# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208085Orig1s000

# OTHER REVIEW(S)

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

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | April 12, 2018 |
| To: | Badrul Chowdhury, MD, PhD<br>Director<br>**Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Marcia Williams, PhD<br>Team Leader, Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Nyedra W. Booker, PharmD, MPH<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Kyle Snyder, PharmD<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Medication Guide (MG) |
| Drug Name (established name): | TRADENAME (hydrocodone bitartrate and guaifenesin) |
| Dosage Form and Route: | tablets, for oral administration, CII |
| Application Type/Number: | NDA 208085 |
| Applicant: | ECI Pharmaceuticals, LLC |

## 1 INTRODUCTION

On October 30, 2017 ECI Pharmaceuticals, LLC submitted for the Agency's review a Resubmission of New Drug Application (NDA) 208085 for hydrocodone bitartrate and guaifenesin tablets, for oral administration. This resubmission was in response to a Complete Response (CR) Letter issued to the Applicant on February 13, 2017 citing Clinical Pharmacology, Product Quality and Facility Inspections deficiencies.

The 505(b)(2) original NDA for hydrocodone bitartrate and guaifenesin tablets, for oral administration was submitted for the Agency's review on April 13, 2016, with the proposed indication to provide symptomatic relief of cough and to loosen mucus associated with the common cold in patients 18 years of age and older.

On January 11, 2018 the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) issued a Safety Labeling Change (SLC) Notification- Prior Approval Supplement (PAS) Request: Update Labeling, to holders of approved drug and biological product applications for codeine and hydrocodone containing opioid antitussives. The purpose of the SLC-PAS was to request updates to the labeling based on new safety information regarding a change in the benefit risk assessment for prescription codeine and hydrocodone containing opioid antitussives, particularly regarding use in children and adolescents.

On March 6, 2018 the Agency provided ECI Pharmaceuticals, LLC with a Medication Guide (MG) template that matches the MGs being implemented as part of the SLC for the codeine and hydrocodone containing opioid antitussives.

On March 12, 2018 the Applicant submitted a Labeling Amendment to provide updated labeling including a revised MG based on the opioid antitussive products MG template.

This collaborative review is written by Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by DPARP on April 3, 2018 and November 13, 2017, respectively, for DMPP and OPDP to review the MG for hydrocodone bitartrate and guaifenesin tablets, for oral administration.

## 2 MATERIAL REVIEWED

- Draft hydrocodone bitartrate and guaifenesin tablets, for oral administration MG received on March 12, 2018 and received by DMPP and OPDP on April 3, 2018.
- Draft hydrocodone bitartrate and guaifenesin tablets, for oral administration Prescribing Information (PI) received on March 12, 2018 and received by DMPP and OPDP on April 3, 2018.
- MG template for opioid antitussive products submitted to the Applicant by DPARP on March 6, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of

60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the MG template for opioid antitussive products, dated March 6, 2018.

## 4 CONCLUSIONS

The MG is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/
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NYEDRA W BOOKER
04/12/2018

KYLE SNYDER
04/12/2018

MARCIA B WILLIAMS
04/12/2018

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

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

# Memorandum

**Date:** April 6, 2018

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

**From:** Kyle Snyder, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Kathleen Klemm
Team Leader (OPDP)

**Subject:** OPDP Labeling Comments for hydrocodone bitartrate and guaifenesin tablets, for oral administration, CII

**NDA**: 208085

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In response to DPARP's consult request dated November 13, 2017, OPDP has reviewed the proposed prescribing information (PI), Medication Guide (MG), and carton/container labels for NDA 208085, hydrocodone bitartrate and guaifenesin tablets, for oral administration, CII.

**PI and MG**: OPDP's comments on the proposed labeling are based on the draft PI and MG received by electronic mail from DPARP on April 3, 2018. Comments on the proposed PI are provided below. A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the MG, and comments on the proposed MG will be sent under separate cover.

**Carton and Container Labeling:** OPDP has reviewed the proposed labels submitted by ECI Pharmaceuticals, LLC, on April 13, 2016, and we have no comments at this time.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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KYLE SNYDER
04/06/2018

**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:** | February 15, 2018 |
| **Requesting Office or Division:** | Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) |
| **Application Type and Number:** | NDA 208085 |
| **Product Name and Strength:** | (b) (4) (hydrocodone bitartrate and guaifenesin) Tablets 5 mg/400 mg |
| **Product Type:** | Multi-ingredient product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | ECI Pharmaceuticals, LLC. |
| **FDA Received Date:** | November 28, 2017 |
| **OSE RCM #:** | 2016-892-1 |
| **DMEPA Safety Evaluator:** | Lissa C. Owens, PharmD |
| **DMEPA Team Leader:** | Sarah K. Vee, PharmD |

## 1 REASON FOR REVIEW

This review evaluates the proposed container labels and prescribing information, for (b) (4) (hydrocodone bitartrate and guaifenesin) tablets, NDA 208085, submitted on November 28, 2017. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the labels and labeling for areas of vulnerability related to medication errors.

## 2 REGULATORY HISTORY

On February 13, 2017, NDA 208085 received a complete response (CR). DMEPA originally reviewed the labels and labeling during the previous review cycle; however, our comments were not sent to the applicant. The application was resubmitted on October 30, 2017.

## 3 MATERIALS REVIEWED

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

**Table 1. Materials Considered for this Label and Labeling Review**

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

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed labels and labeling to determine whether there are any significant concerns in terms of safety, related to preventable medication errors.

We find the proposed container label can be improved; specifically, the usual dosage statement can be improved to maintain consistency with the prescribing information. Therefore, we provide recommendations in Section 5.1 for the Applicant to address this deficiency.

## 5 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container label can be improved to promote the safe use of the product.

## 5.1 RECOMMENDATIONS FOR ECI PHARMACEUTICALS LLC

We recommend the following be implemented prior to approval of this NDA:

**A. Container Label**

1. Revise the usual dosage statement to read 'One tablet every 4 to 6 hours, not to exceed 6 tablets in 24 hours' to maintain consistency with the prescribing information.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

## APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for [redacted] received on November 28, 2017 from ECI.

| **Table 2. Relevant Product Information for** [redacted] | |
|---|---|
| **Initial Approval Date** | N/A |
| **Active Ingredient** | hydrocodone bitartrate and guaifenesin |
| **Indication** | Symptomatic relief of cough, to [redacted] loosen [redacted] (mucus) [redacted] |
| **Route of Administration** | Oral |
| **Dosage Form** | Tablets |
| **Strength** | 5 mg/400 mg |
| **Dose and Frequency** | One tablet every 4 to 6 hours not to exceed 6 tablets in 24 hours |
| **How Supplied** | White, capsule-shaped, debossed "ECI" on one side and "601" on the other containing 5 mg hydrocodone bitartrate and 400 mg guaifenesin. It is available in:<br>White HDPE bottles of 30 Counts: NDC 51293-601-30<br>White HDPE bottles of 100 Counts: NDC 51293-601-01<br>White HDPE bottles of 500 Counts: NDC 51293-601-05 |
| **Storage** | Store at 20° to 25°C (68° to 77°F) |
| **Container Closure** | White high-density polyethylene (HDPE) round bottles with a CRC closure and cottons |

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 13, 2018, we searched DMEPA's previous reviews using the terms, hydrocodone bitartrate and guaifenesin. Our search identified one previous review[a], the application received a Complete Response (CR) and therefore our recommendations were not sent to the Applicant.

