

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22279Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Submission Number	22-279
Submission Code	N-043
Letter Date	12/02/2014
Stamp Date	12/04/2014
PDUFA Goal Date	06/04/2015
Reviewer Name	Xu Wang, M.D., Ph.D.
Review Completion Date	04/29/2015
Established Name	hydrocodone, pseudoephedrine and guaifenesin
(Proposed) Trade Name	Hycofenix Oral Solution
Therapeutic Class	antitussive/decongestant/expectorant
Applicant	Mikart, Inc.
Priority Designation	S
Formulation	Oral solution
Dosing Regimen	10 mL (hydrocodone bitartrate 5 mg/ pseudoephedrine hydrochloride 60 mg/guaifenesin 400 mg) every 4 to 6 hours, not to exceed 4 doses (40 mL) in 24 hours
Indication	For symptomatic relief of cough, nasal congestion, and to loosen mucus associated with the common cold
Intended Population	Adults <span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span>

## Table of Contents

<b>1 EXECUTIVE SUMMARY .....</b>	<b>5</b>
<b>1 EXECUTIVE SUMMARY .....</b>	<b>5</b>
1.1 RECOMMENDATION ON REGULATORY ACTION .....	5
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS .....	5
1.2.1 Risk Management Activity.....	5
1.2.2 Required Phase 4 Commitments .....	6
1.2.3 Other Phase 4 Requests.....	6
1.3 SUMMARY OF CLINICAL FINDINGS.....	7
1.3.1 Brief Overview of Clinical Program .....	7
1.3.2 Efficacy .....	7
1.3.3 Safety .....	7
1.3.4 Dosing Regimen and Administration .....	8
1.3.5 Drug-Drug Interactions .....	8
1.3.6 Special Populations .....	9
<b>2 INTRODUCTION AND BACKGROUND.....</b>	<b>9</b>
2.1 PRODUCT INFORMATION .....	9
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	11
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES.....	11
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS .....	12
2.5 PRESUBMISSION REGULATORY ACTIVITY .....	12
<b>3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES.....</b>	<b>14</b>
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) .....	14
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY .....	15
<b>4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY .....</b>	<b>15</b>
4.1 SOURCES OF CLINICAL DATA.....	15
4.2 TABLES OF CLINICAL STUDIES .....	15
4.3 REVIEW STRATEGY .....	16
4.4 DATA QUALITY AND INTEGRITY .....	16
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES .....	17
4.6 FINANCIAL DISCLOSURES .....	17
<b>5 CLINICAL PHARMACOLOGY.....</b>	<b>17</b>
<b>6 INTEGRATED REVIEW OF EFFICACY.....</b>	<b>19</b>
6.1 INDICATION.....	19
<b>7 INTEGRATED REVIEW OF SAFETY.....</b>	<b>19</b>
7.1 METHODS AND FINDINGS.....	19
7.1.1 Deaths .....	19
7.1.2 Other Serious Adverse Events.....	21
7.1.3 Dropouts and Other Significant Adverse Events.....	20
7.1.5 Common Adverse Events.....	21
7.1.6 Less Common Adverse Events .....	22
7.1.7 Laboratory Findings .....	22
7.1.8 Vital Signs.....	23
7.1.9 Electrocardiograms (ECGs).....	23
7.1.13 Withdrawal Phenomena and/or Abuse Potential .....	23
7.1.14 Human Reproduction and Pregnancy Data .....	23
7.1.16 Overdose Experience .....	24

7.1.17 Postmarketing Experience.....	24
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS.....	25
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety.....	26
7.2.3 Adequacy of Overall Clinical Experience.....	26
7.2.9 Additional Submissions, Including Safety Update.....	26
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS.....	26
<b>8 ADDITIONAL CLINICAL ISSUES.....</b>	<b>27</b>
8.1 DOSING REGIMEN AND ADMINISTRATION.....	27
8.2 DRUG-DRUG INTERACTIONS.....	27
8.3 SPECIAL POPULATIONS.....	27
8.4 PEDIATRICS.....	27
8.6 LITERATURE REVIEW.....	28
8.7 POSTMARKETING RISK MANAGEMENT PLAN.....	29
<b>9 OVERALL ASSESSMENT.....</b>	<b>30</b>
9.1 CONCLUSIONS.....	30
9.2 RECOMMENDATION ON REGULATORY ACTION.....	31
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS.....	31
9.4 LABELING REVIEW.....	31

**Table of Tables**

Table 1 Formulation of Hycufenix Oral Solution.....	14
Table 2 Summary of clinical pharmacology studies in the submission.....	16
Table 3 Summary of guaifenesin BA/BE, study 11467601.....	18
Table 4 Summary of PK data, study S11-0028 (reviewed in previous review cycle).....	19
Table 5 Adverse events reported in study 11467601.....	22
Table 6 Post-marketing adverse events (AERS database, 01/01/2003 to 12/31/2007, incidence >3%).....	25

## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

This reviewer recommends an “Approval” action for hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin oral solution (proposed trade name Hycofenix) for symptomatic relief of cough, nasal congestion, and to loosen mucus associated with the common cold in patients 18 years of age and older.

This is a 505(b)(2) application for an immediate release oral solution fixed dose combination drug product containing hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin (2.5, 30, and 200 mg, respectively, per 5 ml). The development program for the proposed drug product is a clinical pharmacology program. As a basis for the 505(b)(2) submission pathway, the Applicant uses Hycodan (hydrocodone bitartrate and homatropine methylbromide, NDA 5-213) and Hydrocodone Bitartrate and Homatropine Methylbromide Oral Syrup by Hi-Tech Pharmacal (ANDA 40-613) as the reference drug (RLD) for hydrocodone component of the combination product. The Applicant also cites OTC Monograph 21 CFR 341.20 to support pseudoephedrine and 21 CFR 341.18 to support guaifenesin of the combination product. The proposed drug product depends on the bioequivalence to the reference drugs to support its safety and effectiveness. No clinical efficacy and safety studies were submitted to support this application.

This is the 4<sup>th</sup> submission for this NDA (the 3<sup>rd</sup> complete response submission). The hydrocodone and pseudoephedrine components of the proposed drug were shown to be bioequivalent to reference drugs in clinical pharmacology studies submitted and reviewed in previous submissions. However, the guaifenesin component of the proposed drug product was not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence). In this submission, the clinical pharmacology study demonstrated that the guaifenesin in the proposed drug product was bioequivalent to a commercially available guaifenesin product. The clinical pharmacology program, as presented in this submission for guaifenesin bioequivalence plus the demonstrated bioequivalence for hydrocodone and pseudoephedrine components in the previous submission, supports the approval for the proposed drug product.

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

The Applicant did not submit a risk management plan for the proposed drug product. There is no Risk Minimization Action Plan in place for other immediate release hydrocodone-containing products. Routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of Hycofenix Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

## 1.2.2 Required Phase 4 Commitments

No special Phase 4 commitments are recommended at this time since the recommended regulatory action is Complete Response.

## 1.2.3 Other Phase 4 Requests

The clinical pharmacology studies to support this NDA were conducted in subjects 18 years of age and older. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The agreement has been reached between the Applicant and the Division to partially waive pediatric studies in patients below 6 years of age because the use of hydrocodone in children less than 6 years of age has been associated with fatal respiratory depression, and to conduct pediatric studies as post-marketing requirements in the population from 6 to less than 18 years of age for pharmacokinetics (PK) and safety data in this age group. The Pediatric Review Committee (PeRC) PREA Subcommittee meeting had previously agreed with the Division in other immediate release hydrocodone-containing cough and cold drug programs to grant a partial waiver for pediatric studies below 6 years of age and to grant a deferral for the PK and safety studies in the pediatric population from 6 to less than 18 years of age to a post-approval phase because adult studies are completed and the product is ready for approval in adults. The agreed on post-approval pediatric studies are listed below:

- A. A single-dose pharmacokinetic study whose primary objective is to identify the dose(s) of Hycofenix Oral Solution that results in exposures of hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin in children (aged 6 to 11) and adolescents (aged 12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. The population eligible for enrollment should be otherwise healthy children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The timelines for final protocol submission, trial completion, and final report submission are set to be 01/2016, 07/2017, and 01/2018, respectively.
- B. An open-label multi-dose safety and tolerability study at the dose(s) that result in drug exposures in children (aged 6 to 11) and adolescents (aged 12 to 17 years) that are similar to the exposures seen in adults at the recommended dose. 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 (6-11 years, 12 to 17 years). The timelines for final protocol submission, trial completion, and final report submission are set to be 07/2019, 01/2023, and 07/2023, respectively.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

The development program for the proposed drug product is a clinical pharmacology program. As a basis for the 505(b)(2) submission pathway, the Applicant uses Hycodan (hydrocodone bitartrate and homatropine methylbromide, NDA 5-213) and Hydrocodone Bitartrate and Homatropine Methylbromide Oral Syrup by Hi-Tech Pharmacal (ANDA 40-613) as the reference drug (RLD) for hydrocodone component of the combination product. The Applicant also cites OTC monograph 21 CFR 341.20 to support pseudoephedrine and 21 CFR 341.18 to support guaifenesin of the combination product. The proposed drug product depends on the bioequivalence to the reference drugs to support its safety and effectiveness.

This is a Complete Response submission. In previous review cycle, the clinical pharmacology studies demonstrated the bioequivalence between the hydrocodone and pseudoephedrine components of the proposed drug product and the reference drugs. However, the guaifenesin component of the proposed drug product was not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence). In this submission, the bioequivalent data for guaifenesin component of the proposed drug product come from the clinical pharmacology studies 11467601. There are no clinical efficacy or safety studies in this application.

#### 1.3.2 Efficacy

No clinical efficacy studies were submitted to support this application. This is a 505(b)(2) application using clinical pharmacology studies to support approval. The Agency's previous findings of efficacy and safety of approved hydrocodone products (Hycodan Syrup and Tablets, NDA 5-213) and the OTC monograph for pseudoephedrine and guaifenesin are being used to substantiate the efficacy and safety of this combination drug product.

#### 1.3.3 Safety

The safety of the proposed drug product is based on establishing bioequivalence of the proposed drug product compared to the approved reference drug for hydrocodone and the OTC monograph drugs for pseudoephedrine and guaifenesin. In addition, the Applicant provided clinical summary for the safety data from the clinical pharmacology studies, post-marketing adverse event searches, and a literature survey. In the pivotal clinical pharmacology study (study 11467601) in this complete response submission, a total of 36 healthy subjects received single dose of the test drug. There were no death or serious adverse event occurred in the clinical pharmacology study. The only adverse event reported more than once for the test drug was nausea (2 reports). Other AEs reported as single case included headache, dizziness, hyperhidrosis, asthenia, paraesthesia, and anxiety. These general adverse events occurred in the clinical pharmacology study did not reveal a safety signal. Also, the clinical pharmacology studies submitted and reviewed in the previous review cycle did not reveal safety signals for the proposed drug product.

In previous submission, the Applicant submitted post-marketing adverse events from the AERS database covered the period from January 1, 2003 through December 31, 2007. The AERS database search using combinations hydrocodone plus pseudoephedrine plus guaifenesin (HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The search included the generic names and the trade name medications obtained from internet sites. Combination products containing antihistamines were excluded from the search result. There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The Applicant also searched MEDLINE and EMBASE for the medical literature relevant to safety of hydrocodone, pseudoephedrine and guaifenesin in previous submission. The literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years. The Applicant's search of the medical literature for safety information related to hydrocodone, pseudoephedrine and guaifenesin identified no new safety signals.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. The Applicant submitted a safety update, and identified no new safety signals for the proposed drug product.

#### 1.3.4 Dosing Regimen and Administration

The application is for Hycofenix Oral Solution. The proposed drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The indication is for symptomatic relief of cough, nasal congestion, and to (b) (4) loosen mucus associated with the common cold. The dosage is 10 mL every 4 to 6 hours, not to exceed (NTE) 4 doses (40 mL) in 24 hours for adults (b) (4) 18 years of age and older.

#### 1.3.5 Drug-Drug Interactions

There is no drug-drug interaction study conducted in this NDA submission. The Applicant submitted literature references to address the drug-drug interaction potential of the triple combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone, pseudoephedrine, and guaifenesin are administered together.

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The Applicant's proposed labeling appropriately addresses the potential for these drug-drug interactions.

### 1.3.6 Special Populations

There were no studies in special populations for Hycofenix Oral Solution. The Applicant's proposed labeling indicates that the drug product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. A literature search showed a report that two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Hycofenix Oral Solution is administered to nursing mothers.

*Reviewer's comments:*

*On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received a long-acting hydrocodone-containing cough product.*

*[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>,  
<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>].*

*Although hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age, safety concerns of dose-related respiratory depression over the last few years raise the issue of the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression cases, including fatalities due to respiratory failure have been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products. Tussionex Pennkinetic ER suspension (NDA 19111), a long-acting hydrocodone-containing cough and cold drug, indicates in the product labeling that Tussionex is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. Also all immediate release hydrocodone-containing cough and cold drugs carry a labeling statement in Pediatric Use section that the use of hydrocodone in children less than 6 years of age has been associated with fatal respiratory depression.*

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The Applicant has developed an immediate release oral solution formulation of hydrocodone, pseudoephedrine, and guaifenesin. The drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The labeled indication is for symptomatic relief of cough, nasal congestion, and to <sup>(b) (4)</sup> loosen mucus associated with the common cold. The sponsor's proposed proprietary name, Hycofenix Oral Solution, has been accepted. [Proprietary Name Request Conditionally Acceptable Letter, Division of Medical Error Prevention and Analysis, OSE, 03/02/2015] The dosage is 10 mL every 4 to 6 hours, not to exceed (NTE) 4 doses (40 mL) in 24 hours for adults <sup>(b) (4)</sup> 18 years of age and older.

Hydrocodone (HC) is a commonly used antitussive. The safety and effectiveness of HC as a prescription drug for the symptomatic relief of cough are supported by DESI review and by the FDA approved product Hycodan (NDA 5-213). HC is an opioid, a Schedule II controlled substance as a single ingredient (21 CFR 1308.12), and, according to 21 CFR 1308 published on February 27, 2014 in Federal Register Volume 79, Number 39, all HC combination products (analgesic and antitussive) are placed into Schedule II controlled substance as well.

Hycodan Tablets and Syrup (HC 5 mg plus homatropine methylbromide (HTM) 1.5 mg, and HC 5 mg plus HTM 1.5 mg per 5 mL, NDA 5-213) were classified in the DESI review as safe and effective for prescription drug for the symptomatic relief of cough (DESI Notice #5123). The approved dosages are:

- Adults: One tablet or one teaspoonful of the syrup (5 mg HC) every 4 to 6 hours as needed; not to exceed (NTE) 6 tablets or 6 teaspoonfuls (30 mg HC) in 24 hours
- Children 6 to 12 years of age: One-half (1/2) tablet or one-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 tablets or 3 teaspoonfuls (15 mg HC) in 24 hours
- Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age is contraindicated due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic product labeling].

Pseudoephedrine (PSE) is considered to be GRASE as an oral nasal decongestant [21 CFR 341.20] in the following age groups at the following oral doses [21 CFR 341.80(d)]:

- Adults and children 12 years of age and over: 60 mg every 4 to 6 hours NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 to 6 hours NTE 120 mg in 24 hours
- Children 2 to under 6 years of age: 15 mg every 4 to 6 hours NTE 60 mg in 24 hours
- Children under 2 years of age: consult a doctor

Guaifenesin (GU) is considered to be generally recognized as safe and effective (GRASE) as an expectorant [21 CFR 341.18] in the following age groups at the following oral doses [21 CFR 341.78]:

- Adults and children 12 years of age and older: 200 to 400 mg every 4 hours, NTE 2400 mg in 24 hours
- Children 6 to under 12 years of age: 100 to 200 mg every 4 hours, NTE 1200 mg in 24 hours
- Children 2 to under 6 years of age: 50 to 100 mg every 4 hours, NTE 600 mg in 24 hours
- Children under 2 years of age: consult a doctor

The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single nasal decongestant (such as pseudoephedrine) and any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

*Reviewer's comments:*

*Hydrocodone, a Schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in*

*compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50).*

*However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product, which can be found in detail in Medical Officer Review, IND (b)(4) M-001, MR, Charles E. Lee, M.D., 9/25/2006. Briefly, during the FDA deliberations on the approvability of Tussionex Pennkinetic extended release suspension (NDA 19-111) at the Center Level the FDA determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. The development program for Tussionex Pennkinetic was comprised of 3 bioavailability studies and no clinical studies. Based on this prior precedent, the Division has accepted the conclusion that for a HC combination product containing monograph active ingredients, a drug development plan does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the efficacy and safety of the combination product, and that approval can be based on establishment of bioequivalence.*

## 2.2 Currently Available Treatment for Indications

Hydrocodone is currently approved in the United States in tablet and syrup as an immediate release antitussive drug (Hycodan, NDA 5-213). The owner of NDA 5-213, Endo Pharmaceuticals, had withdrawn the products voluntarily not because of reasons of safety or efficacy. The company keeps the NDA 5-213 current, but stopped manufacturing and marketing the Hycodan Tablets and Solution on January 4 and May 14, 2008, respectively. Hydrocodone is approved in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111). Also, hydrocodone is approved as immediate release formulations in combination with guaifenesin (Obredon, NDA 205-474), chlorpheniramine maleate (Vituz, NDA 204-307), pseudoephedrine HCl (Rezira, NDA 22-442), and chlorpheniramine maleate and pseudoephedrine HCl (Zutripro, NDA 22-439).

There are other generic hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussigon (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). Pseudoephedrine and guaifenesin are readily available OTC monograph drugs, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph doses for the temporary relief of nasal congestion, and to help loosen phlegm (mucus) and thin bronchial secretions.

## 2.3 Availability of Proposed Active Ingredient in the United States

Hydrocodone is currently available in combination with guaifenesin, chlorpheniramine maleate, and pseudoephedrine HCl in NDAs and multiple generic antitussive drugs. In addition, hydrocodone is available in the United States in tablet and capsule formulations as analgesic medications at higher doses than antitussives, such as Vicoprofen (NDA 20716), Vicodin and Vicodin HP (ANDA 88058, ANDA 40117), Lortab (ANDA 40100, ANDA 87722), and Anexsia (ANDA 40405, ANDA 40409, ANDA (b)(4), ANDA 40686, ANDA 89160).

Pseudoephedrine is currently approved in the United States in tablet (Afrinol, NDA 18-191), in combination with chlorpheniramine (Chlor-Trimeton, NDA 18-397), with ibuprofen and chlorpheniramine (Advil Allergy Sinus Caplet, NDA 21-441), and with guaifenesin (Mucinex™ D, NDA 21-585). These products are extended release formulations. Pseudoephedrine is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

Guaifenesin is currently approved in the United States in tablet (Mucinex ER, NDA 21-282), in combination with dextromethorphan (Mucinex™ DM, NDA 21-620), and with pseudoephedrine (Mucinex™ D, NDA 21-585). These products are extended release formulations. Guaifenesin is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

## 2.4 Important Issues With Pharmacologically Related Products

Hydrocodone is a semi-synthetic opioid that has the potential for abuse. Dependence and tolerance may develop upon repeated administration. Hydrocodone is a Schedule II controlled substance as a single ingredient (21 CFR 1308.12). Also, according to 21 CFR 1308 published on February 27, 2014 in Federal Register Volume 79, Number 39, all HC combination products (analgesic and antitussive) are placed into Schedule II controlled substance as well.

The Controlled Substances Staff (CSS) was consulted to advice on the abuse potential for the proposed drug product in previous review cycle. The CSS concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies (Memorandum, Consult on NDA 22-279, N000, Controlled Substance Staff, March 27, 2009). On June 12, 2009, a CDER regulatory briefing was held to discuss the need for abuse potential studies for these products. The consensus from the panel was that abuse potential assessment was not required for these combination products. These types of combinations have been on the market for years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The panel recommended that a post-marketing signal could trigger the need for abuse potential studies for these products.

Pseudoephedrine is an OTC monograph drug of oral nasal decongestant [21 CFR 341.20]. Pseudoephedrine can be unlawfully used to make the illicit drug methamphetamine. The Combat Methamphetamine Act restricts the access of pseudoephedrine by requiring retailers to place OTC drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase.

## 2.5 Presubmission Regulatory Activity

- 03/26/2007: The Applicant ( [REDACTED] (b) (4) ) had a pre-IND meeting with the Division to discuss the plans to develop two immediate release oral solutions of hydrocodone and guaifenesin and hydrocodone, pseudoephedrine and guaifenesin.

- 09/25/2007: The Applicant submitted an opening IND for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (IND 76,365). The opening IND study was a single dose, open label bioavailability study that was determined safe to proceed.
- 08/22/2008: The Applicant filed a 505(b)(2) NDA (NDA 22-279 N000, the 1st submission) for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. The submission included a single arm study to assess the BA of the proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution.
- 04/22/2009: Notice received that the NDA was transferred ownership from (b) (4) (b) (4).
- 06/22/2009: A **Complete Response Letter** was issued, stating that “The open-label bioavailability study submitted is inadequate to evaluate the bioequivalence, drug-drug interaction, and food effect of the proposed combination product.” In order to support the proposed drug product, the Applicant needs to “(1) Conduct a single-dose clinical pharmacology study to establish the bioequivalence of the proposed Hydrocodone 2.5 mg/Pseudoephedrine 30 mg/Guaifenesin 200 mg per 5 mL Oral Solution to the reference products; and (2) Conduct a food effect study of the proposed drug product under fed and fasted conditions.”
- 07/26/2010: The Applicant resubmitted the NDA (NDA 22-279 N019, the 2nd submission) including PK data obtained from two clinical pharmacology studies.
- 01/25/2011: A **Complete Response Letter** was issued, stating that the pharmacology studies submitted in the NDA cannot be relied upon to support the clinical pharmacology of hydrocodone, pseudoephedrine, and guaifenesin oral solution, because an audit performed by the Agency of the pharmacology studies identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site.
- 07/18/2011: The Applicant resubmitted the NDA (NDA 22-279 N030, the 3rd submission) presenting PK data from a single dose BA/BE study and a food effect study.
- 11/04/2011: Notice received that the NDA was transferred ownership from (b) (4) (b) (4).
- 11/04/2011: Notice received that the NDA was transferred ownership from (b) (4) (b) (4) to the present owner of the NDA, Mikart, Inc.
- 01/11/2012: A **Complete Response Letter** was issued, stating that “The clinical pharmacology studies submitted to support this application show that the guaifenesin component of your oral solution product is not bioequivalent to the reference guaifenesin product. This deficiency may be addressed by (1) Assess the design of your relative bioavailability study and, if appropriate, correct design deficiencies and repeat the single-dose clinical pharmacology study; or (2) Evaluate whether there is a formulation effect with your proposed combination product and reformulate the product if necessary. If you reformulate the product you must repeat the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the individual reference products. You may also need to repeat the food effect study if the product is reformulated; or (3) Conduct a clinical development program with clinical efficacy and safety studies to support your combination product.”
- 12/02/2014: The present complete response resubmission (NDA 22-279 N043, the 4th submission) was filed. In this submission, the Applicant included 5 clinical pharmacology studies to compare the relative BA/BE of their proposed drug product (not

reformulated) to 6 commercially available guaifenesin products. While fail to meet the BE criteria for guaifenesin in 4 exploratory studies, the pivotal clinical pharmacology study (11467601) demonstrated that the guaifenesin in the proposed drug product was BE to a commercially available guaifenesin product. The successful study was presented as the support for the proposed drug product. The clinical pharmacology program, as presented in this submission for guaifenesin BE and the BE for hydrocodone and pseudoephedrine in previous submission, is considered acceptable by the Agency's clinical pharmacology review team. [NDA 22-279 N043, Clinical Pharmacology Review, by Yunzhao Ren, Ph. D.]

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 CMC (and Product Microbiology, if Applicable)

The drug product is an oral aqueous solution containing hydrocodone bitartrate USP 2.5 mg, pseudoephedrine hydrochloride USP 30 mg, and guaifenesin USP 200 mg per 5 mL. This is an immediate release formulation. The excipients in the test formulation include sorbitol, glycerin, polyethylene glycol, methylparaben, propylparaben, citric acid, sodium citrate, saccharin, D&C Red #33 and FD&C Blue (b)(4) black raspberry flavor. The proposed combination drug is manufactured by Mikart, Inc.

The formulation of Hycofenix Oral Solution is displayed in Table 1. The experimental formulation is supplied by Mikart, Inc.

**Table 1 Formulation of Hycofenix Oral Solution**

Ingredient	% w/v	mg/5 mL	g/liter
Hydrocodone bitartrate USP	0.050	2.5	0.50
Guaifenesin USP	4.000	200	40.00
Pseudoephedrine hydrochloride USP	0.600	30	6.00
Sorbitol (b)(4) USP	(b)(4)		(b)(4)
Glycerine USP			
Polyethylene glycol (b)(4) NF			
Methylparaben NF			
Propylparaben NF			
Citric acid (b)(4) USP			
Sodium citrate (b)(4) USP			
Saccharin sodium			
D & C red #33			
FD & C blue #1			
(b)(4) black raspberry flavor (b)(4)			
Purified water USP			

Hydrocodone bitartrate USP used in the rest formulation was manufactured by (b)(4)  
 (b)(4) Pseudoephedrine hydrochloride USP (b)(4)  
 used in the rest formulation was manufactured by (b)(4)  
 (b)(4) Guaife  
 manufactured by (b)(4)

A detailed review of the CMC portion of the application may be found in the ONDQA review by Arthur Shaw, Ph. D.

### 3.2 Animal Pharmacology/Toxicology

No new animal data or toxicology data were submitted. No new pre-clinical toxicology studies were required or performed for this application.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The application was submitted under Section 505(b)(2) of the Food, Drug & Cosmetic Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of approved or OTC monograph reference products. The Applicant's drug development program for Hycofenix Oral Solution is based on establishing that their combination drug product produces exposures equivalent to that of approved and marketed products for hydrocodone and to that of OTC monograph drugs pseudoephedrine and guaifenesin. This application refers to the pivotal clinical pharmacology study 11467601. There were no clinical efficacy or safety studies in this application.

The Applicant also included brief overviews for 4 exploratory clinical pharmacology studies (11267601, 11267602, 11267603, and 11267604) comparing the relative bioavailability of guaifenesin from the test formulation with marketed guaifenesin drugs. Because these studies were exploratory in nature and were not used to support the proposed drug product, the 4 studies are only briefly mentioned in this review.

In the previous review cycle, the bioequivalence on hydrocodone and pseudoephedrine components of the proposed drug product were demonstrated in clinical pharmacology studies. For detailed review of those studies, readers are referred to the medical officer review. [NDA 22-279 S030, Medical Officer Review, Xu Wang, M.D., Ph.D. 11/02/2011]

### 4.2 Table of Clinical Studies

The Applicant included 5 clinical pharmacology studies in this submission (Table 2). The 4 studies (11267601, 11267602, 11267603, and 11267604) were exploratory in nature. The study 11467601 was the pivotal study providing support for the bioequivalence of the guaifenesin component between the test drug and the reference drug.

**Table 2 Summary of clinical pharmacology studies in the submission**

StudyNo. (StudyTime)	Study type	Treatment group	Design	Subject No.	Subjects	Guaifenesin BE Result
11267601 (03/03/2012-03/05/2012)	BA/BE	A: Test drug*  B: Children's Mucinex (guaifenesin)200mg/10mL  C: Guaifenesin Syrup 200 mg/10 mL	Randomized, single dose, 2-way crossover	18	Healthy adult males and females	Test drug was BE to reference C;  Cmax of reference B failed to meet BE criteria
11267602 (04/14/2012-04/15/2012)	BA/BE	A: Test drug*  B: Guaifenesin Syrup 200 mg/10 mL	Randomized, single dose, 2-way crossover	30	Healthy adult males and females	Cmax failed to meet BE criteria
11267603 (06/27/2012-06/28/2012)	BA/BE	A: Test drug*  B: Children's Mucinex (guaifenesin)200mg/10mL	Randomized, single dose, 2-way crossover	30	Healthy adult males and females	AUC and Cmax failed to meet BE criteria
11267604 (09/26/2012-009/27/2012)	BA/BE	A: Test drug*  B: Children's Mucinex (guaifenesin)200mg/10mL co-administered with hydrocodone and pseudoephedrine	Randomized, single dose, 2-way crossover	36	Healthy adult males and females	AUC and Cmax failed to meet BE criteria
<b>11467601</b> (pivotal PK study) (07/18/2014-07/19/2014)	BA/BE	A: Test drug*  B: Mucus Relief (guaifenesin) 200 mg/5mL	Randomized, single dose, 2-way crossover	36	Healthy adult males and females	<b>Test drug was BE to reference</b>

\* Hydrocodone bitartrate 2.5mg/pseudoephedrine HCl 30mg/guaifenesin 200mg per 5 mL

#### 4.3 Review Strategy

This is mainly a review of the data from the pivotal clinical pharmacology study (11467601) that demonstrated that the guaifenesin in the proposed drug product was bioequivalent to a commercially available guaifenesin drug (Mucus Relief). Detailed review of the clinical pharmacology data can be found in the Clinical Pharmacology Review. [NDA 22-279, N043, Clinical Pharmacology Review by Yunzhao Ren, Ph. D.] Also included in this review are the adverse event data from AERS database for post-marketing and spontaneous adverse event reports and the literature review for hydrocodone and guaifenesin in previous submission.

#### 4.4 Data Quality and Integrity

The review team requested the inspection for the clinical and analytical sites of the clinical pharmacology studies. 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, because the sites were inspected within the last 4 years and the inspection outcomes were No Action Indicated. [NDA 22-424 and NDA 22-279, Recommendation to accept data without on-site inspection, Division of New Drug Bioequivalence Evaluation (DNDBE), Office of Study Integrity and Surveillance (OSIS), 02/04/2015]

#### 4.5 Compliance with Good Clinical Practices

The clinical pharmacology studies in this application were conducted in accordance with Good Clinical Practices. The applicant certified that the clinical contractor complied with all applicable federal, state and local laws, codes, regulations, and orders, including, but not limited to, the Federal Food, Drug, and Cosmetic Act and regulations promulgated there under, and Institutional Review Board requirements relative to clinical studies.

#### 4.6 Financial Disclosures

The applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The Applicant stated that the clinical investigator of the clinical pharmacology study in this application certified that he did not have a proprietary interest in the proposed product or a significant equity in the Applicant.

### 5 CLINICAL PHARMACOLOGY

There were 5 clinical pharmacology studies in the submission (Table 2). One study (11467601) is the pivotal study to demonstrate that the guaifenesin in the proposed drug product was bioequivalent to a commercially available guaifenesin drug. A summary of data from the Applicant's clinical pharmacology studies follows below. Detailed information can be found in the Clinical Pharmacology Review by Yunzhao Ren, Ph. D.

**Study 11467601** is a clinical pharmacology study to evaluate the relative bioavailability of guaifenesin from the test formulation of hydrocodone bitartrate/pseudoephedrine HCl/guaifenesin 2.5 mg/30 mg/200 mg per 5 mL oral solution compared to a marketed formulation of guaifenesin 100 mg/5 mL oral solution in healthy volunteers under fasting condition.

This was an open-label, randomized, single-dose, 2-treatment, 2-period, crossover study under fasting conditions comparing equal doses of guaifenesin (10 mL or 400 mg) from the test drug (A) and reference drug (B). The study was conducted with 36 healthy adult subjects. The subjects received the test product in one of the study periods and the reference product in the other study period according to a 2-sequence randomization schedule. The test product was hydrocodone bitartrate/ pseudoephedrine HCl/guaifenesin 2.5 mg/30 mg/200 mg per 5 mL and the reference product was Refenesen™ Mucus Relief Expectorant (guaifenesin), 200 mg/5 mL (distributed by Reese Pharmaceutical). Subjects were confined at the clinical facility from at least 10 hours before dosing until after the 5-hour blood sample collection in Period II (about 30 hours after dosing in Period I). The interval (wash-out) between doses was 24 hours.

Nineteen (19) blood samples were collected from each subject during each period of the study: up to 60 minutes before dosing (0 hr), and then at 0.08, 0.17, 0.25, 0.33, 0.42, 0.50, 0.58, 0.67, 0.83, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 5.0 hours post-dose for measurement of plasma guaifenesin concentrations. The analytical data were used to estimate the pharmacokinetic parameters: AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, C<sub>max</sub>, T<sub>max</sub>, K<sub>el</sub> and T<sub>1/2</sub> for guaifenesin. The t in AUC<sub>0-t</sub> is

the time at which the last measurable concentration was recorded. The Statistical Analysis System (SAS®, Version 9.4) was used for all pharmacokinetic and statistical calculations.

The PK data were summarized in Table 3 below. The test formulation of hydrocodone bitartrate/pseudoephedrine HCl/guaifenesin 2.5 mg/30 mg/200 mg per 5 mL oral solution ( (b) (4) ) met the 90% CI criterion for bioequivalence compared to an equal dose of guaifenesin in reference product, Refenesen™ Mucus Relief Expectorant (guaifenesin), 200 mg/5 mL (distributed by Reese Pharmaceutical). The geometric mean ratio (test/listed) of AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> were 0.9687 (90% CI = 0.9203, 1.0197), 0.9674 (90% CI = 0.9188, 1.0186), and 0.9253 (90% CI = 0.8500, 1.0072), respectively.

**Table 3 Summary of guaifenesin BA/BE, Study 11467601**

Parameter	Trt	# Datasets	LS Geometric Mean	Contrast (# subjects)	LSGM Ratio (%)	90% Confid. Interval
AUC <sub>0-t</sub> (ng·hr/mL)	A	36	2519	A vs B (n=36)	96.87	92.03-101.97
	B	36	2601			
AUC <sub>0-∞</sub> (ng·hr/mL)	A	36	2603	A vs B (n=36)	96.74	91.88-101.86
	B	36	2690			
C <sub>max</sub> (ng/mL)	A	36	2015	A vs B (n=36)	92.53	85.00-100.72
	B	36	2178			

Source: NDA 22-279 S043, Attachment 1. Overview of Pharmacology, page 75.

