

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22279Orig1s000

OTHER REVIEW(S)

There are known safety issues of hydrocodone in the pediatric population and the lack of adequate PK and safety data to inform dosing in the pediatric population. The results of this study will be used to determine the appropriate dose of the proposed drug product to evaluate in a safety study in children ages 6–17 years.

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.

Pharmacokinetics of each active component in proposed drug product in children ages 6–17 years with symptoms of cough associated with upper and lower respiratory tract congestion.

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)
- 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

Continuation of Question 4

- 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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
05/11/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 22279/Hydrocodone/Guaifenesin/pseudoephedrine
Product
Name:Hycofenix

PMR/PMC Description: Conduct an open-label, multi-dose safety and tolerability study in children (aged 6 to 11) and adolescents (aged 12 to 17 years). The population eligible for the study would be children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The study will enroll a total of approximately 400 children aged 6 to 17 inclusive in two cohorts (6-11years, 12 to 17 years). The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6 to 17 years.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/2019</u>
	Study/Trial Completion:	<u>01/2023</u>
	Final Report Submission:	<u>07/2023</u>

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

This product will be approved in the adult population. There are known safety issues of hydrocodone in the pediatric population and the lack of adequate safety data of the proposed drug in the pediatric patient' population ages 6-17.

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."

There are known safety issues of hydrocodone in the pediatric population and the lack of adequate PK and safety data to inform dosing in the pediatric population. The preceding PK study will determine the appropriate dose of the proposed drug product to be evaluated in this safety study in children ages 6–17 years. Safety evaluation will include physical examination, vital signs, ECG, and laboratory tests. The adverse event profile of the patient, as recorded by a parent or guardian, will be the primary endpoint. Although this study is primarily a safety study, the effectiveness of the proposed drug will be assessed. The secondary endpoints will include changes of symptom scores from baseline.

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)
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- Pediatric Research Equity Act
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- 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.

Safety of the proposed drug product in approximately 400 ^{(b) (4)} children ages 6–17 years with symptoms of cough associated with upper and lower respiratory tract congestion.

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

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If so, does the clinical trial meet the following criteria?

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(signature line for BLAs)

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/s/

SALLY M SEYMOUR
05/11/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: May 4, 2015
Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number: NDA 206323
Product Name and Strength: Codeine Phosphate and Chlorpheniramine Maleate Extended-release Tablets, 40 mg/8 mg
Product Type: Multi-ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Spriaso LLC.
Submission Date: August 22, 2014
OSE RCM #: 2014-1976
DMEPA Primary Reviewer: Lissa C. Owens, PharmD
DMEPA Team Leader: Kendra Worthy, PharmD

This review can be found on Drugs@FDA: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206323Orig1s000OtherR.pdf

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/s/

LISSA C OWENS
05/04/2015

KENDRA C WORTHY
05/04/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: April 28, 2015

To: Laura Musse, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Senior Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: NDA 022279
OPDP labeling comments for Hycofenix (hydrocodone bitartrate,
pseudoephedrine hydrochloride, and guaifenesin) Oral Solution CII

In response to DPARP's consult request dated January 13, 2015, OPDP has reviewed the draft labeling (Package Insert [PI] and Carton/Container Labeling) for Hycofenix (hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin) Oral Solution CII (Hycofenix).

PI:

OPDP's comments on the PI are provided directly below and are based on the draft labeling titled "NDA 22279 PI Word.doc" (attached) that was provided via email from DPARP on April 16, 2015.

Carton/Container Labeling:

OPDP has reviewed the proposed container labeling submitted by the sponsor on February 18, 2015 (attached) and available at:
<\\cdsesub4\NONECTD\NDA022279\5752352>. We offer the following comments:

- The proposed container labeling includes the text, [REDACTED] (b) (4)
[REDACTED] This text makes a representation
regarding [REDACTED] (b) (4), thereby creating the need for balancing

risk information on the proposed container labeling. We recommend that this text be deleted.

- We recommend that the established name be presented in a manner consistent with 21 CFR 201.10(g)(2) which requires that the established name be at least half the size of the letters comprising the proprietary name and have a prominence consistent with the proprietary name in terms of type, size, color, and font.

Thank you for your consult. If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
04/28/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 13, 2015

Requesting Office or Division: Division of Pulmonary, Allergy, & Rheumatology Products (DPARP)

Application Type and Number: NDA 22279

Product Name and Strength: Hycofenix (hydrocodone, pseudoephedrine, guaifenesin) Oral Solution 2.5 mg/30 mg/200 mg Per 5 mL

Product Type: Multi-Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Mikart, Inc.

Submission Date: February 20, 2015

OSE RCM #: 2015-82

DMEPA Primary Reviewer: Matthew Barlow, RN, BSN

DMEPA Team Leader: Kendra Worthy, PharmD

1 REASON FOR REVIEW

This is in response to the request by Division of Pulmonary, Allergy, & Rheumatology (DPARP) for DMEPA to review the labels and labeling for any areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The active ingredients hydrocodone, pseudoephedrine, and guaifenesin are currently marketed both separate and in combination as other products. This is a 505(b) (2) submission.

We performed a risk assessment of the proposed container labels and prescribing information to evaluate any areas that may lead to medication errors.

DMEPA finds the proposed prescribing information acceptable. However, the container labeling can be modified to improve readability and differentiation between other Mikart, Inc. products.