[a] Owens, L. Label and Labeling Review for (b) (4) *** NDA 208085. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 2. RCM No.: 2016-892.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

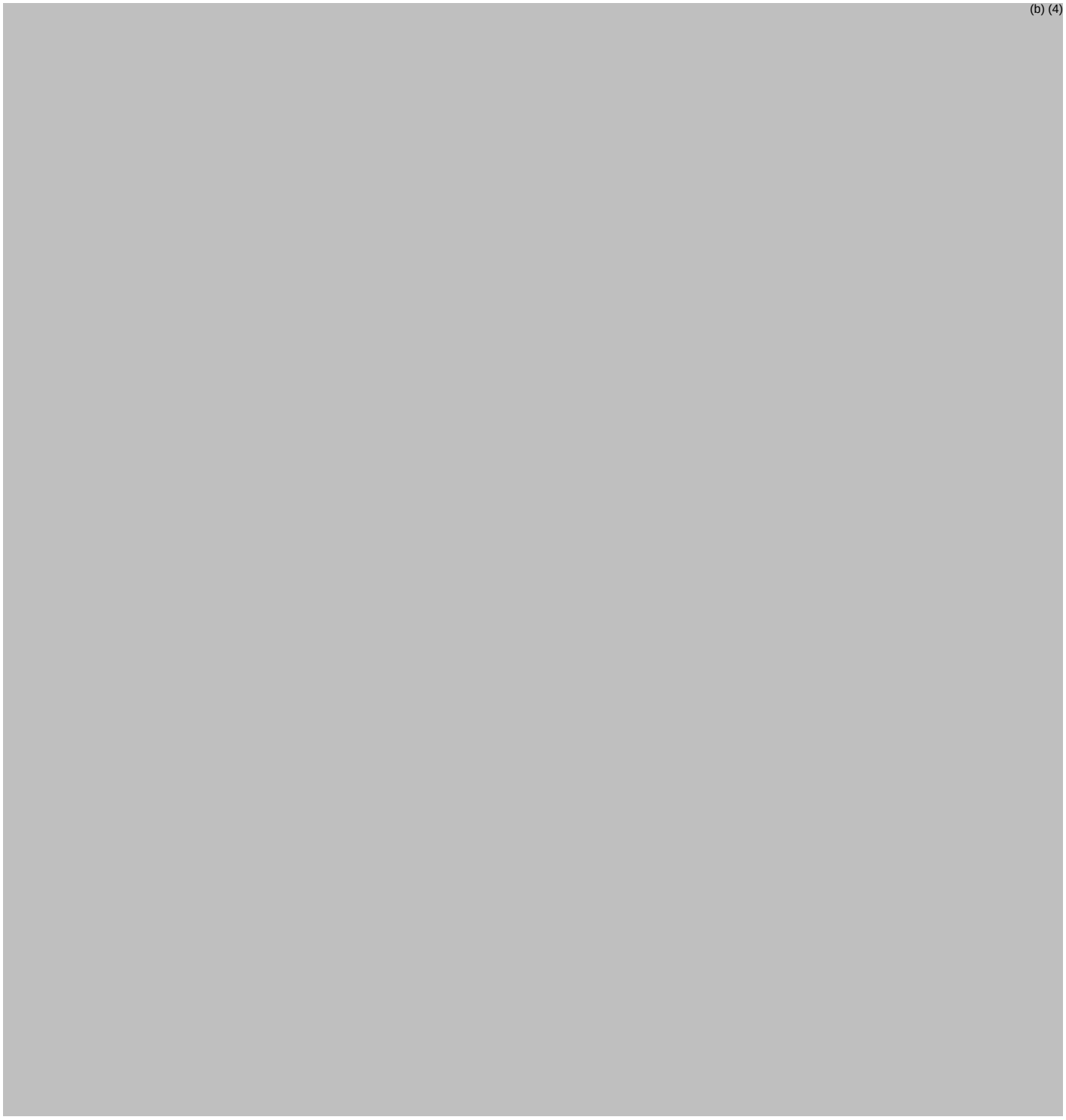
Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by ECI.

- Container label received on November 28, 2017
- Prescribing Information (Image not shown) received on November 28, 2017

### G.2 Label and Labeling Images

(b) (4)

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


(b) (4)

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LISSA C OWENS
02/15/2018

SARAH K VEE
02/15/2018

**M E M O R A N D U M**

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

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DATE: 11/29/2017

TO: Division of Pulmonary, Allergy and Rheumatology Products
Office of Drug Evaluation II

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

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

RE: NDA 208085

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.

**Rationale**

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

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

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SHILA S NKAH
11/30/2017

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

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

# Memorandum

**Date:** **January 31, 2017**

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

**From:** **Kyle Snyder, Regulatory Review Officer**
**Office of Prescription Drug Promotion (OPDP)**

**Subject:** **NDA 208085**
**OPDP labeling comments for (b) (4) (hydrocodone bitartrate and guaifenesin) Tablets CII**

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OPDP acknowledges receipt of DPARP's May 6, 2016, consult request to review the proposed product labeling (package insert and carton/container labeling) for (b) (4) (hydrocodone bitartrate and guaifenesin) Tablets CII. Reference is made to DPARP's email to OPDP on January 20, 2017, conveying that a Complete Response action will be taken and that labeling will not be sent to OPDP for review. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DPARP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Kyle Snyder at 240-402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

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KYLE SNYDER
01/31/2017

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

**Division of Pediatric and Maternal Health Memorandum**

**Date:** January 23, 2017 **Date Consulted:** June 16, 2016

**From:** Jane Liedtka MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

**Through:** Miriam Dinatale, DO, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

**To:** LeAnn Brodhead, Regulatory Project Manager (RPM)
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

**Drug:** (b) (4) (Hydrocodone Bitartrate/Guaifenesin 5mg/400mg) tablet

**NDA:** NDA 208085

**Indication:** (b) (4) is a combination of hydrocodone, an opioid (b) (4) and guaifenesin, an expectorant indicated for use in symptomatic relief of cough, to (b) (4) loosen (b) (4) (mucus) (b) (4)

**Applicant:** ECI Pharmaceuticals, LLC

**Subject:** Pregnancy and Lactation labeling

**Materials Reviewed:**

- Applicant's submitted background package for NDA 208085
- Applicant's revised label, literature review and summary of pharmacovigilance database submitted as SD#5 on August 17, 2016.

- DPMH review of Zohydro ER, NDA 202880. Carol H. Kasten, MD, Medical Officer. January 28, 2015. DARRTS Reference ID 3693127.

**Consult Question:** Request review of PLLR content of PI.

## INTRODUCTION

On June 16, 2016, DPARP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of (b) (4) (Hydrocodone Bitartrate /Guaifenesin 5mg/400mg) tablet labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

## REGULATORY HISTORY

On April 13, 2016, ECI Pharmaceuticals, LLC submitted a new NDA. NDA 208085 is for (b) (4), which is a combination of hydrocodone, an opioid (b) (4) and guaifenesin, an expectorant, indicated for use in symptomatic relief of cough, to (b) (4) loosen (b) (4) (mucus) (b) (4) On August 5, 2016, the Agency sent the Applicant an advice letter requesting that they submit a review and summary of the available published literature and a summary of the Applicant's pharmacovigilance database regarding hydrocodone and guaifenesin use in pregnant and lactating women. On August 17, 2016, the Applicant submitted the requested supporting information which was adequate.