**Other studies**

The Applicant also submitted brief overviews for 4 exploratory clinical pharmacology studies (studies 11267601, 11267602, 11267603, and 11267604) comparing the relative bioavailability of guaifenesin from the test formulation of hydrocodone bitartrate/pseudoephedrine HCl/guaifenesin in healthy volunteers under fasting conditions. As shown in the summaries of the 4 exploratory studies (Table 1), the test drug was bioequivalent to one in 5 commercially available guaifenesin references, and failed to demonstrate BE to other 4 guaifenesin references. These exploratory PK studies were used only to assist the design of the pivotal PK study, and not for providing the support for the proposed drug product.

*Reviewer's comments:*

*In the previous review cycle, the clinical pharmacology studies demonstrated the bioequivalence between the hydrocodone and pseudoephedrine components of the proposed drug product and the reference drugs. However, the guaifenesin component of the proposed drug product was not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence). Table 4 below summarized the PK data supporting the bioequivalence between the hydrocodone and pseudoephedrine components of the proposed drug product and the reference drugs. Detailed information regarding the clinical*

*pharmacology studies reviewed in previously can be found in NDA 22-279 S030, Medical Officer Review, Xu Wang, M.D., Ph.D. 11/02/2011.*

**Table 4 Summary of PK data, study S11-0028 (reviewed in previous review cycle)**

	<b>Test</b>	<b>Reference</b>	<b>% Ratio</b>	<b>90% CI</b>
<i>Hydrocodone</i>				
<i>AUC<sub>0-t</sub> (ng.h/mL)</i>	56.65	57.21	99.01	94.73, 103.49
<i>AUC<sub>0-inf</sub> (ng.h/mL)</i>	61.15	61.40	99.60	95.20, 204.30
<i>C<sub>max</sub> (ng/mL)</i>	9.00	10.33	87.12	82.54, 91.96
<i>Pseudoephedrine</i>				
<i>AUC<sub>0-t</sub> (ng.h/mL)</i>	1916.40	2016.98	95.01	92.32, 97.79
<i>AUC<sub>0-inf</sub> (ng.h/mL)</i>	1977.99	2081.19	95.04	92.30, 97.87
<i>C<sub>max</sub> (ng/mL)</i>	190.21	222.32	85.56	83.03, 88.16
<i>Guaiifenesin</i>				
<i>AUC<sub>0-t</sub> (ng.h/mL)</i>				
<i>AUC<sub>0-inf</sub> (ng.h/mL)</i>				
<i>C<sub>max</sub> (ng/mL)</i>				

(b) (4)

Source: NDA 22-279 S030, MO Re

## 6 INTEGRATED REVIEW OF EFFICACY

This is a clinical pharmacology program. The NDA submission is supported by comparison of the bioavailability of the proposed drug product to reference. No clinical efficacy studies were conducted to support this application.

### 6.1 Indication

Hycufenix (hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin) Oral Solution is indicated for symptomatic relief of cough, nasal congestion, and to loosen mucus associated with the common cold in patients 18 years of age and older.

## 7 INTEGRATED REVIEW OF SAFETY

The safety of the proposed drug product relies primarily on the Agency's previous findings of approved hydrocodone products (Hycodan Syrup and Tablets, NDA 5-213) and the OTC monograph for guaifenesin. Therefore the safety of the proposed drug product is determined by the bioequivalence to the reference drugs. Since the guaifenesin component of the proposed drug product previously failed to meet the BE criterion, the safety of the proposed drug product could not be supported by the Agency's previous findings. The Applicant needs to provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs or conduct clinical studies to support its safety and efficacy.

The Applicant submitted a Clinical Summary including the safety data from the clinical pharmacology study 11467601. The safety data did not identify a safety signal. There were 36 subjects received single dose of the proposed drug product in the study, and the adverse event data from the study reveal no new safety signals. The Applicant also provided brief summaries for the 4 exploratory clinical pharmacology studies (11267601, 11267602, 11267603, and

11267604) that failed in BE for the guaifenesin between the test drug and reference drugs. The adverse events reported in the 4 studies were rare and mild in nature, and did not show significant difference in subjects with the test drug and references.

In previous submission, the Applicant submitted post-marketing adverse event reports from the search result of AERS database covering the period from January 1, 2003 through December 31, 2007, and a brief literature review for safety of hydrocodone, pseudoephedrine, and guaifenesin. The Applicant also conducted an AERS database search using combinations hydrocodone plus pseudoephedrine plus guaifenesin (HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The search included the generic names and the trade name medications obtained from internet sites. Combination products containing antihistamines were excluded from the search result. The presence or absence of acetaminophen was disregarded. The AEs reported from the USA were included.

The Applicant also submitted 2 volumes of compiled published literature references related to the safety of their product in the previous review cycle [Volume 5.8 – 5.9, Section 5.4.2]. The literature survey did not reveal new safety signals for the proposed drug product.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. There are no animal studies and clinical safety studies conducted for the test drug and the test drug was not manufactured and marketed. The safety update identified no new safety information for the proposed drug product.

## 7.1 Methods and Findings

### 7.1.1 Deaths

There were no deaths in the clinical pharmacology studies 11467601.

In searching AERS database in previous submission covering the period from January 1, 2003 through December 31, 2007, there were 6,668 adverse event reports with 2,545 deaths (38.17%) for the search terms of hydrocodone plus pseudoephedrine plus guaifenesin HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The most death reports (2,327) came from searching with hydrocodone, accounting for 62.15% of the adverse event reports (3,744). The four most commonly reported adverse event terms were completed suicide (25.08%, 939/3,744), multiple drug overdose (22.97%, 860/3,744), overdose (13.41%, 502/3,744), and cardiorespiratory arrest (8.87%, 332/3,744). Noticeably, the overall adverse events and death reports for hydrocodone did not differentiate if the hydrocodone was taken as antitussive doses or as much higher analgesic doses. Because the data reflect a large fraction of suicide and overdoses, the dosage forms of hydrocodone for the deaths and adverse events were most possibly higher than doses as an antitussive. There were 194 and 19 death reports for pseudoephedrine and guaifenesin, respectively. The data also reflect a large portion of suicide and overdoses.

*Reviewer's comment:*

*The AERS database search shows the death rate is high in the AE reports for hydrocodone. The death reports reflects a large fraction of suicide and overdoses reported for hydrocodone use. Also, hydrocodone is known to be used in symptomatic treatment for many end stage diseases. Without the knowledge of dosage forms, diseases, co-administered medications, a simple search of AERS, a spontaneous post-marketing adverse event reporting database, does not provide meaningful safety information for hydrocodone use. In the previous review cycle for NDA 22-279, the OSE consult was requested to evaluate the AERS data regarding the high incidence of death reports related to hydrocodone use. The OSE safety evaluator concluded that "the high number of death reports for hydrocodone 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" [NDA 22-279 Review of Fatalities, Division of Pharmacovigilance I, Debra Ryan, Pharm.D., MBA, Safety Evaluator, May 15, 2009].*

### 7.1.2 Other Serious Adverse Events

There were no serious adverse events in the clinical pharmacology studies in this application.

The search of the AERS database covering the period from January 1, 2003 through December 31, 2007 does not identify new safety signals for hydrocodone, pseudoephedrine, and guaifenesin.

### 7.1.3 Dropouts and Other Significant Adverse Events

There were no dropouts in the clinical pharmacology study 11467601. There were no significant adverse events in the 2 clinical pharmacology studies in this submission.

### 7.1.4 Other Search Strategies

No other search strategies were used in this application.

### 7.1.5 Common Adverse Events

In the study 11467601, there were 9 of the 36 subjects reported 16 mild adverse events. Nine (9) and 7 AEs were reported from subjects who had test drug product and reference drug, respectively. The case report review revealed that all adverse events were mild in nature and no treatment was required. The most frequently reported adverse event for the test and reference products was nausea (2 subjects in test drug and 1 subject in the reference). Table 5 summarizes the adverse events occurred in study 11467601.

Note that the reference was guaifenesin only and the test drug contained hydrocodone, pseudoephedrine and guaifenesin. The reported AEs in study 11467601 did not identify a safety signal.

**Table 5 Adverse events reported in study 11467601**

Body System/Adverse Event	Bioequivalence Study Study No. 11467601	
	Test A N (%)	Reference B N (%)
<b>Gastrointestinal disorders</b>		
Diarrhoea	0 (0.00%)	1 (2.78%)
Nausea	2 (5.56%)	1 (2.78%)
<b>General disorders and administration site conditions</b>		
Asthenia	1 (2.78%)	0 (0.00%)
Chills	0 (0.00%)	1 (2.78%)
<b>Nervous system disorders</b>		
Dizziness	1 (2.78%)	1 (2.78%)
Headache	1 (2.78%)	1 (2.78%)
Paraesthesia	1 (2.78%)	0 (0.00%)
Tremor	0 (0.00%)	1 (2.78%)
<b>Psychiatric disorders</b>		
Anxiety	1 (2.78%)	0 (0.00%)
<b>Skin and subcutaneous tissue disorders</b>		
Hyperhidrosis	1 (2.78%)	1 (2.78%)
Macule	1 (2.78%)	0 (0.00%)
<b>Total N%</b>	<b>6 (16.67%)</b>	<b>3 (8.33%)</b>

Treatment A: Test drug Hydrocodone bitartrate 2.5mg/pseudoephedrine 30mg/guaifenesin 200mg per 5 mL.  
 Treatment B: Refenesen™ Mucus Relief Expectoant (guaifenesin), 200 mg/5 mL (distributed by Reese Pharmaceutical).  
 Source: Study 11467601 Report, page 37.

The Applicant also provided brief summaries for the 4 exploratory clinical pharmacology studies (11267601, 11267602, 11267603, and 11267604) that failed in BE for the guaifenesin between the test drug and references. The adverse events reported in the 4 studies were rare and mild in nature, and did not show significant difference in subjects with the test drug and references.

*Reviewer's comment:*

*Because of the small number of the subjects and the low reporting rate for adverse events, there was no meaningful information in differences in adverse events in gender, age, and race/ethnicity.*

7.1.6 Less Common Adverse Events

Adverse events occurring in the clinical pharmacology studies in adults are reviewed in Section 7.1.5. Less common adverse events did not suggest a safety signal.

7.1.7 Laboratory Findings

Laboratory examinations were not safety endpoints in the clinical pharmacology studies of this application.

### 7.1.8 Vital Signs

Vital sign assessments were conducted before and the end of the clinical pharmacology studies. No clinically significant changes from baseline data were reported.

### 7.1.9 Electrocardiograms (ECGs)

ECGs were not safety endpoints in the clinical pharmacology studies of this application.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. Adams EH, Breiner S, Cicero TJ, et al. reported a 12-month study in chronic pain patients that showed an abuse rate of 1.2% for hydrocodone<sup>1</sup>. The applicant provided data regarding the drug-related ED visits in 2005, collected by the Drug Abuse Warning Network (DAWN). The data show that hydrocodone/combinations accounted for 51,225 (6.27%) of the 816,696 total illicit drug-related ED visits in 2005<sup>2</sup>. Although hydrocodone dosages as an antitussive is much lower than that of analgesics and illicit drugs, hydrocodone-containing medications should be prescribed and administered with caution. The proposed Hycufenix Oral Solution is a Schedule II prescription drug, which provides limitation to its accessibility for the unlawful use.

Pseudoephedrine is a sympathomimetic amine used as an oral nasal decongestant. It can be unlawfully used to make illicit drug methamphetamine<sup>3</sup>. The Combat Methamphetamine Act restricts the access of pseudoephedrine by requiring retailers to place drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase. The potential of unlawfully using pseudoephedrine in the proposed drug to make methamphetamine is addressed by the access restriction required in the Combat Methamphetamine Act.

The Controlled Substances Staff (CSS) was consulted to advice on the abuse potential during previous review cycle. The CSS concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies (Memorandum, Consult on NDA 22-279, N000, Controlled Substance Staff, March 27, 2009). On June 12, 2009, a CDER regulatory briefing was held to discuss the need for abuse potential studies for these products. The consensus from the panel was that abuse potential assessment was not required for these combination products.

### 7.1.14 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected in the clinical pharmacological study. The Applicant has not observed or reported adverse events associated with drug exposure during pregnancy in the post-marketing surveillance. The Applicant's proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies

---

1 Adams EH, Breiner S, Cicero TJ, et al. J Pain Symptom Manage. May 2006;31(5):465-476

2 Manchikanti L. Pain Physician 2007;10:399-424

3 [www.streetdrugs.org](http://www.streetdrugs.org), accessed on March 5, 2009

in pregnant women. The Applicant searched MEDLINE database for hydrocodone and human reproduction. A report revealed 2 cases of hydrocodone excretion in breast milk<sup>4</sup>. The infants of the mothers who were taking hydrocodone received an estimated 3.1% and 3.7% of the maternal weight-adjusted dosage. The absolute hydrocodone doses the infants received were 8.58 mcg/kg and 3.07 mcg/kg per day. One infant (18-day-old) became groggy and slept for most of the day while the mother was taking 20 mg hydrocodone every 4 hours. The infant's symptoms improved when mother decrease her hydrocodone dose by half. Another infant (5-week-old) became cyanotic and required intubation while the mother was taking hydrocodone and methadone for migraine headache. The infant was positive for opioids in urinary test and responded well to naloxone treatment. There are no reports of hydrocodone in breast milk while a mother takes hydrocodone at a much lower antitussive dosage. The prescribers and patients should be aware of the potential hydrocodone excretion into breast milk and use Hycofenix Oral Solution with caution.

#### 7.1.16 Overdose Experience

There was no overdose experience reported in the clinical pharmacological studies. The applicant searched the AERS database and the result shows that 36.38% of the reported adverse events associated with hydrocodone were overdose or multiple-drug overdose. In the literature review, the Applicant summarized that hydrocodone had the potential of being overdosed by self-medication and abuse, like other opioids. The AERS database search and literature review did not differentiate whether the hydrocodone was taken as antitussives or at much higher dosages as analgesics. The Applicant identified no new pattern of overdose for the ingredients of the proposed drug.

#### 7.1.17 Postmarketing Experience

The proposed drug product Hycofenix Oral Solution has not been marketed. But there have been multiple illegally marketed hydrocodone-containing products in the U.S. market. The FDA has announced its intention to take enforcement actions against unapproved drug products containing hydrocodone bitartrate if such drug products are manufactured and marketed on or after October 31, 2007 [Federal Register Vol. 72, No 189, October 1, 2007]. The post-marketing experiences were obtained from AERS database search covering hydrocodone and guaifenesin drug products, including approved and unapproved drug products containing hydrocodone as antitussives and analgesics.

Table 6 below summarized the results of the AERS search covering the period from January 1, 2003 through December 31, 2007. The adverse events with an incidence >3% are listed. The AERS search data were reviewed in the previous review cycle, and did not reveal a new safety signal.

---

4 Anderson PO, Sauberan JB, Lane JR, et al. Breastfeeding Med March 2007;2(1):10-14

**Table 6 Post-marketing adverse events (AERS database, 01/01/2003 to 12/31/2007, incidence >3%)**

Search term*	HC/PSE/GU (%)	HC/PSE (%)	HC/GU (%)	HC (%)	PSE (%)	GU (%)
Total (n) AEs	2	3	12	3744	2782	125
Serious AEs <sup>#</sup>	0	0	6 (50.0)	3161 (84.43)	333 (11.97)	85 (68.0)
Death	0	0	5 (41.67)	2327 (62.15)	194 (6.97)	19 (15.20)
Completed suicide	0	0	0	939 (25.08)	65 (2.34)	2 (1.60)
Multiple drug overdose	0	0	1 (8.33)	860 (22.97)	29 (1.04)	5 (4.00)
Overdose	0	1 (33.3)	1 (8.33)	502 (13.41)	97 (3.49)	5 (4.00)
Cardiorespiratory arrest		0	1 (8.33)	332 (8.87)	30 (1.08)	2 (1.60)
Drug toxicity	0	0	1 (8.33)	314 (8.39)	77 (2.77)	0
Drug abuser	0	0	0	230 (6.14)	-- <sup>\$</sup>	1 (0.80)
Respiratory arrest	0	0	0	215 (5.74)	29 (1.04)	1 (0.80)
Vomiting	1 (50.0)	0	1 (8.33)	167 (4.46)	61 (2.19)	5 (4.00)
Nausea	0	0	1 (8.33)	161 (4.30)	167 (6.00)	8 (6.40)
Medical error	0	0	1 (8.33)	158 (4.22)	47 (1.69)	13 (10.40)
Increased drug level	0	0	0	154 (4.11)	35 (1.26)	1 (0.80)
Coma	0	0	1 (8.33)	147 (3.93)	37 (1.33)	3 (2.40)
Somnolence	0	0	0	145 (3.87)	0	2 (1.60)
Drug ineffective	0	0	1 (8.33)	137 (3.66)	224 (8.05)	4 (3.20)
Anxiety	1 (50.0)	0	0	44 (1.18)	40 (1.44)	7 (5.60)
Dyspnea	0	1 (33.3)	0	51 (1.36)	68 (2.44)	3 (2.40)
Vision blurred	0	1 (33.3)	0	0	41 (1.47)	0
Loss of consciousness	0	0	1 (8.33)	88 (2.35)	45 (1.62)	7 (5.60)
Insomnia	0	0	0	39 (1.04)	122 (4.39)	3 (2.40)
Dizziness	0	0	0	59 (1.58)	98 (3.52)	10 (8.00)
Headache	0	0	0	54 (1.44)	163 (5.86)	6 (4.80)
Convulsion	0	0	1 (8.33)	60 (1.60)	40 (1.44)	10 (8.00)
Abdominal pain	0	0	1 (8.33)	47 (1.26)	63 (2.26)	6 (4.80)

\* The version of the MedDRA used in searching the database is not specified.

# Serious adverse events include deaths, life threatening, hospitalization, and disabilities.

\$ The term “drug abuser” was not on the list of terms in PSE report.

(Source: Volume 5.9, Section 5.3.1.2, page 128-134, 157-162)

## 7.2 Adequacy of Patient Exposure and Safety Assessments

The safety of the proposed drug product relies primarily on the Agency’s previous findings of approved hydrocodone products (Hycodan Syrup and Tablets, NDA 5-213) and the OTC monograph for guaifenesin. Therefore the safety of the proposed drug product is determined by the bioequivalence to the reference drugs. Since the guaifenesin component of the proposed drug product had previously failed to meet the BE criterion, the safety of the proposed drug product previously could not be supported by the Agency’s previous findings. In the clinical pharmacology study 11467601, a total of 36 healthy adult subjects receive a single dose of 5 mL of an immediate release oral solution of 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine HCl, and 200 mg guaifenesin under fasting condition. There were 9 subjects who reported 16 adverse events. All adverse events were non-specific and mild in nature, and spontaneously resolved without special treatment. These adverse events did not reveal a safety signal. The efficacy and safety of the proposed drug product are now supported by the BE of the test drug to

the approved reference drug for hydrocodone and the OTC monograph for pseudoephedrine and guaifenesin.

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable

### 7.2.2.3 Literature

The Applicant performed a search of the medical literature for information relevant to safety of hydrocodone, pseudoephedrine, and guaifenesin in general in previous submission. The search covered three individual active ingredient (hydrocodone, pseudoephedrine, guaifenesin) for two years (2006 – 2008) and the products containing all three ingredients for 10 years (1998 – 2008). The search was conducted with the MEDLINE and EMBASE database. There were no studies related to safety of products containing all three ingredients. The literature search revealed no new safety signals for hydrocodone, pseudoephedrine and guaifenesin. The result of the literature search is provided in the Section 8.6 of this review.

## 7.2.3 Adequacy of Overall Clinical Experience

This submission includes two single-dose clinical pharmacology studies in 36 healthy subjects. The study was small in size and provides a fairly limited amount of safety information. The efficacy and safety of the proposed drug is supported by DESI review for hydrocodone and by OTC monograph for pseudoephedrine and guaifenesin. The AERS database and literature search revealed no new safety signals for hydrocodone, pseudoephedrine and guaifenesin at proposed doses. Given the extensive experience with use of hydrocodone as an antitussive, pseudoephedrine as a nasal decongestant, and guaifenesin as an expectorant, this reviewer concludes that the overall clinical exposure to the proposed drug is adequate.

## 7.2.9 Additional Submissions, Including Safety Update

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. There were no animal studies and clinical safety studies conducted for the test drug and the test drug was not manufactured and marketed. The safety update identified no new safety information for the proposed drug product.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the clinical pharmacology studies, the number of subjects treated was small and AEs were infrequent. No new safety concerns have become apparent in the clinical pharmacology studies.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The application is for Hycofenix Oral Solution. The proposed drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription fixed dose combination of antitussive, decongestant and expectorant. The indication is for symptomatic relief of cough, nasal congestion, and to loosen mucus associated with the common cold. The dosage is 10 mL every 4 to 6 hours, not to exceed (NTE) 4 doses (40 mL) in 24 hours for adults (b) (4) 18 years of age and older.

### 8.2 Drug-Drug Interactions

The Applicant submitted literature references to address the drug-drug interaction potential of the triple combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone, pseudoephedrine and guaifenesin are administered together.

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or codeine. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The applicant's proposed labeling appropriately addresses the potential these drug-drug interactions.

### 8.3 Special Populations

There were no studies in special populations for Hycofenix Oral Solution. The Applicant's proposed labeling indicates that the drug product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. A literature search showed a report that two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Hycofenix Oral Solution is administered to nursing mothers.

### 8.4 Pediatrics

The clinical pharmacology studies to support this NDA were conducted in subjects 18 years of age and older. The Applicant conducted the post-marketing adverse event search in AERS for hydrocodone, pseudoephedrine, and guaifenesin in age groups of 0 to under 18, 18 to under 35, 35 to under 50, 50 to under 65, 65 to under 80, and above 80 years. The adverse events in the 0 to 18 age groups were less than most other age groups, accounting for 2.4%, 9.6%, and 8.8% of all adverse events for hydrocodone, pseudoephedrine and guaifenesin, respectively. The Applicant conducted the literature review that revealed no new pediatric safety concerns for hydrocodone, pseudoephedrine and guaifenesin when used for approved indications at the proposed dose.

On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough and cold

drug in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received long-acting hydrocodone-containing cough product.

[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>,  
<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>].

Although hydrocodone is currently labeled for use in children down to 6 years of age, safety concerns regarding dose-related respiratory depression identified by the Agency over the last few years raises the question regarding the most appropriate dose for the pediatric population. There is not enough information regarding the exposure and safety of the proposed drug product in pediatric population. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The agreement has been reached between the Applicant and the Division to partially waive pediatric studies in patients less than 6 years of age because the use of hydrocodone in this age group has been associated with fatal respiratory depression, and to conduct pediatric studies as post-marketing requirements in the population from 6 to less than 18 years of age for pharmacokinetics (PK) and safety data in this age group. The Pediatric Review Committee (PeRC) PREA Subcommittee meeting has previously agreed with the Division in other hydrocodone-containing cough and cold drug programs to grant a partial waiver for pediatric studies below 6 years of age and to grant a deferral for the PK and safety studies in the pediatric population from 6 to less than 18 years of age to a post-approval phase because adult studies are completed and the product is ready for approval in adults. The intent would be for Mikart to also conduct pediatric PK and safety studies as post-market required studies (PMRs) to support pediatric use. This was communicated to Mikart and they agreed on 04/20/2015.

## 8.6 Literature Review

The applicant performed a search of the medical literature for information relevant to hydrocodone, pseudoephedrine and guaifenesin in general in previous submission. The search covered three individual active ingredient hydrocodone, pseudoephedrine, guaifenesin) for a period of two years (January 1, 2006 – June 24, 2008) and the products containing all three ingredients for a period of 10 years (January 1, 1998 – June 24, 2008). There were no new safety signals revealed through the literature search.

There were four case reports, two observational studies, five clinical trials, and one drug-drug interaction study involving hydrocodone adverse events. All four clinical trials were to study hydrocodone in different types of pain patients. All adverse events reported were consistent with what would be expected in use of any opiate (nausea, vomiting, dizziness, somnolence, constipation, etc.)<sup>1-5</sup> The drug-drug interaction study in chronic pain patients demonstrated that serum nicotine levels were negatively correlated with serum hydrocodone levels in smokers.<sup>6</sup> The observational studies and case reports were involved lethal hydrocodone intoxication cases,<sup>7</sup> traffic related deaths with hydrocodone and alcohol use,<sup>8</sup> multiple drug abuse including

hydrocodone,<sup>9</sup> and breast milk hydrocodone excretion in mothers taking prescribed hydrocodone for pain.<sup>10</sup>

There were eight case reports, two observational studies and ten clinical trials involving pseudoephedrine adverse events. There were reported death cases related to multiple drug intoxication including pseudoephedrine.<sup>11</sup> A report of 15 deaths of children younger than 17 months involved OTC medications containing pseudoephedrine.<sup>12</sup> The reported adverse events related to pseudoephedrine use included insomnia, hypertension,<sup>13</sup> two case of myocardial infarction,<sup>14</sup> and a case of transient ischemic attack.<sup>15</sup> It appeared that these serious adverse events involved serious diseases and other concomitant treatments.

There were no reported adverse events related to guaifenesin use. There were no studies related to safety of products containing all three ingredients. The literature search revealed no new safety signals for hydrocodone, pseudoephedrine and guaifenesin.

#### Reference

1. Adams EH, Breiner S, Cicero TJ, et al. *J Pain Symptom Manage*. May 2006;31(5):465-476
2. Chelly JE, Nissen CW, Rodgers AJ, et al. *Curr Med Res Opin*. Jan 2007 ;23(1):195-206
3. Church CA, Stewart CT, et al. *Laryngoscope*. April 2006;116(4):602-606
4. Hewitt DJ, Todd KH, Xiang J, et al. *Am Emerg Med*. April 2007;49(4):468-480
5. Rodriguez RF, Bravol LE, Castro F, et al. *J Palliat Med*. Feb 2007 ;10(1) :56-60
6. Ackerman WE, Ahmad M. *J Ark Med Soc*. July 2007;104(1):19-21
7. Baker DD, Jenkins AJ. *J Anal Toxicol*. March 2008;32(2):165-171
8. Schwilke EW, Sampario MI. et al. *J Forensic Sci*. Sept 2006;51(5):1191-1198
9. Kyle PB, Daley WP. *J Anal Toxicol*. Sept 2007;31(7):415-418
10. Anderson PO, Sauberan JB, Lane JR, et al. *Breastfeeding Med* March 2007;2(1):10-14
11. Carson HJ. *Legal Med*. 2008;10(2):92-95
12. Wingert WE, Mundy LA, Collins GL, et al. *J Forensic Sci*. March 2007;52(2):487-490
13. Latte J, Taverner D. *Am J Rhinol*. 2007;21(4):452-455
14. Biyik I, Ergene O. *Can J Cardiol*. March 2006;22(3):254-256
15. Profice P, Pilato F, Michetti F, et al. *Acta Neurol Scand*. Nov 2006 ;114(5) :358-359

#### 8.7 Postmarketing Risk Management Plan

Hydrocodone is a Schedule II controlled substance that is known to have a certain level of abuse potential. The risk associated with Hycofenix Oral Solution is expected being similar to the risks of other hydrocodone-containing antitussives. The Controlled Substances Staff (CSS) was consulted for advice on the abuse potential for this combination product in the first review cycle. The CSS concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies (Memorandum, Consult on NDA 22-279, N000, Controlled Substance Staff, 03/27/2009). On June 12, 2009, a CDER regulatory briefing was held to discuss the need for abuse potential studies for these products. The consensus from the panel was that abuse potential assessment was not required for these combination products.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The Applicant seeks the approval of Hycofenix, an immediate release oral solution formulation of hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin. The product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription combination drug of antitussive, decongestant and expectorant. The indication is for symptomatic relief of cough, nasal congestion, and to loosen mucus associated with the common cold in patients 18 years of age and older. The dosage is 10 mL every 4 to 6 hours, not to exceed (NTE) 4 doses (40 mL) in 24 hours for adults and adolescents 18 years of age and older.

Guaifenesin and pseudoephedrine are OTC monograph drugs, being considered to be generally recognized as safe and effective (GRASE) in specified doses as an expectorant and an oral nasal decongestant, respectively. The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single nasal decongestant (such as pseudoephedrine) and any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40]. Hydrocodone, a Schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combination is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50). However, there is a regulatory precedent regarding the combination of hydrocodone with an OTC monograph product. The FDA has previously determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. Based on this policy, the Division has approved drug development programs for hydrocodone and OTC monograph product combinations, concluding that a drug development plan does not need to establish the efficacy, safety, or the contribution of hydrocodone or an OTC monograph ingredient to the efficacy and safety of the combination product.

The application consists of a clinical pharmacology program, and the present submission is a complete response submission. In previous review cycle, the clinical pharmacology studies demonstrated the bioequivalence between the hydrocodone and pseudoephedrine components of the proposed drug product and the reference drugs. However, the guaifenesin component of the proposed drug product was not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence). In this submission, the pivotal clinical pharmacology study demonstrated that the guaifenesin in the proposed drug product was bioequivalent to a commercially available guaifenesin product. The clinical pharmacology program, as presented in this submission for guaifenesin BE plus the previously demonstrated BE for hydrocodone and pseudoephedrine components in the previous submission, now supports the approval for the proposed drug.

The safety data from the clinical pharmacology studies in adult subjects did not identify a safety signal. Because of the small number of the subjects, there was no meaningful information in differences of adverse events in gender, age, and race/ethnicity. The Applicant's search of the

medical literature for safety information related to hydrocodone, pseudoephedrine and guaifenesin identified no new safety signal for adverse events.

## 9.2 Recommendation on Regulatory Action

This reviewer recommends an “Approval” action for Hycufenix Oral Solution for symptomatic relief of cough, nasal congestion, and to loosen mucus associated with the common cold in patients 18 years of age and older.

## 9.3 Recommendation on Postmarketing Actions

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The Division has agreed upon request from the Applicant to partially waive pediatric studies in patients less than 6 years of age because the use of hydrocodone in this age group has been associated with fatal respiratory depression. Also because of dose-related respiratory depression cases reported with the use of hydrocodone in children, the Division requires pediatric studies for pharmacokinetics (PK) to assess the adequate dose and safety of the proposed drug product in pediatric population from 6 to less than 18 years of age. The Pediatric Review Committee (PeRC) PREA Subcommittee meeting had previously agreed with the Division in other hydrocodone-containing cough and cold drug programs to grant a partial waiver for pediatric studies below 6 years of age and to grant a deferral for the PK and safety studies in the pediatric population from 6 to less than 18 years of age to a post-approval phase because adult studies are completed and the product is ready for approval in adults.

## 9.4 Labeling Review

Proposed labeling was submitted in Physician’s Labeling Rule (PLR) format. The negotiation of the final labeling is ongoing at the time of this review, and will be harmonized with the labels of other hydrocodone-containing cough and cold drug products.

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

/s/  
-----

XU WANG  
04/29/2015

ANTHONY G DURMOWICZ  
04/29/2015

Clinical Investigator Financial Disclosure  
Review Template

Application Number: 22-279

Submission Date(s): December 4, 2014

Applicant: Mikart Inc.

Product: Hydrocodone/Guaifenesin/Pseudoephedrine

Reviewer: Xu Wang, M.D., Ph.D.

Date of Review: 1/28/2015

Covered Clinical Study (Name and/or Number): Study 11467601

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>7</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3454): <u>None</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>None</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.<sup>1</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

---

<sup>1</sup> See [web address].

## SUMMARY REVIEW OF REGULATORY ACTION

<b>Date</b>	January 11, 2012
<b>From</b>	Lydia Gilbert-McClain, MD, FCCP
<b>Subject</b>	Deputy Division Director Memorandum
<b>NDA/BLA#</b>	NDA 22-279
<b>Applicant</b>	Mikart, Inc
<b>Date of Submission</b>	July 18, 2011
<b>PDUFA Goal Date</b>	January 19, 2012
<b>Proprietary Name/Established (USAN) Names</b>	No acceptable proprietary name/hydrocodone bitartrate/pseudoephedrine HCl/Guaifenesin
<b>Dosage forms/strengths</b>	Oral solution/hydrocodone bitartrate 2.5 mg/pseudoephedrine HCl 30 mg/guaifenesin 200 mg/5 mL
<b>Proposed indication (s)</b>	For symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)
<b>Action/Recommended action for NME</b>	<i>Complete Response</i>
<b>Material Reviewed/consulted</b>	<b>Names of discipline reviewers</b>
Action package including:	
Medical officer review	Xu Wang, MD, PhD
CDTL	Anthony Durmowicz, MD
Clinical Pharmacology review	Arun Agrawal, PhD
CMC review	Arthur Shaw, PhD
Microbiology review	John W. Metcalfe, PhD

### 1. Introduction

This is a second complete response submission to a Complete Response (CR) action taken by the Division on this 505(b)(2) new drug application. The application was originally submitted on August 22, 2008 (received on August 22, 2008, CDER stamp date) by (b) (4). This NDA changed ownership twice since its original submission; first being owned by (b) (4) to the current owner Mikart Inc. as of November 2011. The application is for a fixed dose combination oral solution comprised of hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin as an antitussive, nasal decongestant, and expectorant (b) (4). This is the third review cycle for this NDA. The CR actions the first on June 22, 2009 second CR action on January 25, 2011 have been primarily for clinical pharmacology deficiencies. The Applicant submitted a complete response to the second CR action dated July 18, 2011. The same information was submitted to support the Hydrocodone/guaifenesin NDA 22-424 for which a complete response action was taken on

September 29, 2011 because of clinical pharmacology deficiencies. In the submitted studies, the applicant failed to establish bioequivalence for the guaifenesin component of the combination product. This review will summarize the salient findings from the complete response to support the Division's regulatory action on the application.