4 CONCLUSION & RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

4.1 RECOMMENDATIONS FOR MIKART, INC.

A. All Container Labels

- a. Revise the presentation of the proprietary name from all caps (i.e. HYCOFENIX) to title case (i.e. Hycofenix) to improve readability of the name.

b.

(b) (4)

Consider revising the container labels to adequately differentiate the products to eliminate selection error as they may have the potential to be near each other on a shelf in a pharmacy.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Hycofenix that Mikart, Inc. submitted on February 20, 2015.

Table 2. Relevant Product Information for Hycofenix	
Initial Approval Date	N/A
Active Ingredient	Hydrocodone; Pseudoephedrine; Guaifenesin
Indication	Indicated for symptomatic relief of cough, (b) (4) nasal congestion, and to loosen mucus associated with the common cold.
Route of Administration	Oral
Dosage Form	Oral Solution
Strength	2.5 mg/30 mg/ 200 mg PER 5 mL
Dose and Frequency	10 mL every 4 to 6 hours, not to exceed 4 doses (40 mL) in 24 hours.
How Supplied	Supplied as a violet-colored, black raspberry flavored liquid containing 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin in each 5 mL. It is available in: White HDPE bottles of 16 fl. oz. (473 mL) White HDPE bottles of 4 fl. oz. (118 mL)
Storage	Store solution at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Container Closure	See How Supplied

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Hycofenix labels and labeling submitted by Mikart, Inc. on February 20, 2015.

- Container label
- Full Prescribing Information

(b) (4)



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



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/s/

MATTHEW J BARLOW
03/16/2015

KENDRA C WORTHY
03/16/2015

MEMORANDUM

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

DATE: February 04, 2015

TO: Division of Pulmonary, Allergy, and Rheumatology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 022279 and NDA 022424

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSIS inspected the site listed below within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)
Clinical	Novum Pharmaceutical Research Services	3760 Pecos McLeod, Las Vegas, NV, 89121

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/s/

SHILA S NKAH
02/04/2015

MEMORANDUM

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

DATE: January 20, 2011

TO: Badrul A. Chowdhury, M.D.
Director
Division of Pulmonary and Allergy Products (DPAP)

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

FROM: Martin K. Yau, Ph.D.
Acting Team Leader (Bioequivalence)
Division of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph. *Sam H. Haidar*
Chief, GLP and Bioequivalence Branch
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-279, Hydrocodone
Bitartrate/Pseudoephedrine HCl/Guaifenesin Oral
Solution, Sponsored by (b) (4)

At the request of DPAP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following phase I studies supporting NDA 22-279:

Study Number: S09-0009

Study Title: "A drug-drug interaction and relative bioavailability study of hydrocodone bitartrate 5 mg/guaifenesin 400 mg/pseudoephedrine HCl 60 mg oral solution"

Study Number: S09-0010

Study Title: "A food effect study of hydrocodone bitartrate 5 mg/guaifenesin 400 mg/pseudoephedrine HCl 60 mg oral solution"

The clinical portions of Studies S09-0009 and S09-0010 were conducted at Cetero Research, St. Charles, MO (Cetero - St. Charles). The analytical portions (b) (4)

Following inspection of the clinical (December 28 - 30, 2010) and analytical sites (b) (4) Form FDA 483 was issued at each site (Attachments 1 and 2).

In addition to the studies mentioned above, the inspection at the analytical site also included a follow-up 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. As of this writing, Cetero-St Charles's response to the Form FDA-483 has not been received by DSI. The (b) (4) response to the Form FDA-483 was received on (b) (4) electronically via an e-mail. The 483 observations, (b) (4) written response, and our evaluations follow:

Clinical Site: Cetero Research, St. Charles, MO

1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, you failed to follow the exclusion criteria in protocols S09-0009 and S09-0010. Both protocols state an exclusion criteria of: "Reports a history of clinically significant allergies including food or drug allergies." One subject (009, (b) (6)) from protocol S09-0009, and three subjects (015 (b) (6); 007 (b) (6); 001 (b) (6)) from protocol S09-0010 reported clinically significant drug allergies.

As the four subjects cited in the above 483 observation failed to meet the inclusion/exclusion criteria, data generated from these subjects should be excluded from data analysis.

2. You failed to follow your Standard Operating Procedures regarding transferring subjects from a different study.

Specifically, for protocol S09-0009 an alternate subject (b) (6) was used to replace subject number 015 in the study. This alternate signed the informed consent form on the day of dosing, and exact time was not documented as required by Cetero Research's Standard Operating Procedures (SOP) STL_WI_03_SCT_007, Version 2, "Conducting Inter-study Subject Transfer". This SOP states "If informed consent is obtained on the study day, ensure to document the exact time the informed consent was obtained."

In addition, you failed to follow SOP STL_WI_03_SCT_007, Version 2, "Conducting Inter-study Subject Transfer" regarding the obtaining of the investigator's signature when transferring a subject into a different study. The SOP states "obtain investigator dated signature confirming subject eligibility for study participation in instances when inter-study transfer involves two unrelated studies. In instances when inter-study transfer involves two related studies (e.g., fast / fed), enter N/A in the space provided." This space on subject SAP's Subject Transfer form for the Investigator's signature was left blank.

3. Not all changes in research activity or documentation were approved by the Institutional Review Board prior to implementation.