## BACKGROUND

### Opioids and Pregnancy

Opioids are known to cross the placental barrier, and may cause respiratory depression in neonates, and may also prolong labor. Opioid medications may be needed during pregnancy to manage severe pain associated with many conditions, including both acute and chronic medical conditions and surgical procedures. Recent studies show that the prevalence of opioid use among pregnant women ranges from 2% to 20%, and usage of opioids in pregnancy has been increasing.[1]

### Hydrocodone Drug Characteristics[2]

(b) (4) oral tablets contain hydrocodone bitartrate 5 mg and guaifenesin 400 mg.

Hydrocodone bitartrate is derived from the opium alkaloid, thebaine. Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive

[1] Sahin, Leyla. DPMH Review- Xartemis XR (NDA 204031). 10/28/2013.
[2] (b) (4)

doses, hydrocodone will depress respiration. Hydrocodone can produce miosis, euphoria, and physical and physiological dependence. The mean plasma half-life of hydrocodone is ≈ 5.45 hours. The molecular weight of hydrocodone bitartrate is ≈ 495 Daltons and it is 19-45 % protein bound in plasma.

Hydrocodone is biotransformed to the opioid hydromorphone, a more potent opioid. Its analgesic effect is attributable to both hydrocodone and hydromorphone.[3] Both CYPs 3A4 and 2D6 metabolize hydrocodone, the first cytochrome to the inactive metabolite norhydromorphone; the second cytochrome to hydromorphone.[2]

When guaifenesin and hydrocodone were administered in combination, the pharmacokinetics for each component was similar to those observed when each component was administered separately. The most common adverse reactions observed in clinical trials of (b) (4) included dizziness, headache, sedation, nausea and decreased blood pressure.

**Opioid Analgesic Drug Products' Class Labeling**

On September 10, 2013, the FDA implemented safety labeling changes related to neonatal opioid withdrawal syndrome (NOWS) for extended-release/long-acting (ER/LA) opioid analgesics. The Office of Regulatory Policy received a citizen petition from the National Advocates for Pregnant Women on October 17, 2013. On April 11, 2014, DPMH completed a review in response to the citizen's petition and discussed recommended labeling for NOWS.[4] Class labeling for opioid analgesic drug products originally applied to Schedule II controlled substances that are extended release or long acting (ER/LA). However, DAAAP has expanded class labeling for opioid analgesics to include IR opioid formulations as well. As part of the opioid class labeling, boxed warnings are required for addiction, abuse and misuse, respiratory depression (that can lead to overdose and death) and NOWS (which may be life threatening in neonates whose mothers required prolonged opioid therapy while pregnant). In addition to the boxed warnings, there is class labeling in several sections and sub-sections.[5] Class labeling for the pregnancy and lactation subsections are presented below.

**Guaifenesin Drug Characteristics[6]**

Guaifenesin is an expectorant, the action of which promotes or facilitates the removal of secretions from the respiratory tract. The precise mechanism of action of guaifenesin is not known; however, it is thought to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi. In turn, this may increase the efficiency

[3] Clinical pharmacology online©, www.clinicalpharmacology-ip.com/ Elsevier. Gold Standard. Revision date: November 26, 2015. Accessed January 11, 2015.
[4] Leyla Sahin, MD, Amy Taylor, MD, MHS. Citizen Petition and Petition for Stay regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes. April 11, 2014. DARRTS Reference ID: 3488324
[5] *Draft Guidances for Industry Analgesic Indications Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).*
[6] Briggs GG, Freeman RK, Yaffee SJ. Drugs in pregnancy and lactation. 6th ed. Philadelphia, PA: Lippincott Williams &Wilkins; 2002: 636-7/g.

of the cough reflex and facilitate removal of the secretions. The mean plasma half-life of guaifenesin is approximately 1.13 hours and the molecular weight is ≈ 198 Daltons.

**Pregnancy and Lactation Labeling**

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[7] also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[8] format to include information about the risks and benefits of using these products during pregnancy and lactation.

**REVIEW**

**PREGNANCY**

**Hydrocodone and Guaifenesin**

Nonclinical Experience

In animal reproduction studies, hydrocodone was teratogenic when given to pregnant hamsters at a single dose of 102 mg/kg subcutaneously (approximately 27 times the maximum recommended human daily dose, MRHDD) during organogenesis. Guaifenesin was also teratogenic when given to pregnant rats at oral doses greater than or equal to the MRHDD.

For further details, the reader is directed to the Nonclinical Review by Yu-Mee Kim, PhD.

Applicant's Review of Literature Regarding Hydrocodone Use in Pregnant Women

The Applicant conducted a literature search on the use of hydrocodone in pregnant women in PubMed, Science Direct and FDA databases. Nine publications regarding use of hydrocodone in pregnant women were identified and are summarized below.

- Schick, *et al.*[9], published a preliminary analysis of first trimester exposure to oxycodone and hydrocodone in 118 (n=40 for hydrocodone and n=78 for oxycodone) pregnant women and compared them with a matched group using codeine. Diagnoses included

[7] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[8] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[9] Schick, B et al. Preliminary analysis of first trimester exposure to oxycodone and hydrocodone. Reproductive Toxicology. 1996; 10(2), 162.

postoperative pain, general pain, or upper respiratory infection in both groups. Six (5.1 %) of the infants exposed to hydrocodone or oxycodone had malformations, an odds ratio of 2.61 (95% confidence interval 0.6-11.5) (p = 0.13). There was no pattern evident among the six malformations. The authors found no correlation with either congenital malformations or miscarriage.

- Broussard, *et al.*[10], conducted a population based case-control study examining the association between maternal use of opioid analgesics and > 30 types of major structural birth defects. In 17,449 case mothers, therapeutic opioid use was reported by 454 (2.6%) compared with 134 (2.0%) of 6701 control mothers. Indications for use of opioid analgesics were surgical procedures (41 %), infections (34%), chronic diseases (20%), and injuries (18%). Dose, duration, and frequency were not evaluated. The exposure period evaluated was from 1 month before to 3 months after conception. Limiting the exposure period to the first 2 months after conception produced similar results. Cases of exposure to hydrocodone were included but numbers for individual drugs were not specified. The birth defect, total number, number exposed, and the adjusted odds ratio (aOR) with 95% confidence interval (CI) were as follows:

| Birth Defect | Total | Cases | aOR (95% CI) |
|---|---|---|---|
| Spina bifida | 718 | 26 | 2.0 (1.3–3.2) |
| *Any heart defect (20 types)* | 7724 | 211 | 1.4 (1.1–1.7) |
| Atrioventricular septal defect | 175 | 9 | 2.4 (1.2–4.8) |
| Teratology of Fallot | 672 | 21 | 1.7 (1.1–2.8) |
| Conotruncal defect | 1481 | 41 | 1.5 (1.0–2.1) |
| Conoventricular septal defect | 110 | 6 | 2.7 (1.1–6.3) |
| Left ventricular outflow tract obstruction defect | 1195 | 36 | 1.5 (1.0–2.2) |
| Hypoplastic left heart syndrome | 357 | 17 | 2.4 (1.4–4.1) |
| Right ventricular outflow tract obstruction defect | 1175 | 40 | 1.6 (1.1–2.3) |
| Pulmonary valve stenosis | 867 | 34 | 1.7 (1.2–2.6) |
| Atrial septal defect (ASD) | 511 | 17 | 2.0 (1.2–3.6) |
| Ventricular septal defect + ASD | 528 | 17 | 1.7 (1.0–2.9) |
| Hydrocephaly | 301 | 11 | 2.0 (1.0–3.7) |
| Glaucoma/anterior chamber defects | 103 | 5 | 2.6 (1.0–6.6) |
| Gastroschisis | 726 | 26 | 1.8 (1.1–2.9) |