## 2. Background

FDA published a final Federal Register (FR) notice of its intention to take enforcement action against illegally marketed cough/cold drug products containing hydrocodone on October 1, 2007 [Docket No. 2007N-0353]. Manufacturers who wish to market a cough/cold product containing hydrocodone must obtain FDA approval via the new drug application (NDA) or an abbreviated new drug application (ANDA) process. Based on the FR notice, manufacturing of unapproved hydrocodone-containing products have ceased and sponsors are conducting development programs for hydrocodone-containing products for cough/cold/upper respiratory allergy indications. Hydrocodone is used as an antitussive agent. It belongs to the opioid class of drugs and it is derived from codeine but unlike codeine, hydrocodone is not a monograph ingredient. Hydrocodone as a single ingredient is a Schedule II narcotic and combination products containing hydrocodone with other non-narcotic active ingredients are Schedule III. Until recently, the only FDA-approved and marketed combination product containing hydrocodone was a hydrocodone polistirex and chlorpheniramine polistirex combination suspension extended-release product (NDA 19-1111) marketed as TUSSIONEX.

The other two ingredients in the proposed combination product guaifenesin and pseudoephedrine are monograph ingredients. However, since hydrocodone is not a monograph product, clinical studies would normally be required to support a combination product containing hydrocodone and other active ingredients in order to show the contribution of each component to the combination product as required by regulation (21CFR 300.50). However, because of the prior regulatory precedent of approving Tussionex Pennkinetic (the combination of hydrocodone and chlorpheniramine) based on demonstration of bioequivalence, hydrocodone-containing combination products that are combined with active ingredients that are listed in the OTC monograph as permitted combinations of active ingredients as per 21CFR 341.40, can satisfy the regulatory requirement for efficacy and safety by demonstration of bioequivalence to appropriate reference products. Therefore, clinical efficacy and safety trials may not be necessary to support a hydrocodone-containing combination product provided that the applicant carries out a satisfactory clinical pharmacology program. The FDA approved 2 new hydrocodone-containing oral solution products on June 8, 2011 Zutripro (hydrocodone/chlorpheniramine and pseudoephedrine) (b) (4)

Approval of these two new products was based on satisfactory demonstration of bioequivalence for each of the active ingredients to an appropriate reference.

The Agency's reliance on safety and efficacy for hydrocodone in the proposed combination product comes from Hycodan [ ENDDO Phamaceuticals] (NDA 05-213) . Note that since Hycodan is no longer marketed (not because of safety or efficacy reasons) the Applicant used

a hydrocodone bitartrate/homatropine methylbromide product from Morton Grove (ANDA 88-088) as the hydrocodone reference product in their clinical pharmacology studies.

### 3. CMC/Device

The proposed product in this NDA is for an aqueous oral solution containing hydrocodone bitartrate (HC) 2.5 mg, pseudoephedrine hydrochloride (PSE) 30 mg, and guaifenesin (GU) 200 mg per 5 mL. The product will be available in 16 oz plastic HDPE bottles containing 473 ml of solution. These active substances are USP ingredients that have been previously assessed to support other NDA applications in the past. There are no unresolved DMF issues. There are no issues with the inactive ingredients which are all compendial except for the (b) (4) (FD&C red and blue) and the flavoring (raspberry flavor). The inactive ingredients include methyl- and propyl-parabens (b) (4) glycerin and water (b) (4) polyethylene glycol (b) (4) citric acid and sodium citrate (b) (4) sorbitol and saccharin (b) (4). Stability data conducted in 16 oz and 4 oz HDPE bottles support a 24 month expiry. There are no outstanding facilities issues with this application. There is one outstanding product quality (microbiology) issue with the application. Although the product is a non-sterile solution, adequate acceptance criterion for *Burkholderia cepacia* an organism considered objectionable in non-sterile aqueous drug products is lacking. Therefore, this deficiency will be conveyed to the applicant as a deficiency.

### 4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology studies were required or performed for this application.

### 5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted two clinical pharmacology studies to address the deficiencies in the action letter: a single dose bioequivalence study (Study S11-0028) and a food effect study (Study 11-0029). Study S11-0028 was a single-dose, randomized, three-period, three-treatment crossover study under fasting conditions with a wash-out period of at least 7 days between treatments. The study investigated the relative bioavailability of the Applicant's hydrocodone bitartrate/pseudoephedrine hydrochloride/guaifenesin oral solution (Test) to the reference products hydrocodone oral solution (the generic hydrocodone oral solution product from Morton Grove [ANDA 88-008] and Robitussin Chest congestion (contains PSE and GU). The study was conducted in 42 healthy adult male and female volunteers. The hydrocodone and pseudoephedrine components of the combination product were bioequivalent to the reference products, in that the 90% CI for the ratios of the geometric means of the test/reference products for the AUC and Cmax were within 80 – 125%. However, the guaifenesin component of the combination product was not bioequivalent to

the reference product (b) (4)

**Table 1 Results for Guaifenesin test/reference**

Parameter	Test	Reference	% Ratio	90% CI
AUC0-4 (ng.h/mL)	(b) (4)			
AUC0-inf (ng h/mL)	(b) (4)			
Cmax (ng/mL)	(b) (4)			

*Test: Hydrocodone bitartrate 5 mg /pseudoephedrine hydrochloride 60 mg/guaifenesin 400 mg oral solution*

*Reference: Combination of pseudoephedrine hydrochloride 60 mg and Robitussin Chest Congestion (guaifenesin 400 mg) oral solution.*

The food effect study was an open-label, single-dose, randomized, two-period, two-treatment crossover study under fasting and fed conditions that assessed the impact of food on the bioavailability of Hydrocodone bitartrate 5 mg /pseudoephedrine hydrochloride 60 mg/guaifenesin 400 mg oral solution. (b) (4)

. The results of the food effect study for the guaifenesin component are shown in Table 2.

**Table 2: Food effect study results for guaifenesin**

Parameter	Guaifenesin (fed) N = 15	Guaifenesin (fasted) N = 15	% Ratio	90% CI
AUC0-4 (ng h/mL)	(b) (4)			
AUC0-inf (ng h/mL)	(b) (4)			
Cmax (ng/mL)	(b) (4)			

## 6. Clinical Microbiology

This is a non-sterile solution and clinical microbiology is not applicable. There is a microbiology quality issue regarding acceptance criteria for *Burkholderia Cepacia* as noted in the CMC section.

## 7. Clinical/Statistical- Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of approved reference products Hycodan and the OTC monograph products pseudoephedrine, and guaifenesin. No clinical studies were required to support the application.

## 8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to approved reference products. The applicant did not submit any new safety data in the complete response. In the original application the applicant conducted a review of the literature (via a MEDLINE and EMBASE search), and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof, for the period from January 1, 2003 – December 31, 2007. These searches did not reveal any new safety signals. The clinical pharmacology studies did not reveal any new safety concerns.

## 9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. The three active ingredients present in this product are not new molecules and there are no issues that need to be discussed at an advisory committee meeting.

## 10. Pediatrics

(b) (4) the Applicant requested a waiver for children under 6 years of age. Since the application is not going to be approved, the application was not presented to PERC. (b) (4)

(b) (4) The request for waiver for children under 6 years of age is based on the fact that the proposed product contains hydrocodone which is contraindicated for use in children less than 6 years of age (because of the risk of respiratory depression). It would be appropriate to waive studies for pediatric patients less than 6 years of age because of this safety concern. (b) (4)

(b) (4) Dose-related respiratory depression including fatalities due to respiratory failure has been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children less than 6 years of age and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require the sponsor to establish the appropriate dose of hydrocodone for the pediatric (less than 18 years) population. Hydrocodone was approved under Drug Efficacy Study Implementation (DESI) review and the basis for the dose selection for the pediatric population is unclear. Further, the appropriate dose of the cough/cold monograph ingredients for the pediatric population are currently under evaluation and whether the currently approved monograph doses of guaifenesin and pseudoephedrine will be considered appropriate for children (b) (4) is unknown.

Whether additional data will be required to support the dose of PSE and GU to support the combination product is unclear but the Agency is not aware of any new safety concerns with these ingredients. However, given the safety concern with hydrocodone, additional PK and safety data will be required to support dosing recommendations in the combination product for children 6 to < 18 years of age.

## 11. Other Relevant Regulatory Issues

### Data Quality, Integrity, and Financial Disclosure

A DSI audit was not conducted in this review cycle because the clinical pharmacology studies failed to establish bioequivalence.

## 12. Labeling

Given the clinical pharmacology data are not acceptable to support the application; a labeling review was not conducted during this cycle. The applicant does not have an acceptable proprietary name at this time and have submitted several proprietary names that have been rejected by the Agency. The most recent proposed proprietary names (b)(4) was reviewed and deemed unacceptable. The applicant has not proposed an alternative trade name (b)(4) that is currently under review.

## 13. Action and Risk Benefit Assessment

### Regulatory action

The regulatory action on the application will be a complete response. The Applicant has not submitted adequate data to support approval of Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution for use as an antitussive, decongestant, and expectorant in patients (b)(4). The open-label bioavailability study submitted failed to show bioequivalence for the guaifenesin component.

The comments below are for the Complete Response action letter:

The clinical pharmacology studies submitted to support this application (studies S11-028 a single-dose bioavailability study and S11-0029 a single-dose crossover food effect study) show that the guaifenesin component of your oral solution product is not bioequivalent to the reference guaifenesin product (b)(4)

This deficiency may be addressed by doing the following:

- a) Assess the design of your relative bioavailability study and, if appropriate, correct design deficiencies and repeat the single-dose clinical pharmacology study to evaluate the bioavailability of your proposed hydrocodone 2.5 mg/guaifenesin 200 mg per 5 mL oral solution combination product compared to the individual reference products,

using the bioequivalence goal post of 80– 125% geometric mean ratio of the AUC and  $C_{\max}$  for your proposed product and the reference products.

OR

b) Evaluate whether there is a formulation effect with your proposed combination product and reformulate the product if necessary. If you reformulate the product you must provide complete CMC information for the new product, repeat the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the individual reference products, using the bioequivalence goal post of 80 – 125%. You may also need to repeat the food effect study if the product is reformulated.

OR

c) Conduct a clinical development program with clinical efficacy and safety studies to support your combination product.

- Risk Benefit Assessment

The overall risk and benefit assessment of the individual ingredients hydrocodone, pseudoephedrine, and guaifenesin does not suggest an unfavorable risk benefit for these individual ingredients. However, for this combination product, a risk benefit assessment cannot be made because the applicant has not conducted the appropriate studies to demonstrate the bioequivalence of this product in comparison to reference listed products. These data are lacking and therefore the product cannot be approved at this time.

- Recommendations for Postmarketing Risk Management Activities

Hydrocodone is a controlled substance known to have a certain level of abuse potential. This combination product if approved will be labeled as a Schedule <sup>(b)</sup><sub>(4)</sub> narcotic and will be available by prescription only. The abuse potential will be managed with appropriate labeling and routine pharmacovigilance.

- Recommendations for other Postmarketing Study Commitments

Not applicable as the product is not going to be approved at this time. However, should the product be approved, the applicant will be required to conduct pharmacokinetic and safety studies in the pediatric (under 18 years) population.

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

/s/  
-----

LYDIA I GILBERT MCCLAIN  
01/11/2012  
Deputy Division Director

## Cross-Discipline Team Leader Review

<b>Date</b>	December 20, 2011
<b>From</b>	Anthony G. Durmowicz, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	22-279
<b>Supplement#</b>	
<b>Applicant</b>	Mikart, Inc.
<b>Date of Submission</b>	July 19, 2011
<b>PDUFA Goal Date</b>	January 19, 2012
<b>Proprietary Name / Established (USAN) names</b>	hydrocodone bitartrate, pseudoephedrine, and guaifenesin oral solution
<b>Dosage forms / Strength</b>	Oral Solution/2.5 mg, 30 mg, and 200 mg, respectively, in each 5 ml
<b>Proposed Indication(s)</b>	For symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)
<b>Recommended Action:</b>	Complete Response

### 1. Introduction

This second complete response submission by the Applicant, received July 19, 2011, is a 505(b)(2) new drug application based on a clinical pharmacology program for a hydrocodone bitartrate, pseudoephedrine, and guaifenesin combination immediate release oral solution with a proposed indication for the symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4). The original NDA, submitted

bioavailability study, which was determined to be inadequate to evaluate the bioequivalence (BE), drug-drug interaction, and food effect of the proposed combination product and a complete response action was taken on June 22, 2009. On July 26, 2010, the Applicant filed the first complete response resubmission, which included data from a single-dose BE study and a food effect study. However, an audit conducted by the Agency identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies were not acceptable to support this NDA submission and a second complete response action was taken on January 25, 2011. Subsequently, the Applicant re-conducted the clinical pharmacology program consisting of single-dose relative bioavailability and food-effect studies and filed this complete response resubmission received on 7/19/2011. Of note is that these same studies were submitted to support approval of a related dual hydrocodone and guaifenesin combination product also being developed by the Applicant (NDA 22-424), however, upon review bioequivalency criteria were not met for the guaifenesin drug component and a complete response action was taken for NDA 22-424 on September 29, 2011. Also of note is that on November 4, 2011, the Division received notice that the owner of the NDA was transferred

Anthony Durmowicz M.D.

Cross Discipline Team Leader Review

NDA 22-279, hydrocodone bitartrate, pseudoephedrine, and guaifenesin oral solution

from (b) (4) to Mikart, Inc. This CDTL review will provide an overview of the application, with a focus on the two newly conducted clinical pharmacology studies which have already been reviewed by FDA reviewers for NDA 22-424. The PDUFA date for this application is January 19, 2012.

## 2. Background

The product under development is one of the hydrocodone-containing cough/cold products belonging to a group of previously illegally marketed products. According to the Agency's Federal Register notice [(published on October 1, 2007 [Docket No. 2007N-0353], all manufacturers of hydrocodone-containing products had to stop manufacturing these products by December 31, 2007. The Agency has encouraged manufacturers of these and other unapproved products to submit NDAs to obtain approval for marketing these products in the United States. This application is to market a combination product containing hydrocodone bitartrate, pseudoephedrine, and guaifenesin, as an immediate release oral solution containing 2.5 mg, 30 mg, and 200 mg of hydrocodone, pseudoephedrine, and guaifenesin, per 5 mL respectively. Guaifenesin and pseudoephedrine are a well known expectorant and decongestant products, respectively, found in many cough and cold products and listed in the OTC monograph (21 CFR 341.40). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses (40 mL) in 24 hours for adults (b) (4)

The Applicant had a pre-IND meeting on March 26, 2007 with the Division to discuss plans to develop two immediate release oral cough and cold solutions, the current NDA 22-279 and the already mentioned related NDA 22-424 hydrocodone and guaifenesin double combination product. The formulations for the proposed drugs (b) (4) for the double and triple combination products (b) (4) in the triple combination product which is the subject of this review. The Applicant planned to conduct all pharmacological studies using the triple combination product in order to obtain data to support both combination products. The Applicant submitted an opening IND on September 25, 2007 for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin triple combination oral solution (IND 76,365). As stated above, the original NDA was submitted on August 22, 2008, and was determined to be inadequate to evaluate the BE, drug-drug interaction, and food effect of the triple combination product and a complete response action was taken on June 22, 2009. On July 26, 2010, the Applicant filed the first complete response resubmission, which included data from a single-dose BE study and a food effect study. However, an audit conducted by the Agency identified deficiencies at the analytical site and, as a result, the studies were not acceptable to support this NDA submission and a second complete response action was taken on January 25, 2011. Subsequently, the Applicant re-conducted the clinical pharmacology program consisting of single-dose relative bioavailability and food-effect studies and filed this complete response resubmission received on 7/19/2011.

As the Applicant has not conducted clinical trials to assess the safety and efficacy of their proposed combination product, the development program for this application is based on demonstration of bioequivalence to the reference ingredients of the combination product. Since

Anthony Durmowicz M.D.

Cross Discipline Team Leader Review

NDA 22-279, hydrocodone bitartrate, pseudoephedrine, and guaifenesin oral solution

hydrocodone is not a monograph product, clinical studies would normally be required to support a combination product containing hydrocodone and other active ingredients in order to demonstrate the contribution of each component to the combination product as required by regulation (21CFR 300.50). However, because of the prior regulatory precedent of approving Tussionex Pennkinetic (the combination of hydrocodone and chlorpheniramine) with clinical pharmacology data only, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combinations can be developed under a clinical pharmacology program only. Therefore, clinical efficacy and safety studies may not be necessary to support this combination product provided that the applicant carries out a satisfactory clinical pharmacology program. However, lack of such a program (lack of bioequivalence) would not allow the Applicant to rely on the Agency's previous determination of safety and efficacy for the reference products and therefore require the Applicant to support any differences with clinical studies or evaluate and correct the reason(s) for lack of bioequivalence and repeat the bioequivalence studies.

Of note is that Hycodan (ENDO Pharmaceuticals) was the initial hydrocodone reference product as listed in the Orange Book. However, the manufacturer of Hycodan discontinued marketing Hycodan solution. The Applicant is using a generic hydrocodone bitartrate product as the hydrocodone reference product in this application, however, Hycodan is still the reference drug for reliance for safety and efficacy of hydrocodone.

### 3. CMC/Device

The proposed product is an aqueous oral immediate release solution containing hydrocodone bitartrate 2.5 mg, pseudoephedrine hydrochloride 30 mg, and guaifenesin 200 mg per 5 mL. Inactive ingredients (excipients) include sorbitol, glycerin, polyethylene glycol, methylparaben, propylparaben, citric acid, sodium citrate, saccharin, D&C Red #33 and FD&C Blue (b) (4) black raspberry flavor.

Hydrocodone bitartrate USP used in the test formulation was manufactured by (b) (4) (b) (4) Guaifenesin USP used in the test formulation was manufactured by (b) (4) (b) (4) and the pseudoephedrine hydrochloride USP used in the test formulation was manufactured by (b) (4) (b) (4)

The proposed combination drug product is manufactured and supplied by Mikart, Inc. 2090 Marietta Blvd, Atlanta, GA 30318. This facility's EES status is acceptable. The drug product release specifications include appearance, pH, specific gravity, identification, and assays for preservatives, impurity, (b) (4) and microbial limits.

Stability data conducted in 16 oz and 4 oz HDPE bottles support a 24 month expiry.

There is one outstanding product quality issue with this product which is also an issue with the related hydrocodone/guaifenesin double combination product (NDA 22424). The proposed triple combination product is a non-sterile solution for oral ingestion which contains (b) (4) (b) (4) The ONDQA microbiology reviewer has

Anthony Durmowicz M.D.

Cross Discipline Team Leader Review

NDA 22-279, hydrocodone bitartrate, pseudoephedrine, and guaifenesin oral solution

identified a CMC deficiency in that the drug product release specification lacks a test and acceptance criterion for *Burkholderia cepacia*, an organism considered objectionable in non-sterile aqueous drug products. Therefore, the microbiology recommendation is that the product is approvable pending resolution of the deficiency.

## 4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology studies were required or performed for this application.

## 5. Clinical Pharmacology/Biopharmaceutics

This review will focus on data submitted for studies S11-0028 and S11-0029, the recently performed clinical pharmacology studies conducted to support NDA.

**Table 1. Summary of pharmacology studies**

Study No.	Study type	Treatment group	Design	Subject No.	Subjects	Materials submitted
S11-0028	BE	A: HC 5/PSE 60/GU 400mg B: HC 5 mg C: PSE 60/GU 400mg	Randomized, single dose, 3-treatment crossover	42	Healthy males and females, 18-64 yrs	Study report
S11-0029	Food effect	HC 5/PSE 60/GU 400mg, fed and fasted conditions	Randomized, open-label, single dose, 2-treatment crossover	18	Healthy males and females, 18-64 yrs	Study report

HC=hydrocodone, PSE=pseudoephedrine, GU=guaifenesin

### Study S11-0028:

#### Design

The study was designed to investigate the relative bioavailability of the Test and Reference solutions by comparing the rate and extent of exposure of (b) (4) (now Mikart's) triple combination solution to the reference solutions. It was a single-dose, randomized, three-treatment crossover study under fasting condition in 42 male and female healthy volunteers aged 18 to 64 years old participated this study. There was at least a 7 day washout period between doses. Safety evaluation includes adverse events and vital signs during the study.

Treatment A (Applicant Test Product): Applicant's hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution

Treatment B (Hydrocodone Reference Product): Hydrocodone bitartrate 5 mg oral solution (Morton Grove, ANDA 88-088).

Treatment C (Guaifenesin Reference Product): the combination of pseudoephedrine HCl 60 mg and Robitussin Chest Congestion (guaifenesin 400 mg) oral solution

#### Results

The hydrocodone and pseudoephedrine components of the combination product were bioequivalent to the respective reference products, in that the 90% CI for the ratio of the geometric means of the test/reference products for the AUC and C<sub>max</sub> were within 80 – 125%. However, the guaifenesin component of the combination product was not bioequivalent to the reference product (b) (4)

**Table 2. Results for guaifenesin test/reference**

Parameter	Test	Reference	% Ratio	90% CI
AUC <sub>0-t</sub> (ng.h/mL)	(b) (4)			
AUC <sub>0-inf</sub> (ng h/mL)				
C <sub>max</sub> (ng/mL)				

**Study S11-0029:**

Design

This was a single-dose food effect cross-over study to assess the impact of food on the bioavailability of the Applicant’s hydrocodone, pseudoephedrine, and guaifenesin oral solution. Eighteen healthy male and female subjects 18 to 64 years of age were randomized to receive a single open-label of dose of the proposed hydrocodone, pseudoephedrine, and guaifenesin oral solution under fed and fasting conditions with 15 subjects completing the study. Again, at least a 7-day washout period was observed between the doses. Safety evaluation included adverse events and vital signs monitoring during the study.

Results

The data demonstrated that food had an impact on the systemic exposure and bioavailability for the hydrocodone and guaifenesin drug substances. Food did not have an impact on the systemic exposure or bioavailability of pseudoephedrine as the test ratios of geometric means and 90% CI for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> were all contained within the protocol defined acceptance range of 80.00 -125.00%.

For hydrocodone, (b) (4)

**Table 3: Food effect study results for hydrocodone**

Parameter	Hydrocodone (fed) N = 15	Hydrocodone (fasted) N = 15	% Ratio	90% CI
AUC <sub>0-t</sub> (ng h/mL)	(b) (4)			
AUC <sub>0-inf</sub> (ng h/mL)				
C <sub>max</sub> (ng/mL)				

For guaifenesin (b) (4)

**Table 4: Food effect study results for guaifenesin**

Parameter	Guaifenesin (fed) N = 15	Guaifenesin (fasted) N = 15	% Ratio	90% CI
AUC <sub>0-t</sub> (ng h/mL)				
AUC <sub>0-inf</sub> (ng h/mL)				
C <sub>max</sub> (ng/mL)				

(b) (4)

## 6. Clinical Microbiology

While this is a non-sterile solution and clinical microbiology is not applicable, the ONDQA microbiology reviewer has identified a CMC deficiency in that the drug product release specification lacks a test and acceptance criterion for *Burkholderia cepacia*, an organism considered objectionable in non-sterile aqueous drug products (see Section 3).

## 7. Clinical/Statistical- Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of approved reference products hydrocodone, pseudoephedrine, and guaifenesin. No clinical efficacy studies were conducted to support this application.

## 8. Safety

The safety of the product is based on establishing bioequivalence of the proposed combination product compared to the approved reference product, Hycodan Syrup and Tablets, (NDA 5-213) and the OTC monograph for pseudoephedrine and guaifenesin. Since the guaifenesin component of the proposed drug product failed to meet the bioequivalency criteria, the safety of the proposed drug product can not be supported by the Agency's previous findings for single ingredient or combination products containing guaifenesin. The Applicant needs to provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs or conduct clinical studies to support its safety and efficacy.

In the clinical pharmacology program (including adverse event reports from earlier performed clinical pharmacology studies #S09-0009 and #S09-0010) in which a total of 120 healthy adult subjects received a single dose of 10 mL of an immediate release oral solution containing 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin, there were a total of 34 adverse events (13 headache, 8 dizziness, 4 lightheaded, 3 hot flush, 3 hyperhidrosis, 2 pallor, and 1 drowsiness). These events were mild and resolved without intervention.

A review of the literature (via a MEDLINE and EMBASE search), and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof were also conducted to support the safety of the proposed product. The post-marketing adverse events from the AERS database covered the period from January 1,

Anthony Durmowicz M.D.

Cross Discipline Team Leader Review

NDA 22-279, hydrocodone bitartrate, pseudoephedrine, and guaifenesin oral solution

2003 through December 31, 2007 while the literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years.

While no new safety issues regarding hydrocodone and guaifenesin were detected, because of the failure to demonstrate bioequivalency to guaifenesin in the clinical pharmacology studies, the above AERS database and literature searches are insufficient in and of themselves to support the safety of the proposed hydrocodone and guaifenesin combination product.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required. However, there are no additional animal or clinical safety studies the Applicant has conducted for the test drug and the test drug has not been manufactured and marketed. Thus, there was no new information to include in the safety update.

## 9. Advisory Committee Meeting

An advisory committee meeting is not necessary for this application. The active ingredients present in this product are well known as individual drug substances, and as previously discussed, based on the current monograph and the Agency's prior precedent, the combination of products of these classes are accepted for the proposed indications.

## 10. Pediatrics

[REDACTED] (b) (4)

The request for waiver for children under 6 years of age is based on the fact that the proposed product contains hydrocodone which is contraindicated for use in children less than 6 years of age (because of the risk of respiratory depression). It would be appropriate to waive studies for pediatric patients less than 6 years of age because of this safety concern [REDACTED] (b) (4)

[REDACTED] Dose-related respiratory depression including fatalities due to respiratory failure has been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e., that hydrocodone is contraindicated in children less than 6 years of age and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require the sponsor to establish the appropriate dose of hydrocodone for the pediatric (less than 18 years) population. Hydrocodone was approved under Drug Efficacy Study Implementation (DESI) review and the basis for the dose selection for the pediatric population is unclear. [REDACTED] (b) (4)

[REDACTED]

## 11. Other Relevant Regulatory Issues

### Withdrawal and Abuse Potential

The Controlled Substances Staff (CSS) was consulted to give their opinion on the abuse potential for the Applicant's hydrocodone containing triple combination product during a previous review cycle. The CSS was concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies (Memorandum, Consult on NDA 22-279, N000, Controlled Substance Staff, March 27, 2009). On June 12, 2009, a CDER regulatory briefing was held to discuss the need for abuse potential studies for these products. The consensus from the panel was that abuse potential assessment was not required for these combination products. These combinations are currently in Schedule III and have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The panel recommended that a post-marketing signal could trigger the need for abuse potential studies for these products.

### Inspections

The Division of Scientific Investigation (DSI) audits were not conducted for studies S11-0028 and S11-0029 because the studies have failed to establish the bioequivalence between the proposed combination drug product and reference drugs and, as such, the studies could not be used to support approval of the product based on establishing bioequivalency.

### Compliance with Good Clinical Practices

The clinical pharmacology study in this application was conducted in accordance with Good Clinical Practices, and in particular with the requirements of 21 CFR Part 314.50(3)(i). The Applicant certified that the clinical contractor conducted the study in compliance with Institutional Review Board regulations and with Informed Consent Regulations.

### Financial Disclosures

The Applicant certified that there was no financial arrangement with the clinical investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant stated that the clinical investigator of the clinical pharmacology studies in this application certified that he did not have a proprietary interest in the proposed product or a significant equity in the Applicant.

## 12. Labeling

### Proprietary Name

The previously proposed trade name (b) (4) was reviewed and deemed to be unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA). The Applicant has not proposed a replacement trade name.

### Physician Labeling

Label and carton/container review were not conducted during this review cycle as the product had not established bioequivalency and could not be approved based on bioequivalency.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is for a Complete Response as (b) (4) (b) (4) Mikart, Inc. has not submitted adequate data to support approval of their hydrocodone, pseudoephedrine, and guaifenesin oral solution for use as an antitussive, decongestant, and expectorant in patients (b) (4). The submitted open-label bioavailability study failed to demonstrate bioequivalence for the guaifenesin drug component and, as a result, cannot rely on the Agency's previous determinations of safety and efficacy. As the Applicant was relying on establishing bioequivalence as the means for approval, they did not conduct clinical studies to support the safety and efficacy of the proposed product.

- Risk Benefit Assessment

While the overall risk and benefit assessment of the individual ingredients hydrocodone, pseudoephedrine, and guaifenesin does not suggest an unfavorable risk benefit, for this combination product, a risk benefit assessment cannot be made because the Applicant has not established bioequivalence of the combination product to the individual reference products (guaifenesin specifically) and therefore cannot rely on the Agency's previous determination of safety and efficacy.

- Recommendation for Postmarketing Risk Management Activities

Hydrocodone is a controlled substance known to have a certain level of abuse potential. Therefore, this combination product, if approved, will be labeled as a Schedule (b) (4) narcotic and will be available by prescription only. The abuse potential will be managed with appropriate labeling and routine pharmacovigilance.

- Recommendation for other Postmarketing Study Commitments

None, as the recommendation is for a Complete Response for this application.

- Deficiencies for the Complete Response Letter

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form for the following reasons:

1. Your clinical pharmacology 505(b)(2) application is based on being able to demonstrate bioequivalency of the test drugs to the reference drugs and the guaifenesin component in the test oral solution is not bioequivalent to the reference product with the 90% CI for the geometric mean ratio of Cmax falling outside of the 80.00% to 125.00% acceptance range for BE.

To address this deficiency you should do the following:

- If you believe the failure to demonstrate bioequivalency is because of study design issues, repeat the single dose bioavailability study between your product and the reference products under fasted state by appropriately redesigning the study. To gain approval based on bioequivalency criteria, bioequivalence must be established between your proposed product and the reference products under a fasted state.

Or

- If you believe the failure to demonstrate bioequivalency is due to formulation issues, reformulate the product and repeat the clinical pharmacology program to demonstrate BE between the reformulated product and the reference products under a fasted state, and repeat the food effect study if necessary.

Or

- Develop your combination product by conducting clinical trials to support its safety and efficacy.

2. Your proposed drug product release specification lacks a test and acceptance criterion for *Burkholderia cepacia*, an organism considered objectionable in non-sterile aqueous drug products.

To address this deficiency you should do the following:

- Incorporate testing and acceptance criteria for the bacteria, *Burkholderia cepacia*, into the release specification for your proposed hydrocodone and guaifenesin combination product.
- Provide test method(s) for *Burkholderia cepacia* and the relevant method validations. The test method(s) validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

Additional Comments:

1. To control the objectionable microorganism *Burkholderia cepacia*, we recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
2. Update the revised acceptance limits for impurities and Total Combined Mold/Yeast Count in the stability data summary table in your next stability data update.

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

/s/  
-----

ANTHONY G DURMOWICZ  
12/20/2011

## CLINICAL REVIEW

Application Type	NDA
Submission Number	22-279
Submission Code	N-030
Letter Date	07/18/2011
Stamp Date	07/19/2011
PDUFA Goal Date	01/19/2012
Reviewer Name	Xu Wang, M.D., Ph.D.
Review Completion Date	11/02/2011
Established Name	Hydrocodone, Pseudoephedrine, and Guaifenesin
(Proposed) Trade Name	Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)
Therapeutic Class	Antitussive/Nasal decongestant/Expectorant
Applicant	(b) (4)
Priority Designation	S
Formulation	Oral solution
Dosing Regimen	For adults (b) (4) 10 mL (hydrocodone bitartrate 5 mg/pseudoephedrine hydrochloride 60 mg/guaifenesin 400 mg) every 4 hours, not to exceed 40 mL in 24 hours (b) (4)
Indication	For symptomatic relief of cough (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)
Intended Population	Adults (b) (4)

## Table of Contents

<b>1 EXECUTIVE SUMMARY .....</b>	<b>5</b>
<b>1 EXECUTIVE SUMMARY .....</b>	<b>5</b>
1.1 RECOMMENDATION ON REGULATORY ACTION .....	5
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS .....	5
1.2.1 Risk Management Activity.....	5
1.2.2 Required Phase 4 Commitments .....	5
1.2.3 Other Phase 4 Requests.....	5
1.3 SUMMARY OF CLINICAL FINDINGS.....	6
1.3.1 Brief Overview of Clinical Program .....	6
1.3.2 Efficacy.....	6
1.3.3 Safety .....	7
1.3.4 Dosing Regimen and Administration.....	8
1.3.5 Drug-Drug Interactions .....	8
1.3.6 Special Populations.....	8
<b>2 INTRODUCTION AND BACKGROUND.....</b>	<b>9</b>
2.1 PRODUCT INFORMATION .....	9
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	11
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES.....	11
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS .....	12
2.5 PRESUBMISSION REGULATORY ACTIVITY .....	13
<b>3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES.....</b>	<b>14</b>
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) .....	14
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY .....	15
<b>4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY .....</b>	<b>15</b>
4.1 SOURCES OF CLINICAL DATA.....	15
4.2 TABLES OF CLINICAL STUDIES .....	15
4.3 REVIEW STRATEGY .....	16
4.4 DATA QUALITY AND INTEGRITY .....	16
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES .....	16
4.6 FINANCIAL DISCLOSURES .....	16
<b>5 CLINICAL PHARMACOLOGY.....</b>	<b>17</b>
<b>6 INTEGRATED REVIEW OF EFFICACY.....</b>	<b>19</b>
6.1 INDICATION.....	19
<b>7 INTEGRATED REVIEW OF SAFETY.....</b>	<b>20</b>
7.1 METHODS AND FINDINGS .....	19
7.1.1 Deaths .....	19
7.1.2 Other Serious Adverse Events.....	22
7.1.3 Dropouts and Other Significant Adverse Events.....	20
7.1.5 Common Adverse Events.....	22
7.1.6 Less Common Adverse Events .....	23
7.1.7 Laboratory Findings.....	23
7.1.8 Vital Signs.....	23
7.1.9 Electrocardiograms (ECGs).....	23
7.1.13 Withdrawal Phenomena and/or Abuse Potential .....	24
7.1.14 Human Reproduction and Pregnancy Data .....	24
7.1.16 Overdose Experience .....	25

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

7.1.17 Postmarketing Experience.....	25
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS .....	26
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety .....	26
7.2.3 Adequacy of Overall Clinical Experience .....	26
7.2.9 Additional Submissions, Including Safety Update.....	27
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS .....	27
<b>8 ADDITIONAL CLINICAL ISSUES.....</b>	<b>27</b>
8.1 DOSING REGIMEN AND ADMINISTRATION.....	27
8.2 DRUG-DRUG INTERACTIONS .....	28
8.3 SPECIAL POPULATIONS .....	28
8.4 PEDIATRICS.....	28
8.6 LITERATURE REVIEW .....	29
8.7 POSTMARKETING RISK MANAGEMENT PLAN.....	30
<b>9 OVERALL ASSESSMENT .....</b>	<b>30</b>
9.1 CONCLUSIONS .....	30
9.2 RECOMMENDATION ON REGULATORY ACTION .....	31
9.4 LABELING REVIEW.....	31
9.5 COMMENTS TO APPLICANT.....	31

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

**Table of Tables**

Table 1 Summary of pharmacology studies..	15
Table 2 Formulation of Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution.....	17
Table 3 Summary of PK data, Study S11-0028.....	18
Table 4 Summary of PK data, Study S11-0029.....	19
Table 5 Post-marketing adverse events (AERS database, Jan. 1, 2003 to Dec. 31, 2007, incidence >3%).....	21
Table 6 Adverse events reported in study S11-0028.....	23

## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

In the present NDA resubmission the Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only) has failed to meet bioequivalence criteria and I recommend that the application be given a Complete Response action.