Specifically, revisions to the informed consent forms for protocol numbers S09-0009 and S09-0010 were only reviewed by the Institutional Review Board Chairman and not by the entire Institutional Review Board before implementation.

Although the observations cited in Items 2 and 3 above are objectionable, these observations should not affect the study outcomes. However, Cetero-St. Charles should correct these objectionable practices in their current and future studies.

4. You failed to retain an adequate quantity of the investigational drug, Hydrocodone Bitartrate 5 mg/Guaifenesin 400 mg/Pseudoephedrine HCL 60 mg oral solution, for protocols S09-0009 and S09-0010, in order to permit FDA to perform five times all relevant tests required in the application.

Although the study reserves retained at the clinical site are less the 'five times' quantity, the volumes of test and reference oral solutions collected by the ORA field investigator during the FDA inspection should be sufficient to allow the FDA lab in St. Louis to carry out the necessary testing.

Analytical Site: [REDACTED] (b) (4)

1. Failure to identify and document procedures for "prep" run injections as described in the Form FDA-483 issued to [REDACTED] (b) (4). Specifically, in studies S09-009 and S09-0010, analytical runs were 'prep' for one to several times using run samples (i.e., samples could be uninjected subject samples, calibration standard and/or quality control samples (QCs)), and the number of samples in the 'prep' runs varied greatly. No explanation, rationale, or justification of how the 'prep' runs were carried out was provided by [REDACTED] (b) (4). Analysts that conducted the 'prep' runs did not follow any written procedure and did not document any of the actions they completed during the performance of the "prep" runs.

In their written response (Attachment 3), [REDACTED] (b) (4) stated that 'prep' runs were performed to equilibrate and to ensure optimal performance of the LC/MS/MS system before being used for study sample analysis. However, they also acknowledged that study samples not yet analyzed should not be used to equilibrate the LC/MS/MS system. They said that the practice of using study samples not yet analyzed in the 'prep' runs was stopped in May 2009 shortly after the bioanalytical work of studies S09-0009 and S09-0010 was completed.

The above 483 observation was issued to [REDACTED] (b) (4) because the sample analyses of studies S09-009 and S09-0010 were conducted at the time period when study samples not yet analyzed were used in the 'prep' run. DSI has concerns regarding the integrity of the bioanalytical data generated in these two studies due to the following reasons:

- A. In a letter dated [REDACTED] (b) (4) a former employee alleged that laboratory staff of [REDACTED] (b) (4) altered the outcome of analytical runs (i.e., runs were 'fixed' through 'prep' runs injected prior to the actual subject sample batch). An evaluation of the

allegations by a third party [REDACTED] (b) (4) [REDACTED] for the audit report) as well as by DSI during the [REDACTED] (b) (4) [REDACTED] inspections raised concerns regarding the integrity of the bioanalytical work generated by [REDACTED] (b) (4) [REDACTED]. Specifically, the basic elements of the analytical process are in questions due to documentation irregularities. For example:

(a) In studies S09-0009 and S09-0010, there is no SOP nor any Analytical Procedure (AP) sheets to document what samples was injected to condition the LC/MS/MS system or what was done afterwards. Many prep runs were repeated several times and the number of samples in the 'prep' runs varied greatly, but the rationale behind these variations, what if anything was altered between the prep runs, and the outcome of the prep run injections were not documented. For example, DSI found during the [REDACTED] (b) (4) [REDACTED] inspection that samples in pseudoephedrine run 16 in study S09-0009 were injected multiple times. Specifically, the 'prep' run for pseudoephedrine run 16 contained 20 samples listed as standards, QCs, and blanks. After the official injections on LC/MS/MS system 92, all samples in run 16 were re-injected officially as run 17 on LC/MS/MS system 75 with a 'prep' run for run 17 containing 51 samples. The type of samples in 'prep' run 17 was not listed and only vial number was assigned to each of these prep samples. The pseudoephedrine QCs results of runs 16 and 17 were similar (mean difference = 1.5%) but the pseudoephedrine concentrations of the subjects samples in runs 16 and 17 were very different (about 14%), suggesting possible manipulation of standard and QC samples to impact the results. After the official runs 16 and 17, all samples in these two runs were re-injected again, but these re-injections were not recorded on the AP sheets and pseudoephedrine concentration of these re-injections were not included in the run study binders. The above example of documentation and procedural irregularities makes it difficult to dismiss allegations of improper procedures and possible data manipulation.

According to the complainant's allegations, certain chemist in the laboratory would 'prep' the calibration standards and quality control samples in an attempt to review the results and make correction (i.e., by

substituting or spiking standard and QC samples) to the standard curve and quality control samples prior to injecting the run into the pertinent project folder; blank & blank/blank were fixed to assure they were clean. No direct evidence was uncovered during the inspection to confirm these allegations. Overall, due to documentation irregularities, it is difficult to dismiss allegations of improper procedures and possible data manipulation to cause official runs to pass, when in fact they would have failed.

(b) During the [REDACTED] (b)(4) inspections, DSI scientists only looked at prep runs that were provided in the electronic study folder (i.e., official prep runs). It is possible that there were other prep runs injected but were not put in the electronic study folders, as alleged by the complainant. DSI found that it is impossible to determine this during the inspection.