Source: Broussard, *et al*[10]

The exposure data were obtained by retrospective maternal self-report; the authors acknowledged that recall bias and misclassification might have affected their results. The

[10] Broussard, CS *et al*. Maternal treatment with opioid analgesics and risk for birth defects. American Journal of Obstetrics and Gynecology. 2011; 204(4), 314.e311-314.e311.

average recall periods were different for cases and controls. Some mothers were queried about exposures that may have occurred up to three years prior to their interview. Exposures to hydrocodone could have occurred at any time during pregnancy, at an unknown dose and duration. The authors concluded that the absolute risk was a modest absolute increase above the baseline risk for birth defects.

- Briggs, *et al*.[6], discussed a surveillance study of Michigan Medicaid recipients involving 229,101 completed pregnancies conducted between 1985 and 1992, 332 newborns had been exposed to hydrocodone during the 1st trimester (F. Rosa, personal communication, FDA, 1993). A total of 24 (7.2%) major birth defects were observed (14 expected), 5 of which were cardiovascular defects (3 expected). No anomalies were observed in five other defect categories (oral clefts, spina bifida, polydactyly, limb reduction defects, and hypospadias) for which specific data were available. The total number of malformations is suggestive of a possible association but other factors, including the mother's disease, concurrent drug use, and chance, may be involved. The authors also note that "Because of its narcotic properties, withdrawal could theoretically occur in infants exposed *in utero* to prolonged maternal ingestion of hydrocodone".

- Cook, *et al*.[11], examined newly diagnosed cases of neuroblastoma (n = 504) in the United States and Canada which were identified between 1992 and 1994 at 139 hospitals affiliated with the Pediatric Oncology Group or the Children's Cancer Group clinical trial programs. "One age-matched control was sampled from the community of each case by means of random digit dialing. Exposure information was ascertained retrospectively from mothers in a structured telephone interview. Mothers of cases were more likely to report using medications containing opioid agonists while they were pregnant or nursing than were mothers of controls (odds ratio = 2.4, 95% confidence interval: 1.3, 4.3). Although, for the study more mothers of cases reported using medications containing codeine while hydrocodone was clubbed with other opioids for analysis".

- Yazdy, *et al*.[12], used data from 1998 to 2010 from the Slone Epidemiology Center Birth Defects Study, an ongoing case–control study. Mothers were interviewed by telephone within 6 months of delivery about sociodemographic factors and exposures during pregnancy including detailed questions on type and timing of medication use. A higher percentage of mothers of offsprings with neural tube defects (3.9%) reported using an opioid medication than mothers of offsprings in the normal formed control group (1.6%) and offsprings in the malformed control group (2.0%) with adjusted odds ratios (ORs) of 2.2 (95% CI 1.2 24.2) and 1.9 (95% CI 1.0 23.4), respectively. When offsprings were restricted to those with spina bifida, the adjusted ORs were 2.5 (95% CI 1.3–5.0) and 2.2 (95% CI 1.1–4.1), respectively.

[11] Cook, MN *et al.* Maternal Medication Use and Neuroblastoma in Offspring. American Journal of Epidemiology. 2004; 159(8), 721-731.
[12] Yazdy, MM *et al.* Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol. 2013; 122(4), 838-844.

- Kellogg, *et al.*[13], conducted a retrospective cohort study of all deliveries at Mayo Clinic from 1998 through 2009; the data was obtained from prospectively maintained obstetrics and neonatal databases to evaluate trends and prevalence of chronic prescription narcotic use during pregnancy and the subsequent neonatal outcomes. The authors concluded that chronic narcotic use during pregnancy is increasing in prevalence. Neonatal withdrawal syndrome (NOWS) occurred in 5.6% of the exposed neonates. NOWS is associated with lower than normal birth weight and require lengthier neonatal intensive care for treatment of NOWS.

- Patrick, *et al.*[14], conducted a retrospective, serial, cross-sectional analysis of a nationally representative sample of newborns with neonatal abstinence syndrome (NAS). NAS is a drug withdrawal syndrome in newborns following birth most commonly occurs in the context of antepartum opiate use. Newborns with NAS were more likely than all other hospital births to have low birth weight and have respiratory complications and require lengthier neonatal intensive care.

- Maeda, *et al.*[15], conducted an analysis of hospitalizations for delivery data from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project and concluded opioid abuse or dependence during pregnancy is associated with considerable obstetrical morbidity and mortality, and its prevalence is dramatically increasing in the United States.

- Nocon[16], stated that for some opioid-only-dependent chronic pain patients, where switching to methadone or buprenorphine may not be possible it was recommended that pregnant women maintain their current opioid regimens to avoid withdrawal. Specifically, hydrocodone (with acetaminophen) 5/325 or 10/325 (up to two tabs q 6h) were deemed acceptable since a low rate of NAS has been noted with these doses.

DPMH's Review of Literature Regarding Hydrocodone Use in Pregnant Women

Reviews by both TERIS[17] and Reprotox[18] state that there is a minimal to small risk for teratogenesis from hydrocodone exposure *in utero* based on limited to fair data. Two epidemiological studies are discussed in both the TERIS and Reprotox reviews. In the first, the Collaborative Perinatal Project, data on medication use was collected on 50,282 pregnant

[13] Kellogg, *et al.* Current trends in narcotic use in pregnancy and neonatal outcomes. American Journal of Obstetrics and Gynecology. 2011; 204(3), 259.e251-259.e254.
[14] Patrick, SW *et al.* Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. JAMA. 2012; 307 (18), 1934-1940.
[15] Maeda, A *et al*. Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes. Anesthesiology. 2014; 1(6), 1158-1165.
[16] Nocon, JJ. (2013). 15 - Substance Use Disorders A2 - Mattison, Donald R *Clinical Pharmacology during Pregnancy* (pp. 217-256): Academic Press.
[17] TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Review date 07/14. Accessed January 13, 2015. http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/
[18] http://www.reprotox.org/. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed January 13, 2015.

women enrolled from 1958 to 1965.[19] In the study there were 60 children who were prenatally exposed to hydrocodone, only 12 of which were exposed during organogenesis. No increase was found in the number of malformations observed over expected.

The second study was the Broussard[10] publication (already discussed under the section of this review entitled Applicant's Review of the Literature). In this report, statistically significant associations between hydrocodone exposure at any time in pregnancy and congenital malformations were reported for spina bifida (n=11; OR 2.5 (95% CI 1.3-4.8)), gastroschisis (n=15; OR 3.3 (95% CI 1.8-6.1)) and a subset of four different cardiovascular malformations: atrioventricular septal defect, Tetralogy of Fallot, hypoplastic left heart, and pulmonary valve stenosis (n=70; OR=1.4 (95% CI 0.99-2.1)). As previously noted, limitations included potential recall bias and misclassification.