This NDA is a 505(b)(2) new drug application based on a clinical pharmacology program. There are no efficacy and safety studies in this NDA. While 505(b)2 applications do not necessarily require the Applicant to meet strict bioequivalence criteria, for this program the Applicant relies on demonstrating bioequivalence to the approved product for hydrocodone and to OTC monograph drugs for pseudoephedrine and guaifenesin to support the efficacy and safety of the proposed drug product. The clinical pharmacology studies submitted are not adequate to support this application because the result does not fulfill the bioavailability criteria for combination products as per 21 CFR 320.25 (g). Specifically, the guaifenesin component of the proposed product is not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence). To support the registration of the proposed drug product, the Applicant needs to either provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs and therefore be able to rely on the Agency's previous determination of efficacy and safety for hydrocodone, pseudoephedrine, and guaifenesin or conduct clinical studies to support its efficacy and safety.

### **1.2 Recommendation on Postmarketing Actions**

#### **1.2.1 Risk Management Activity**

No special post-marketing risk management activities are recommended at this time.

#### **1.2.2 Required Phase 4 Commitments**

No special Phase 4 commitments are recommended at this time since the recommended regulatory action is Complete Response.

#### **1.2.3 Other Phase 4 Requests**

There are no Phase 4 requests for this application.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

This is a Complete Response (CR) resubmission based on the deficiencies outlined in the Complete Response letter dated January 25, 2011. The original NDA, submitted on August 22, 2008, presented a single dose bioavailability study, which was determined inadequate to evaluate the bioequivalence, drug-drug interaction, and food effect of the proposed combination product. On July 26, 2010, the Applicant filed a CR resubmission, presented data from a single-dose BE study (S09-0009) and a food effect study (S09-0010). An audit conducted by the Agency identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies were not acceptable to support this NDA submission [MEMORANDUM Division of Scientific Investigation, Martin K. Yau, Ph.D., 1/20/2011]. The second CR letter was issued on 1/25/2011. Subsequently, the Applicant re-conducted the clinical pharmacology program and filed this CR resubmission on 7/18/2011. In this NDA resubmission, the Applicant referenced the previously reviewed clinical pharmacology studies and included two additional clinical pharmacology studies. Study S11-0028 is a single-dose, randomized, three-treatment crossover study to assess the relative bioavailability and bioequivalence of the test drug, (b) (4) triple combination solution), and reference solutions. The results of this study demonstrated that hydrocodone and pseudoephedrine met the bioequivalence criteria. However, the guaifenesin component of the proposed product is not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence).

Study S11-0029 is a food effect study to assess the impact of food on the bioavailability of (b) (4) triple combination solution. This is a single-dose, randomized, two-treatment crossover study under fed and fasting conditions. The results of this study demonstrated that the ratio of fed vs. fasting for the hydrocodone and guaifenesin component the point estimates and their 90% CIs for C<sub>max</sub> were not contained within the acceptance range of 80.00 - 125.00%, and for guaifenesin the point estimate and its 90% CI for AUC was not contained within the acceptance range of 80.00 - 125.00% as well, suggesting that food had an overall impact on the systemic bioavailability of the hydrocodone and guaifenesin component.

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology studies S11-0028 and S11-0029, a search of the AERS database for post-marketing spontaneous adverse events, and a literature survey to provide support for the safety of the proposed drug product.

#### 1.3.2 Efficacy

This is a 505(b)(2) application using clinical pharmacology studies to support approval. No clinical efficacy studies were submitted to support this application. The Agency's previous findings of efficacy and safety of approved hydrocodone products (Hycodan Syrup and Tablets, NDA 5-213) and the OTC monograph for pseudoephedrine and guaifenesin are being used to substantiate the efficacy and safety of this triple combination product. Because the clinical pharmacology studies in this NDA failed to meet the bioequivalence criterion, the Applicant

needs to provide new data to demonstrate the bioequivalence of the proposed drug product to reference drugs or conduct clinical studies to support its safety and efficacy for the proposed indication.

### 1.3.3 Safety

The safety of the proposed drug product relies primarily on the Agency's previous findings of approved hydrocodone products (Hycodan Syrup and Tablets, NDA 5-213) and the OTC monograph for pseudoephedrine and guaifenesin. Therefore the safety of the proposed drug product is determined by the bioequivalence to the reference drugs. Since the guaifenesin component of the proposed drug product failed to meet the BE criterion, the safety of the proposed drug product can not be supported by the Agency's previous findings of safety for single ingredient or combination products containing guaifenesin. The Applicant needs to provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs or conduct clinical studies to support its safety and efficacy.

In the clinical pharmacology studies S11-0028 and S11-0029, a total of 60 healthy, adult subjects aged 18 to 64 years receive a single dose of 10 mL of an immediate release oral solution containing 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin under fasting condition. There were a total of 17 adverse events in these two clinical pharmacology studies (7 headache, 3 hot flush, 3 hyperhidrosis, 2 dizziness, and 2 pallor). All adverse events were mild in nature and spontaneously resolved without special treatment. The safety data from these two clinical pharmacology studies in healthy adult subjects did not identify a safety signal.

The post-marketing adverse events from the AERS database covered the period from January 1, 2003 through December 31, 2007. The AERS database search using combinations hydrocodone plus pseudoephedrine plus guaifenesin (HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The search included the generic names and the trade name medications obtained from internet sites. Combination products containing antihistamines were excluded from the search result. There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The Applicant searched MEDLINE and EMBASE for the medical literature relevant to safety of hydrocodone, pseudoephedrine, and guaifenesin. The literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years. The Applicant's search of the medical literature for safety information related to hydrocodone, pseudoephedrine, and guaifenesin identified no new safety signals.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the test drug and the test drug has not been manufactured and marketed. Thus, there is no new information to include in the safety update.

### 1.3.4 Dosing Regimen and Administration

The application is for Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only). The proposed drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed indications are “for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4).

### 1.3.5 Drug-Drug Interactions

The applicant submitted literature references to address the drug-drug interaction potential of the triple combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone, pseudoephedrine, and guaifenesin are administered together.

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The Applicant’s proposed labeling appropriately addresses the potential for these drug-drug interactions.

### 1.3.6 Special Populations

There were no studies in special populations for Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution in this submission to review. The Applicant’s proposed labeling indicates that the drug product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. A literature search shows a report of two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution is administered to nursing mothers.

*Reviewer comment:*

*On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received a long-acting hydrocodone-containing cough product.*

*[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>,*

*<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>].*

(b) (4)

(b) (4)

*Dose-related respiratory depression cases, including fatalities due to respiratory failure have been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children under 6 years of age, and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require that the sponsor establish the appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population. The Applicant will be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age.*

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The Applicant has developed an immediate release oral solution formulation of hydrocodone, pseudoephedrine, and guaifenesin. The drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed labeled indications are “for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)

(b) (4) The sponsor’s proposed name is Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4)

(b) (4)

The Applicant has provided a paper submission.

Hydrocodone (HC) is a commonly used antitussive. The safety and effectiveness of HC as a prescription drug for the symptomatic relief of cough are supported by DESI review and by the FDA approved product Hycodan (NDA 5-213). HC is an opioid, a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in combination with active non-narcotic ingredients and if the product contains not more than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15).

Hycodan Tablets and Syrup (HC 5 mg plus homatropine methylbromide (HTM) 1.5 mg, and HC 5 mg plus HTM 1.5 mg per 5 mL, NDA 5-213) was classified in the DESI review as safe and effective for prescription drug for the symptomatic relief of cough (DESI Notice #5123). The approved dosages are:

- Adults: One tablet or one teaspoonful of the syrup (5 mg HC) every 4 to 6 hours as needed; not to exceed (NTE) 6 tablets or 6 teaspoonfuls (30 mg HC) in 24 hours

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

- Children 6 to 12 years of age: One-half (1/2) tablet or one-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 tablets or 3 teaspoonfuls (15 mg HC) in 24 hours
- Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age is contraindicated due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic product labeling].

Pseudoephedrine (PSE) is considered to be GRASE as an oral nasal decongestant [21 CFR 341.20] in the following age groups at the following oral doses [21 CFR 341.80(d)]:

- Adults and children 12 years of age and over: 60 mg every 4 to 6 hours NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 to 6 hours NTE 120 mg in 24 hours
- Children 2 to under 6 years of age: 15 mg every 4 to 6 hours NTE 60 mg in 24 hours
- Children under 2 years of age: consult a doctor

Guaifenesin (GU) is considered to be generally recognized as safe and effective (GRASE) as an expectorant [21 CFR 341.18] in the following age groups at the following oral doses [21 CFR 341.78]:

- Adults and children 12 years of age and older: 200 to 400 mg every 4 hours, NTE 2400 mg in 24 hours
- Children 6 to under 12 years of age: 100 to 200 mg every 4 hours, NTE 1200 mg in 24 hours
- Children 2 to under 6 years of age: 50 to 100 mg every 4 hours, NTE 600 mg in 24 hours
- Children under 2 years of age: consult a doctor

The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single nasal decongestant (such as pseudoephedrine) and any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

*Reviewer comment:*

*Hydrocodone, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50).*

*However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product, which can be found in detail in Medical Officer Review, (b) (4), M-001, MR, Charles E. Lee, M.D., 9/25/2006. Briefly, during the FDA deliberations on the approvability of Tussionex Pennkinetic extended release suspension (NDA 19-111) at the Center Level the FDA determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. The development program for Tussionex Pennkinetic was comprised of 3 bioavailability studies and no clinical studies. Based on this prior precedent, the Division has accepted the conclusion that for a HC combination product containing monograph active ingredients, a drug development plan does not always need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the*

*efficacy and safety of the combination product, and that approval can be based on establishment of bioequivalence.*

(b) (4)

*Dose-related respiratory depression cases, including fatalities due to respiratory failure have been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children under 6 years of age, and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require that the sponsor establish the appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population. The Applicant will be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age.*

## **2.2 Currently Available Treatment for Indications**

Hydrocodone is currently approved in the United States in tablet and syrup as an immediate release antitussive drug (Hycodan, NDA 5-213). The owner of NDA 5-213, Endo Pharmaceuticals, had withdrawn the products voluntarily not because of reasons of safety or efficacy. The company keeps the NDA 5-213 current, but stopped manufacturing and marketing the Hycodan Tablets and Solution on January 4 and May 14, 2008, respectively. Hydrocodone is also approved in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111).

There are other generic Hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussionon (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). Pseudoephedrine and guaifenesin are readily available OTC monograph drugs, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph doses for the temporary relief of nasal congestion, and to help loosen phlegm (mucus) and thin bronchial secretions.

## **2.3 Availability of Proposed Active Ingredient in the United States**

Hydrocodone is currently available in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111) and generic antitussive drugs Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussionon (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). In addition, hydrocodone is available in the United States in tablet and capsule formulations as analgesic medications at higher doses than antitussives, such as Vicoprofen (NDA 20716), Vicodin and Vicodin HP (ANDA 88058, ANDA 40117), Lortab (ANDA 40100, ANDA 87722), and Anexsia (ANDA 40405, ANDA 40409, (b) (4))

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

ANDA 40686, ANDA 89160). There have been multiple illegally marketed hydrocodone-containing products in the U.S. market. The FDA has announced its intention to take enforcement actions against unapproved drug products containing hydrocodone bitartrate if such drug products are manufactured and marketed on or after October 31, 2007 [Federal Register Vol. 72, No 189, October 1, 2007].

Pseudoephedrine is currently approved in the United States in tablet (Afrinol, NDA 18-191), in combination with chlorpheniramine (Chlor-Trimeton, NDA 18-397), with ibuprofen and chlorpheniramine (Advil Allergy Sinus Caplet, NDA 21-441), and with guaifenesin (Mucinex<sup>TM</sup> D, NDA 21-585). These products are extended release formulations. Pseudoephedrine is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

Guaifenesin is currently approved in the United States in tablet (Mucinex ER, NDA 21-282), in combination with dextromethorphan (Mucinex<sup>TM</sup> DM, NDA 21-620), and with pseudoephedrine (Mucinex<sup>TM</sup> D, NDA 21-585). These products are extended release formulations. Guaifenesin is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

## **2.4 Important Issues With Pharmacologically Related Products**

Hydrocodone is a semi-synthetic opioid that has the potential for abuse. Dependence and tolerance may develop upon repeated administration. Hydrocodone is a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in combination with active non-narcotic ingredients and if the product contains not more than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15).

The Controlled Substances Staff (CSS) was consulted to advise on the abuse potential for the related triple combination product in the previous review cycle. The CSS concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies (Memorandum, Consult on NDA 22-279, N000, Controlled Substance Staff, March 27, 2009). On June 12, 2009, a CDER regulatory briefing was held to discuss the need for abuse potential studies for these products. The consensus from the panel was that abuse potential assessment was not required for these combination products. These combinations are currently in Schedule III and have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The panel recommended that a post-marketing signal could trigger the need for abuse potential studies for these products.

Pseudoephedrine is an OTC monograph drug of oral nasal decongestant [21 CFR 341.20]. Pseudoephedrine can be unlawfully used to make the illicit drug methamphetamine. The Combat Methamphetamine Act restricts the access of pseudoephedrine by requiring retailers to

place OTC drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase.

## 2.5 Presubmission Regulatory Activity

The Applicant had a pre-IND meeting on March 26, 2007 with the Division to discuss the plans to develop two immediate release oral cough and cold solutions: (1) hydrocodone and guaifenesin and (2) hydrocodone, pseudoephedrine, and guaifenesin. The formulations for the proposed drugs [REDACTED] (b) (4) for the double and triple combination products [REDACTED] (b) (4) in the triple combination product. The Applicant planned to conduct all pharmacological studies using the triple combination product in order to obtain data to support both combination products.

The Applicant submitted an opening IND on September 25, 2007 for the proposed Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (IND 76,365). The opening IND study was a single dose, open label bioavailability study that was determined safe to proceed. The Applicant filed a 505(b)(2) NDA (NDA 22-279, N000) for the proposed Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution on August 22, 2008. A Complete Response Letter was issued to the submission on June 22, 2009, stating that "The open-label bioavailability study submitted is inadequate to evaluate the bioequivalence, drug-drug interaction, and food effect of the proposed combination product." In order to support the proposed drug product, the Applicant needs to "(1) conduct a single-dose clinical pharmacology study to establish the bioequivalence of the proposed Hydrocodone 2.5 mg/Pseudoephedrine 30 mg/Guaifenesin 200 mg per 5 mL Oral Solution to the reference products; and (2) conduct a food effect study of the proposed drug product under fed and fasted conditions."

The Applicant resubmitted the NDA (NDA 22-279, N019) on July 26, 2010, including data obtained from two clinical pharmacology studies (S09-0009 and S09-0010). On January 25, 2011, the Agency issued a Complete Response letter for the resubmission, stating that "An audit performed by the Agency of studies S09-0009 (a drug-drug interaction and relative bioavailability study) and S09-0010 (a food effect study) identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies cannot be relied upon to support the clinical pharmacology of hydrocodone, pseudoephedrine, and guaifenesin oral solution." Because of these deficiencies, these studies were not acceptable to support this NDA submission [MEMORANDUM Division of Scientific Investigation, Martin K. Yau, Ph.D., 1/20/2011]. The second CR letter was issued on 1/25/2011. Subsequently, the Applicant re-conducted the clinical pharmacology program and filed this CR resubmission on 7/18/2011.

In the present CR resubmission, the Applicant reported data from 2 clinical pharmacology studies S11-0028 and S11-0029. Study S11-0028 was a single-dose BE study to compare the proposed product to the reference products. Study S11-0029 was a single-dose food effect study. These 2 studies were previously submitted to support NDA 22-424 (Hydrocodone and Guaifenesin Oral Solution) that was also filed by the Applicant. The review of the NDA 22-424 has found that the clinical pharmacology studies submitted failed to demonstrate bioequivalence

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

for the guaifenesin component of the proposed product. Also both hydrocodone and guaifenesin did not meet the BE criteria when administered under fed conditions versus fasted conditions [NDA 22-424 N000, Clinical Pharmacology Review, Arun Agrawal, Ph.D. 08/23/2011]. Because the present submission (NDA 22-279) is supported by the same clinical pharmacology data that have been determined not supporting the proposed product, the approvability of the NDA 22-279 has been preempted. However, from a regulatory perspective, the Division has decided that NDA 22-279 is reviewable because the submission meets the requirement for submission of an NDA (21 CFR 314.54).

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 CMC (and Product Microbiology, if Applicable)

The drug product is an oral aqueous solution containing hydrocodone bitartrate USP 2.5 mg, pseudoephedrine hydrochloride USP 30 mg, and guaifenesin 200 mg per USP 5 mL. This is an immediate release formulation. The excipients in the test formulation include sorbitol, glycerin, polyethylene glycol, methylparaben, propylparaben, citric acid, sodium citrate, saccharin, D&C Red #33 and FD&C Blue (b) (4) black raspberry flavor. The proposed combination drug is manufactured by (b) (4)

Hydrocodone bitartrate USP used in the test formulation was manufactured (b) (4)

Pseudoephedrine hydrochloride USP used in the test formulation was manufactured (b) (4)

Guaifenesin USP used in the test formulation was manufactured (b) (4)

The excipients in the test formulation include (b) (4)

The proposed product was previously owned by (b) (4). The Agency was informed in a facsimile dated April 15, 2009 that the ownership of NDA 22-279 has been transferred to (b) (4) C. The new ownership of the NDA was effective on March 25, 2009.

A detailed review of the CMC portion of the application may be found in the ONDQA review [NDA 22-279 N-030, ONDQA Review, Arthur Shaw, Ph. D.].

### 3.2 Animal Pharmacology/Toxicology

No new animal data or toxicology data were submitted. No new pre-clinical toxicology studies were required or performed for this application.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The application was submitted under Section 505(b)(2) of the Food, Drug & Cosmetic Act, which permits approvals to be based on the Agency’s previous findings of efficacy and safety of approved or OTC monograph reference products. This application relies on a comparison of the bioavailability of the proposed drug product to the reference drugs. The applicant’s drug development program for Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution is based on establishing bioequivalence between the proposed combination product and reference drugs. This application refers to clinical pharmacology studies S11-0028 and S11-0029. There were no clinical efficacy or safety studies in this application to support any differences in safety or efficacy based on lack of establishing bioequivalency to the reference products.

The Applicant is also developing a double combination product, Hydrocodone and Guaifenesin Oral Solution, (b) (4) with the proposed triple combination product Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution. The Applicant has conducted all pharmacologic studies using the triple combination.

### 4.2 Table of Clinical Studies

The Applicant has submitted the results from 4 clinical pharmacology studies. Studies S09-0009 and S09-0010 were submitted and reviewed during the last review cycle and the two studies were determined unacceptable due to the deficiencies found in the Agency’s inspection. The studies in this application are summarized below in Table 1.

**Table 1 Summary of pharmacology Studies**

Study No.	Study type	Treatment group	Design	Subject No.	Subjects	Materials submitted
S09-0009*	BE	A: HC 5/PSE 60/GU 400mg B: HC 5 mg C: PSE 60/GU 400mg	Randomized, single dose, 3-treatment crossover	42	Healthy males and females, 18-64 yrs	Study report
S09-0010*	Food effect	HC 5/PSE 60/GU 400mg, fed and fasted conditions	Randomized, single dose, 2-treatment crossover	18	Healthy males and females, 19-65 yrs	Study report
S11-0028	BE	A: HC 5/PSE 60/GU 400mg B: HC 5 mg	Randomized, single dose, 3-treatment	42	Healthy males and females, 18-	Study report

		C: PSE 60/GU 400mg	crossover		64 yrs	
S11-0029	Food effect	HC 5/PSE 60/GU 400mg, fed and fasted conditions	Randomized, open-label, single dose, 2-treatment crossover	18	Healthy males and females, 18- 64 yrs	Study report

\* Studies S11-0009 and S11-0010 have been reviewed in the previously review cycle. The 2 studies were determined unacceptable due to the deficiencies found in the Agency's inspection. This review only includes data from studies S11-0028 and S11-0029.

### 4.3 Review Strategy

This is a review of the data from studies S11-0028 and S11-0029. Studies S11-0009 and S11-0010 were reviewed in the previously review cycle. The 2 studies (S11-0009 and S11-0010) were determined unacceptable due to the deficiencies found in the Agency's inspection. Data from AERS database for post-marketing and spontaneous adverse event reports and the literature review for hydrocodone, pseudoephedrine, and guaifenesin are also reviewed. Detailed review of the clinical pharmacology data can be found in the Clinical Pharmacology Review [NDA 22-279, N-030, Clinical Pharmacology Review, Arun Agrawal, Ph.D.].

### 4.4 Data Quality and Integrity

Not applicable. For studies S11-0028 and S11-0029, DSI audit is not conducted because the studies have failed to establish the bioequivalence between the proposed drug product and reference drugs.

### 4.5 Compliance with Good Clinical Practices

The clinical pharmacology studies in this application were conducted in accordance with Good Clinical Practices. The applicant certified that the clinical contractor complied with all applicable federal, state and local laws, codes, regulations, and orders, including, but not limited to, the Federal Food, Drug, and Cosmetic Act and regulations promulgated there under, and Institutional Review Board requirements relative to clinical studies [m5, Section 5.3.1.2.5, page 10 and 5.3.1.2.6, pages 8].

### 4.6 Financial Disclosures

The applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The Applicant stated that the clinical investigator of the clinical pharmacology study in this application certified that he did not have a proprietary interest in the proposed product or a significant equity in the Applicant [m1, Section 1.3.4, page 1].

## 5 CLINICAL PHARMACOLOGY

There were 4 clinical pharmacology studies in the submission. Because the 2 studies (S11-0009 and S11-0010) were reviewed in the previously submitted NDA 22-279 and determined unacceptable due to the deficiencies found in the Agency's inspection, this review only includes data from studies S11-0028 and S11-0029. A summary of data from the Applicant's clinical pharmacology studies follows below. Detailed information can be found in the Clinical Pharmacology Review [NDA 22-279, N-030, Clinical Pharmacology Review, Arun Agrawal, Ph.D.].

The formulation of Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution is displayed in Table 2. The experimental formulation is manufactured and supplied by (b) (4) [Volume 2.1, Section 2.3, page 19].

**Table 2 Formulation of Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution**

Ingredient	% w/v	mg/5 mL	g/liter
Hydrocodone bitartrate USP	0.05	2.5	0.50
Guaifenesin USP	4.00	200	40.00
Pseudoephedrine hydrochloride USP	0.60	30	6.00
Sorbitol (b) (4) USP	(b) (4)		(b) (4)
Glycerine USP			
Polyethylene glycol (b) (4) NF			
Methylparaben NF			
Propylparaben NF			
Citric acid (b) (4) USP			
Sodium citrate (b) (4) USP			
Saccharin sodium			
D & C red #33			
FD & C blue #1			
(b) (4) black raspberry flavor (b) (4)			
Purified water USP			

**Study S11-0028** is a single-dose, randomized, three-treatment crossover study under fasting condition. Forty-two male and female healthy volunteers aged 18 to 64 years old participated this study. Subjects were generally healthy as documented by the medical history, physical examination, vital sign, clinical laboratory tests, and ECG. Subjects did not receive any investigational drug within the past 30 days, any prescription drug (except contraceptives for females) within past 14 days, and any OTC medications (except multivitamins) within past 7 days. At least 7-day washout period was observed between the doses. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24 and 36 hours post-dose. Blood samples were collected only up to 16 hours for hydrocodone bitartrate/homatropine methylbromide arm (Treatment B). Safety evaluation includes adverse events and vital signs during the study.

This study investigated the relative bioavailability of the Test and Reference solutions by comparing the rate and extent of exposure of (b) (4) triple combination solution.

Treatment A (Test): (b) (4) hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution

Treatment B (References 1): Hydrocodone bitartrate 5 mg oral solution

Treatment C (References 2): the combination of pseudoephedrine HCl 60 mg and Robitussin Chest Congestion (guaifenesin 400 mg) oral solution

Results are summarized in Table 3 below:

**Table 3 Summary of PK data, Study S11-0028**

	Test	Reference	% Ratio	90% CI
Hydrocodone				
AUC <sub>0-t</sub> (ng.h/mL)	56.65	57.21	99.01	94.73, 103.49
AUC <sub>0-inf</sub> (ng.h/mL)	61.15	61.40	99.60	95.20, 204.30
Cmax (ng/mL)	9.00	10.33	87.12	82.54, 91.96
Pseudoephedrine				
AUC <sub>0-t</sub> (ng.h/mL)	1916.40	2016.98	95.01	92.32, 97.79
AUC <sub>0-inf</sub> (ng.h/mL)	1977.99	2081.19	95.04	92.30, 97.87
Cmax (ng/mL)	190.21	222.32	85.56	83.03, 88.16
Guaifenesin				
AUC <sub>0-t</sub> (ng.h/mL)				
AUC <sub>0-inf</sub> (ng.h/mL)				
Cmax (ng/mL)				

(b) (4)

Hydrocodone (Treatment A versus Treatment B): The ratios of geometric means were 99.01% (90% CI 94.73% - 103.49%) for AUC<sub>0-t</sub>, 99.60% (90% CI 95.10% - 104.30%) for AUC<sub>0-inf</sub>, and 87.12% (90% CI 82.54% - 91.96%) for Cmax. The point estimates and their 90% CIs were all contained within the protocol defined acceptance range of 80.00 - 125.00%.

Pseudoephedrine (Treatment A versus Treatment C): The test ratios of geometric means were 95.01% (90% CI 92.32% - 97.79%) for AUC<sub>0-t</sub>, 95.04% (90% CI 92.30% - 97.87%) for AUC<sub>0-inf</sub>, and 85.56% (90% CI 83.03% - 88.16%) for Cmax. The point estimates and their 90% CIs were all contained within the protocol defined acceptance range of 80.00 - 125.00%.

Guaifenesin (Treatment A versus Treatment C): The ratios of geometric means were

(b) (4)

(b) (4)

**Study S11-0029** is a food effect study to assess the impact of food on the bioavailability of (b) (4) Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (5/60/400 mg). This is a single-dose, randomized, open-label, two-treatment crossover study under fed and fasting conditions. Eighteen male and female healthy volunteers aged 18 to 64 years old participated this study. Subjects were generally healthy as documented by the medical history, physical examination, vital sign, clinical laboratory tests, and ECG. Subjects did not receive any investigational drug within the past 30 days, any prescription drug (except contraceptives for females) within past 14 days, and any OTC medications (except multivitamins) within past 7 days. At least a 7-day washout period was observed between the doses. Blood samples were

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

collected at 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24 and 36 hours post-dose. Safety evaluation includes adverse events and vital signs monitoring during the study. Results are summarized in Table 4 below:

**Table 4 Summary of PK data, Study S11-0029**

	Fed	Fasted	% Ratio	90% CI
Hydrocodone	(b) (4)			
AUC <sub>0-t</sub> (ng.h/mL)				
AUC <sub>0-inf</sub> (ng.h/mL)				
Cmax (ng/mL)				
Pseudoephedrine				
AUC <sub>0-t</sub> (ng.h/mL)	1963.44	2049.65	95.79	88.55, 103.63
AUC <sub>0-inf</sub> (ng.h/mL)	2004.33	2100.57	95.42	88.13, 103.31
Cmax (ng/mL)	196.54	199.96	98.29	94.53, 102.19
Guaifenesin	(b) (4)			
AUC <sub>0-t</sub> (ng.h/mL)				
AUC <sub>0-inf</sub> (ng.h/mL)				
Cmax (ng/mL)				

Hydrocodone: (b) (4)

Pseudoephedrine: The test ratios of geometric means and 90% CI were 95.79% (90% CI 88.55% - 103.63%) for AUC<sub>0-t</sub>, 95.42% (90% CI 88.13% - 103.31%) for AUC<sub>0-inf</sub>, and 98.29% (90% CI 95.53% - 102.19%) for Cmax. The point estimates and their 90% CIs were all contained within the protocol defined acceptance range of 80.00 -125.00%.

Guaifenesin: (b) (4)

## 6 INTEGRATED REVIEW OF EFFICACY

This is a clinical pharmacology program. The NDA submission is supported by comparison of the bioavailability of the proposed drug product to reference. No clinical efficacy studies were conducted to support this application.

### 6.1 Indication

The proposed indication for this product follows below:

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only) is for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus) (b) (4)

## 7 INTEGRATED REVIEW OF SAFETY

The safety of the proposed drug product relies primarily on the Agency's previous findings of approved hydrocodone products (Hycodan Syrup and Tablets, NDA 5-213) and the OTC monograph for guaifenesin. Therefore the safety of the proposed drug product is determined by the bioequivalence to the reference drugs. Since the guaifenesin component of the proposed drug product failed to meet the BE criterion, the safety of the proposed drug product can not be supported by the Agency's previous findings. The Applicant needs to provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs or conduct clinical studies to support its safety and efficacy.

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology studies S11-0028 and S11-0029, post-marketing spontaneous adverse events report, and literature survey. The safety was assessed through adverse events and vital signs in the two single dose clinical pharmacology studies S11-0028 and S11-0029. The safety data from these two single-dose clinical pharmacology studies in adult subjects did not identify a safety signal. Due to their small size and design, these studies alone are not sufficient to support the safety of the proposed HC and GA combination product.

The post-marketing adverse event reports from the search result of AERS database covering the period from January 1, 2003 through December 31, 2007, and a brief literature review for safety of hydrocodone, pseudoephedrine, and guaifenesin [Volume 2.1, Section 2.7.4, pages 34 – 44]. The Applicant also submitted 2 volumes of compiled published literature references related to the safety of their product [Volume 5.8 – 5.9, Section 5.4.2].

The Applicant conducted an AERS database search using combinations hydrocodone plus pseudoephedrine plus guaifenesin (HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The search included the generic names and the trade name medications obtained from internet sites. Combination products containing antihistamines were excluded from the search result. The presence or absence of acetaminophen was disregarded. The AEs reported from the USA were included.

The Applicant searched MEDLINE and EMBASE for the medical literature relevant to safety of hydrocodone, pseudoephedrine, and guaifenesin. The literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years. The Applicant's search of the medical literature for safety information related to hydrocodone, pseudoephedrine, and guaifenesin identified no new safety signals.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, as there are no animal studies and clinical safety studies conducted for the test drug and the test

drug has not been manufactured and marketed. There are no new data which could be submitted as a safety update.

## 7.1 Methods and Findings

Table 5 summarizes the results of the AERS search covering the period from January 1, 2003 through December 31, 2007. The adverse events with an incidence >3% are listed.

**Table 5 Post-marketing adverse events (AERS database, Jan. 1, 2003 to Dec. 31, 2007, incidence >3%)**

Search term*	HC/PSE/GU (%)	HC/PSE (%)	HC/GU (%)	HC (%)	PSE (%)	GU (%)
Total (n) AEs	2	3	12	3744	2782	125
Serious AEs <sup>#</sup>	0	0	6 (50.0)	3161 (84.43)	333 (11.97)	85 (68.0)
Death	0	0	5 (41.67)	2327 (62.15)	194 (6.97)	19 (15.20)
Completed suicide	0	0	0	939 (25.08)	65 (2.34)	2 (1.60)
Multiple drug overdose	0	0	1 (8.33)	860 (22.97)	29 (1.04)	5 (4.00)
Overdose	0	1 (33.3)	1 (8.33)	502 (13.41)	97 (3.49)	5 (4.00)
Cardiorespiratory arrest		0	1 (8.33)	332 (8.87)	30 (1.08)	2 (1.60)
Drug toxicity	0	0	1 (8.33)	314 (8.39)	77 (2.77)	0
Drug abuser	0	0	0	230 (6.14)	-- <sup>\$</sup>	1 (0.80)
Respiratory arrest	0	0	0	215 (5.74)	29 (1.04)	1 (0.80)
Vomiting	1 (50.0)	0	1 (8.33)	167 (4.46)	61 (2.19)	5 (4.00)
Nausea	0	0	1 (8.33)	161 (4.30)	167 (6.00)	8 (6.40)
Medical error	0	0	1 (8.33)	158 (4.22)	47 (1.69)	13 (10.40)
Increased drug level	0	0	0	154 (4.11)	35 (1.26)	1 (0.80)
Coma	0	0	1 (8.33)	147 (3.93)	37 (1.33)	3 (2.40)
Somnolence	0	0	0	145 (3.87)	0	2 (1.60)
Drug ineffective	0	0	1 (8.33)	137 (3.66)	224 (8.05)	4 (3.20)
Anxiety	1 (50.0)	0	0	44 (1.18)	40 (1.44)	7 (5.60)
Dyspnea	0	1 (33.3)	0	51 (1.36)	68 (2.44)	3 (2.40)
Vision blurred	0	1 (33.3)	0	0	41 (1.47)	0
Loss of consciousness	0	0	1 (8.33)	88 (2.35)	45 (1.62)	7 (5.60)
Insomnia	0	0	0	39 (1.04)	122 (4.39)	3 (2.40)
Dizziness	0	0	0	59 (1.58)	98 (3.52)	10 (8.00)
Headache	0	0	0	54 (1.44)	163 (5.86)	6 (4.80)
Convulsion	0	0	1 (8.33)	60 (1.60)	40 (1.44)	10 (8.00)
Abdominal pain	0	0	1 (8.33)	47 (1.26)	63 (2.26)	6 (4.80)

\* The version of the MedDRA used in searching the database is not specified.