(c) There were notes found written by laboratory staff suggesting improper conduct. Specifically, a note written by [REDACTED] (b)(6) the MS supervisor was found and it stated "*Please correct AP sheets to read guard column - Onyx C18. We may not have had them for this study but always refer to what's on the AP sheet*" This was cited in the third party audit report as clearly a directive to falsify data. In addition, the third party auditor also reported there are notes to the instrument operators that said "*if the 'prep' does not pass, save the run for the supervisor to inject the following days*". This practice by staff in the laboratory raised questions on the integrity of their work.

B. In agreement with the [REDACTED] (b)(4) DSI inspectional findings, the present DSI inspection also concludes that the firm's investigation was insufficient to thoroughly address the allegation of "fixing" runs. As stated in the [REDACTED] (b)(4) EIR cover memo, [REDACTED] (b)(4) [REDACTED] lacked adequate documentation and written procedures to verify the identity of samples in the 'prep' runs. Instead, [REDACTED] (b)(4) made assumptions about the identity of such samples for the conduct of their investigation. Given the lack of confirmatory information, it is not possible to determine if the

firms's investigation could identify runs affected by "fixing" versus those without such manipulation.

C. As reported in the previous EIR cover memo to DPAP and OCP2 on (b)(4) internal investigations of (b)(4) (b)(4) found unexplained discrepancies between the initial system equilibration result ('prep' run) and the actual rerun results 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. In the (b)(4) FDA inspection, (b)(4) (b)(4) still could not explain the discrepancy. Thus falsification of analytical batches can not be ruled out for studies conducted by (b)(4) before June 2009.

2. Review of the records for the extraction of subject samples for the determination of guaifenesin and pseudoephedrine concentrations in plasma verified that the records were falsified as described in the Form FDA-483 issued to (b)(4). Examples include analytical Run 5 and Run 6 for guaifenesin and analytical Run 4 for pseudoephedrine in Study S09-0010.

As cited above, extraction records of some analytical runs in Study S09-0010 were falsified. Moreover, during the (b)(4) inspection, DSI inquired and learned that falsification occurred during weekday extractions as well, although it was not as frequent as on weekends. (b)(4) confirmed that some analysts that falsified extraction records on the weekends also committed falsifications on weekdays as well. In the written response, (b)(4) stated that the falsification was limited to the date/time of extraction. However, from DSI viewpoint, the falsification itself along with the concerns stated in Item 1 above, question the integrity of the activities carried out at (b)(4)

3. Stability was not demonstrated under the same conditions as in the study samples. Specifically, samples in stability experiments contained either hydrocodone/chlorpheniramine, fexofenadine/pseudoephedrine, or guaifenesin, whereas study samples in Study S09-0010 contained hydrocodone, pseudoephedrine, and guaifenesin; study samples in Study S09-0009 contained combinations of

hydrocodone, pseudoephedrine, and guaifenesin or hydrocodone and homatropine.

(b) (4) acknowledged this observation and agreed to establish storage stability for all analytes (hydrocodone, guaifenesin, pseudoephedrine, and homatropine) in the presence of each other. In the written response, (b) (4) stated these stability experiments should be completed in May 2011.

4. Documentation for re-injections of analytical runs was not contemporaneous. For example, samples in Study S09-0009 Run 5 were analyzed for guaifenesin on April 4, 2009. Majority of samples in Run 5 were re-injected on April 7, 2009. However, there was no documentation at that time to explain or justify these re-injections. Explanation was later provided, during the course of an investigation of allegations of improprieties, in a LC/MS/MS supervisor memo

(b) (4)

(b) (4) acknowledged the lack of contemporaneous documentation in their written response and said their practices now mandate documenting all sample re-injections with an appropriate reason for the activity. This observation added to DSI's concerns for documentation irregularities found at this firm

Conclusions

Following DSI's evaluation of the inspectional findings, DSI recommends the following:

- Study S09-0009 and S09-0010 should not be accepted for review at this time due to concerns raised by DSI and the incomplete investigation of complaint allegations by (b) (4) (see analytical 483 items 1 and 2 above).
- Appropriate freeze/thaw and long term frozen storage stability to demonstrate analyte stability under the same conditions as the subject samples (i.e., hydrocodone, guaifenesin, pseudoephedrine, and/or homatropine combinations) are needed to confirm samples integrity during sample processing and storage.

Page 9 - NDA 22-279, Hydrocodone Bitartrate/Pseudoephedrine
HCl/Guaifenesin Oral Solution

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

Martin K. Yau 1/20/11

Martin K. Yau, Ph.D.

Final Classification:

Cetero Research, St. Charles, MO - VAI

(b) (4)

cc:

CDER DSI PM TRACK (e-mail)
OC DSI/Ball/Viswanathan/Haidar/Yau/CF
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OTS/OCP/DCPII/Agrawal/Wang/Xu
HFR-SW1580/Peacock
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XIKUI CHEN
01/21/2011



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

Date: July 30, 2009

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

Through: Solomon Iyasu, MD, MPH
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Subject: Epidemiological Analysis of Hydrocodone containing Products

Drug Name(s): hydrocodone containing products

Submission Number: various

Application Number: 22-279, (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)¹ 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.

¹ 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 (b) (4) over (b) (4) prescriptions in 2004 (b) (4) prescriptions in 2007 (b) (4) (%). The number of prescriptions for respiratory hydrocodone products were (b) (4) prescriptions in 2004 to (b) (4) in 2007.