Applicant's Review of Literature Regarding Guaifenesin Use in Pregnant Women

The Applicant conducted a literature search on the use of guaifenesin in pregnant women in PubMed, Science Direct and FDA databases. Three publications regarding use of guaifenesin in pregnant women were identified and are summarized below.

- Aselton, *et al*.[20], determined the prevalence of certain major congenital disorders among live-born infants of 6509 mothers in a prepaid health plan for the 30-month period of January 1, 1980 through June 30, 1982 who used a wide variety of drugs during the first trimester of pregnancy. Guaifenesin was used in combination with codeine in 85 recipients and was not associated with an increased incidence of congenital disorders.

- Shaw *et al*.[21], in a report of a case-control study, noted that researchers identified 538 fetuses and live-born infants with neural tube defects between 1989 and 1991. Twelve patients with neural tube defects were exposed to Guaifenesin during gestation; 6 in the control group reported exposure. The authors reported a trend towards increased risk of neural tube defects in offspring of guaifenesin-exposed mothers (odds ratio=2.04; 95% CI, 0.79-5.28). However, since the results were not statistically significant, the authors concluded that guaifenesin had not contributed to the occurrence of neural tube defects.

- In the same report by Briggs[6] previously discussed under hydrocodone, 141 newborns had been exposed to guaifenesin during the 1st trimester (F. Rosa, personal communication, FDA, 1993). Nine (6.4%) major birth defects were observed (6 expected), including two cardiovascular defects (1.4 expected). No anomalies were observed in five other categories of defects (oral clefts, spina bifida, polydactyly, limb reduction defects, and hypospadias) for which specific data were available. The author concluded that the data do not support an association between guaifenesin and congenital defects.

[19] Heinonen OP, Slone D, Shapiro S: Birth Defects and Drugs in Pregnancy. Publishing Sciences Group Inc., Littleton, MA, pages 287, 434, 1977.
[20] Aselton, P *et al*. First-trimester drug use and congenital disorders. Obstet Gynecol. 1985; 65(4), 451-455.
[21] Shaw, GM *et al*. Maternal illness, including fever and medication use as risk factors for neural tube defects. Teratology. 1998; 57(1), 1-7.

DPMH's Review of the Literature Regarding Guaifenesin Use in Pregnant Women

DPMH conducted a review of the literature and identified the following publications (in addition to those cited by the Applicant)

- Jick, *et al.*[22], reported that the frequency of malformations was no greater than expected among the children of more than 925 women who took guaifenesin in the first trimester of pregnancy in the Boston Collaborative Drug Surveillance Program.

- Heinonen, *et al*.[19], reported that the frequency of congenital anomalies was not increased among the infants of 197 women who used guaifenesin in the first four lunar months, or the infants of 1336 women who used the drug anytime in pregnancy in the Collaborative Perinatal Project.

Summary

Human pregnancy outcome data specific for hydrocodone and guaifenesin are limited in the published literature. There were no cases from the applicant's pharmacovigilance database. The findings in animal studies concluded that hydrocodone was teratogenic when given to pregnant hamsters at a single dose of 102 mg/kg subcutaneously (approximately 27 times the maximum recommended human daily dose, MRHDD) during organogenesis. Guaifenesin was also teratogenic when given to pregnant rats at oral doses greater than or equal to the MRHDD.

The consensus among experts referenced in review articles on use of drugs during pregnancy was that use of hydrocodone posed a minimal to small risk of teratogenicity to the fetus at usual doses for short duration and that the data do not support an association between guaifenesin and congenital defects. DPMH agrees with this assessment and recommends the standard class labeling opioid language as well as the following statement be included in (b) (4) labeling:

> Published studies and postmarketing reports on hydrocodone and guafenesin use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes.

**LACTATION**

**Hydrocodone**

Applicant's Review of Literature

The Applicant conducted a literature search in PubMed, Science Direct and FDA databases for literature available references regarding hydrocodone impact on lactation. The Applicant identified five relevant publications which are summarized below

[22] Jick, H *et al*. First-trimester drug use and congenital disorders. JAMA.1981; 246(4):343-346.

- Anderson, *et al*.[23], reported milk concentrations of hydrocodone in two women. In the first case, a 22-year-old, 63.6 kg woman was treated during the 3rd trimester with hydrocodone/acetaminophen two tablets every 3-4 hours to control headaches caused by left-sided temporal schwannoma (skull-based tumor). She continued the analgesic combination after delivery at 35 weeks' gestation. On postpartum day 7, the patient underwent a craniotomy to remove the tumor and was continued on 5 mg of hydrocodone/acetaminophen one to two tablets every 4 hours as needed. She received 105 mg hydrocodone over 81 hours. During that time, an electric pump was used to obtain breast milk for her infant. The milk hydrocodone concentrations were 8.6-127.3 mcg/L with the levels dependent upon the mother's dose and the time interval from the last dose. The average milk concentration, based on AUC, was 57.2 mcg/L. The infant dose, if exclusively breastfed, was 8.58 meg/kg/day, or 3.1% of the mother's weight-adjusted dose.

  In the second case, a 22-year-old, 73.5 kg woman at 16 days postpartum was admitted to the hospital for treatment of mastitis and urosepsis. In addition to antibiotics, she received hydrocodone/ acetaminophen (5/500 mg) every 6 hours, but only took three doses (15 mg hydrocodone) over a 24-hour period. Milk was obtained as in the first case. Milk concentrations of the opioid were 5.2-47.2 mcg/L depending on the time from the last dose. The average milk concentration, based on AUC, was 20.4 mcg/L. The infant dose, if exclusively breastfed, was 3.07 mcg/kg/day, or 3.7% of the mother's weight-adjusted dose.

  The authors noted that although the infant doses relative to their mother's weight-adjusted dose were nearly the same (3.1% vs. 3.7%), the absolute infant doses were much different (8.58 vs. 3.07 mcg/kg/day). Because the infants were not hospitalized, the authors could not determine if either infant experienced an adverse reaction. However, toxicity would have been more likely in the first infant because of the higher dose.

- Meyer, *et al*.[24], described a five week old breastfed infant with severe apnea who was found cyanotic and unresponsive after maternal exposure to methadone and hydrocodone/acetaminophen (neither dose nor duration were indicated) for a migraine headache prior to breastfeeding. The infant was intubated and administered naloxone which improved his respiratory effort. He required ventilator support for 48 hours. All of the infant’s laboratory evaluations were within normal limits, with the exception of a urine screen which was positive for opioids. The authors could not determine if the infant toxicity was due to methadone, hydrocodone or a combination of the two agents.

[23] Anderson, PO *et al.* Hydrocodone excretion into breast milk: the first two reported cases. Breastfeed Med. 2007; 2(1), 10-14.
[24] Meyer D, Tobias J. Adverse Effects Following the Inadvertent Administration of Opioids to Infants and Children. Clinical Pediatrics 2005; 499 -503.

- Sauberan, *et al.*,[25] presented data on hydrocodone and hydromorphone levels in breast milk from 30 women treated with a hydrocodone immediate release - acetaminophen combination product; dosages were not specified. The breast milk specimens were collected from 24 to 96 hours postpartum or until discharge. Both hydrocodone and hydromorphone levels were measured to provide the total opioid exposure; however, hydromorphone was detectable in the milk of only 12 of the 30 women. Neither the hydrocodone nor hydromorphone levels were normally distributed. Breast milk hydrocodone data from 125 milk samples provided by the study patients revealed an average milk hydrocodone concentration of 25.9 (16–35.9) micrograms/L. The mean neonatal dose was 3.9 (2.4–5.4) micrograms/kg/d. This yields a mean relative infant dose of 2.4% (1.4% -- 3.3%).