# Serious adverse events include deaths, life threatening, hospitalization, and disabilities.

\$ The term "drug abuser" was not on the list of terms in PSE report.

(Source: Volume 5.9, Section 5.3.1.2, page 128-134, 157-162)

### 7.1.1 Deaths

There was no death in the clinical pharmacology studies S11-0028 and S11-0029 in this application.

In searching AERS database covering the period from January 1, 2003 through December 31, 2007, there were 6,668 adverse event reports with 2,545 deaths (38.17%) for the search terms of hydrocodone plus pseudoephedrine plus guaifenesin HC+PSE+GU), hydrocodone plus

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The most death reports (2,327) came from searching with hydrocodone, accounting for 62.15% of the adverse event reports (3,744). The four most commonly reported adverse event terms were completed suicide (25.08%, 939/3,744), multiple drug overdose (22.97%, 860/3,744), overdose (13.41%, 502/3,744), and cardiorespiratory arrest (8.87%, 332/3,744). Noticeably, the overall adverse events and death reports for hydrocodone did not differentiate if the hydrocodone was taken as antitussive doses or as much higher analgesic doses. Because the data reflect a large fraction of suicide and overdoses, the dosage forms of hydrocodone for the deaths and adverse events were most possibly higher than doses as an antitussive. There were 194 and 19 death reports for pseudoephedrine and guaifenesin, respectively. The data also reflect a large portion of suicide and overdoses.

*Reviewer comment:*

*The AERS database search shows the death rate is high in the AE reports for hydrocodone. The death reports reflects a large fraction of suicide and overdoses reported for hydrocodone use. Also, hydrocodone is known to be used in symptomatic treatment for many end stage diseases. Without the knowledge of dosage forms, diseases, co-administered medications, a simple search of AERS, a spontaneous post-marketing adverse event reporting database, does not provide meaningful safety information for hydrocodone use. In the previous review cycle for NDA 22-279, the OSE consult was requested to evaluate the AERS data regarding the high incidence of death reports related to hydrocodone use. The OSE safety evaluator concluded that “the high number of death reports for hydrocodone 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” [NDA 22-279 Review of Fatalities, Division of Pharmacovigilance I, Debra Ryan, Pharm.D., MBA, Safety Evaluator, May 15, 2009].*

### 7.1.2 Other Serious Adverse Events

There was no other serious adverse event in the clinical pharmacology studies in this application.

The search of the AERS database covering the period from January 1, 2003 through December 31, 2007 does not identify new safety signals for hydrocodone, pseudoephedrine, and guaifenesin.

### 7.1.3 Dropouts and Other Significant Adverse Events

There was no dropout or withdrawal from the clinical pharmacology studies S11-0028 and S11-0029 due to adverse events. There was no significant adverse event in the clinical pharmacology studies in this application.

### 7.1.4 Other Search Strategies

No other search strategies were used in this application.

### 7.1.5 Common Adverse Events

In the clinical pharmacology study S11-0028, a total of 12 mild adverse events occurred. The case report review revealed that all adverse events were mild in nature and no treatment was required. Table 6 summarizes the adverse events occurred in study S11-0028.

**Table 6 Adverse events reported in study S11-0028**

Adverse event	Treatment A	Treatment B	Treatment C	Total
Headache	2	1	1	4
Dizziness	1	1	--	2
Hot flush	1	1	--	2
Hyperhidrosis	--	1	1	2
Pallor	--	2	--	2
<b>Total</b>	4	6	2	12

Treatment A: Hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution

Treatment B: Hydrocodone bitartrate 5 mg oral solution

Treatment C: Pseudoephedrine HCl 60 mg and Robitussin Chest Congestion (guaifenesin 400 mg) oral solution

In the clinical pharmacology study S11-0029, four subjects experienced a total of 5 AEs across all treatments over the course of the study. A total of 2 AEs (a hot flush and a hyperhidrosis) occurred in subjects after they received the test product under fed condition, and 3 AEs (3 headache) occurred in subjects after they received the test product under fasting condition. All adverse events were mild in nature and no treatment was required.

*Reviewer comment:*

*These data do not identify a safety signal. Because of the small number of the subjects, there was no meaningful information in differences in adverse events in gender, age, and race/ethnicity.*

### 7.1.6 Less Common Adverse Events

Adverse events occurring in the clinical pharmacology studies in adults are reviewed in Section 7.1.5. Less common adverse events did not suggest a safety signal.

### 7.1.7 Laboratory Findings

Laboratory examinations were not safety endpoints in the clinical pharmacology studies of this application.

### 7.1.8 Vital Signs

Vital sign assessments were conducted before and the end of the clinical pharmacology studies. No clinically significant changes from baseline data were reported.

### 7.1.9 Electrocardiograms (ECGs)

ECGs were not safety endpoints in the clinical pharmacology studies of this application.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. Adams EH, Breiner S, Cicero TJ, et al. reported a 12-month study in chronic pain patients that showed an abuse rate of 1.2% for hydrocodone<sup>1</sup>. The applicant provided data regarding the drug-related ED visits in 2005, collected by the Drug Abuse Warning Network (DAWN). The data show that hydrocodone/combinations accounted for 51,225 (6.27%) of the 816,696 total illicit drug-related ED visits in 2005<sup>2</sup>. Although hydrocodone dosages as an antitussive is much lower than that of analgesics and illicit drugs, hydrocodone-containing medications should be prescribed and administered with caution. The proposed Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution is a prescription drug, which provides limitation to its accessibility for the unlawful use.

The Controlled Substances Staff (CSS) was consulted to advise on the abuse potential for the Applicant's another hydrocodone containing triple combination product (NDA 22-279) during its review cycle. The CSS concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies (Memorandum, Consult on NDA 22-279, N000, Controlled Substance Staff, March 27, 2009). On June 12, 2009, a CDER regulatory briefing was held to discuss the need for abuse potential studies for these products. The consensus from the panel was that abuse potential assessment was not required for these combination products. These combinations are currently in Schedule III and have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The panel recommended that a post-marketing signal could trigger the need for abuse potential studies for these products.

Pseudoephedrine is a sympathomimetic amine used as an oral nasal decongestant. It can be unlawfully used to make illicit drug methamphetamine<sup>3</sup>. The Combat Methamphetamine Act, signed into law by President Bush on March 9, 2005, restricts the access of pseudoephedrine by requiring retailers to place drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase. The potential of unlawfully using pseudoephedrine in the proposed drug to make methamphetamine is addressed by the access restriction required in the Combat Methamphetamine Act. The proposed Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution is a prescription drug, which provides limitation to its accessibility for the unlawful use.

### 7.1.14 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected in the clinical pharmacological study. The Applicant has not observed or reported adverse events associated with drug exposure during pregnancy in the post-marketing surveillance. The Applicant's proposed labeling indicates that

---

1 Adams EH, Breiner S, Cicero TJ, et al. J Pain Symptom Manage. May 2006;31(5):465-476

2 Manchikanti L. Pain Physician 2007;10:399-424

3 [www.streetdrugs.org](http://www.streetdrugs.org), accessed on March 5, 2009

the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. The Applicant searched MEDLINE database for hydrocodone and human reproduction. A report revealed 2 cases of hydrocodone excretion in breast milk<sup>4</sup>. The infants of the mothers who were taking hydrocodone received an estimated 3.1% and 3.7% of the maternal weight-adjusted dosage. The absolute hydrocodone doses the infants received were 8.58 mcg/kg and 3.07 mcg/kg per day. One infant (18-day-old) became groggy and slept for most of the day while the mother was taking 20 mg hydrocodone every 4 hours. The infant's symptoms improved when mother decrease her hydrocodone dose by half. Another infant (5-week-old) became cyanotic and required intubation while the mother was taking hydrocodone and methadone for migraine headache. The infant was positive for opioids in urinary test and responded well to naloxone treatment. There are no reports of hydrocodone in breast milk while a mother takes hydrocodone at a much lower antitussive dosage. The prescribers and patients should be aware of the potential hydrocodone excretion into breast milk and use Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution with caution.

#### 7.1.16 Overdose Experience

There is no overdose experience reported in the clinical pharmacological studies. The Applicant searched the AERS database and the result shows that 36.38% of the reported adverse events associated with hydrocodone were overdose or multiple-drug overdose. In the literature review, the Applicant summarized that hydrocodone had the potential of being overdosed by self-medication and abuse, like other opioids. The AERS database search and literature review did not differentiate whether the hydrocodone was taken as antitussives or at much higher dosages as analgesics. The Applicant identified no new pattern of overdose for the ingredients of the proposed drug.

*Reviewer comment:*

*The reviewer concurs with the Applicant that there are no new concerns regarding overdose with the ingredients of their proposed drug product.*

#### 7.1.17 Postmarketing Experience

The proposed drug product Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution has not been marketed. But there have been multiple illegally marketed hydrocodone-containing products in the U.S. market. The FDA has announced its intention to take enforcement actions against unapproved drug products containing hydrocodone bitartrate if such drug products are manufactured and marketed on or after October 31, 2007 [Federal Register Vol. 72, No 189, October 1, 2007]. The post-marketing experiences were obtained from AERS database search covering pseudoephedrine, guaifenesin and hydrocodone drug products, including approved and unapproved drug products containing hydrocodone as antitussives and analgesics.

---

4 Anderson PO, Sauberan JB, Lane JR, et al. Breastfeeding Med March 2007;2(1):10-14

## 7.2 Adequacy of Patient Exposure and Safety Assessments

The safety of the proposed drug product relies primarily on the Agency's previous findings of approved hydrocodone products (Hycodan Syrup and Tablets, NDA 5-213) and the OTC monograph for pseudoephedrine and guaifenesin. Therefore the safety of the proposed drug product is determined by the bioequivalence to the reference drugs. Since the guaifenesin component of the proposed drug product has failed to meet the BE criterion, the safety of the proposed drug product can not be supported by the Agency's previous findings. In the clinical pharmacology studies S11-0028 and S11-0029, a total of 60 healthy, adult subjects aged 18 to 64 years receive a single dose of 10 mL of an immediate release oral solution containing 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin under fasting condition. There were a total of 17 adverse events in these two clinical pharmacology studies (7 headache, 3 hot flush, 3 hyperhidrosis, 2 dizziness, and 2 pallor). All adverse events were mild in nature and spontaneously resolved without special treatment. The safety data from these two clinical pharmacology studies in healthy adult subjects did not identify a safety signal. However, the exposure in the 2 clinical pharmacology studies is not enough for a safety assessment. The Applicant needs to provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs or conduct clinical studies to support its safety.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable

#### 7.2.2.3 Literature

The Applicant performed a search of the medical literature for information relevant to safety of hydrocodone, pseudoephedrine, and guaifenesin in general. The search covered three individual active ingredient hydrocodone, pseudoephedrine, and guaifenesin) for two years (2006 – 2008) and the products containing all three ingredients for 10 years (1998 – 2008). The search was conducted with the MEDLINE and EMBASE database. There were no studies related to safety of products containing all three ingredients. The literature search revealed no new safety signals for hydrocodone, pseudoephedrine, and guaifenesin. The result of the literature search is provided in the Section 8.6 of this review. However, because of the failure to demonstrate bioequivalency to approved marketed guaifenesin-containing products, the data from the literature search are of limited value in supporting the safety of the proposed combination product.

### 7.2.3 Adequacy of Overall Clinical Experience

This submission includes data from two single-dose clinical pharmacology studies in 60 healthy subjects. The study was small in size and provides a fairly limited amount of safety information. The efficacy and safety of the proposed drug relies on the Agency's DESI review for hydrocodone and OTC monograph for pseudoephedrine and guaifenesin. Since the guaifenesin component of the proposed drug product has failed to meet the BE criterion, the safety of the

proposed drug product can not be supported by the Agency's previous findings. The clinical experience from the 2 clinical pharmacology studies submitted is not adequate to evaluate the efficacy and safety of the proposed drug product. The Applicant needs to provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs or conduct clinical studies to support its safety.

### 7.2.9 Additional Submissions, Including Safety Update

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the proposed drug and the proposed drug has not been manufactured and marketed so there is no new information to submit in a safety update.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the clinical pharmacology studies, the number of subjects treated was small and AEs were infrequent. No new safety concerns have become apparent in the clinical pharmacology studies.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The application is for Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only). The proposed drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed indications are "for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4).

(b) (4)

Dose-related respiratory depression cases, including fatalities due to respiratory failure have been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children under 6 years of age, and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require that the sponsor establish the

appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population. The Applicant will be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age.

## 8.2 Drug-Drug Interactions

The applicant submitted literature references to address the drug-drug interaction potential of the triple combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone, pseudoephedrine, and guaifenesin are administered together.

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or codeine. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The applicant's proposed labeling appropriately addresses the potential these drug-drug interactions.

## 8.3 Special Populations

There were no studies in special populations for Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution in this submission to review. The applicant's proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. (b) (4)

A literature search shows a report that two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution is administered to nursing mothers.

## 8.4 Pediatrics

The clinical pharmacology studies S11-0028 and S11-0029 included no pediatric subjects.

On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received long-acting hydrocodone-containing cough product.

[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>,  
<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>].

The Applicant is requesting a waiver for pediatric studies below 6 years of age, and provides the following justification for the waiver:

(b) (4)

(b) (4)

This reviewer considers that the request for a waiver for pediatric studies below 6 years of age is appropriate. (b) (4)

Dose-related respiratory depression cases, including fatalities due to respiratory failure have been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children under 6 years of age, and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require that the sponsor establish the appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population. The Applicant will be requested to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age.

## 8.6 Literature Review

The applicant performed a search of the medical literature for information relevant to hydrocodone, pseudoephedrine, and guaifenesin in general. The search covered three individual active ingredient hydrocodone, pseudoephedrine, and guaifenesin) for a period of two years (January 1, 2006 – June 24, 2008) and the products containing all three ingredients for a period of 10 years (January 1, 1998 – June 24, 2008). There was no new safety signal revealed through the literature search.

There were four case reports, two observational studies, five clinical trials, and one drug-drug interaction study involving hydrocodone adverse events. All four clinical trials were to study hydrocodone in different types of pain patients. All adverse events reported were consistent with what would be expected in use of any opiate (nausea, vomiting, dizziness, somnolence, constipation, etc.)<sup>1-5</sup> The drug-drug interaction study in chronic pain patients demonstrated that serum nicotine levels were negatively correlated with serum hydrocodone levels in smokers.<sup>6</sup> The observational studies and case reports were involved lethal hydrocodone intoxication cases,<sup>7</sup> traffic related deaths with hydrocodone and alcohol use,<sup>8</sup> multiple drug abuse including hydrocodone,<sup>9</sup> and breast milk hydrocodone excretion in mothers taking prescribed hydrocodone for pain.<sup>10</sup>

There were eight case reports, two observational studies and ten clinical trials involving pseudoephedrine adverse events. There were reported death cases related to multiple drug intoxication including pseudoephedrine.<sup>11</sup> A report of 15 deaths of children younger than 17 months involved OTC medications containing pseudoephedrine.<sup>12</sup> The reported adverse events related to pseudoephedrine use included insomnia, hypertension,<sup>13</sup> two case of myocardial

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

infarction,<sup>14</sup> and a case of transient ischemic attack.<sup>15</sup> It appears that these serious adverse events involved serious diseases and other concomitant treatments.

There were no reported adverse events related to guaifenesin use. There were no studies related to safety of products containing all three ingredients.

#### Reference

1. Adams EH, Breiner S, Cicero TJ, et al. J Pain Symptom Manage. May 2006;31(5):465-476
2. Chelly JE, Nissen CW, Rodgers AJ, et al. Curr Med Res Opin. Jan 2007 ;23(1):195-206
3. Church CA, Stewart CT, et al. Laryngoscope. April 2006;116(4):602-606
4. Hewitt DJ, Todd KH, Xiang J, et al. Am Emerg Med. April 2007;49(4):468-480
5. Rodriguez RF, Bravol LE, Castro F, et al. J Palliat Med. Feb 2007 ;10(1) :56-60
6. Ackerman WE, Ahmad M. J Ark Med Soc. July 2007;104(1):19-21
7. Baker DD, Jenkins AJ. J Anal Toxicol. March 2008;32(2):165-171
8. Schwilke EW, Sampario MI. et al. J Forensic Sci. Sept 2006;51(5):1191-1198
9. Kyle PB, Daley WP. J Anal Toxicol. Sept 2007;31(7):415-418
10. Anderson PO, Sauberan JB, Lane JR, et al. Breastfeeding Med March 2007;2(1):10-14
11. Carson HJ. Legal Med. 2008;10(2):92-95
12. Wingert WE, Mundy LA, Collins GL, et al. J Forensic Sci. March 2007;52(2):487-490
13. Latte J, Taverner D. Am J Rhinol. 2007;21(4):452-455
14. Biyik I, Ergene O. Can J Cardiol. March 2006;22(3):254-256
15. Profice P, Pilato F, Michetti F, et al. Acta Neurol Scand. Nov 2006 ;114(5) :358-359

## 8.7 Postmarketing Risk Management Plan

As the recommendation is for a Complete Response action, no special post-marketing risk management activities are recommended at this time.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The Applicant seeks the approval of an immediate release oral solution formulation of hydrocodone, pseudoephedrine, and guaifenesin. This NDA is a 505(b)(2) new drug application based on a clinical pharmacology program. There are no efficacy and safety studies in this NDA. The Applicant relies on the bioequivalence to the approved product for hydrocodone and OTC monograph for pseudoephedrine and guaifenesin to support the efficacy and safety of the proposed drug product. No clinical efficacy studies were submitted to support this application. The clinical pharmacology studies submitted in this application are not adequate to support approval of this application because this study does not fulfill the bioavailability criteria for combination products as per 21 CFR 320.25 (g). Specifically, the guaifenesin component of the proposed product is not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio for C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence). The clinical experience

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-030, Resubmission/Class 2, 07/18/2011, Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only)

from the 2 clinical pharmacology studies submitted is not adequate to evaluate the safety or efficacy of the proposed drug product. For approval, the Applicant needs to provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs or conduct clinical studies to support its efficacy and safety.

## **9.2 Recommendation on Regulatory Action**

The Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only) has failed to meet bioequivalence criteria and I recommend that the application be given a Complete Response action.

This NDA is a 505(b)(2) new drug application based on a clinical pharmacology program. There are no efficacy and safety studies in this NDA. The Applicant relies on the bioequivalence to the approved product for hydrocodone and to OTC monograph drugs for pseudoephedrine and guaifenesin to support the efficacy and safety of the proposed drug product. The clinical pharmacology studies submitted are not adequate to support this application because the result does not fulfill the bioavailability criteria for combination products as per 21 CFR 320.25 (g). Specifically, the guaifenesin component of the proposed product is not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence). To support the registration of the proposed drug product, the Applicant needs to either provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs and therefore be able to rely on the Agency's previous determination of efficacy and safety for hydrocodone, pseudoephedrine, and guaifenesin or conduct clinical studies to support its efficacy and safety.

## **9.3 Recommendation on Postmarketing Actions**

No special post-marketing risk management activities are recommended at this time.

## **9.4 Labeling Review**

Proposed labeling was submitted in Physician's Labeling Rule (PLR) format. Labeling review is not conducted because the proposed product is not ready for approval in the present NDA submission.

## **9.5 Comments to Applicant**

Following comments should be sent to the Applicant:

- (1) The clinical pharmacology studies submitted are not adequate to support this application because the study result does not fulfill the bioavailability criteria for combination products as per 21 CFR 320.25 (g). Specifically, the guaifenesin component of the proposed product is not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence). To support

the registration of the proposed drug product, the Applicant needs to either provide data to demonstrate the bioequivalence of the proposed drug product to reference drugs and therefore be able to rely on the Agency's previous determination of efficacy and safety for hydrocodone, pseudoephedrine, and guaifenesin or conduct clinical studies to support its efficacy and safety.

- (2) Although Hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age, safety concerns of dose-related respiratory depression over the last few years raise the issue of the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression cases, including fatalities due to respiratory failure have been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children under 6 years of age, and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to establish the appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, you need to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age to support the proper dose in this pediatric population.

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

/s/  
-----

XU WANG  
11/02/2011

ANTHONY G DURMOWICZ  
11/02/2011

## SUMMARY REVIEW OF REGULATORY ACTION

<b>Date</b>	January 25, 2010
<b>From</b>	Lydia Gilbert-McClain, MD, FCCP
<b>Subject</b>	Deputy Division Director Memorandum
<b>NDA/BLA#</b>	NDA 22-279
<b>Applicant</b>	(b) (4)
<b>Date of Submission</b>	July 26, 2010
<b>PDUFA Goal Date</b>	January 26, 2011
<b>Proprietary Name/Established (USAN) Names</b>	No acceptable proprietary name/hydrocodone bitartrate/pseudoephedrine HCl/Guaifenesin
<b>Dosage forms/strengths</b>	Oral solution/hydrocodone bitartrate 2.5 mg/pseudoephedrine HCl 30 mg/guaifenesin 200 mg/5 mL
<b>Proposed indication (s)</b>	For symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)
<b>Action/Recommended action for NME</b>	<i>Complete Response</i>
<b>Material Reviewed/consulted</b>	<b>Names of discipline reviewers</b>
Action package including:	
Medical officer review	Xu Wang, MD, PhD
Clinical Pharmacology review	Arun Agrawal, PhD
CMC review	Arthur Shaw, PhD, Prasad Peri, PhD
DMEPA consult	Nichelle Rashid, Lubna Merchant, Pharm D, Denise Toyer, Pharm D
DSI consult	Martin K. Yau, PhD, Sam H. Haidar, PhD, R. Ph

### 1. Introduction

This is a complete response submission to a CR action taken by the Division on this 505(b)(2) new drug application. The application was originally submitted on August 22, 2008 (received on August 22, 2008, CDER stamp date) by (b) (4). During the original review cycle, (b) (4) sold the NDA to (b) (4) with Mikart Inc as their regulatory agent (effective March 25 2009) and (b) (4) became the sole owner of the NDA. The application is for a fixed dose combination oral solution comprised of hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin as an antitussive, nasal decongestant, and expectorant (b) (4). The NDA was given a complete response action on June 22, 2009 because of clinical pharmacology deficiencies and because the manufacturing site described in the application was not going to be used to manufacture drug product for the marketing of this drug. The Applicant submitted a complete response on July 26, 2010, including information regarding a

new drug product manufacturing site.. This review will summarize the salient findings from the complete response to support the Division's regulatory action on the application.

## 2. Background

FDA published a final Federal Register (FR) notice of its intention to take enforcement action against illegally marketed cough/cold drug products containing hydrocodone on October 1, 2007 [Docket No. 2007N-0353]. Manufacturers who wish to market a cough/cold product containing hydrocodone must obtain FDA approval via the new drug application (NDA) or an abbreviated new drug application (ANDA) process. Based on the FR notice, manufacturing of unapproved hydrocodone-containing products have ceased and sponsors are conducting development programs for hydrocodone-containing products for cough/cold/upper respiratory allergy indications. (b) (4) triple-combination product is one such product. The product was originally submitted August 22, 2008 but was given a complete response action. In the action letter, the Division noted that the clinical pharmacology study submitted was not adequate to support the application because of inadequacies in the design. As designed, the study did not allow for comparison of the rate and extent of absorption of each active drug ingredient in the proposed fixed dose combination solution. In addition, the formulation contained a significant amount (b) (4) % w/v of sorbitol and the applicant had not conducted a food effect study. The applicant submitted two studies in the complete response: a drug-drug interaction oral bioavailability study to compare the rate and extent of absorption of each active ingredient in the combination oral solution compared to the reference products (S09-0009), and a single dose food effect study (S09-0010) to compare the rate and extent of absorption of the combination product in the fasted vs. fed state.

In addition, the manufacturing site that had been used to prepare the drug product used in the pivotal clinical studies was not going to be used to manufacture the drug product for marketing. The applicant had not submitted any data concerning a new site for manufacturing the drug product for marketing.

## 3. CMC/Device

The proposed product in this NDA is for an aqueous oral solution containing hydrocodone bitartrate (HC) 2.5 mg, pseudoephedrine hydrochloride (PSE) 30 mg, and guaifenesin (GU) 200 mg per 5 mL. The product will be available in 16 oz plastic HDPE bottles containing 473 ml of solution. These active substances are USP ingredients that have been previously assessed to support other NDA applications in the past. There are no unresolved DMF issues. There are no issues with the inactive ingredients which are all compendial except for the (b) (4) (FD&C red and blue) and the flavoring (raspberry flavor). The inactive ingredients include methyl- and propyl-parabens (b) (4) glycerin and water (b) (4) polyethylene glycol (b) (4) citric acid and sodium citrate (b) (4) sorbitol and saccharin (b) (4).

The Office of Compliance issued a withhold status for the application, All manufacturing, testing, and release facilities were found to be acceptable. However the NDA was given an Overall Withhold Status because (b) (4) is affiliated with (b) (4). The Office of Compliance

has found a number of CGMP violations for (b) (4). There is no specific CMC deficiency to cite in the action letter per se for (b) (4).

#### 4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology studies were required or performed for this application.

#### 5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted two clinical pharmacology studies to address the deficiencies in the action letter: a single dose bioequivalence study (Study #S09-0009) and a food effect study (Study #09-0010). Study #S09-0009 was a single-dose, randomized, three-period, three-treatment crossover study under fasting conditions with a wash-out period of at least 7 days between treatments. The study investigated the relative bioavailability of (b) (4) hydrocodone bitartrate/pseudoephedrine hydrochloride/guaifenesin oral solution (Test) to the reference products hydrocodone oral solution (the generic hydrocodone oral solution product from ANDA 88-008 (b) (4) and Robitussin Chest congestion (contains PSE and GU). The study was conducted in 42 healthy adult male and female volunteers. The hydrocodone and pseudoephedrine components of the combination product were bioequivalent to the reference products, in that the 90% CI for the ratios of the geometric means of the test/reference products for the AUC and Cmax were within 80 – 125%. (b) (4)

**Table 1 Results for Guaifenesin test/reference**

Parameter	Test	Reference	% Ratio	90% CI
AUC0-4 (ng.h/mL)	(b) (4)			
AUC0-inf (ng h/mL)				
Cmax (ng/mL)				

*Test: Hydrocodone bitartrate 5 mg /pseudoephedrine hydrochloride 60 mg/guaifenesin 400 mg oral solution*

*Reference: Combination of pseudoephedrine hydrochloride 60 mg and Robitussin Chest Congestion (guaifenesin 400 mg) oral solution.*

The food effect study was an open-label, single-dose, randomized, two-period, two-treatment crossover study under fasting and fed conditions that assessed the impact of food on the bioavailability of Hydrocodone bitartrate 5 mg /pseudoephedrine hydrochloride 60 mg/guaifenesin 400 mg oral solution. (b) (4)

respectively. The results of the food effect study for the guaifenesin component are shown in Table 2.

**Table 2: Food effect study results for guaifenesin**

Parameter	Guaifenesin (fed) N = 18	Guaifenesin (fasted) N = 18	% Ratio	90% CI
AUC0-4 (ng h/mL)	(b) (4)			
AUC0-inf (ng h/mL)				
Cmax (ng/mL)				

*Given the results of the Division of Scientific Investigations (DSI) report, these clinical pharmacology studies cannot be used to support the NDA at this time (see section 11)*

## 6. Clinical Microbiology

This is a non-sterile solution and clinical microbiology is not applicable.

## 7. Clinical/Statistical- Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of approved reference products Hycodan and the OTC monograph products pseudoephedrine, and guaifenesin. No clinical studies were required to support the application.

## 8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to approved reference products. Of the 60 healthy adult subjects exposed to the hydrocodone/pseudoephedrine/guaifenesin oral solution, there were 10 subjects who reported adverse events. These adverse events were mild and resolved without treatment and included headache (6), dizziness (6), lightheaded (4) and drowsiness (1). Other anticipated serious adverse events with this product are events known to occur with opioids such as CNS and respiratory depression. Pseudoephedrine is also known to cause CNS effects and also has the potential to cause cardiovascular effects and increase blood pressure. The applicant did not submit any new safety data in the complete response. In the original application the applicant conducted a review of the literature (via a MEDLINE and EMBASE search), and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof, for the period from January 1, 2003 – December 31, 2007. These searches did not reveal any new safety signals.

## 9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. The three active ingredients present in this product are not new molecules and there are no issues that need to be discussed at an advisory committee meeting.

## 10. Pediatrics

The proposed indication is (b) (4) the Applicant requested a waiver for children under 6 years of age. Since the application is not going to be approved, the application was not presented to PERC. (b) (4)

(b) (4). The request for waiver for children under 6 years of age is based on the fact that the proposed product contains hydrocodone which is contraindicated for use in children less than 6 years of age (because of the risk of respiratory depression). It would be appropriate to waive studies for pediatric patients less than 6 years of age because of this safety concern. However, although hydrocodone is currently labeled for use in children down to 6 years of age, safety concerns regarding dose-related respiratory depression identified over the last few years raises the issue of the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression including fatalities due to respiratory failure has been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children less than 6 years of age and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require the sponsor to establish the appropriate dose of hydrocodone for the pediatric (less than 18 years) population. Hydrocodone was approved under Drug Efficacy Study Implementation (DESI) review and the basis for the dose selection for the pediatric population is unclear. Further, the appropriate

## 11. Other Relevant Regulatory Issues

### Data Quality, Integrity, and Financial Disclosure

A DSI audit was conducted of the clinical and analytical portions studies S09-0009 (the relative bioavailability and drug-drug interaction study) and study S09-0010 (the food effect study). The clinical portions of the studies were conducted at Cetero Research, St Charles, MO and the analytical portions were conducted at (b) (4) The evaluation of the clinical portions of the studies revealed several violations however, these violations (failure to document the time the consent from was obtained, violations of exclusion criteria in that a patient with allergies was included, failure to have the IRB review all changes prior to implementation) should not affect the study outcomes. Several violations were found at the analytical portions of the studies. These violations included not having the

required number of samples available in order for FDA to perform the required relevant tests, failure to identify and document procedures for analytical testing (“prep” runs). In addition, the inspection at the analytical site also included a follow-up investigation of a complaint received by the Agency in June 2009, in which an ex-employee of (b) (4) alleged misconduct in a number of bioanalytical studies. In that complaint, the former employee alleged that laboratory staff of (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 as well as by DSI during the May and December 2010 inspections raised concerns regarding the integrity of the bioanalytical work generated by (b) (4). In a follow up email from DSI January 24, 2011, the DSI reviewer Martin Yau, noted that (b) (4) has claimed to have implemented corrections to assure the alleged complaint of misconduct will not occur again. DSI has posed an option for the sponsor to reanalyze the study samples to demonstrate that the study samples have no stability problems. If there are no stability issues with the samples the data may be used to support the NDA. The (b) (4) site will need to be re-inspected again if the sponsor chooses to reanalyze the samples.

## 12. Labeling

Given the clinical pharmacology data are not acceptable to support the application; a labeling review was not conducted during this cycle. The applicant does not have an acceptable proprietary name at this time and have submitted several proprietary names that have been rejected by the Agency. The most recent proposed proprietary names - (b) (4) have also been rejected. The Applicant proposes to use the (b) (4). Due to concerns with the use of an untested and potentially vulnerable (b) (4) the proposed proprietary (b) (4) were denied.

## 13. Action and Risk Benefit Assessment

### Regulatory action

The regulatory action on the application will be a complete response. (b) (4) has not submitted adequate data to support approval of Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution for use as an antitussive, decongestant, and expectorant in patients (b) (4). The open-label bioavailability study submitted failed to show bioequivalence for the guaifenesin component. Furthermore, an inspection conducted by the Department of Scientific Investigations (DSI) in the office of compliance found violations in the analytical portions of the studies which render the data unacceptable for use in the NDA to make regulatory decisions. The failure to demonstrate bioequivalence for the GU component of the combination product is preempted by the DSI inspection issues.

The comments below are for the Complete Response action letter

An audit performed by the Agency of studies S09-0009 (a drug-drug interaction and relative bioavailability study) and S09-0010 (a food effect study) identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies cannot be relied upon to support the clinical pharmacology of your Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution.

This deficiency may be addressed by doing one of the following:

1) If stability data can be provided to show that the study samples are still stable and have no stability problems, reanalyze all subject plasma samples from studies S09-0009, and S09-0010.

OR

2) Repeat the clinical pharmacology program to evaluate the rate and extent of absorption between your proposed product and the reference product under the fasted state, and repeat the food effect study. Use the bioequivalence goal post of 80 – 125% for the 90% CI for the geometric mean ratio of the AUC and  $C_{max}$  for your proposed product and the reference products.

OR

3) Conduct clinical efficacy and safety studies to support your combination product.

- Risk Benefit Assessment

The overall risk and benefit assessment of the individual ingredients hydrocodone, pseudoephedrine, and guaifenesin does not suggest an unfavorable risk benefit for these individual ingredients. However, for this combination product, a risk benefit assessment cannot be made because the applicant has not conducted the appropriate studies to demonstrate the bioequivalence, evaluate the drug-drug interaction, and the food effect of this product in comparison to reference listed products. These data are lacking and therefore the product cannot be approved at this time.