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)
Hydrocodone Prescriptions				
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
Abuse Ratios*				
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⁺</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
Hydrocodone Prescriptions				
TOTAL Hydrocodone Market	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
Adverse Reaction Ratios*				
Both Analgesic and Respiratory Products	2.4	3.7	4.3	4.9
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>	<i>2004</i>	<i>2005</i>	<i>2006</i>	<i>2007</i>
Analgesic and Respiratory Products	46,924	56,037	67,043	77,560
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>				
Analgesic and Respiratory Products	26,756	44,221	54,533	64,779
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	1.8	1.3	1.2	1.2
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

⁺ 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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/s/

CATHERINE M DORMITZER
08/21/2009

HINA S MEHTA
08/26/2009

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Pulmonary and Allergy Products

Application Number: NDA 22-279

Name of Drug: hydrocodone bitartrate, pseudoephedrine hydrochloride and guaifenesin Oral Solution

Applicant: [REDACTED] (b) (4)

Material Reviewed:

Submission Date(s): August 22, 2008

Receipt Date(s): August 22, 2008

Submission Date of Structure Product Labeling (SPL): August 22, 2008

Type of Labeling Reviewed: Word/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the proposed labeling.

General Comments

1. For specific requirements on the content and format of labeling for human prescription drug and biologic products refer to 21 CFR 201.57. Also see Draft Guidance for Industry: Labeling for human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements (Implementation Guidance).
2. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling format.
3. Ensure that the type size for all labeling information, headings, and subheadings are a minimum of 8 points except for trade labeling. This also applies to Contents and the full prescribing information (FPI). 21 CFR 201.57(d)(5).

Highlights

4. [REDACTED] (b) (4) This applies only to Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions.

Indications and Usage

5. A colon needs to be placed after the words “indicated for”.

Dosage Forms and Strengths

6. [REDACTED] (b) (4)
This section should contain a concise summary of dosage forms and strengths

Full Prescribing Information Contents

7. [REDACTED] (b) (4)

Full Prescribing Information

8. Any required section, subsection or specific information that is clearly inapplicable may be omitted from the FPI. However, the numbering does not change. The subsection Pharmacokinetics should continue to be numbered as 12.3 [REDACTED] (b) (4)

Recommendations

The recommendations and comments were conveyed to the applicant in the filing letter issued on November 3, 2008.

Carol Hill
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: chill/June 18, 2009
Revised/Initialed: Barnes/ June 19, 2009
Finalized: chill/June 19, 209

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/s/

Carol F. Hill
6/19/2009 07:51:24 PM
CSO

Sandra Barnes
7/23/2009 01:05:00 PM
CSO



**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 15, 2009

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

Through: Mark Avigan, MD, CM, Director
Lanh Green, Pharm.D., MPH, Team Leader
Division of Pharmacovigilance (DPV) I
Office of Surveillance and Epidemiology (OSE), CDER

From: Debra Ryan, Pharm.D., MBA, Safety Evaluator
Division of Pharmacovigilance (DPV) I

Subject: Review of fatalities

Drug Name(s): Hydrocodone/Pseudoephedrine/Guaifenesin Oral Solution

Application Type/Number: NDA# 22-279

Applicant/sponsor: (b) (4)

OSE RCM #: 2009-632

1 INTRODUCTION

This consult is in response to a request from the Division of Pulmonary and Allergy Products (DPAP) to assess the high death rates in the sponsor's (b) (4) data analysis submitted for New Drug Application (NDA) # 22-279. The submitted NDA is for a combination antitussive, decongestant, expectorant oral solution containing hydrocodone, pseudoephedrine, and guaifenesin.

Referencing the FDA's Adverse Event Reporting System (AERS), (b) (4), submitted "FDA Adverse Event Reporting System Summarization Report" which identified death as an outcome in 62.15% of the adverse events (AEs) reported for hydrocodone, 6.97% of the AEs reported for pseudoephedrine, and 15.2% for AEs reported for guaifenesin. In the report summary the authors state the following reasons for the high percentage of deaths: a) the reporting collection appears to have been influenced significantly by multiple product exposures and co-reporting, b) sources of data and reporter profile are strongly shifted toward serious (including fatal) reporting, and c) the AE profile for reports is typical of prescription narcotics and therefore show a disproportionate reporting of overdoses, suicides, central nervous system depression, medication misuse, and addiction liability. In conclusion, (b) (4) identified no new AE issues of importance as a result of their analysis of AERS data.

The original DPAP request was to provide an analysis of AERS data for deaths, several AEs with high "incidence" and by various age groups to confirm the adverse event profile submitted by the sponsor. Upon further discussion with DPAP the consult is amended to review the sponsor's analysis and the high rate of death associated with the use of hydrocodone.

2 MATERIAL REVIEWED

2.1 AERS Search Strategy

Four separate searches were conducted.