  In their discussion, the authors cautioned that the neonates were not followed for evidence of hypersomnolence, poor feeding or other possible adverse reactions to opiates so no conclusions regarding safety may be made. The authors also emphasized that these data represent neonatal pharmacodynamics. Hydrocodone metabolism in older infants has been shown to be different due to maturation of the CYP enzymes.

- Bodley and Powers[26] described a mother who experienced severe pain from cracked nipples associated with a fungal infection while breast feeding her 18 day old infant. After acetaminophen alone or combined with codeine could not provide desired relief, hydrocodone/acetaminophen (1 0/650 mg/tablet) two tablets every 4 hours was initiated and found effective. However, both the mother and infant were groggy and sleepy most of the day, symptoms that alleviated upon decreasing the dose to 1 tablet every 3-5 hours. Although hydrocodone milk concentrations were not measured, the authors concluded that the marked sedation in the infant was a result of hydrocodone excretion into the mother's milk.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*[27], the Drugs and Lactation Database (LactMed),[28] Micromedex[29], and of published literature. No reports of adequate and well-controlled studies of hydrocodone use in lactating women were found.

[25] Sauberan JB, Anderson, PO *et al.* Breast milk hydrocodone and hydromorphone levels in mothers using hydrocodone for postpartum pain. Obstet Gynecol 2011; 117:611 – 617.
[26] Bodley, V., & Powers, D. Long-term treatment of a breastfeeding mother with fluconazole-resolved nipple pain caused by yeast: a case study. J Hum Lact. 1997; 13(4), 307-311.
[27] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 422-423.
[28] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[29] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/1/16.

In *Medications and Mother's Milk*, Dr. Thomas Hale, a breastfeeding expert, notes that cases of hydrocodone use during lactation have resulted in relative infant doses ranging between 1.4 and 3.7% (he references the previously cited publications by Anderson[23] and Sauberan[25] for these numbers) and makes the following recommendation:

> It is recommended that for the treatment of postpartum pain, hydrocodone dosages should be limited to no more than 30mg/day. If higher doses are required, then an infant should be closely monitored for possible untoward effects such as sedation and apnea. Doses more than 40mg/day should be avoided.

Hydrocodone is referenced in LactMed. The summary of use states:

> Maternal use of oral narcotics during breastfeeding can cause infant drowsiness, central nervous system depression and even death. Newborn infants seem to be particularly sensitive to the effects of even small dosages of narcotic analgesics. Once the mother's milk comes in, it is best to provide pain control with a nonnarcotic analgesic and limit maternal intake of oral hydrocodone to a few days at a maximum dosage of 30 mg daily with close infant monitoring. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately.[30]

Micromedex notes the following regarding hydrocodone; "Infant risk cannot be ruled out".

**Guaifenesin**

Nonclinical Experience

There is no nonclinical information regarding the presence of guaifenesin in animal milk.

Applicant's Review of the Literature

A literature search by the Applicant did not identify any published information regarding Guaifenesin's impact on lactation.

DPMH Review of Literature

In *Medications and Mother's Milk*, Dr. Hale, notes that there is no information on the use of guaifenesin during lactation or the presence of the drug in breastmilk. Dr Hale notes that guafenesin is "probably compatible" with breastfeeding.

Guaifenesin is referenced in LactMed. The summary of use states:

[30] Noti A et al. Exposure of babies to C (15)-C (45) mineral paraffins from human milk and breast salves. Regul Toxicol Pharmacol. 2003; 38:317-25.

> Neither the excretion of guaifenesin in milk nor its effect on breastfed infants have been studied. It is unlikely that with usual maternal doses amounts in breastmilk would harm the nursing infant, especially in infants over 2 months of age. It is best to avoid the use of products with a high alcohol content while nursing

Micromedex notes the following regarding guaifenesin: "Infant risk cannot be ruled out. Until more data is available, use caution when considering the use of guaifenesin in lactating women."

Summary

Hydrocodone appears to be transferred into breast milk with reported relative infant doses ranging between 1.4 and 3.7%. There are two cases that report adverse effects of hydrocodone on breastfed infants, including sedation and respiratory depression. However, in the case report involving respiratory depression, the infant was also exposed to methadone. There is no information about the presence of guaifenesin in breast milk.

Since (b) (4) includes an immediate-release opioid product, (b) (4) labeling will be structured in the PLLR format using IR opioid labeling and will include the following risk/benefit statement in section 8.2, Risk Summary:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) and any potential adverse effects on the breastfed infant from (b) (4) or from the underlying maternal condition.

In addition, the following information will appear in section 8.2, Clinical Considerations:

> Infants exposed to (b) (4) through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

**Use in Females and Males of Reproductive Potential**

**Hydrocodone**

Nonclinical Experience

No effects on male fertility were observed with hydrocodone at doses equivalent to 10 times the human dose of 100 mg/day, however, decreases in the weight of male reproductive organs were observed in all treated groups at doses equivalent to 2.4 times the human dose of 100 mg/day and above. Reductions in female fertility indices were observed at doses of hydrocodone equivalent to 2 times the human dose of 100 mg/day and above. These changes are attributed to a hydrocodone-mediated decrease in prolactin levels in the rat. Unique to

rodents, prolactin is required for normal estrous cycling and the effects on fertility observed in this study are most likely rodent-specific and not believed to be clinically relevant

For further details, the reader is directed to the Nonclinical Review by Yu-Mee Kim, PhD.

Applicant's Review of Literature

Literature review did not present information for hydrocodone's adverse impact on fertility.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding hydrocodone and its effects on fertility and found no relevant literature.

However, the effects of opioids (as a class) on fertility are known to the Agency. In 2014, the Division of Bone, Reproductive and Urologic Products (DBRUP) reviewed the literature to evaluate the association between chronic opioid administration and hypogonadism. Based on that review, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) updated the immediate and extended release opioid labelings to include information about the potential for chronic opioid use to influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency. It was determined that Section 8.3, Females and Males of Reproductive Potential, of opioid labeling will now include the following statement:

> Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

*Reviewers Comment*

*The division clinical team was queried as to whether they wished to include the class labeling information regarding effects on fertility in the* (b) (4) *label. They opted to defer a decision for now. If the pending decision is to include this material, then information on androgen deficiency will need to be added to Sections 6 Adverse Reactions and 12.2 Pharmacokinetics.*

**Guaifenesin**

Applicant's Review of Literature

The Applicant's literature review did not present information for guaifenesin's adverse impact on fertility.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding guaifenesin and its effects on fertility and found two relevant publications summarized below

- Check, *et al*.[31], reported on a small uncontrolled study of 40 infertile couples, treated with guaifenesin, among whom 23 (57%) of the women showed marked improvement and 7 (17.5%) showed slight improvement in cervical mucous. This improvement was followed by a subsequent pregnancy in 15/23 (65.2%) couples with marked improvement but in only 1/7 couples with slight improvement.
- Means, *et al*.[32], reported a 32year old male with a history of infertility who had low sperm count and motility on examination. He was treated with guaifenesin 600 mg extended release tablets twice daily and two months later, the semen analysis was repeated and demonstrated marked improvement in both total sperm count and motility.