- Recommendations for Postmarketing Risk Management Activities

Hydrocodone is a controlled substance known to have a certain level of abuse potential. This combination product if approved will be labeled as a Schedule <sup>(b)</sup><sub>(4)</sub> narcotic and will be available by prescription only. The abuse potential will be managed with appropriate labeling and routine pharmacovigilance.

- Recommendations for other Postmarketing Study Commitments

There are no recommended postmarketing study commitments for this application.

APPEARS THIS WAY ON ORIGINAL

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

/s/  
-----

LYDIA I GILBERT MCCLAIN  
01/25/2011  
Deputy Division Director

### **Addendum**

This is a correction to Section 4.4 Data Quality and Integrity of the CLINICAL REVIEW for NDA 22-279 N019 that had been finalized and filed on January 6, 2011. The original Section 4.4 stated: “There was no DSI audit conducted for the study site or data analyses.”

The corrected review for this section follows below:

#### **Section 4.4 Data Quality and Integrity**

The Division of Scientific Investigations (DSI) conducted the audit on the bioanalytical site of the clinical pharmacology studies S09-0009 and S09-0010. The final DSI report is pending at the time of finalizing this review. A draft report by DSI raises concerns to the data quality and integrity and recommends that the clinical pharmacology data submitted in this NDA not be accepted for review. The draft recommendation of the DSI states: “Study S09-0009 and S09-0010 should not be accepted for review at this time due to concerns raised by DSI and incomplete investigation of complaint allegations by (b) (4). 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 sample integrity during sample processing and storage.”

Readers are referred to the full DSI report that is yet to be finalized.

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

/s/  
-----

XU WANG  
01/19/2011

ANTHONY G DURMOWICZ  
01/19/2011  
I concur

## CLINICAL REVIEW

Application Type	NDA
Submission Number	22-279
Submission Code	N-019
Letter Date	07/26/2010
Stamp Date	07/26/2010
PDUFA Goal Date	01/26/2011
Reviewer Name	Xu Wang, M.D., Ph.D.
Review Completion Date	12/30/2010
Established Name	Hydrocodone, Pseudoephedrine and Guaifenesin
(Proposed) Trade Name	Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)
Therapeutic Class	Antitussive/Decongestant/Expectorant
Applicant	(b) (4)
Priority Designation	S
Formulation	Oral solution
Dosing Regimen	For adults (b) (4): 10 mL (hydrocodone bitartrate 5 mg/pseudoephedrine hydrochloride 60 mg/guaifenesin 400 mg) every 4 hours, not to exceed 40 mL in 24 hours
	(b) (4)
Indication	For symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)
Intended Population	Adults (b) (4)

## Table of Contents

<b>1 EXECUTIVE SUMMARY .....</b>	<b>5</b>
<b>1 EXECUTIVE SUMMARY .....</b>	<b>5</b>
1.1 RECOMMENDATION ON REGULATORY ACTION .....	5
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS .....	5
1.2.1 Risk Management Activity.....	5
1.2.2 Required Phase 4 Commitments .....	5
1.2.3 Other Phase 4 Requests.....	5
1.3 SUMMARY OF CLINICAL FINDINGS.....	5
1.3.1 Brief Overview of Clinical Program .....	5
1.3.2 Efficacy.....	6
1.3.3 Safety .....	6
1.3.4 Dosing Regimen and Administration.....	7
1.3.5 Drug-Drug Interactions .....	7
1.3.6 Special Populations.....	7
<b>2 INTRODUCTION AND BACKGROUND.....</b>	<b>9</b>
2.1 PRODUCT INFORMATION .....	9
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	10
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES.....	11
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS .....	11
2.5 PRESUBMISSION REGULATORY ACTIVITY .....	12
<b>3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES.....</b>	<b>12</b>
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) .....	12
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY .....	13
<b>4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY .....</b>	<b>13</b>
4.1 SOURCES OF CLINICAL DATA.....	13
4.2 TABLES OF CLINICAL STUDIES .....	13
4.3 REVIEW STRATEGY .....	14
4.4 DATA QUALITY AND INTEGRITY .....	14
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES .....	14
4.6 FINANCIAL DISCLOSURES .....	14
<b>5 CLINICAL PHARMACOLOGY.....</b>	<b>14</b>
<b>6 INTEGRATED REVIEW OF EFFICACY.....</b>	<b>17</b>
6.1 INDICATION.....	17
<b>7 INTEGRATED REVIEW OF SAFETY.....</b>	<b>17</b>
7.1 METHODS AND FINDINGS.....	19
7.1.1 Deaths .....	19
7.1.2 Other Serious Adverse Events.....	19
7.1.3 Dropouts and Other Significant Adverse Events.....	20
7.1.5 Common Adverse Events.....	19
7.1.6 Less Common Adverse Events .....	20
7.1.7 Laboratory Findings.....	20
7.1.8 Vital Signs.....	20
7.1.9 Electrocardiograms (ECGs).....	20
7.1.13 Withdrawal Phenomena and/or Abuse Potential.....	21
7.1.14 Human Reproduction and Pregnancy Data .....	21
7.1.16 Overdose Experience .....	22

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-019, Resubmission/Class 2, 07/26/2010, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)

7.1.17 Postmarketing Experience.....	22
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS .....	22
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety .....	22
7.2.3 Adequacy of Overall Clinical Experience .....	23
7.2.9 Additional Submissions, Including Safety Update.....	23
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS .....	23
<b>8 ADDITIONAL CLINICAL ISSUES.....</b>	<b>23</b>
8.1 DOSING REGIMEN AND ADMINISTRATION.....	23
8.2 DRUG-DRUG INTERACTIONS .....	24
8.3 SPECIAL POPULATIONS .....	24
8.4 PEDIATRICS.....	24
8.6 LITERATURE REVIEW .....	25
8.7 POSTMARKETING RISK MANAGEMENT PLAN.....	26
<b>9 OVERALL ASSESSMENT .....</b>	<b>27</b>
9.1 CONCLUSIONS .....	27
9.2 RECOMMENDATION ON REGULATORY ACTION .....	28
9.4 LABELING REVIEW.....	28
9.5 COMMENTS TO APPLICANT.....	28

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-019, Resubmission/Class 2, 07/26/2010, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)

**Table of Tables**

Table 1 Summary of two pharmacology studies S09-0009 and S09-0010.....	14
Table 2 Formulation of Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution.....	15
Table 3 Post-marketing adverse events (AERS database, Jan. 1, 2003 to Dec. 31, 2007, incidence >3%).....	18
Table 4 Adverse events reported in study S09-0009.....	20

## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

In the present NDA resubmission the Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only) has failed to meet bioequivalence criteria and I recommend that the application be given a Complete Response action.

This drug development program is a clinical pharmacology program. The clinical pharmacology studies submitted are not adequate to support this application because these studies do not fulfill the bioavailability criteria for combination products as per 21 CFR 320.25 (g). Specifically, the guaifenesin component of the proposed product is not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence).

### **1.2 Recommendation on Postmarketing Actions**

#### **1.2.1 Risk Management Activity**

No special post-marketing risk management activities are recommended at this time.

#### **1.2.2 Required Phase 4 Commitments**

No special Phase 4 commitments are recommended at this time since the recommended regulatory action is Complete Response.

#### **1.2.3 Other Phase 4 Requests**

There are no Phase 4 requests for this application.

### **1.3 Summary of Clinical Findings**

#### **1.3.1 Brief Overview of Clinical Program**

This is a Complete Response resubmission based on the deficiencies outlined in the Complete Response letter dated June 22, 2009. The original NDA, submitted on August 22, 2008, presented a single dose bioavailability study, which was determined “inadequate to evaluate the bioequivalence, drug-drug interaction, and food effect of the proposed combination product.” In this NDA resubmission, the Applicant included two clinical pharmacology studies. Study S09-0009 is a single-dose, randomized, three-treatment crossover study to assess the relative bioavailability and bioequivalence of the test drug, (b) (4) triple combination solution, and reference solutions. The results of this study demonstrated that hydrocodone and

pseudoephedrine met the bioequivalence criteria. However, the guaifenesin component of the proposed product is not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence).

Study S09-0010 is a food effect study to assess the impact of food on the bioavailability of (b) (4) triple combination solution. This is a single-dose, randomized, two-treatment crossover study under fed and fasting conditions. The results of this study demonstrated that for guaifenesin (but not for hydrocodone or pseudoephedrine) the point estimates and their 90% CIs for AUC and C<sub>max</sub> were not contained within the acceptance range of 80.00 - 125.00%, suggesting that food had an overall impact on the systemic bioavailability of guaifenesin as compared to the fasted state.

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology studies S09-0009 and S09-0010, a search of the AERS database for post-marketing spontaneous adverse events, and a literature survey to provide support for the safety of the proposed drug product.

### 1.3.2 Efficacy

No clinical efficacy studies were submitted to support this application. This is a 505(b)(2) application using clinical pharmacology studies to support approval. The Agency's previous findings of efficacy and safety of approved hydrocodone products (Hycodan Syrup and Tablets, NDA 5-213) and the OTC monograph for pseudoephedrine and guaifenesin are being used to substantiate the efficacy and safety of this triple combination product.

### 1.3.3 Safety

In the clinical pharmacology studies S09-0009 and S09-0010, a total of 60 healthy, adult subjects aged 18 to 65 years received a single dose of 10 mL of an immediate release oral solution of 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin under fasting conditions. There were 10 subjects who reported 18 adverse events in these two clinical pharmacology studies (6 headaches, 6 dizziness, 4 lightheaded, 1 drowsiness, and 1 abnormal white blood cell count). All adverse events were mild in nature and spontaneously resolved without special treatment. The safety data from the clinical pharmacology studies in adult subjects did not identify a safety signal.

The post-marketing adverse events from the AERS database covered the period from January 1, 2003 through December 31, 2007. The AERS database search using combinations hydrocodone plus pseudoephedrine plus guaifenesin (HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The search included the generic names and the trade name medications obtained from internet sites. Combination products containing antihistamines were excluded from the search result. There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The Applicant searched MEDLINE and EMBASE for the medical literature relevant to safety of hydrocodone, pseudoephedrine and guaifenesin. The literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years. The Applicant's search of the medical literature for safety information related to hydrocodone, pseudoephedrine and guaifenesin identified no new safety signals.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the test drug and the test drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the test drug.

#### 1.3.4 Dosing Regimen and Administration

The application is for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only). The proposed drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed indications are "for symptomatic relief of cough, (b)(4) nasal congestion, and to (b)(4) loosen (b)(4) mucus (b)(4). The proposed dosage is two te (b)(4) 8 teaspoonfuls) (b)(4) in 24 hours for adults (b)(4)

#### 1.3.5 Drug-Drug Interactions

The applicant submitted literature references to address the drug-drug interaction potential of the triple combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone, pseudoephedrine and guaifenesin are administered together.

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The Applicant's proposed labeling appropriately addresses the potential for these drug-drug interactions.

#### 1.3.6 Special Populations

There were no studies in special populations for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution in this submission to review. The Applicant's proposed labeling indicates that the drug product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. (b)(4)

(b)(4) A literature search shows a report of two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Hydrocodone, Pseudoephedrine and

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-019, Resubmission/Class 2, 07/26/2010, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)

Guaifenesin Oral Solution is administered to nursing mothers. The information about the hydrocodone excreted in breast milk and the potential risks of hydrocodone use in nursing women should be added to the proposed labeling when it is considered for approval.

*Reviewer comment:*

*On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received a long-acting hydrocodone-containing cough product.*

*[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>,*

*<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>].*

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The Applicant has developed an immediate release oral solution formulation of hydrocodone, pseudoephedrine and guaifenesin. The drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed labeled indications are “for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4).” The sponsor’s proposed name is Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4).

(b) (4) The Applicant has provided a paper submission.

Hydrocodone (HC) is a commonly used antitussive. The safety and effectiveness of HC as a prescription drug for the symptomatic relief of cough are supported by DESI review and by the FDA approved product Hycodan (NDA 5-213). HC is an opioid, a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in combination with active non-narcotic ingredients and if the product contains not more than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15).

Hycodan Tablets and Syrup (HC 5 mg plus homatropine methylbromide (HTM) 1.5 mg, and HC 5 mg plus HTM 1.5 mg per 5 mL, NDA 5-213) was classified in the DESI review as safe and effective for prescription drug for the symptomatic relief of cough (DESI Notice #5123). The approved dosages are:

- Adults: One tablet or one teaspoonful of the syrup (5 mg HC) every 4 to 6 hours as needed; not to exceed (NTE) 6 tablets or 6 teaspoonfuls (30 mg HC) in 24 hours
- Children 6 to 12 years of age: One-half (1/2) tablet or one-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 tablets or 3 teaspoonfuls (15 mg HC) in 24 hours
- Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age is contraindicated due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic product labeling].

Pseudoephedrine (PSE) is considered to be GRASE as an oral nasal decongestant [21 CFR 341.20] in the following age groups at the following oral doses [21 CFR 341.80(d)]:

- Adults and children 12 years of age and over: 60 mg every 4 to 6 hours NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 to 6 hours NTE 120 mg in 24 hours

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-019, Resubmission/Class 2, 07/26/2010, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)

- Children 2 to under 6 years of age: 15 mg every 4 to 6 hours NTE 60 mg in 24 hours
- Children under 2 years of age: consult a doctor

Guaifenesin (GU) is considered to be generally recognized as safe and effective (GRASE) as an expectorant [21 CFR 341.18] in the following age groups at the following oral doses [21 CFR 341.78]:

- Adults and children 12 years of age and older: 200 to 400 mg every 4 hours, NTE 2400 mg in 24 hours
- Children 6 to under 12 years of age: 100 to 200 mg every 4 hours, NTE 1200 mg in 24 hours
- Children 2 to under 6 years of age: 50 to 100 mg every 4 hours, NTE 600 mg in 24 hours
- Children under 2 years of age: consult a doctor

The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single nasal decongestant (such as pseudoephedrine) and any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

*Reviewer comment:*

*Hydrocodone, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50).*

*However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product, which can be found in detail in Medical Officer Review, IND (b) (4) M-001, MR, Charles E. Lee, M.D., 9/25/2006. Briefly, during the FDA deliberations on the approvability of Tussionex Pennkinetic extended release suspension (NDA 19-111) at the Center Level the FDA determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. The development program for Tussionex Pennkinetic was comprised of 3 bioavailability studies and no clinical studies. Based on this prior precedent, the Division has accepted the conclusion that for a HC combination product containing monograph active ingredients, a drug development plan does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the efficacy and safety of the combination product, and that approval can be based on establishment of bioequivalence.*

## **2.2 Currently Available Treatment for Indications**

Hydrocodone is currently approved in the United States in tablet and syrup as an immediate release antitussive drug (Hycodan, NDA 5-213). The owner of NDA 5-213, Endo Pharmaceuticals, had withdrawn the products voluntarily not because of reasons of safety or efficacy. The company keeps the NDA 5-213 current, but stopped manufacturing and marketing the Hycodan Tablets and Solution on January 4 and May 14, 2008, respectively. Hydrocodone is also approved in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111).

There are other generic Hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussion (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). Pseudoephedrine and guaifenesin are readily available OTC monograph drugs, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph doses for the temporary relief of nasal congestion, and to help loosen phlegm (mucus) and thin bronchial secretions.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Hydrocodone is currently available in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111) and generic antitussive drugs Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussion (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). In addition, hydrocodone is available in the United States in tablet and capsule formulations as analgesic medications at higher doses than antitussives, such as Vicoprofen (NDA 20716), Vicodin and Vicodin HP (ANDA 88058, ANDA 40117), Lortab (ANDA 40100, ANDA 87722), and Anexsia (ANDA 40405, ANDA 40409, ANDA (b) (4) ANDA 40686, ANDA 89160). There have been multiple illegally marketed hydrocodone-containing products in the U.S. market. The FDA has announced its intention to take enforcement actions against unapproved drug products containing hydrocodone bitartrate if such drug products are manufactured and marketed on or after October 31, 2007 [Federal Register Vol. 72, No 189, October 1, 2007].

Pseudoephedrine is currently approved in the United States in tablet (Afrinol, NDA 18-191), in combination with chlorpheniramine (Chlor-Trimeton, NDA 18-397), with ibuprofen and chlorpheniramine (Advil Allergy Sinus Caplet, NDA 21-441), and with guaifenesin (Mucinex<sup>TM</sup> D, NDA 21-585). These products are extended release formulations. Pseudoephedrine is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

Guaifenesin is currently approved in the United States in tablet (Mucinex ER, NDA 21-282), in combination with dextromethorphan (Mucinex<sup>TM</sup> DM, NDA 21-620), and with pseudoephedrine (Mucinex<sup>TM</sup> D, NDA 21-585). These products are extended release formulations. Guaifenesin is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

### **2.4 Important Issues With Pharmacologically Related Products**

Hydrocodone is a semi-synthetic opioid that has the potential for abuse. Dependence and tolerance may develop upon repeated administration. Hydrocodone is a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in combination with active non-narcotic ingredients and if the product contains not more than 300

milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15).

Pseudoephedrine is an OTC monograph drug of oral nasal decongestant [21 CFR 341.20]. Pseudoephedrine can be unlawfully used to make the illicit drug methamphetamine. The Combat Methamphetamine Act restricts the access of pseudoephedrine by requiring retailers to place OTC drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase.

## 2.5 Presubmission Regulatory Activity

The Applicant had a pre-IND meeting on March 26, 2007 with the Division to discuss the plans to develop two immediate release oral solutions of hydrocodone and guaifenesin and hydrocodone, pseudoephedrine and guaifenesin. The formulations for the proposed drugs were not provided in the briefing package. The Applicant submitted an opening IND on September 25, 2007 for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (IND 76,365). The opening IND study was a single dose, open label bioavailability study that was determined safe to proceed. The Applicant filed a 505(b)(2) NDA (NDA 22-279, N000) for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution on August 22, 2008. A Complete Response Letter was issued to the submission on June 22, 2009, stating that "The open-label bioavailability study submitted is inadequate to evaluate the bioequivalence, drug-drug interaction, and food effect of the proposed combination product." In order to support the proposed drug product, the Applicant needs to "(1) conduct a single-dose clinical pharmacology study to establish the bioequivalence of the proposed Hydrocodone 2.5 mg/Pseudoephedrine 30 mg/Guaifenesin 200 mg per 5 mL Oral Solution to the reference products; and (2) conduct a food effect study of the proposed drug product under fed and fasted conditions." The Applicant resubmitted the NDA (NDA 22-279, N019) on July 26, 2010, including data obtained from two clinical pharmacology studies.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 3.1 CMC (and Product Microbiology, if Applicable)

The drug product is an oral aqueous solution containing hydrocodone bitartrate USP 2.5 mg, pseudoephedrine hydrochloride USP 30 mg, and guaifenesin 200 mg per USP 5 mL. This is an immediate release formulation. The excipients in the test formulation include sorbitol, glycerin, polyethylene glycol, methylparaben, propylparaben, citric acid, sodium citrate, saccharin, D&C Red #33 and FD&C Blue (b) (4) black raspberry flavor. The proposed combination drug is manufactured by (b) (4)

Hydrocodone bitartrate USP used in the rest formulation was manufactured by (b) (4)

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-019, Resubmission/Class 2, 07/26/2010, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)

Pseudoephedrine hydrochloride USP used in the rest formulation was manufactured by (b) (4)

Guaifenesin USP used in the test formulation was manufactured by (b) (4)

The Applicant, (b) (4) informed the Agency in a facsimile dated April 15, 2009, that the ownership of NDA 22-279 has been transferred to (b) (4). The new ownership of the NDA was effective on March 25, 2009. The proposed drug product will be manufactured by a new contractor that has not been announced by the new owner of this NDA.

A detailed review of the CMC portion of the application may be found in the ONDQA review [NDA 22-279 N-019, ONDQA Review, Arthur Shaw, Ph. D.].

### **3.2 Animal Pharmacology/Toxicology**

No new animal data or toxicology data were submitted. No new pre-clinical toxicology studies were required or performed for this application.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

The application was submitted under Section 505(b)(2) of the Food, Drug & Cosmetic Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of approved or OTC monograph reference products. This application relies on a comparison of the bioavailability of the proposed drug product to the reference drugs. The applicant's drug development program for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution is based on establishing that their combination product produces exposures are equivalent to that of approved and marketed products for hydrocodone and to that of OTC monograph doses of pseudoephedrine and guaifenesin. This application refers to clinical pharmacology studies S09-0009 and S09-0010. There were no clinical efficacy or safety studies in this application.

### **4.2 Table of Clinical Studies**

The Applicant has submitted the results from studies S09-0009 and S09-0010. The studies in this application are summarized below in Table 1.

**Table 1. Summary of two pharmacology Studies S09-0009 and S09-0010**

Study No.	Study type	Treatment group	Design	Subject No.	Subjects	Materials submitted
S09-0009	BE	A: HC 5/PSE 60/GU 400mg B: HC 5 mg C: PSE 60/GU 400mg	Randomized, single dose, 3- treatment crossover	42	Healthy males and females, 18- 64 yrs	Study report
S09-0010	Food effect	HC 5/PSE 60/GU 400mg, fed and fasted conditions	Randomized, single dose, 2- treatment crossover	18	Healthy males and females, 19- 65 yrs	Study report

### 4.3 Review Strategy

This is a review of the data from studies S09-0009 and S09-0010, and of the data from AERS database for post-marketing and spontaneous adverse event reports and the literature review for hydrocodone, pseudoephedrine and guaifenesin. Detailed review of the clinical pharmacology data can be found in the Clinical Pharmacology Review [NDA 22-279, N-019, Clinical Pharmacology Review, Arun Agrawal, Ph. D.].

### 4.4 Data Quality and Integrity

Not applicable. There was no DSI audit conducted for the study site or data analyses.

### 4.5 Compliance with Good Clinical Practices

The clinical pharmacology studies in this application were conducted in accordance with Good Clinical Practices. The applicant certified that the clinical contractor complied with all applicable federal, state and local laws, codes, regulations, and orders, including, but not limited to, the Federal Food, Drug, and Cosmetic Act and regulations promulgated there under, and Institutional Review Board requirements relative to clinical studies [Volume 5.1, Section 5.3.1.1.1, page 18, and Volume 5.9, Section 5.3.1.1.2, page 16].

### 4.6 Financial Disclosures

The applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The Applicant stated that the clinical investigator of the clinical pharmacology study in this application certified that he did not have a proprietary interest in the proposed product or a significant equity in the applicant [Volume 1.1, Section 1.3.4, pages 1-2].

## 5 CLINICAL PHARMACOLOGY

There were two clinical pharmacology studies in the submission. A summary of data from the Applicant's clinical pharmacology studies follows below. Detailed information can be found in

The formulation of Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution is displayed in Table 2. The experimental formulation is manufactured and supplied by (b) (4) [Volume 2.1, Section 2.3, page 19].

**Table 2. Formulation of Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution**

Ingredient	% w/v	mg/5 mL	g/liter
Hydrocodone bitartrate USP	0.05	2.5	0.50
Guaifenesin USP	4.00	200	40.00
Pseudoephedrine hydrochloride USP	0.60	30	6.00
Sorbitol (b) (4) USP	(b) (4)		(b) (4)
Glycerine USP			
Polyethylene glycol (b) (4) NF			
Methylparaben NF			
Propylparaben NF			
Citric acid (b) (4) USP			
Sodium citrate (b) (4) USP			
Saccharin sodium			
D & C red #33			
FD & C blue #1			
(b) (4) black raspberry flavor (b) (4)			
Purified water USP			

**Study S09-0009** is a single-dose, randomized, three-treatment crossover study under fasting condition. Forty-two male and female healthy volunteers aged 18 to 64 years old participated this study. Subjects were generally healthy as documented by the medical history, physical examination, vital sign, clinical laboratory tests, and ECG. Subjects did not receive any investigational drug within the past 30 days, any prescription drug (except contraceptives for females) within past 14 days, and any OTC medications (except multivitamins) within past 7 days. At least 7-day washout period was observed between the doses. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24 and 36 hours post-dose. Blood samples were collected only up to 16 hours for hydrocodone bitartrate/homatropine methylbromide arm (Treatment B). Safety evaluation includes adverse events and vital signs monitoring during the study.

This study investigated the relative bioavailability of the Test and Reference solutions by comparing the rate and extent of exposure of (b) (4) triple combination solution.

Treatment A (Test): (b) (4) hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution

Treatment B (References 1): Hydrocodone bitartrate 5 mg oral solution

Treatment C (References 2): the combination of pseudoephedrine HCl 60 mg and Robitussin Chest Congestion (guaifenesin 400 mg) oral solution

Results are summarized below:

**Hydrocodone (Treatment A versus Treatment B):** The test ratios of geometric means were 100.87% (90% CI 98.21% - 103.60%) for  $AUC_{0-t}$ , 101.12% (90% CI 98.28% - 104.04%) for  $AUC_{0-inf}$ , and 89.80% (90% CI 85.81% - 93.98%) for  $C_{max}$ . The point estimates and their 90% CIs were all contained within the protocol defined acceptance range of 80.00 - 125.00%.

**Pseudoephedrine (Treatment A versus Treatment C):** The test ratios of geometric means were 100.48% (90% CI 96.54% - 104.57%) for  $AUC_{0-t}$ , 100.75% (90% CI 96.92% - 104.73%) for  $AUC_{0-inf}$ , and 85.68% (90% CI 82.08% - 89.44%) for  $C_{max}$ . The point estimates and their 90% CIs were all contained within the protocol defined acceptance range of 80.00 - 125.00%.

**Guaifenesin (Treatment A versus Treatment C):** The test ratios of geometric means were (b) (4)

**Study S09-0010** is a food effect study to assess the impact of food on the bioavailability of (b) (4) hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution. This is a single-dose, randomized, two-treatment crossover study under fed and fasting conditions. Eighteen male and female healthy volunteers aged 19 to 65 years old participated this study. Subjects were generally healthy as documented by the medical history, physical examination, vital sign, clinical laboratory tests, and ECG. Subjects did not receive any investigational drug within the past 30 days, any prescription drug (except contraceptives for females) within past 14 days, and any OTC medications (except multivitamins) within past 7 days. At least a 7-day washout period was observed between the doses. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24 and 36 hours post-dose. Safety evaluation includes adverse events and vital signs monitoring during the study. Results are summarized below:

**Hydrocodone:** The test ratios of geometric least squares means (LSM) and 90% CI were 115.7% (90% CI 111.86% - 119.66%) for  $AUC_{0-t}$ , 117.0% (90% CI 112.94% - 121.0%) for  $AUC_{0-inf}$ , and 102.6% (90% CI 97.17% - 108.28%) for  $C_{max}$ . The point estimates and their 90% CIs were all contained within the protocol defined acceptance range of 80.00 -125.00%.

**Pseudoephedrine:** The test ratios of geometric least squares means (LSM) and 90% CI were 94.9% (90% CI 87.68% - 102.70%) for  $AUC_{0-t}$ , 94.8% (90% CI 87.37% - 102.83%) for  $AUC_{0-inf}$ , and 97.3% (90% CI 92.70% - 102.10%) for  $C_{max}$ . The point estimates and their 90% CIs were all contained within the protocol defined acceptance range of 80.00 -125.00%.

**Guaifenesin:** The test ratios of geometric least squares means (LSM) and 90% CI were (b) (4)

. Thus, for guaifenesin (but not for hydrocodone or pseudoephedrine) the point estimates and their 90% CIs for AUC and  $C_{max}$  were not contained within the acceptance range of 80.00 - 125.00%, suggesting that food had an overall impact on the systemic bioavailability of guaifenesin as compared to the fasted state.

## 6 INTEGRATED REVIEW OF EFFICACY

This is a clinical pharmacology program. The NDA submission is supported by comparison of the bioavailability of the proposed drug product to reference. No clinical efficacy studies were conducted to support this application.

### 6.1 Indication

The proposed indication for this product follows below:

Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only) is for symptomatic relief of cough, (b) (4) of nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)

## 7 INTEGRATED REVIEW OF SAFETY

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology studies S09-0009 and S09-0010, post-marketing spontaneous adverse events report, and literature survey. The safety was assessed through adverse events and vital signs in the two single dose clinical pharmacology studies S09-0001 and S09-0010. The safety data from these two clinical pharmacology studies in adult subjects did not identify a safety signal. There were 60 subjects participated in two studies, and the adverse event data from the studies are not enough to evaluate the association of adverse events and gender or race/ethnicity.

The post-marketing adverse event reports from the search result of AERS database covering the period from January 1, 2003 through December 31, 2007, and a brief literature review for safety of hydrocodone, pseudoephedrine, and guaifenesin [Volume 2.1, Section 2.7.4, pages 34 – 44]. The Applicant also submitted 2 volumes of compiled published literature references related to the safety of their product [Volume 5.8 – 5.9, Section 5.4.2].

The Applicant conducted an AERS database search using combinations hydrocodone plus pseudoephedrine plus guaifenesin (HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The search included the generic names and the trade name medications obtained from internet sites. Combination products containing antihistamines were excluded from the search result. The presence or absence of acetaminophen was disregarded. The AEs reported from the USA were included.

The Applicant searched MEDLINE and EMBASE for the medical literature relevant to safety of hydrocodone, pseudoephedrine and guaifenesin. The literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years. The Applicant's search of the medical literature for safety information related to hydrocodone, pseudoephedrine and guaifenesin identified no new safety signals.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the test drug and the test drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the test drug.

## 7.1 Methods and Findings

Table 3 summarizes the results of the AERS search covering the period from January 1, 2003 through December 31, 2007. The adverse events with an incidence >3% are listed.

**Table 3. Post-marketing adverse events (AERS database, Jan. 1, 2003 to Dec. 31, 2007, incidence >3%)**

Search term*	HC/PSE/GU (%)	HC/PSE (%)	HC/GU (%)	HC (%)	PSE (%)	GU (%)
Total (n) AEs	2	3	12	3744	2782	125
Serious AEs <sup>#</sup>	0	0	6 (50.0)	3161 (84.43)	333 (11.97)	85 (68.0)
Death	0	0	5 (41.67)	2327 (62.15)	194 (6.97)	19 (15.20)
Completed suicide	0	0	0	939 (25.08)	65 (2.34)	2 (1.60)
Multiple drug overdose	0	0	1 (8.33)	860 (22.97)	29 (1.04)	5 (4.00)
Overdose	0	1 (33.3)	1 (8.33)	502 (13.41)	97 (3.49)	5 (4.00)
Cardiorespiratory arrest		0	1 (8.33)	332 (8.87)	30 (1.08)	2 (1.60)
Drug toxicity	0	0	1 (8.33)	314 (8.39)	77 (2.77)	0
Drug abuser	0	0	0	230 (6.14)	-- <sup>\$</sup>	1 (0.80)
Respiratory arrest	0	0	0	215 (5.74)	29 (1.04)	1 (0.80)
Vomiting	1 (50.0)	0	1 (8.33)	167 (4.46)	61 (2.19)	5 (4.00)
Nausea	0	0	1 (8.33)	161 (4.30)	167 (6.00)	8 (6.40)
Medical error	0	0	1 (8.33)	158 (4.22)	47 (1.69)	13 (10.40)
Increased drug level	0	0	0	154 (4.11)	35 (1.26)	1 (0.80)
Coma	0	0	1 (8.33)	147 (3.93)	37 (1.33)	3 (2.40)
Somnolence	0	0	0	145 (3.87)	0	2 (1.60)
Drug ineffective	0	0	1 (8.33)	137 (3.66)	224 (8.05)	4 (3.20)
Anxiety	1 (50.0)	0	0	44 (1.18)	40 (1.44)	7 (5.60)
Dyspnea	0	1 (33.3)	0	51 (1.36)	68 (2.44)	3 (2.40)
Vision blurred	0	1 (33.3)	0	0	41 (1.47)	0
Loss of consciousness	0	0	1 (8.33)	88 (2.35)	45 (1.62)	7 (5.60)
Insomnia	0	0	0	39 (1.04)	122 (4.39)	3 (2.40)
Dizziness	0	0	0	59 (1.58)	98 (3.52)	10 (8.00)
Headache	0	0	0	54 (1.44)	163 (5.86)	6 (4.80)
Convulsion	0	0	1 (8.33)	60 (1.60)	40 (1.44)	10 (8.00)
Abdominal pain	0	0	1 (8.33)	47 (1.26)	63 (2.26)	6 (4.80)

\* The version of the MedDRA used in searching the database is not specified.

# Serious adverse events include deaths, life threatening, hospitalization, and disabilities.

\$ The term "drug abuser" was not on the list of terms in PSE report.

(Source: Volume 5.9, Section 5.3.1.2, page 128-134, 157-162)

### 7.1.1 Deaths

There was no death in the clinical pharmacology studies S09-0009 and S09-0010 in this application.

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-019, Resubmission/Class 2, 07/26/2010, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)

In searching AERS database covering the period from January 1, 2003 through December 31, 2007, there were 6,668 adverse event reports with 2,545 deaths (38.17%) for the search terms of hydrocodone plus pseudoephedrine plus guaifenesin (HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The most death reports (2,327) came from searching with hydrocodone, accounting for 62.15% of the adverse event reports (3,744). The four most commonly reported adverse event terms were completed suicide (25.08%, 939/3,744), multiple drug overdose (22.97%, 860/3,744), overdose (13.41%, 502/3,744), and cardiorespiratory arrest (8.87%, 332/3,744). Noticeably, the overall adverse events and death reports for hydrocodone did not differentiate if the hydrocodone was taken as antitussive doses or as much higher analgesic doses. Because the data reflect a large fraction of suicide and overdoses, the dosage forms of hydrocodone for the deaths and adverse events were most possibly higher than doses as an antitussive. There were 194 and 19 death reports for pseudoephedrine and guaifenesin, respectively. The data also reflect a large portion of suicide and overdoses.