- The AERS database was searched for all events using product names: hydrocodone, hydrocodone amberlite, hydrocodone bitartrate, hydrocodone polistirex, hydrocodone resin complex, hydrocodone tannate, hydrocodone terephthalate, hydrocodone, H-2 from January 1, 2003 through December 31, 2007. The time frame coincides with the time frame used by the sponsor.
- The same criteria were used on the second search further selecting for those cases that reported death as an outcome.
- The AERS database was searched for all events for product combinations: hydrocodone & guaifenesin, hydrocodone & pseudoephedrine, and hydrocodone & pseudoephedrine & guaifenesin for the time period January 1, 2003 through December 31, 2007.
- An additional customized search of the AERS database, performed by Lynette Swartz, for the brand names of antitussive products containing hydrocodone was also conducted.

¹ (b) (4). New Drug Application #022-279. Module 5.3.1.2 Safety Report and related information. Adverse Event Reporting System Summarization Report. August 15, 2008. Located at Food and Drug Administration, White Oak, Silver Spring, MD.

Results of the search selecting death as an outcome (N=2141) were exported to Excel and systematically searched as follows:

- Filtered data and selected for all reports designating the reporting source as literature and searched the narratives for the word “literature” (N=1329)
- Searched the narrative and reaction fields for the word “overdose” (N=518)
- Searched the narrative and reaction fields for the word “suicide” (N=59)
- Searched the narrative for the word “medical examiner” (N=80)
- Searched the narrative and reaction fields for the words “drug abuse”, “polypharmacy”, “polysubstance” and “drug toxicity” (N=24)
- Searched the narrative and reaction field for the word “methamphetamine” (N=17)
- Searched the narrative and reaction field for the word “accident” (N=7)
- Searched the narrative for the word “cancer” (N=8)

2.2 Limitations of AERS

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2.3 Results

The search of the AERS database retrieved 3641 reports (crude counts) from January 1, 2003 through December 31, 2007; all for products containing hydrocodone (e.g., Vicodin, Lortab, Tussionex, etc). Of these reports, 2141 (59%) reported death as an outcome.

These 2141 reports are associated with a variety of combination products containing hydrocodone in various dosage forms. The ingredient hydrocodone is only available in combination with other ingredients. A spontaneous reporting system such as AERS cannot reliably pull out reports for a specific product. Even the customized search was unable to narrow the number of meaningful reports.

A number of reports (N=1329) are generated from sponsor identified events from the literature as required by regulation 21CFR 600.80. The events are published in reports of exposure to substances for overdoses, accidents, and deaths from unknown causes. The majority of these reports originated from:

- “Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System” (TESS), published in the American Journal of Emergency Medicine.

- Florida Department of Law Enforcement (FDLE) titled: "Report of Drugs Identified in Deceased Persons by Florida Medical Examiners" in the United States of America.
- Medical Examiners Commission and Florida Department of Law Enforcement (FDLE) publication report from the USA of "HYDROCODONE toxicity and OXYCODONE toxicity coincident with HYDROCODONE therapy".

In addition to the above literature sources there are reports from professional journals, litigations, and criminal investigations.

The search strategy identified 2042 cases of what can generally be described as intentional or accidental overdose with multiple drugs and the resultant sequelae. Reading through the remaining case narratives (N=99) there are reports of multiple drug ingestion with cause of death being undetermined or secondary to cardiac arrest, multiple organ failure, hypoxemia, shock, hypersensitivity reaction, ischemic cardiomyopathy, adult respiratory distress syndrome, post-operative complications, and cancer (N=89).

Only 10 of the 2141 cases identified one hydrocodone combination as a sole suspect product. There are two duplicate reports leaving a total of 8 case reports. Four of the 8 reports are for oral tablet formulations and cause of death reported is: cardiac arrest, cancer, and two consumer reports that pain medication had contributed to the death. Four of the 8 reports are for Tussionex and in 3 of the Tussionex cases the cause of death is not reported. One case associated with Tussionex reports death due to cardiac arrhythmia secondary to a viral process.

AERS identified 20 cases (crude counts) reporting events associated with hydrocodone & guaifenesin (N=16) and hydrocodone & pseudoephedrine (N=4). Six of the cases (30%) report death as an outcome. Death was due to multiple drug ingestion (N=3), overdose secondary to a medication error (N=1), and cause not reported (N=2). Seven of the cases report CNS events (N=3), gastrointestinal event and hypersensitivity (N=1), hypersensitivity reaction (N=1), increased blood pressure and palpitations (N=1), and drug ineffective (N=1). Seven of the cases are excluded from review because: hydrocodone combination product is not the suspect drug (N=4), combination product reported does not include hydrocodone (N=1), and report is notification of potential for error due to product labeling (N=2).

AERS identified no reports for products containing hydrocodone and pseudoephedrine and guaifenesin.

3 DISCUSSION

The high percentage of deaths reported in this case series reflects a reporting bias from three major sources (eg. TESS and FDLE). These sources only report fatal events associated with exposure to toxic substances or opioid related products. Nearly 99% (2131 of 2141) of the AERS reports include the ingestion of multiple opioid containing products and multiple adverse reactions including overdoses, suicides, polypharmacy, and polysubstance abuse. Generally, in the narrative, hydrocodone is just one of many opiates identified and opiates are only one class of drug reported as suspect products. This high percentage and causality of death associated with hydrocodone mirror the results submitted by (b) (4)

AERS cases for antitussive liquid formulations containing the same ingredients, though not in the same combination as the proposed NDA, report labeled events. Those reporting death as an outcome mirror the causes of death reported for hydrocodone containing products: multiple drug ingestion and intentional or accidental overdose.