*Reviewers Comments*

*Though interesting, these two publications are insufficient to determine if guaifenesin has a positive impact on fertility.*

Summary

There are no data on an effect of hydrocodone on human fertility. The effects of hydrocodone on fertility were felt to be species specific to rodents. The pharmacology/toxicology reviewer recommended (b) (4). There is limited published literature that suggests a possibility of an improvement in fertility with guaifenesin (b) (4).

However, as noted above, there are class effects of opioids on fertility. Therefore, Section 8.3, Females and Males of Reproductive Potential, of opioid labeling will now include the following statement:

> Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

**CONCLUSIONS**

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for (b) (4) hydrocodone bitartrate/guaifenesin 5mg/400mg) labeling:

- **Warnings and Precautions, Section 5.x**
  - Based on the increased likelihood of adverse infant effects due to clinical experience with opioids in pregnant women, a subsection describing embryo- and/or fetal risks ("Neonatal Opioid Withdrawal Syndrome") as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4).

[31]Check, JH *et al*. Improvement of cervical factor with guaifenesin. Fertil Steril. 1982; 37(5), 707-708.
[32] Means G *et al*. Guaifenesin and increased sperm motility: a preliminary case report. International Journal of General Medicine. 2011:4; 13–14.

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of (b) (4) labeling was structured in the PLLR format to include the "Risk Summary", "Clinical Considerations" and "Data" sections.[33]
- **Lactation, Section 8.2**
  - The "Lactation" subsection of (b) (4) labeling was formatted in the PLLR format to include the "Risk Summary" and "Clinical Considerations" sections.[34]
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" section of (b) (4) labeling was formatted in the PLLR format to include the "Infertility" section to discuss the potential for chronic use of opioids to cause reduced fertility in females and males.[35]
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of (b) (4) labeling was updated to correspond with changes made to sections 5 x, 8.1, 8.2 and 8.3 of labeling.

**LABELING RECOMMENDATIONS**

DPMH revised the HPI and sections 5.x, 8.1, 8.2, 8.3 and 17 of (b) (4) (hydrocodone bitartrate/guaifenesin 5mg/400mg) labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DAAAP on January 9, 2017. See Appendix A for the Applicant's proposed labeling. DPMH refers to the final NDA action for final labeling.

**DPMH Proposed (b) (4) Pregnancy and Lactation Labeling**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**WARNING: NEONATAL OPIOID WITHDRAWAL SYNDROME**
***See full prescribing information for complete boxed warning.***

- **Prolonged use of (b) (4) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**

**---------- USE IN SPECIFIC POPULATIONS ----------**

- Pregnancy: May cause fetal harm. (8.1)

[33] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.
[34] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.
[35] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

**FULL PRESCRIBING INFORMATION**

**WARNING: NEONATAL OPIOID WITHDRAWAL SYNDROME**

**Neonatal Opioid Withdrawal Syndrome**

**Prolonged use of (b) (4) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [*see Warnings and Precautions (5.3)*].**

**5 WARNINGS AND PRECAUTIONS**

**5.x Neonatal Opioid Withdrawal Syndrome**

Prolonged use of (b) (4) during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [*see Use in Specific Populations (8.1)*].

**8 Use in Specific Populations**

**8.1 Pregnancy**

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3), Clinical Considerations]*. Published studies and postmarketing reports on hydrocodone and guaifenesin use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes [*see Data]*. In animal reproduction studies, hydrocodone was teratogenic when given to pregnant hamsters at a single dose of 102 mg/kg subcutaneously (approximately 27 times the maximum recommended human daily dose, MRHDD) during organogenesis. Guaifenesin was also teratogenic when given to pregnant rats at oral doses greater than or equal to the MRHDD *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

*Fetal/neonatal adverse reactions*

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset of neonatal withdrawal symptoms usually occurs in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.3)]*.

*Labor or Delivery*
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. (b) (4) is not recommended for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including (b) (4) can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data
*Human Data*
A limited number of pregnancies have been reported in published observational studies and postmarketing reports describing hydrocodone and guaifenesin use during pregnancy. However, these data cannot definitely establish or exclude any drug-associated risk during pregnancy. Methodological limitations of these observational studies include small sample size and lack of details regarding dose, duration and timing of exposure.

*Animal Data*
Reproduction and developmental studies have not been conducted with (b) (4) however, published information is available for the individual active ingredients or related active ingredients.
In an embryo-fetal study, pregnant hamsters received a single subcutaneous dose of hydrocodone during the period of organogenesis (gestation day 8) at 102 mg/kg (approximately (b) (4) times the MRHDD on a mg/m$^2$ basis). Hydrocodone induced malformations (cranioschisis) in this study. Reproductive toxicology studies were also conducted with codeine, an opiate related to hydrocodone. In an embryo-fetal study, pregnant rats received an oral dose of codeine throughout organogenesis at (b) (4) (approximately (b) (4) times the MRHDD of hydrocodone on a mg/m$^2$ basis). Codeine induced increased resorptions and decreased fetal weight, however, these effects occurred in the presence of maternal toxicity. In embryo-fetal studies in which pregnant rabbits and mice received oral doses of codeine throughout organogenesis at 30 and 600 mg/kg/day, respectively (up to approximately (b) (4) times, respectively, the MRHDD of hydrocodone on a mg/m$^2$ basis), there were no adverse developmental effects.

In an embryo-fetal study, pregnant rats received oral doses of guaifenesin during the period of organogenesis at 250, 350, 500, or 600 mg/kg/day. Guaifenesin resulted in fetal death at doses greater than or equal to 350 mg/kg/day (1.4 times the MRHDD). Guaifenesin also induced hemorrhagic spots and decreases in fetal weight and lengths of full body, skull, fore- and hind-limbs, and tail in all treated groups at doses greater than or equivalent to 250 mg/kg/day (equivalent to the MRHDD). Limb and tail defects, increased intercostal space and improper development of limbs were observed at 500 or 600 mg/kg/day, equivalent to 2 or 2.4 times the MRHDD.

### 8.2 Lactation

Risk Summary
There are no data on the presence of (b) (4) in human milk, the effects on the breastfed infant, or the effects on milk production. Hydrocodone, a component of (b) (4) is transferred into human milk. Published cases report variable concentrations of hydrocodone and hydromorphone (an active metabolite) in breast milk with administration of immediate-release hydrocodone to nursing mothers in the early post-partum period with relative infant doses of hydrocodone ranging between 1.4 and 3.7%. There are reports of excessive sedation and respiratory depression in breastfed infants exposed to hydrocodone. However, there is no information on the effects of hydrocodone on milk production. There are no data on the presence of guaifenesin in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) and any potential adverse effects on the breastfed infant from (b) (4) or from the underlying maternal condition.

Clinical Considerations
Infants exposed to (b) (4) through breast milk should be monitored for excess sedation and respiratory depression due to the hydrocodone component of (b) (4) Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic, such as hydrocodone, a component of (b) (4) is stopped, or when breast-feeding is stopped.

### 8.3 Females and Males of Reproductive Potential

Infertility
Chronic use of opioids, such as hydrocodone, a component of (b) (4) may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2)], Nonclincical Pharmacology (13.1)]*.