*Reviewer comment:*

*The AERS database search shows the death rate is high in the AE reports for hydrocodone. The death reports reflects a large fraction of suicide and overdoses reported for hydrocodone use. Also, hydrocodone is known to be used in symptomatic treatment for many end stage diseases. Without the knowledge of dosage forms, diseases, co-administered medications, a simple search of AERS, a spontaneous post-marketing adverse event reporting database, does not provide meaningful safety information for hydrocodone use. The OSE consult has been requested to evaluate the AERS data regarding the high incidence of death reports related to hydrocodone use.*

### 7.1.2 Other Serious Adverse Events

There was no serious adverse event in the clinical pharmacology studies in this application.

The search of the AERS database covering the period from January 1, 2003 through December 31, 2007 does not identify new safety signals for hydrocodone, pseudoephedrine and guaifenesin.

### 7.1.3 Dropouts and Other Significant Adverse Events

There was no dropout or withdrawal from the clinical pharmacology studies S09-0009 and S09-0010 due to adverse events. There was no significant adverse event in the clinical pharmacology studies in this application.

### 7.1.4 Other Search Strategies

No other search strategies were used in this application.

### 7.1.5 Common Adverse Events

In the clinical pharmacology study S09-0009, there were eight subjects reported 15 mild adverse events. The case report review revealed that all adverse events were mild in nature and no treatment was required. Table 4 summarizes the adverse events occurred in study S09-0009.

Table 4. Adverse events reported in study S09-0009

Adverse event	Treatment A	Treatment B	Treatment C	Total
Headache	3	1	2	6
Dizziness	2	2		4
Lightheaded	2	1	1	4
Abnormal WBC		1		1
<b>Total</b>	<b>7</b>	<b>5</b>	<b>3</b>	<b>15</b>

Treatment A: Hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution

Treatment B: Hydrocodone bitartrate 5 mg oral solution

Treatment C: Pseudoephedrine HCl 60 mg and Robitussin Chest Congestion (guaifenesin 400 mg) oral solution

In the clinical pharmacology study S09-0010, two subjects experienced three adverse events (two dizziness and one drowsiness) during the study. All adverse events were mild in nature and no treatment was required.

*Reviewer comment:*

*These data do not identify a safety signal. Because of the small number of the subjects, there was no meaningful information in differences in adverse events in gender, age, and race/ethnicity.*

### 7.1.6 Less Common Adverse Events

Adverse events occurring in the clinical pharmacology studies in adults are reviewed in Section 7.1.5. Less common adverse events did not suggest a safety signal.

### 7.1.7 Laboratory Findings

Laboratory examinations were not safety endpoints in the clinical pharmacology studies of this application.

### 7.1.8 Vital Signs

Vital sign assessments were conducted before and the end of the clinical pharmacology studies. No clinically significant changes from baseline data were reported.

### 7.1.9 Electrocardiograms (ECGs)

ECGs were not safety endpoints in the clinical pharmacology studies of this application.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. Adams EH, Breiner S, Cicero TJ, et al. reported a 12-month study in chronic pain patients that showed an abuse rate of 1.2% for hydrocodone<sup>1</sup>. The applicant provided data regarding the drug-related ED visits in 2005, collected by the Drug Abuse Warning Network (DAWN). The data show that hydrocodone/combinations accounted for 51,225 (6.27%) of the 816,696 total illicit drug-related ED visits in 2005<sup>2</sup>. Although hydrocodone dosages as an antitussive is much lower than that of analgesics and illicit drugs, hydrocodone-containing medications should be prescribed and administered with caution.

Pseudoephedrine is a sympathomimetic amine used as an oral nasal decongestant. It can be unlawfully used to make illicit drug methamphetamine<sup>3</sup>. The Combat Methamphetamine Act, signed into law by President Bush on March 9, 2005, restricts the access of pseudoephedrine by requiring retailers to place drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase. The potential of unlawfully using pseudoephedrine in the proposed drug to make methamphetamine is addressed by the access restriction required in the Combat Methamphetamine Act. The proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution is a prescription drug, which provides limitation to its accessibility for the unlawful use.

### 7.1.14 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected in the clinical pharmacological study. The Applicant has not observed or reported adverse events associated with drug exposure during pregnancy in the post-marketing surveillance. The Applicant's proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. The Applicant searched MEDLINE database for hydrocodone and human reproduction. A report revealed 2 cases of hydrocodone excretion in breast milk<sup>4</sup>. The infants of the mothers who were taking hydrocodone received an estimated 3.1% and 3.7% of the maternal weight-adjusted dosage. The absolute hydrocodone doses the infants received were 8.58 mcg/kg and 3.07 mcg/kg per day. One infant (18-day-old) became groggy and slept for most of the day while the mother was taking 20 mg hydrocodone every 4 hours. The infant's symptoms improved when mother decrease her hydrocodone dose by half. Another infant (5-week-old) became cyanotic and required intubation while the mother was taking hydrocodone and methadone for migraine headache. The infant was positive for opioids in urinary test and responded well to naloxone treatment. There are no reports of hydrocodone in breast milk while a mother takes hydrocodone at a much lower antitussive dosage. The prescribers and patients should be aware of the potential hydrocodone excretion into breast milk and use Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution with caution.

---

1 Adams EH, Breiner S, Cicero TJ, et al. J Pain Symptom Manage. May 2006;31(5):465-476

2 Manchikanti L. Pain Physician 2007;10:399-424

3 [www.streetdrugs.org](http://www.streetdrugs.org), accessed on March 5, 2009

4 Anderson PO, Sauberan JB, Lane JR, et al. Breastfeeding Med March 2007;2(1):10-14

### 7.1.16 Overdose Experience

There is no overdose experience reported in the clinical pharmacological studies. The applicant searched the AERS database and the result shows that 36.38% of the reported adverse events associated with hydrocodone were overdose or multiple-drug overdose. In the literature review, the Applicant summarized that hydrocodone had the potential of being overdosed by self-medication and abuse, like other opioids. The AERS database search and literature review did not differentiate whether the hydrocodone was taken as antitussives or at much higher dosages as analgesics. The Applicant identified no new pattern of overdose for the ingredients of the proposed drug.

*Reviewer comment:*

*The reviewer concurs with the Applicant that there are no new concerns regarding overdose with the ingredients of their proposed drug product.*

### 7.1.17 Postmarketing Experience

The proposed drug product Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution has not been marketed. But there have been multiple illegally marketed hydrocodone-containing products in the U.S. market. The FDA has announced its intention to take enforcement actions against unapproved drug products containing hydrocodone bitartrate if such drug products are manufactured and marketed on or after October 31, 2007 [Federal Register Vol. 72, No 189, October 1, 2007]. The post-marketing experiences were obtained from AERS database search covering pseudoephedrine, guaifenesin and hydrocodone drug products, including approved and unapproved drug products containing hydrocodone as antitussives and analgesics.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

In the clinical pharmacology studies S09-0009 and S09-0010, a total of 60 healthy, adult subjects aged 18 to 65 years receive a single dose of 10 mL of an immediate release oral solution of 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin under fasting condition. There were 10 subjects who reported 18 adverse events in these two clinical pharmacology studies (6 headaches, 6 dizziness, 4 lightheaded, 1 drowsiness, and 1 abnormal white blood cell count). All adverse events were mild in nature and spontaneously resolved without special treatment.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable

#### 7.2.2.3 Literature

The Applicant performed a search of the medical literature for information relevant to safety of hydrocodone, pseudoephedrine, and guaifenesin in general. The search covered three individual active ingredient hydrocodone, pseudoephedrine, guaifenesin) for two years (2006 – 2008) and

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-019, Resubmission/Class 2, 07/26/2010, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)

the products containing all three ingredients for 10 years (1998 – 2008). The search was conducted with the MEDLINE and EMBASE database. There were no studies related to safety of products containing all three ingredients. The literature search revealed no new safety signals for hydrocodone, pseudoephedrine and guaifenesin. The result of the literature search is provided in the Section 8.6 of this review.

*Reviewer comment:*

*The Applicant's search strategies and search terms are acceptable and provide an acceptable approach to identify relevant safety information on the use of hydrocodone, pseudoephedrine and guaifenesin.*

### 7.2.3 Adequacy of Overall Clinical Experience

This submission includes two single-dose clinical pharmacology studies in 60 healthy subjects. The study was small in size and provides a fairly limited amount of safety information. The efficacy and safety of the proposed drug is supported by DESI review for hydrocodone and by OTC monograph for pseudoephedrine and guaifenesin. The AERS database and literature search revealed no new safety signals for hydrocodone, pseudoephedrine and guaifenesin at proposed doses. Given the extensive experience with use of hydrocodone as an antitussive, pseudoephedrine as a nasal decongestant, and guaifenesin as an expectorant, this reviewer concludes that the overall clinical exposure to the proposed drug is adequate.

### 7.2.9 Additional Submissions, Including Safety Update

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. The Applicant submitted the required safety data with the original NDA submission. Since that time no animal studies or clinical safety studies have been conducted for the proposed drug and the proposed drug has not been manufactured and marketed. Thus, the determination of safety made during the first submission has not changed.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the clinical pharmacology studies, the number of subjects treated was small and AEs were infrequent. No new safety concerns have become apparent in the clinical pharmacology studies.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The application is for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only). The proposed drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug

combination of antitussive, decongestant and expectorant. The proposed indications are “for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4).

## 8.2 Drug-Drug Interactions

The applicant submitted literature references to address the drug-drug interaction potential of the triple combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone, pseudoephedrine and guaifenesin are administered together.

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or codeine. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The applicant’s proposed labeling appropriately addresses the potential these drug-drug interactions.

## 8.3 Special Populations

There were no studies in special populations for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution in this submission to review. The applicant’s proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. (b) (4)

(b) (4) A literature search shows a report that two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution is administered to nursing mothers. The information about the hydrocodone excreted in breast milk and the potential risks of hydrocodone use in nursing women should be added to the proposed labeling when it is considered for approval.

## 8.4 Pediatrics

The clinical pharmacology studies S09-0009 and S09-0010 included no pediatric subjects. The Applicant conducted the post-marketing adverse event search in AERS for age groups of 0 to under 18, 18 to under 35, 35 to under 50, 50 to under 65, 65 to under 80, and above 80 years. The adverse events in the 0 to 18 age groups were less than most other age groups, accounting for 2.4%, 9.6%, and 8.8% of all adverse events for hydrocodone, pseudoephedrine and guaifenesin, respectively. No pediatric subgroup analyses were conducted for the post-market adverse events for the proposed drug. The Applicant conducted the literature review that revealed no new pediatric safety concerns for hydrocodone, pseudoephedrine and guaifenesin when used for approved indications at approved doses.

On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received long-acting hydrocodone-containing cough product.

[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>,  
<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>].

Although hydrocodone is currently labeled for use in children down to 6 years of age, safety concerns regarding dose-related respiratory depression identified by the Agency over the last few years raises the question regarding the most appropriate dose for the pediatric population.

The Applicant is requesting a waiver for pediatric studies below 6 years of age, and this reviewer considers that the request for a waiver for pediatric studies below 6 years of age is appropriate. However, with regard to the pediatric patient population from 6 to under 18 years of age, based on continuing safety concerns with the use of hydrocodone-containing cough and cold products in the pediatric population, [REDACTED] <sup>(b) (4)</sup> the Applicant will need to conduct pharmacokinetic studies to determine the exposure of hydrocodone in the pediatric population (i.e. patients under 18 years of age) to provide data to guide dose selection.

## 8.6 Literature Review

The applicant performed a search of the medical literature for information relevant to hydrocodone, pseudoephedrine and guaifenesin in general. The search covered three individual active ingredient hydrocodone, pseudoephedrine, guaifenesin) for a period of two years (January 1, 2006 – June 24, 2008) and the products containing all three ingredients for a period of 10 years (January 1, 1998 – June 24, 2008). There was no new safety signal revealed through the literature search.

There were four case reports, two observational studies, five clinical trials, and one drug-drug interaction study involving hydrocodone adverse events. All four clinical trials were to study hydrocodone in different types of pain patients. All adverse events reported were consistent with what would be expected in use of any opiate (nausea, vomiting, dizziness, somnolence, constipation, etc.)<sup>1-5</sup> The drug-drug interaction study in chronic pain patients demonstrated that serum nicotine levels were negatively correlated with serum hydrocodone levels in smokers.<sup>6</sup> The observational studies and case reports were involved lethal hydrocodone intoxication cases,<sup>7</sup> traffic related deaths with hydrocodone and alcohol use,<sup>8</sup> multiple drug abuse including hydrocodone,<sup>9</sup> and breast milk hydrocodone excretion in mothers taking prescribed hydrocodone for pain.<sup>10</sup>

There were eight case reports, two observational studies and ten clinical trials involving pseudoephedrine adverse events. There were reported death cases related to multiple drug intoxication including pseudoephedrine.<sup>11</sup> A report of 15 deaths of children younger than 17 months involved OTC medications containing pseudoephedrine.<sup>12</sup> The reported adverse events related to pseudoephedrine use included insomnia, hypertension,<sup>13</sup> two case of myocardial

Clinical Review, Xu Wang, M.D., Ph.D.

NDA 22-279, N-019, Resubmission/Class 2, 07/26/2010, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)

infarction,<sup>14</sup> and a case of transient ischemic attack.<sup>15</sup> It appears that these serious adverse events involved serious diseases and other concomitant treatments.

There were no reported adverse events related to guaifenesin use. There were no studies related to safety of products containing all three ingredients. The literature search revealed no new safety signals for hydrocodone, pseudoephedrine and guaifenesin.

#### Reference

1. Adams EH, Breiner S, Cicero TJ, et al. *J Pain Symptom Manage.* May 2006;31(5):465-476
2. Chelly JE, Nissen CW, Rodgers AJ, et al. *Curr Med Res Opin.* Jan 2007 ;23(1):195-206
3. Church CA, Stewart CT, et al. *Laryngoscope.* April 2006;116(4):602-606
4. Hewitt DJ, Todd KH, Xiang J, et al. *Am Emerg Med.* April 2007;49(4):468-480
5. Rodriguez RF, Bravol LE, Castro F, et al. *J Palliat Med.* Feb 2007 ;10(1) :56-60
6. Ackerman WE, Ahmad M. *J Ark Med Soc.* July 2007;104(1):19-21
7. Baker DD, Jenkins AJ. *J Anal Toxicol.* March 2008;32(2):165-171
8. Schwilke EW, Sampario MI. et al. *J Forensic Sci.* Sept 2006;51(5):1191-1198
9. Kyle PB, Daley WP. *J Anal Toxicol.* Sept 2007;31(7):415-418
10. Anderson PO, Sauberan JB, Lane JR, et al. *Breastfeeding Med* March 2007;2(1):10-14
11. Carson HJ. *Legal Med.* 2008;10(2):92-95
12. Wingert WE, Mundy LA, Collins GL, et al. *J Forensic Sci.* March 2007;52(2):487-490
13. Latte J, Taverner D. *Am J Rhinol.* 2007;21(4):452-455
14. Biyik I, Ergene O. *Can J Cardiol.* March 2006;22(3):254-256
15. Profice P, Pilato F, Michetti F, et al. *Acta Neurol Scand.* Nov 2006 ;114(5) :358-359

## 8.7 Postmarketing Risk Management Plan

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The risk associated with Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only) is expected being similar to the risks of other hydrocodone-containing antitussives. The Controlled Substances Staff (CSS) was consulted to advise on the abuse potential for this combination product in the first review cycle. The CSS concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies (Memorandum, Consult on NDA 22-279, N000, Controlled Substance Staff, March 27, 2009). On June 12, 2009, a CDER regulatory briefing was held to discuss the need for abuse potential studies for these products. The consensus from the panel was that abuse potential assessment was not required for these combination products. These combinations are currently in Schedule III and have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The panel recommended that a post-marketing signal could trigger the need for abuse potential studies for these products.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The Applicant seeks the approval of an immediate release oral solution formulation of hydrocodone, pseudoephedrine, and guaifenesin. The product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4)

Guaifenesin and pseudoephedrine are OTC monograph drugs, being considered to be generally recognized as safe and effective (GRASE) in specified doses as an expectorant and an oral nasal decongestant, respectively. The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single nasal decongestant (such as pseudoephedrine) and any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

Hydrocodone, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50). However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product. The FDA has previously determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. Based on this policy, the Division has approved drug development programs for HC and OTC monograph product combinations, concluding that a drug development plan does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the efficacy and safety of the combination product.

The application consists of a clinical pharmacology program. No clinical efficacy studies were submitted to support this application. The clinical pharmacology studies submitted in this application are not adequate to support approval of this application because this study does not fulfill the bioavailability criteria for combination products as per 21 CFR 320.25 (g). Specifically, the guaifenesin component of the proposed product is not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence).

The safety data from the clinical pharmacology studies in adult subjects did not identify a safety signal. Because of the small number of the subjects, there was no meaningful information in differences of adverse events in gender, age, and race/ethnicity. The Applicant's search of the medical literature for safety information related to hydrocodone, pseudoephedrine and guaifenesin identified no new safety signal for adverse events.

## **9.2 Recommendation on Regulatory Action**

The Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only) has failed to meet bioequivalence criteria and I recommend that the application be given a Complete Response action.

This drug development program is a clinical pharmacology program. The clinical pharmacology studies submitted are not adequate to support this application because the studies do not fulfill the bioavailability criteria for combination products as per 21 CFR 320.25 (g). Specifically, the guaifenesin component of the proposed product is not bioequivalent to the reference drug (the 90% CI of the geometric mean ratio of C<sub>max</sub> is outside of the 80 -125% goal post for bioequivalence).

## **9.3 Recommendation on Postmarketing Actions**

No special post-marketing risk management activities are recommended at this time.

## **9.4 Labeling Review**

Proposed labeling was submitted in Physician's Labeling Rule (PLR) format. Labeling review is not conducted because the proposed product is not ready for approval in the present NDA submission.

## **9.5 Comments to Applicant**

Deficiency comments will be sent to the applicant in the complete response letter.

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

/s/  
-----

XU WANG  
01/06/2011

ANTHONY G DURMOWICZ  
01/06/2011

## SUMMARY REVIEW OF REGULATORY ACTION

Date: June 22, 2009

From: Lydia I. Gilbert-McClain, MD, FCCP  
Deputy Director, Division of Pulmonary and Allergy Products, CDER,  
FDA

Subject: Deputy Director Summary Review

NDA Number: 22-279

Applicant Name: (b) (4) /Mikhart Inc. U.S. Regulatory Agent

Date of Submission: August 22, 2008

PDUFA Goal Date: June 22, 2009

Proprietary Name: None

Established Name: Hydrocodone, Pseudoephedrine, and Guaifenesin

Dosage form: Oral solution

Strength: 2.5 mg/30 mg/200mg/5 mL

Proposed Indications: For the symptomatic relief of cough, (b) (4) nasal  
congestion and to (b) (4) loosen (b) (4) mucus (b) (4)  
(b) (4)

Action: Complete Response

### 1. Introduction

(b) (4) submitted a 505 (b)(2) new drug application (NDA 22-279) on August 22, 2008 (received on August 22, 2008, CDER stamp date) for use of a combination oral solution comprised of hydrocodone, pseudoephedrine and guaifenesin as an antitussive, nasal decongestant, and expectorant in patients (b) (4). The PDUFA due date for this application is June 22<sup>nd</sup>, 2009. The applicant cites NDA 19-111 (Tussionex, UCB Inc), NDA 05-213 (Hycodan Tablets and Syrup, ENDO Pharma), and NDA 21-441 (Advil Allergy Sinus Caplets, Whitehall-Robbins Healthcare) as references for this application.

During the review cycle the NDA was transferred to a new owner (b) (4) with Mikart Inc. as their regulatory agent. The new ownership became effective March 25<sup>th</sup>, 2009. The data submitted do not support approval of this application. Specifically, the clinical pharmacology study submitted is not adequate to support this application because this study does not fulfill the bioavailability criteria for combination products as per 21 CFR 320.25 (g), and secondly, there is no information regarding the manufacturing site that will be manufacturing the drug product. In subsequent sections of this document comments are made on the findings that have direct bearing on the decision for this application.

## 2. Background

Hydrocodone is an opioid derived from codeine that has antitussive and analgesic effects. Hydrocodone is a Schedule II narcotic under the Controlled Substance Act (21 U.S.C. 801 *et seq*) and combination products with hydrocodone and non-narcotic active ingredients are Schedule III. FDA first approved Hydrocodone for use as an antitussive on March 23, 1943 (NDA 05-213, HYCODAN, submitted by ENDO Laboratories Inc.). A subtherapeutic amount of homatropine methylbromide was later added to this product to help prevent abuse or intentional overdose. HYCODAN was reviewed under the DESI program and was found to be effective for the symptomatic relief of cough, and was classified as a new drug product for which an approved NDA was required prior to marketing [47 FR 23809, June 1, 1982]. Hydrocodone products are prescription only products [21 CFR 1306.21, 21 CFR 1308.13].

Approved applications for antitussive formulations of hydrocodone include HYCODAN syrup and tablets and their approved generic equivalents and a hydrocodone polistirex and chlorpheniramine polistirex combination suspension extended-release product (NDA 19-111), marketed as TUSSIONEX. However, there have been hundreds of unapproved hydrocodone-containing products marketed illegally as antitussives<sup>1</sup>. Such products include, but are not limited to, hydrocodone in combination with an expectorant, such as guaifenesin, or a decongestant, such as phenylephrine or pseudoephedrine.

Under the DESI review, FDA determined that hydrocodone bitartrate is a new drug. Therefore, manufacturers must have an approved application before marketing any drug product that contains hydrocodone bitartrate, or any other salt or ester of hydrocodone. In June 2006, the Agency published a final guidance for FDA staff and Industry: *Marketed Unapproved Drugs-Compliance Policy Guide* in which the Agency outlined its plan to address marketed new drugs without NDAs or ANDAs. The compliance policy guide describes how the Agency intends to exercise enforcement discretion with regard to drugs marketed in the United States that do not have the required FDA approval for marketing. To this end, FDA published a Federal Register (FR) notice of its intention to take enforcement action against illegally marketed drug products containing hydrocodone on October 1, 2007 [Docket No. 2007N-0353]. Manufacturers who wish to market a drug containing hydrocodone must obtain FDA approval of a new drug application (NDA) or an abbreviated new drug application (ANDA). Based on the FR notice, manufacturing of unapproved hydrocodone-containing products should have ceased by December 31, 2007, and shipment of currently marketed and listed unapproved hydrocodone-containing products should have ceased by March 31, 2008.

---

<sup>1</sup> Federal Register Notice October 1, 2007 Docket No. 2007N-0353

The Agency has encouraged manufacturers of these and other unapproved products to obtain approval for marketing in the United States. This NDA is one of these applications submitted to obtain marketing approval of a combination product containing hydrocodone for a cough/cold indication.

The current application is to market a combination product containing hydrocodone bitartrate (HC), pseudoephedrine hydrochloride (PSE) and guaifenesin (GU), as an immediate release oral solution containing 2.5mg, 30 mg, and 200 mg of HC, PSE, and GU per 5 mL respectively. Pseudoephedrine is a well known sympathomimetic amine used for nasal decongestion and guaifenesin is an expectorant found in many OTC cough/cold products. Both PSE and GU are listed in the OTC monograph and are permitted to be combined together (21 CFR 341.40).

Since HC is not a monograph product, clinical studies would normally be required to support a combination product containing hydrocodone and other active ingredients in order to demonstrate the contribution of each component to the combination product as required by regulation (21CFR 300.50). However, because of the prior regulatory precedent of approving Tussionex Pennkinetic (the combination of hydrocodone and chlorpheniramine) with clinical pharmacology data only, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combinations can be developed under a clinical pharmacology program only. Therefore, clinical efficacy and safety studies may not be necessary to support this combination product provided that the applicant carries out a satisfactory clinical pharmacology program.

The development program for this triple combination product was done under IND 76,365. A pre-IND meeting was held on March 26, 2007. In the Pre-IND meeting package, the sponsor proposed to provide bioavailability data for their immediate release formulation with reference to the literature as the only bioavailability study for their application. The sponsor was advised at that time that this was sufficient and no additional comments about the development program were provided to the sponsor after the IND was submitted.

During the 45-day review of the NDA submission, it was observed that the proposed formulation contains sorbitol, in significant amounts ( $\frac{(b)}{(4)}$ % w/v). Sorbitol has been found to affect the bioavailability (BA) of some compounds with low permeability in a dose-proportional manner. Therefore, the single dose BA study that was submitted to support the application would be inadequate to support approval. However, since the contents of the application were consistent with the Agency's advice to the sponsor at the pre-IND meeting, and given the Agency's commitment to work with sponsors seeking to develop HC-containing combinations for cough/cold/allergy indications, the application was filed.

The application was filed on October 21, 2008, and a 74-day filing letter was sent to the sponsor on November 3, 2008. In the 74-day letter, the Division provided the sponsor with advice on the clinical pharmacology studies that would be necessary to support the proposed product.

The Division held a teleconference with the sponsor on October 26<sup>th</sup>, 2008 to explain the clinical pharmacology study requirements outlined in the 74-day filing letter and the rationale for these study requirements. The sponsor subsequently submitted protocols for the proposed studies on January 15, 2009 (FDA receipt date January 16, 2009) and they were reviewed by the clinical pharmacology team. The Division interacted with the applicant via teleconferences to clarify protocol design issues. The proposed studies were ultimately deemed acceptable to fulfill the clinical pharmacology objectives.

### **3. CMC/Device**

The proposed product in this NDA is for an aqueous oral solution containing hydrocodone bitartrate (HC) 2.5 mg, pseudoephedrine hydrochloride (PSE) 30 mg, and guaifenesin (GU) 200 mg per 5 mL. The product will be available in 16 oz plastic HDPE bottles containing 473 ml of solution. These active substances are USP ingredients that have been previously assessed to support other NDA applications in the past. There are no unresolved DMF issues. There was a concern regarding the impurity (b)(4) in the HC in DMF (b)(4) but this was addressed by Dr. Marcus S. Delattee the pharmacology/toxicology reviewer in the Division of Anesthesia, Analgesia, and Rheumatology Products (DARRP). Thus, a separate pharm/tox consult for this impurity was not needed. The conclusion is that (b)(4) is not a genotoxic impurity.

There are no issues with the inactive ingredients which are all compendial except for the (b)(4) (FD&C red and blue) and the flavoring (raspberry flavor). The inactive ingredients include methyl- and propyl-parabens (b)(4) glycerin and water (b)(4) polyethylene glycol (b)(4) citric acid and sodium citrate (b)(4) sorbitol and saccharin (b)(4). The presence of sorbitol in the formulation is the fundamental reason for the need for additional clinical pharmacology studies (discussed later) with this solution formulation.

During the review cycle the NDA changed ownership to (b)(4), and Mikart Laboratories was identified as the new manufacturing and testing site for the drug product. There is no information about the manufacturing procedure or testing at the new site, and this issue will be listed as one of the deficiencies in the action letter.

### **4. Nonclinical Pharmacology/Toxicology**

No new non-clinical pharmacology/toxicology studies were required or performed for this application.

### **5. Clinical Pharmacology/Biopharmaceutics**

The applicant submitted the results of an open-label study in 18 healthy adult subjects in the fasted state (Study S07-0441) to compare the exposure of hydrocodone, guaifenesin, and pseudoephedrine from a single dose of an immediate release solution to the exposure of these ingredients reported in the literature and approved NDAs. The NDAs that the applicant cited

all contain pseudoephedrine as one of the active ingredients [(NDA 21-444 (Advil Allergy Sinus Caplets), NDA 21-373 (Children’s Advil® Cold Suspension), NDA 21-587 (Children’s Advil Allergy Sinus), NDA 21-128 (Children’s Motrin® Cold suspension), and NDA 21-082 (Tavist Allergy Sinus Headache)]. Of these NDAs, only NDA 21-444 (Advil Allergy Sinus Caplets) was certified by the Applicant as one of the reference NDA for this application. The Agency does not need to rely on information in the other NDAs cited in the submission. There were over 100 published articles submitted several of which include pharmacokinetic information for the individual ingredients in the proposed combination product.

The mean C<sub>max</sub> value for HC in the immediate release solution product is similar to that reported in the literature but the mean systemic exposure was about 20% higher. The mean PSE systemic exposure was about 25% higher than that reported in the literature for similar PSE doses. The study did not provide any specific comparison of the GU because there was no available AUC information for the 400 mg dose in the literature and only range data were available for the C<sub>max</sub> for GU. A summary of the open-label bioavailability data in comparison with the literature data is shown in the table below.

**Table 1. Comparative PK study S07-0441 vs. Literature information**

	PK Study S07-0441		Literature information, mean (range)	
	AUC <sub>0-inf</sub> ng/hr/mL	C <sub>max</sub> (ng/mL)	AUC <sub>0-inf</sub> ng hr/mL	C <sub>max</sub> ng/mL
HC	92.2	12.7	77.6 (59.6 -93.7)	12.7 (9.1 -16.4)
PSE	2635.9	241.5	2109 (1800 -2500)	213.2 (169.5 -236.0)
GU	2887.9	2129.7	Not available	(1600-2400)*

\* No mean data reported

The product contains sorbitol ( <sup>(b)</sup>/<sub>(4)</sub> % w/v) an osmotic sugar which can affect the bioavailability of several compounds. The concentration of sorbitol in the proposed formulation is considerably higher than the <sup>(b)</sup>/<sub>(4)</sub> % in the reference product Hycodan. Since sorbitol affects the permeability of many compounds, an assessment of the effect of food on the proposed formulation will be needed in addition to showing bioequivalence to appropriate reference products. These issues will be cited as deficiencies in the action letter; however this information was already conveyed to the sponsor during the review cycle.

## 6. Clinical Microbiology

This is a non-sterile solution and clinical microbiology is not applicable. As noted earlier, the Application was transferred to a new applicant during the review cycle and the manufacturing sites changed. Manufacturing information about the new site has not been submitted and is a deficiency in this application.

## 7. Clinical/Statistical- Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of approved reference products Hycodan and the OTC monograph products pseudoephedrine, and guaifenesin. No clinical studies were required to support the application as discussed in Section 2 (Background).

## 8. Safety

The safety of the product is based on establishing bioequivalence of the product compared to approved reference products. In addition, the applicant conducted a review of the literature (via a MEDLINE and EMBASE search), and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof, for the period from January 1, 2003 – December 31, 2007. These searches did not reveal any new safety signals. In the AERS search, the number of events which identified death as an outcome seemed high (62.15%) for hydrocodone, and OSE was consulted. The OSE consult review commented that the high percentage of deaths reported reflects a reporting bias from sources that only report fatal events associated with exposure to toxic substances, or opioid -related products. Nearly 99% of the AERS reports included the ingestion of multiple opioid-containing products and multiple adverse reactions including overdoses, suicides, polypharmacy, and polysubstance abuse. OSE concluded that these data are not indicative of a new safety signal for hydrocodone.

## 9. Advisory Committee Meeting

An advisory committee meeting was not necessary for this application. The three active ingredients present in this product are well known molecules, and as previously discussed the combination of products of these classes are accepted for the proposed indications.

## 10. Pediatrics

 (b) (4)  
the applicant requested a *partial* waiver for pediatric assessment (i.e. for patients under 6 years of age). Since the proposed product contains hydrocodone which is contraindicated for use in children under 6 years of age (because of the risk of respiratory depression) it would be appropriate to waive studies for pediatric patients less than 6 years of age. The application was not presented to PERC in this review cycle given that the action will be a complete response.

## 11. Other Relevant Regulatory Issues

### Control Substances Staff Consult

Single ingredient hydrocodone is a Schedule II controlled substance and combination products currently approved for use in the United States are placed in Schedule III. The Applicant proposed that the combination product containing hydrocodone, pseudoephedrine, and guaifenesin be placed in Schedule (b) (4)

The Controlled Substances Staff (CSS) was consulted to advise on the abuse potential and the Schedule for this combination product. The CSS staff were concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies. There are currently 5 other NDAs in the Division for hydrocodone -containing combination products for cough/cold/allergy indications and these CSS recommendations would impact all of them. Therefore, a CDER regulatory briefing was held on June 12<sup>th</sup>, 2009 to discuss the need for abuse potential studies for these products. The following questions were posed to the panel:

- 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 (*sic*) or on a case by case basis?

The consensus from the panel was that abuse potential assessment was not required for these combination products. These combinations are currently in Schedule III and have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for several years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The panel recommended that a post-marketing signal could trigger the need for abuse potential studies for these products.

### Data Quality, Integrity, and Financial Disclosure

A DSI audit was not conducted because the study that the applicant conducted cannot support approval of the NDA because of the way it is designed. There are no ethical issues present, and the study that was performed was done in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements.

### Other issues

During the review cycle, the applicant informed us that the reference product for hydrocodone listed in the NDA [Hycodan solution (NDA 05-213)] was discontinued from the market on May 14, 2008, and they were unable to obtain this reference product. The applicant was advised that they could use one of the generic hydrocodone products (ANDA 40-613 Hi-Tech Pharma or ANDA 88-008, Morton Grove) currently on the market. The applicant did not submit new clinical pharmacology studies during this review cycle.

## **12. Labeling**

### **Proprietary name**

The applicant did not submit a proprietary name for their product.

### **Physician labeling**

The applicant submitted a label in the Physician's Labeling Rule Format. Since the product will not be approved, the Division did not discuss detailed labeling language with the applicant.

### **Carton and Immediate Container Labels**

As with physician labeling, detailed review of the carton and immediate container label was not done. Preliminary carton and container labeling comments were conveyed to the applicant in a Chemistry IR during the review cycle.