4 CONCLUSIONS

This review does determine that the high number of death reports for hydrocodone (59%) reported in AERS are secondary to an ingestion of multiple drug products, either accidentally or intentionally, and of themselves do not signal a safety risk for hydrocodone. AERS cases for antitussive liquid formulations that contain similar ingredients as the NDA report labeled events. In addition, AERS database did not identify adverse event reports associated with products containing hydrocodone and pseudoephedrine and guaifenesin. Therefore, a safety profile for this specific combination product, as proposed by (b) (4) can not be assessed based on AERS data.

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/s/

Debra Ryan
5/15/2009 06:28:28 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
5/18/2009 10:11:50 AM
DRUG SAFETY OFFICE REVIEWER

Lanh Green
5/22/2009 03:30:21 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: March 27, 2009

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

Through: Michael Klein, Ph.D., Director
Lori A. Love, M.D., Lead Medical Officer
Controlled Substance Staff (CSS)

From: Jovita Randall-Thompson, Ph.D., Pharmacologist (CSS)

Subject: Consult on NDA 22-279 - Hydrocodone, Pseudoephedrine, Guaifenesin Oral Solution, containing USP 2.5 mg, USP 30 mg and USP 20 mg, respectively per teaspoon (5mL)
Indicated for symptomatic relief of cough, nasal congestion and to loosen
[REDACTED] (b) (4)
Sponsor: [REDACTED] (b) (4).

Materials Reviewed

First submission of NDA 22-279 was on December 5, 2008.

Background

This memorandum provides CSS's consultation on the abuse liability of NDA 22-279. NDA 22-279 included the Sponsor's proposed label for the drug combination, hydrocodone, pseudoephedrine and guaifenesin formulated in an oral solution. The Sponsor provided no other information pertaining to the abuse liability of the combination product. The NDA is a 505(b)(2) application with reference to hydrocodone efficacy established in DESI Notice #5213 (37 F.R. 7827) and NDAs of such products as Hycodan and Tussionex and the OTC Monographs for pseudoephedrine HCl and guaifenesin. Specifically, the Division of Pulmonary and Allergy Products requested that CSS evaluate [REDACTED] (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution for abuse potential.

The proposed recommended dosage for adults [REDACTED] (b) (4) is two teaspoonfuls (10 ml) every 4 hrs not to exceed 4 doses in 24 hrs. [REDACTED] (b) (4)

[REDACTED]

Conclusions and Recommendations (to be conveyed to the Sponsor)

After completing a review of NDA 22-279 - (b)(4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution, CSS concludes the following:

- (b)(4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution appears to meet the statutory definition (b)(4) of the Controlled Substances Act (CSA). This combination drug product, however, contains two drugs, hydrocodone and pseudoephedrine, that each on their own has abuse potential and an additional drug, guaifenesin.
- Current available information in the public domain indicates that products containing hydrocodone alone and in combination with other substances each have an abuse potential.
- The Sponsor has not provided specific data in the NDA to evaluate the abuse potential of (b)(4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution in order to (b)(4) recommend labeling in the *Drug Abuse and Dependence* section.

CSS Recommendation

- The Sponsor needs to fully characterize the abuse potential of the combination product, (b)(4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution, specifically to evaluate how the addition of the nonnarcotic components (pseudoephedrine and guaifenesin) affect the abuse potential of the product relative to hydrocodone alone which is listed as a Schedule II substance in the CSA.
- As part of this assessment, the Sponsor should conduct well designed animal and human abuse potential studies. The human abuse potential studies are pharmacology studies conducted in nondependent, opioid experienced volunteers given a placebo and positive control. In this case, the positive control is hydrocodone given alone that is then compared to the test drug, in this case (b)(4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. Hydrocodone should also be included as a positive control when conducting animal studies.
- CSS will review protocols and provide comments to the Sponsor prior to beginning studies.

CSS Review

Hydrocodone

Hydrocodone is a Schedule II controlled substance, opioid analgesic and antitussive agent, chemically similar to other narcotic agonists (e.g. oxycodone, codeine, morphine). Hydrocodone produces discriminative properties similar to such drugs as fentanyl (¹Meert and Vermeirsch, 2005) and morphine (²Lelas et al., 1999). Hydrocodone also maintains intravenous self-administration behavior in rats (³Tomkins et al., 1997), thereby demonstrating reinforcing efficacy. Currently, all approved hydrocodone combination analgesic and antitussive products are Schedule III controlled substances.

Pseudoephedrine

Pseudoephedrine is a sympathomimetic amine used as a decongestant. There are off-label uses of pseudoephedrine for its stimulant properties to stay awake and to increase alertness or awareness. The discriminative generalization of pseudoephedrine at high doses to an amphetamine interoceptive cue is reported (⁴Tongjaroenbuangam et al., 1998). Isomers of pseudoephedrine display some 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 (⁵Wee et al., 2004), a protein extensively documented to be a major component in mechanisms underlying the reinforcing/rewarding properties of abused drugs. Pseudoephedrine is also regulated under the Comprehensive Methamphetamine Control Act of 1996 (US Public Law 104-237) and the Methamphetamine Anti-Proliferation Act (MAPA [US Public Law 106-310], title XXXVI of the Children's Health Act of 2000).