**Comment [LJ1]:** To Clinical Team
Do you plan to include this information in (b) (4) labeling If so, you will need to add information about Androgen Deficiency in section 6 2 and 12 2, which currently does not appear in (b) (4) labeling DPMH

### 17 PATIENT COUNSELING INFORMATION

Pregnancy
*Neonatal Opioid Withdrawal Syndrome*

Inform female patients of reproductive potential that prolonged use of (b) (4) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.x), Use in Specific Populations (8.1)]*.

*Embryo-Fetal Toxicity*
Inform female patients of reproductive potential that (b) (4) can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation
Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility
Inform patients that chronic use of opioids, such as hydrocodone, a component of (b) (4) may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

**Appendix A:**
**Applicant's Proposed (b) (4) (hydrocodone bitartrate/guaifenesin) Labeling**

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**
*Risk Summary*
Prolonged use of opioid (b) (4) during pregnancy may cause neonatal opioid withdrawal syndrome. There are nc (b) (4) use in pregnant women (b) (4) background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% (b) (4)

*Clinical Considerations*

*Fetal/neonatal adverse reactions*
Prolonged use of opioids during pregnancy for medical or nonmedical purposes can result in physical dependence in the (b) (4) and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal (b) (4) and manage accordingly (b) (4)

*Labor or Delivery*
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist such as naloxone must be available for reversal of opioid induced respiratory depression in the neonate. (b) (4) Opioids, including (b) (4) can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

(b) (4)

*Data*
*Animal Data*
(b) (4)

**8.2 Lactation**
*Risk Summary*
Hydrocodone is present in human milk. Published (b) (4) variable concentrations of hydrocodone and hydromorphone (an active metabolite) in breast milk with administration of immediate-release hydrocodone to nursing mothers in the early post-partum period. (b) (4)

(b) (4)

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with (b) (4)

*Clinical Considerations*

Infants exposed to (b) (4) through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid is stopped, or when breast-feeding is stopped.

(b) (4)

**8.3 Females and Males of Reproductive Potential**

*Infertility*

(b) (4)

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/s/

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JANE E LIEDTKA
01/24/2017

MIRIAM C DINATALE
01/24/2017

LYNNE P YAO
01/25/2017

**M E M O R A N D U M** **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: December 6, 2016

TO: Badrul Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Office of Drug Evaluation II (ODEII)
Office of New Drugs (OND)

FROM: Amanda Lewin, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Directory
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of (b) (4)

**Inspection Summary:**

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of comparative oral bioavailability study (b) (4) (NDA 208085) at (b) (4) (b) (4) At the conclusion of the inspection, no significant deficiencies were observed and no Form FDA 483 was issued. The final classification for this inspection is no action indicated (NAI). After reviewing the inspectional findings, I found the clinical data from the audited study to be reliable. Therefore, I recommend that the data for the clinical portion of study (b) (4) submitted to NDA 208085 be accepted for further agency review.

**Inspected Study:**

**NDA 208085**

**Study Number:** (b) (4)
**Study Title:**

**Study Dates:**

ORA investigator (b) (4) inspected the clinical portion of study (b) (4) (b) (4) The inspection included a thorough review and examination of personnel records, training program, study responsibility and authority, protocols, SOPs, subject consent, IRB documentation, enrolled subject records, test article accountability, locked drug storage, record retention, and interviews and discussions with the firm's management and staff. (b) (4) collected reserve samples at the site and she shipped them to the (b) (4) (b) (4)

(b) (4) did not observe any significant deficiencies and she did not issue Form FDA 483 to the clinical site at the conclusion of the inspection.

**Recommendations:**

After reviewing the EIR and inspectional findings, I found the data from the audited study to be reliable. Therefore I recommend that the data for the clinical portion of study (b) (4) (b) (4) submitted to NDA 208085 be accepted for further agency review.

Amanda Lewin, Ph.D.
DNDBE, OSIS

**Final Classification:**
**NAI –**
**(FEI#** [redacted]

CC:
OTS/OSIS/Kassim/Taylor/Haidar/Kadavil/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDBE/Cho/Murphy/Skelly/Choi/Au
CDER/OND/Chowdhury
[redacted]

Draft: AL 10/14/2016
Edit: RCA 10/17/2016, CB 12/6/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Site/ [redacted]NDA208085_Hydrocodone Bitartrate and Guaifenesin Tablets, 5mg 400mg

BE File #s: [redacted] (NDA 208085)

FACTS: [redacted]

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/s/

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AMANDA E LEWIN
12/07/2016

RUBEN C AYALA
12/07/2016

CHARLES R BONAPACE
12/07/2016

**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:** | August 2, 2016 |
| **Requesting Office or Division:** | Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) |
| **Application Type and Number:** | NDA 208085 |
| **Product Name and Strength:** | (b) (4) (hydrocodone bitartrate and guaifenesin) Tablets 5 mg/400 mg |
| **Product Type:** | Multi-ingredient product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | ECI Pharmaceuticals, LLC. |
| **Submission Date:** | April 13, 2016 |
| **OSE RCM #:** | 2016-892 |
| **DMEPA Primary Reviewer:** | Lissa Owens, PharmD |
| **DMEPA Team Leader:** | Mishale Mistry, PharmD, MPH |

## 1 REASON FOR REVIEW

This review evaluates the proposed container labels and prescribing information, for (b) (4) (hydrocodone bitartrate and guaifenesin) tablets, NDA 208085, submitted on April 13, 2016. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the labels and labeling for areas of vulnerability related 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.

**Table 1. Materials Considered for this Label and Labeling Review**

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

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed labels and labeling to determine whether there are any significant concerns in terms of safety, related to preventable medication errors. We find the proposed label can be improved; specifically, the usual dosage statement can be improved to maintain consistency with the prescribing information. Therefore, we provide recommendations in Section 4.1 for the Applicant to address this deficiency.

## 4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label can be improved to promote the safe use of the product.

### 4.1 RECOMMENDATIONS FOR ECI PHARMACEUTICALS LLC

**A. Container Label**

1. Revise the usual dosage statement to read ‘One tablet every 4 to 6 hours, not to exceed 6 tablets in 24 hours’ to maintain consistency with the prescribing information.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for [redacted] that ECI submitted on April 13, 2016.

| **Table 2. Relevant Product Information for** [redacted] | |
|---|---|
| **Initial Approval Date** | N/A |
| **Active Ingredient** | hydrocodone bitartrate and guaifenesin |
| **Indication** | Symptomatic relief of cough, to [redacted] loosen [redacted] (mucus) [redacted] |
| **Route of Administration** | Oral |
| **Dosage Form** | Tablets |
| **Strength** | 5 mg/400 mg |
| **Dose and Frequency** | One tablet every 4 to 6 hours not to exceed 6 tablets in 24 hours |
| **How Supplied** | White, capsule-shaped, debossed "ECI" on one side and "601" on the other containing 5 mg hydrocodone bitartrate and 400 mg guaifenesin. It is available in:<br>White HDPE bottles of 30 Counts: NDC 51293-601-30<br>White HDPE bottles of 100 Counts: NDC 51293-601-01<br>White HDPE bottles of 500 Counts: NDC 51293-601-05 |
| **Storage** | Store at 20° to 25°C (68° to 77°F) |

## 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 (b) (4) labels and labeling submitted by ECI Pharmaceuticals on April 13, 2016.

- Container labels
- Prescribing Information (no image)

(b) (4)

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


(b) (4)

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/s/

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LISSA C OWENS
08/02/2016

MISHALE P MISTRY
08/02/2016