Guaifenesin

Guaifenesin is an expectorant which increases the output of phlegm (sputum) and bronchial secretions. It is mainly found in over the counter cough and allergy products. Little is known about the abuse or dependence of guaifenesin when taken alone or in

¹ Meert, T.F. and H.A. Vermeirsch. "A preclinical comparison between different opioids: antinociceptive versus adverse effects." *Pharmacol Biochem Behav* 80.2 (2005): 309-26.

² Lelas, S., et al. "Inhibitors of cytochrome P450 differentially modify discriminative-stimulus and antinociceptive effects of hydrocodone and hydromorphone in rhesus monkeys." *Drug Alcohol Depend*, 54.3 (1999): 239-49.

³ Tomkins D.M., Otton S.V., Joharchi N., Li N.Y., Balster R.F., Tyndale R.F. and Sellers E.M. "Effect of cytochrome P450 2D1 inhibition on hydrocodone metabolism and its behavioral consequences in rats. *Journal of Pharmacology and Experimental Therapeutics*." 280 (1997): 1374-1382.

⁴ Tongjaroenbuangam, W., Meksuriyen, D., Govitrapong, P., Kotchabhakdi N. and Baldwin, B.A. "Drug discrimination analysis of pseudoephedrine in rats." *Pharmacol Biochem Behav* 59.2 (1998): 505-10.

⁵ Wee S, Ordway G.A. and Woolverton W.L. "Reinforcing effect of pseudoephedrine isomers and the mechanism of action." *European Journal of Pharmacology*, 493 (2004): 117-125.

combination with other CNS depressants or stimulants. Guaifenesin is known to have some analgesic/sedative and muscle relaxant effects. The effect of guaifenesin on the abuse potential of hydrocodone in combination products has not been formally studied.

Abuse Potential of (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution

Current brands with the hydrocodone, pseudoephedrine and guaifenesin combination include: Drixol HD, Entex HC, Hydro-Tuss XP, Hydrotussin HD, Nalex Expectorant, Poly-Tussin XP, Pseudatex HC, Su-Tuss HD Elixir and Vanacon (see the following link for a list of drugs with this drug combination: <http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=1060&n=Guaifenesin%3b+Hydrocodone%3b+Pseudoephedrine>). Some of these drugs and others formulated with the specific combination hydrocodone, pseudoephedrine and guaifenesin were removed from the market by the FDA (see Guidance for FDA staff and industry: marketed unapproved drugs-compliance policy guide; <http://www.fda.gov/cder/guidance/6911fnl.pdf>). This is due to recent measures taken by the FDA to remove drugs from the market that are not approved under FDA regulation and standards.

Potential adverse effects associated with the extended use of the hydrocodone, pseudoephedrine and guaifenesin combination drug products include substance abuse and or physical dependence with onset of a severe withdrawal syndrome. Clinical and epidemiological reports and controlled clinical abuse liability studies clearly identify a potential for abuse of hydrocodone when administered alone and in combination with other substances (⁶Becker et al., 2008; ⁷Zacny et al., 2005; ⁸Zacny and Gutierrez, 2009). Prolonged use may also lead to tolerance to the therapeutic effects of this combination. Increases in the misuse and diversion of hydrocodone combination drugs are reported (⁶Becker et al., 2008). Recently, the widespread nonmedical use, including abuse, of hydrocodone containing products was documented in a number of epidemiological reports including reports utilizing data from the Drug Abuse Warning Network and the National Survey on Drug Use and Health (⁶Becker et al., 2008; ⁹Kelly et al., 2008; ¹⁰Wu et al., 2008).

⁶ Becker W.C., Sullivan L.E., Tetrault J.M., Desai R.A. and Fiellin D.A. "Non-medical use, abuse and dependence on prescription opioids among U.S. adults: Psychiatric, medical and substance use correlates." *Drug and Alcohol Dependence*, 94 (2008): 38-47

⁷ Zacny, J.P., Gutierrez, S., Bolbolam, S.A. "Profiling the subjective, psychomotor, and physiological effects of a hydrocodone/acetaminophen product in recreational drug abusers." *Drug and Alcohol Dependence*, 78(2005):243-252.

⁸ Zacny, J.P., Gutierrez, S. "Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers." *Drug and Alcohol Dependence*, 101(2009):107-114.

⁹ Kelly J.P., Cook S.F., Kaufman D.W., Anderson T., Rosenberg L. and Mitchell A.A. "Prevalence and characteristics of opioid use in the US adult population." *Pain*, in press (2008).

¹⁰ Wu L.T., Pilowsky D.J and Patkar A.A. "Non-prescribed use of pain relievers among adolescents in the United States." *Drug and Alcohol Dependence*, 94 (2008): 1-11.

Based on all of the above, the information reviewed by CSS supports that (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution has abuse potential and supports its control under the CSA.

Scheduling of (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution

While hydrocodone substance is listed in Schedule II of the Controlled Substances Act, hydrocodone combination products currently approved for use in the United States are all placed in Schedule III.

Under 21 U.S.C. 812(c)(Schedule III)(d)(4), *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.

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

Finally, the components pseudoephedrine and guaifenesin in the (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution each meet the last criteria, namely 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 immediate-release guaifenesin (21 CFR 341.78 (a) and (21 CFR 341.78 (d)) indicate that the pseudoephedrine HCl and guaifenesin present in (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution are at therapeutic doses as a nasal decongestant and expectorant, respectively.