### **Patient Labeling and Medication Guide**

There is no separate patient labeling and medication guide for this product

## **13. Action and Risk Benefit Assessment**

### **Regulatory action**

(b) (4) has not submitted adequate data to support approval of Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution for use as an antitussive, decongestant, and expectorant in patients (b) (4). The open-label bioavailability study submitted is inadequate to evaluate the bioequivalence, drug-drug interaction, and food effect of the proposed combination product. The proposed formulation contains sorbitol which can affect the permeability of many compounds and the applicant will need to conduct studies to establish the bioequivalence of their proposed combination product to appropriate reference products, assess drug-drug interaction, and food effect. Furthermore, (b) (4) has not provided the necessary information on the manufacturing site for the proposed product. The action on this application will be Complete Response.

### **The comments below are for the Complete Response action letter**

- 1) The single-dose, single arm, clinical pharmacology study #S07-0441 is not adequate to support this application because this study does not fulfill the bioavailability criteria for combination products as per 21 CFR 320.25 (g). The study, as designed, does not allow for comparison of the rate and extent of

absorption of each active drug ingredient in your proposed Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution to the rate and extent of absorption of each active drug ingredient administered concurrently in separate single-ingredient preparations.

- 2) Your proposed product contains sorbitol. Sorbitol has been found to affect the bioavailability of some compounds with low permeability in a dose-proportional manner. The permeability of hydrocodone, pseudoephedrine, and guaifenesin are not known and therefore, an assessment of food effect on your proposed product is necessary to support approval.
- 3) The quality information for the manufacturing site described in the application, (b) (4) cannot be used to support the quality of the drug product because, according to the amendment submitted on April 24, 2009, this site will not be used to manufacture drug product for the marketing of this drug.

These deficiencies may be addressed by doing the following:

- 1) Conduct a single-dose clinical pharmacology study to establish the bioequivalence of your proposed Hydrocodone 2.5 mg/Pseudoephedrine 30 mg/Guaifenesin 200 mg per 5 mL Oral Solution to the reference products.
- 2) Conduct a food effect study of your proposed Hydrocodone 2.5 mg/Pseudoephedrine 30 mg/Guaifenesin 200 mg per 5 mL Oral Solution under fed and fasted conditions.
- 3) Provide satisfactory quality information for the drug product manufactured at the new manufacturing site. All drug substance and drug product manufacturing sites must be in compliance with Current Good Manufacturing Practices (CGMP).

#### **Risk Benefit Assessment**

The overall risk and benefit assessment of the individual ingredients hydrocodone, pseudoephedrine, and guaifenesin does not suggest an unfavorable risk benefit for these individual ingredients. However, for this combination product, a risk benefit assessment cannot be made because the applicant has not conducted the appropriate studies to demonstrate the bioequivalence, evaluate the drug-drug interaction, and the food effect of this product in comparison to reference listed products. These data are lacking and therefore the product cannot be approved at this time.

#### **Postmarketing Risk Management Activities**

Hydrocodone is a controlled substance known to have a certain level of abuse potential. This combination product if approved will be labeled as a Schedule (b) (4) narcotic and will be available by prescription only. The abuse potential will be managed with appropriate labeling and routine pharmacovigilance.

### **Postmarketing Study Commitments**

There are no recommended postmarketing study commitments for this application.

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

/s/

-----  
Lydia McClain  
6/22/2009 03:00:40 PM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type	NDA
Submission Number	22-279
Submission Code	N-000
Letter Date	08/22/08
Stamp Date	08/22/08
PDUFA Goal Date	06/22/09
Reviewer Name	Xu Wang, M.D., Ph.D.
Review Completion Date	04/22/09
Established Name	Hydrocodone, Pseudoephedrine and Guaifenesin
(Proposed) Trade Name	Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)
Therapeutic Class	Antitussive/Decongestant/Expectorant
Applicant	(b) (4)
Priority Designation	S
Formulation	Oral solution
Dosing Regimen	For adults (b) (4) 10 mL (hydrocodone bitartrate 5 mg/pseudoephedrine hydrochloride 60 mg/guaifenesin 400 mg) every 4 hours, NTE 40 mL in 24 hours
	(b) (4)
Indication	For symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)
Intended Population	Adults (b) (4)

## Table of Contents

<b>1 EXECUTIVE SUMMARY .....</b>	<b>5</b>
<b>1 EXECUTIVE SUMMARY .....</b>	<b>5</b>
1.1 RECOMMENDATION ON REGULATORY ACTION .....	5
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS .....	5
1.2.1 Risk Management Activity.....	5
1.2.2 Required Phase 4 Commitments .....	5
1.2.3 Other Phase 4 Requests.....	6
1.3 SUMMARY OF CLINICAL FINDINGS.....	6
1.3.1 Brief Overview of Clinical Program .....	6
1.3.2 Efficacy.....	6
1.3.3 Safety .....	6
1.3.4 Dosing Regimen and Administration.....	7
1.3.5 Drug-Drug Interactions .....	7
1.3.6 Special Populations.....	8
<b>2 INTRODUCTION AND BACKGROUND.....</b>	<b>9</b>
2.1 PRODUCT INFORMATION .....	9
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	10
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES.....	11
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS .....	11
2.5 PRESUBMISSION REGULATORY ACTIVITY .....	12
<b>3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES.....</b>	<b>12</b>
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) .....	12
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY .....	13
<b>4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY .....</b>	<b>13</b>
4.1 SOURCES OF CLINICAL DATA.....	13
4.2 TABLES OF CLINICAL STUDIES .....	14
4.3 REVIEW STRATEGY .....	14
4.4 DATA QUALITY AND INTEGRITY .....	14
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES .....	14
4.6 FINANCIAL DISCLOSURES .....	14
<b>5 CLINICAL PHARMACOLOGY.....</b>	<b>15</b>
<b>6 INTEGRATED REVIEW OF EFFICACY.....</b>	<b>17</b>
6.1 INDICATION.....	17
<b>7 INTEGRATED REVIEW OF SAFETY.....</b>	<b>17</b>
7.1 METHODS AND FINDINGS.....	19
7.1.1 Deaths .....	19
7.1.2 Other Serious Adverse Events.....	20
7.1.3 Dropouts and Other Significant Adverse Events.....	20
7.1.5 Common Adverse Events.....	20
7.1.6 Less Common Adverse Events .....	21
7.1.7 Laboratory Findings.....	21
7.1.8 Vital Signs.....	21
7.1.9 Electrocardiograms (ECGs).....	21
7.1.13 Withdrawal Phenomena and/or Abuse Potential.....	21
7.1.14 Human Reproduction and Pregnancy Data .....	22
7.1.16 Overdose Experience .....	23

7.1.17 Postmarketing Experience.....	23
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS .....	23
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety .....	24
7.2.3 Adequacy of Overall Clinical Experience .....	24
7.2.9 Additional Submissions, Including Safety Update.....	24
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS .....	25
<b>8 ADDITIONAL CLINICAL ISSUES.....</b>	<b>25</b>
8.1 DOSING REGIMEN AND ADMINISTRATION.....	25
8.2 DRUG-DRUG INTERACTIONS .....	25
8.3 SPECIAL POPULATIONS .....	26
8.4 PEDIATRICS.....	26
8.6 LITERATURE REVIEW .....	27
8.7 POSTMARKETING RISK MANAGEMENT PLAN.....	28
<b>9 OVERALL ASSESSMENT .....</b>	<b>28</b>
9.1 CONCLUSIONS .....	28
9.2 RECOMMENDATION ON REGULATORY ACTION .....	29
9.4 LABELING REVIEW.....	30
9.5 COMMENTS TO APPLICANT.....	31

**Table of Tables**

Table 1 Summary of Study S07-0441.....	14
Table 2 Study S07-0441, formulation of Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution.....	15
Table 3 Pharmacokinetics results, Study S07-0441.....	16
Table 4 Comparison of PK, Study S07-0441 and published data .....	16
Table 5 Post-marketing adverse events (AERS database, Jan. 1, 2003 to Dec. 31, 2007, incidence >3%).....	19

## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

The Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only) is not ready for approval in the present NDA submission and I recommend that the application be given a Complete Response Action.

This drug development program is a clinical pharmacology program. The formulation of the proposed drug contains sorbitol that affects the bioavailability of the active ingredients, and clinical pharmacology studies are required to establish the bioequivalence (BE) of the proposed drug to the reference products. The present NDA submission only includes a small bioavailability study to characterize the exposure of hydrocodone, pseudoephedrine and guaifenesin in the proposed drug product compared to literature references. In the 74-day Letter issued on November 3, 2008, the Applicant was informed of the clinical pharmacology studies needed to support the new drug product. During this review cycle, the Applicant submitted study protocols to start the clinical pharmacology studies. The clinical pharmacology approvability requirements for this NDA will depend on the review of the new clinical pharmacology data that have not been submitted yet.

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The Controlled substances Staff noted in their recommendation that the applicant needs to fully characterize the abuse potential of the combination product specifically to evaluate how the addition of the non-narcotic 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 Controlled Substances Act (CSA). At the time of finalization of this primary review, it has not been decided whether this recommendation will be an approvability issue or this assessment could be completed as a post marketing commitment.

### **1.2 Recommendation on Postmarketing Actions**

#### **1.2.1 Risk Management Activity**

No special post-marketing risk management activities are recommended at this time. It is unclear if the recommendation from the CSS of the need to assess the abuse potential of this combination product will ultimately result in special post-marketing risk management activities.

#### **1.2.2 Required Phase 4 Commitments**

No special Phase 4 commitments are recommended at this time since the recommended regulatory action is Complete Response.

### 1.2.3 Other Phase 4 Requests

There are no Phase 4 requests for this application.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

This is a clinical pharmacology program. The Applicant included one clinical pharmacology study in the NDA submission. The clinical pharmacology study S07-0441 is an open-label bioavailability study designed to characterize the exposure of hydrocodone, pseudoephedrine and guaifenesin from a single dose of 10 mL immediate release oral solution containing 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin under fasting condition in 18 healthy adult subjects compared to exposure data of the individual ingredients from literature reports.

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology study S07-0441, a search of the AERS database for post-marketing spontaneous adverse events, and a literature survey to provide support for the safety of the proposed drug product.

### 1.3.2 Efficacy

No clinical efficacy studies were submitted to support this application. This is a 505(b)(2) application using clinical pharmacology studies to support approval. The Agency's previous findings of efficacy and safety of approved hydrocodone products (Hycodan Syrup and Tablets, NDA 5-213) and the OTC monograph for pseudoephedrine and guaifenesin are being used to substantiate the efficacy and safety of this triple combination product.

### 1.3.3 Safety

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology study S07-0441, post-marketing spontaneous adverse events report, and a literature survey. Safety was assessed through adverse events recording and vital signs in Study S07-0441. The safety data from this clinical pharmacology study in adult subjects did not identify a safety signal. Study S07-0441 was conducted in 18 adult subjects. Five subjects reported 8 adverse events (3 dizziness, 2 nausea, 2 headaches, and 1 fatigue). These adverse events were mild in nature and spontaneously resolved without special treatment. The safety data from the clinical pharmacology study in adult subjects did not identify a safety signal.

The post-marketing adverse events from the AERS database covered the period from January 1, 2003 through December 31, 2007. The AERS database search using combinations hydrocodone plus pseudoephedrine plus guaifenesin (HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The search included the generic names and the trade name

medications obtained from internet sites. Combination products containing antihistamines were excluded from the search result. There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The Applicant searched MEDLINE and EMBASE for the medical literature relevant to safety of hydrocodone, pseudoephedrine and guaifenesin. The literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years. The Applicant's search of the medical literature for safety information related to hydrocodone, pseudoephedrine and guaifenesin identified no new safety signals.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the test drug and the test drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the test drug.

#### 1.3.4 Dosing Regimen and Administration

The application is for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only). The proposed drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed indications are "for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4).

#### 1.3.5 Drug-Drug Interactions

The applicant submitted literature references to address the drug-drug interaction potential of the triple combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone, pseudoephedrine and guaifenesin are administered together. In the 74-day letter to the applicant (November 3, 2008) the Applicant was informed that the claim of lack of DDI based on the literature information will be a review issue. The primary clinical pharmacology review recommends an *in vivo* clinical pharmacology study to address the potential of DDI of the three active ingredients HC, PSE, and GU and the formulation effect because the test drug formulation contains a significant amount ( (b) (4) % w/v) of sorbitol that has been found to affect the bioavailability of some compounds with low permeability in a dose-proportional manner [74-dayLetter, November 3, 2008]. The Applicant subsequently submitted a DDI study protocol for the proposed drug. More information regarding the recommended clinical pharmacology studies can be found in the Clinical Pharmacology Review, IND 76365, Sandra Suarez-Sharp, Ph. D., January 18, 2009. The Applicant has not yet submitted the result of the proposed DDI study for review.

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The Applicant's proposed labeling appropriately addresses the potential for these drug-drug interactions.

### 1.3.6 Special Populations

There were no studies in special populations for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution in this submission to review. The Applicant's proposed labeling indicates that the drug product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. (b) (4)

A literature search shows a report of two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution is administered to nursing mothers. The information about the hydrocodone excreted in breast milk and the potential risks of hydrocodone use in nursing women should be added to the proposed labeling when it is considered for approval.

*Reviewer comment:*

*On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received a long-acting hydrocodone-containing cough product.*

*[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>,*

*<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>].*

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The Applicant has developed an immediate release oral solution formulation of hydrocodone, pseudoephedrine and guaifenesin. The drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed labeled indications are “for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4). The sponsor’s proposed na

Hydrochloride and Guaifenesin Oral Solution (Rx Only). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4).

(b) (4) The Applicant has provided a paper submission.

Hydrocodone (HC) is a commonly used antitussive. The safety and effectiveness of HC as a prescription drug for the symptomatic relief of cough are supported by DESI review and by the FDA approved product Hycodan (NDA 5-213). HC is an opioid, a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in combination with active non-narcotic ingredients and if the product contains not more than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15).

Hycodan Tablets and Syrup (HC 5 mg plus homatropine methylbromide (HTM) 1.5 mg, and HC 5 mg plus HTM 1.5 mg per 5 mL, NDA 5-213) was classified in the DESI review as safe and effective for prescription drug for the symptomatic relief of cough (DESI Notice #5123). The approved dosages are:

- Adults: One tablet or one teaspoonful of the syrup (5 mg HC) every 4 to 6 hours as needed; not to exceed (NTE) 6 tablets or 6 teaspoonfuls (30 mg HC) in 24 hours
- Children 6 to 12 years of age: One-half (1/2) tablet or one-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 tablets or 3 teaspoonfuls (15 mg HC) in 24 hours
- Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age is contraindicated due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic product labeling].

Pseudoephedrine (PSE) is considered to be GRASE as an oral nasal decongestant [21 CFR 341.20] in the following age groups at the following oral doses [21 CFR 341.80(d)]:

- Adults and children 12 years of age and over: 60 mg every 4 to 6 hours NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 to 6 hours NTE 120 mg in 24 hours

- Children 2 to under 6 years of age: 15 mg every 4 to 6 hours NTE 60 mg in 24 hours
- Children under 2 years of age: consult a doctor

Guaifenesin (GU) is considered to be generally recognized as safe and effective (GRASE) as an expectorant [21 CFR 341.18] in the following age groups at the following oral doses [21 CFR 341.78]:

- Adults and children 12 years of age and older: 200 to 400 mg every 4 hours, NTE 2400 mg in 24 hours
- Children 6 to under 12 years of age: 100 to 200 mg every 4 hours, NTE 1200 mg in 24 hours
- Children 2 to under 6 years of age: 50 to 100 mg every 4 hours, NTE 600 mg in 24 hours
- Children under 2 years of age: consult a doctor

The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single nasal decongestant (such as pseudoephedrine) and any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

*Reviewer comment:*

*Hydrocodone, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50).*

*However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product, which can be found in detail in Medical Officer Review, IND <sup>(b) (4)</sup> M-001, MR, Charles E. Lee, M.D., 9/25/2006. Briefly, during the FDA deliberations on the approvability of Tussionex Pennkinetic extended release suspension (NDA 19-111) at the Center Level the FDA determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. The development program for Tussionex Pennkinetic was comprised of 3 bioavailability studies and no clinical studies. Based on this prior precedent, the Division has accepted the conclusion that for a HC combination product containing monograph active ingredients, a drug development plan does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the efficacy and safety of the combination product, and that approval can be based on establishment of bioequivalence.*

## **2.2 Currently Available Treatment for Indications**

Hydrocodone is currently approved in the United States in tablet and syrup as an immediate release antitussive drug (Hycodan, NDA 5-213). During the review cycle, the Division became aware that the manufacturer for Hycodan syrup and tablets, Endo Pharmaceuticals, had withdrawn the products voluntarily not because of reasons of safety or efficacy. The company keeps the NDA 5-213 current, but stopped manufacturing and marketing the Hycodan Tablets and Solution on January 4 and May 14, 2008, respectively. Hydrocodone is also approved in

combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111).

There are other generic Hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussionex (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). Pseudoephedrine and guaifenesin are readily available OTC monograph drugs, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph doses for the temporary relief of nasal congestion, and to help loosen phlegm (mucus) and thin bronchial secretions.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Hydrocodone is currently available in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111) and generic antitussive drugs Hydrocodone Compound (ANDA 88017), Tussicaps (ANDA 77273), Tussionex (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). In addition, hydrocodone is available in the United States in tablet and capsule formulations as analgesic medications at higher doses than antitussives, such as Vicoprofen (NDA 20716), Vicodin and Vicodin HP (ANDA 88058, ANDA 40117), Lortab (ANDA 40100, ANDA 87722), and Anexsia (ANDA 40405, ANDA 40409, ANDA (b) (4) ANDA 40686, ANDA 89160). There have been multiple illegally marketed hydrocodone-containing products in the U.S. market. The FDA has announced its intention to take enforcement actions against unapproved drug products containing hydrocodone bitartrate if such drug products are manufactured and marketed on or after October 31, 2007 [Federal Register Vol. 72, No 189, October 1, 2007].

Pseudoephedrine is currently approved in the United States in tablet (Afrinol, NDA 18-191), in combination with chlorpheniramine (Chlor-Trimeton, NDA 18-397), with ibuprofen and chlorpheniramine (Advil Allergy Sinus Caplet, NDA 21-441), and with guaifenesin (Mucinex<sup>TM</sup> D, NDA 21-585). These products are extended release formulations. Pseudoephedrine is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

Guaifenesin is currently approved in the United States in tablet (Mucinex ER, NDA 21-282), in combination with dextromethorphan (Mucinex<sup>TM</sup> DM, NDA 21-620), and with pseudoephedrine (Mucinex<sup>TM</sup> D, NDA 21-585). These products are extended release formulations. Guaifenesin is also available in the United States in immediate release formulations and is considered to be GRASE at OTC monograph doses.

### **2.4 Important Issues With Pharmacologically Related Products**

Hydrocodone is a semi-synthetic opioid that has the potential for abuse. Dependence and tolerance may develop upon repeated administration. Hydrocodone is a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in

combination with active non-narcotic ingredients and if the product contains not more than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15).

Pseudoephedrine is an OTC monograph drug of oral nasal decongestant [21 CFR 341.20]. Pseudoephedrine can be unlawfully used to make the illicit drug methamphetamine. The Combat Methamphetamine Act restricts the access of pseudoephedrine by requiring retailers to place OTC drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase.

## 2.5 Presubmission Regulatory Activity

The Applicant had a pre-IND meeting on March 26, 2007 with the Division to discuss the plans to develop two immediate release oral solutions of hydrocodone and guaifenesin and hydrocodone, pseudoephedrine and guaifenesin. The formulations for the proposed drugs were not provided in the briefing package. The Applicant submitted an opening IND on September 25, 2007 for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (IND 76,365). The opening IND study was a single-dose bioavailability study that was determined safe to proceed. The Applicant filed a 505(b)(2) NDA for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution on August 22, 2008. During the 45-day filing review period, the Clinical Pharmacology review team found that the formulation of the proposed drug contains sorbitol. Sorbitol has been found to affect the bioavailability of some compounds with low permeability in a dose-proportional manner. Therefore, clinical pharmacology studies are required to establish the bioequivalence (BE) of the proposed drug to the reference. The clinical pharmacology team also indicated that the Applicant needed to evaluate the potential drug-drug interaction (DDI) between the active ingredients, and to determine the effect of food on the bioavailability the active ingredients [74-day Letter, November 3, 2008]. The Applicant subsequently submitted protocols for three clinical pharmacology studies to evaluate the BE, DDI and food effect of the proposed drug. More information regarding the three clinical pharmacology studies can be found in the Clinical Pharmacology Review, IND 76365, Sandra Suarez-Sharp, Ph. D., January 18, 2009.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 3.1 CMC (and Product Microbiology, if Applicable)

The drug product is an oral aqueous solution containing hydrocodone bitartrate USP 2.5 mg, pseudoephedrine hydrochloride USP 30 mg, and guaifenesin 200 mg per USP 5 mL. This is an immediate release formulation. The excipients in the test formulation include sorbitol, glycerin, polyethylene glycol, methylparaben, propylparaben, citric acid, sodium citrate, saccharin, D&C Red #33 and FD&C Blue (b)(4) black raspberry flavor. The proposed combination drug is manufactured by the Applicant, (b)(4)

Hydrocodone bitartrate USP used in the rest formulation was manufactured (b) (4)

Pseudoephedrine hydrochloride USP used in the rest formulation was manufactured by (b) (4)

Guaifenesin USP used in the test formulation was manufactured by (b) (4)

(b) (4)

The Applicant, (b) (4) informed the Agency in a facsimile dated April 15, 2009, that the ownership of NDA 22-279 has been transferred to (b) (4). The new ownership of the NDA was effective on March 25, 2009. The proposed drug product will be manufactured by a new contractor that has not been announced by the new owner of this NDA.

A detailed review of the CMC portion of the application may be found in the ONDQA review [NDA 22-279 N-000, ONDQA Review, Prasad Peri, Ph.D.].

### 3.2 Animal Pharmacology/Toxicology

No new animal data or toxicology data were submitted. No new pre-clinical toxicology studies were required or performed for this application.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

The application was submitted under Section 505(b)(2) of the Food, Drug & Cosmetic Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of approved or OTC monograph reference products. This application relies on a comparison of the bioavailability of the proposed drug product to the published data (package insert or summary for approval of reference products). The applicant's drug development program for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution is based on establishing that their combination product produces exposures that are equivalent to that of approved and marketed products for hydrocodone and to that of OTC monograph doses of pseudoephedrine and guaifenesin. This application refers to one clinical pharmacology study S07-0441. There were no clinical efficacy or safety studies in this application.

## 4.2 Table of Clinical Studies

The Applicant has submitted the results from Study S07-0441, a single-dose bioavailability study, to characterize the exposure of hydrocodone, guaifenesin, and pseudoephedrine immediate release solution in fasted, healthy, adult subjects. The study in this application is summarized below in Table 1.

**Table 1. Summary of Study S07-0441**

Study number	Study type	Treatment group	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects	Materials submitted
S07-0441	Bioavailability	HC 5mg/ PSE60mg/ GU400mg	Single dose	Open label, single dose	18	Healthy males and females, 19-55 yrs	Study report

## 4.3 Review Strategy

This is a review of the safety data from Study S07-0441, and of the data from AERS database for post-marketing and spontaneous adverse event reports and the literature review for hydrocodone, pseudoephedrine and guaifenesin.

## 4.4 Data Quality and Integrity

Not applicable. There was no DSI audit conducted for the study site or data analyses.

## 4.5 Compliance with Good Clinical Practices

The clinical pharmacology study in this application was conducted in accordance with Good Clinical Practices. The applicant certified that the clinical contractor complied with all applicable federal, state and local laws, codes, regulations, and orders, including, but not limited to, the Federal Food, Drug, and Cosmetic Act and regulations promulgated there under, and Institutional Review Board requirements relative to clinical studies [Volume 5.1, Section 5.3.1.1 page 13].

## 4.6 Financial Disclosures

The applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The Applicant stated that the clinical investigator of the clinical pharmacology study in this application certified that he did not have a proprietary interest in the proposed product or a significant equity in the applicant. The clinical investigator also certified that he was not a recipient of significant payments [Volume 1.1, Section 1.3.4, pages 1-2].

## 5 CLINICAL PHARMACOLOGY

There was one clinical pharmacology study in the submission. A summary of data from the Applicant's clinical pharmacology study follows below. Detailed information can be found in the Clinical Pharmacology Review [NDA 22-279, N-000, Clinical Pharmacology Review, Sandra Suarez-Sharp, Ph. D.].

The formulation of Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution is displayed in Table 2. The experimental formulation is manufactured and supplied by (b) (4) [Volume 2.1, Section 2.7, page 20].

**Table 2. Study S07-0441, formulation of Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution**

Ingredient	% w/v	mg/5 mL	g/liter
Hydrocodone bitartrate USP	0.05	2.5	0.50
Guaifenesin USP	4.00	200	40.00
Pseudoephedrine hydrochloride USP	0.60	30	6.00
Sorbitol (b) (4) USP	(b) (4)		(b) (4)
Glycerine USP			
Polyethylene glycol (b) (4) NF			
Methylparaben NF			
Propylparaben NF			
Citric acid (b) (4) USP			
Sodium citrate (b) (4) USP			
Saccharin sodium			
D & C red #33			
FD & C blue #1			
(b) (4) black raspberry flavor (b) (4)			
Purified water USP			

Study S07-0441 was an open-label bioavailability study designed to characterize the exposure of hydrocodone, guaifenesin, and pseudoephedrine from a single dose of 10 mL of an immediate release oral solution of 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin under fasting condition in 18 healthy adult subjects.

Eighteen male and female healthy volunteers aged 19 to 55 years old were recruited. Subjects were screened 4 weeks prior to study start. At screening each subject had medical history, complete physical examination, laboratory tests including blood counts, serum electrolytes, liver and renal functions, drugs of abuse, pregnancy test for females, and ECG. Exclusion criteria included alcoholism and drug abuse, malignancy or other serious medical problems, history of asthma treatment within the past 5 years, history of body piercing or tattoos within the past 30 days, history of hypersensitivity to test drugs, receipt of any prescription drug (except contraceptives for females) within 14 days, receipt of any OTC medications (except multivitamins) within 7 days, females who were pregnant or lactating. After an over night fast for at least 10 hours, each subject received 10 mL Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only). Blood samples for PK determination were taken immediately before dosing (0 hours), and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours and analyzed for plasma hydrocodone, pseudoephedrine and guaifenesin (up to 4 hrs only). Subjects were confined to the clinic until

after the hour 24 sample was obtained, and returned to the clinic for the hour-36 blood collection. Safety evaluation includes adverse events and vital signs monitoring during the study.

Table 3 shows the PK measurement of the study S07-0441. The study is a single dose PK study without comparators, and the Applicant compared their PK results to the literature PK data (Table 4). The comparison shows that the mean systemic exposures (AUC) to HC and PSE (b) (4) for the proposed drug product (b) (4) ng\*hr/mL and (b) (4) ng\*hr/mL, for HC and PSE, respectively) compared to the data obtained from published literature (77.64 ng\*hr/mL and 2109 ng\*hr/mL for HC and PSE, respectively). No published information was provided on the AUC of GU.

**Table 3. Pharmacokinetics results, Study S07-0441 [Volume 2.1, Section 2.7, page 16 – 17]**

PK parameters	AUC <sub>0-inf</sub> (ng·hr/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	t <sub>1/2</sub> (hr)
HC Mean	(b) (4)			
SD				
90% CI				
PSE Mean				
SD				
90% CI				
GU* Mean				
SD				
90% CI				

\*Guaifenesin PK parameters measured up to 4 hours post-dosing.

**Table 4. Comparison of PK, Study S07-0441 and published data**

	PK, Study S07-0441, mean				PK, from literature, mean (range)			
	AUC <sub>0-inf</sub> ng·hr/mL	C <sub>max</sub> ng/mL	T <sub>max</sub> hr	t <sub>1/2</sub> hr	AUC <sub>0-inf</sub> ng·hr/mL	C <sub>max</sub> ng/mL	T <sub>max</sub> hr	t <sub>1/2</sub> hr
HC	(b) (4)							
PSE								
GU								

\* Guaifenesin PK parameters measured up to 4 hours post-dosing.

*Reviewer comment:*

*This drug development program is a clinical pharmacology program. The Applicant had a pre-IND meeting on March 26, 2007 with the Division to discuss the plans to develop two immediate release oral solutions of hydrocodone and guaifenesin and hydrocodone, pseudoephedrine and guaifenesin. The formulations for the proposed drugs were not provided in the briefing package. Based on the available information the Division agreed that a small bioavailability study is sufficient [Meeting Minutes, Pre-IND 76365, April 11, 2007]. The Applicant submitted an opening IND on September 25, 2007 for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (IND 76,365). The opening IND study was a single-dose bioavailability study that was determined safe to proceed. The Applicant filed a 505(b)(2) NDA for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution on August 22, 2008. The Clinical Pharmacology review team found that the formulation of the proposed drug contains sorbitol that affects the bioavailability of some compounds with low permeability in a dose-proportional manner. Therefore, clinical pharmacology studies are required to establish the bioequivalence (BE) of the proposed drug to the reference. The Applicant was also asked to*

*evaluate the potential drug-drug interaction (DDI) between the active ingredients and to determine the effect of food on the bioavailability the active ingredients [74-day Letter, November 3, 2008]. The Applicant subsequently submitted protocols for three clinical pharmacology studies to evaluate the BE, DDI and food effect of the proposed drug. More information regarding the proposed clinical pharmacology studies can be found in Clinical Pharmacology Review, IND 76365, by Sandra Suarez-Sharp, Ph. D., January 18, 2009. The results of the proposed clinical pharmacology studies have not been submitted yet.*

## 6 INTEGRATED REVIEW OF EFFICACY

This application is supported by comparison of the bioavailability of the proposed drug product to the pharmacokinetic data obtaining from published literature of approved hydrocodone products (Hycodan Syrup and Tablets) and OTC monograph drug pseudoephedrine and guaifenesin. No clinical efficacy studies were conducted to support this application.

### 6.1 Indication

The proposed indication for this product follows below:

Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only) is for symptomatic relief of cough, (b) (4) of nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)

## 7 INTEGRATED REVIEW OF SAFETY

The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology study S07-0441, post-marketing spontaneous adverse events report, and literature survey. The safety was assessed through adverse events and vital signs in Study S07-0441. The safety data from this clinical pharmacology study in adult subjects did not identify a safety signal. Study S07-0441 was conducted in only 18 subjects, and the adverse event data from the study is not enough to evaluate the association of adverse events and gender or race/ethnicity.

The post-marketing adverse event reports from the search result of AERS database covering the period from January 1, 2003 through December 31, 2007, and a brief literature review for safety of hydrocodone, pseudoephedrine, and guaifenesin [Volume 2.1, Section 2.7.4, pages 34 – 44]. The Applicant also submitted 2 volumes of compiled published literature references related to the safety of their product [Volume 5.8 – 5.9, Section 5.4.2].

The Applicant conducted an AERS database search using combinations hydrocodone plus pseudoephedrine plus guaifenesin (HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The search included the generic names and the trade name medications obtained from internet sites. Combination products containing antihistamines were excluded from the search result. The presence or absence of acetaminophen was disregarded. The AEs reported from the USA were included.

The Applicant searched MEDLINE and EMBASE for the medical literature relevant to safety of hydrocodone, pseudoephedrine and guaifenesin. The literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years. The Applicant's search of the medical literature for safety information related to hydrocodone, pseudoephedrine and guaifenesin identified no new safety signals.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the test drug and the test drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the test drug.

## 7.1 Methods and Findings

Table 5 summarizes the results of the AERS search covering the period from January 1, 2003 through December 31, 2007. The adverse events with an incidence >3% are listed.

**Table 5. Post-marketing adverse events (AERS database, Jan. 1, 2003 to Dec. 31, 2007, incidence >3%)**

Search term*	HC/PSE/GU (%)	HC/PSE (%)	HC/GU (%)	HC (%)	PSE (%)	GU (%)
Total (n) AEs	2	3	12	3744	2782	125
Serious AEs <sup>#</sup>	0	0	6 (50.0)	3161 (84.43)	333 (11.97)	85 (68.0)
Death	0	0	5 (41.67)	2327 (62.15)	194 (6.97)	19 (15.20)
Completed suicide	0	0	0	939 (25.08)	65 (2.34)	2 (1.60)
Multiple drug overdose	0	0	1 (8.33)	860 (22.97)	29 (1.04)	5 (4.00)
Overdose	0	1 (33.3)	1 (8.33)	502 (13.41)	97 (3.49)	5 (4.00)
Cardiorespiratory arrest		0	1 (8.33)	332 (8.87)	30 (1.08)	2 (1.60)
Drug toxicity	0	0	1 (8.33)	314 (8.39)	77 (2.77)	0
Drug abuser	0	0	0	230 (6.14)	-- <sup>\$</sup>	1 (0.80)
Respiratory arrest	0	0	0	215 (5.74)	29 (1.04)	1 (0.80)
Vomiting	1 (50.0)	0	1 (8.33)	167 (4.46)	61 (2.19)	5 (4.00)
Nausea	0	0	1 (8.33)	161 (4.30)	167 (6.00)	8 (6.40)
Medical error	0	0	1 (8.33)	158 (4.22)	47 (1.69)	13 (10.40)
Increased drug level	0	0	0	154 (4.11)	35 (1.26)	1 (0.80)
Coma	0	0	1 (8.33)	147 (3.93)	37 (1.33)	3 (2.40)
Somnolence	0	0	0	145 (3.87)	0	2 (1.60)
Drug ineffective	0	0	1 (8.33)	137 (3.66)	224 (8.05)	4 (3.20)
Anxiety	1 (50.0)	0	0	44 (1.18)	40 (1.44)	7 (5.60)
Dyspnea	0	1 (33.3)	0	51 (1.36)	68 (2.44)	3 (2.40)
Vision blurred	0	1 (33.3)	0	0	41 (1.47)	0
Loss of consciousness	0	0	1 (8.33)	88 (2.35)	45 (1.62)	7 (5.60)
Insomnia	0	0	0	39 (1.04)	122 (4.39)	3 (2.40)
Dizziness	0	0	0	59 (1.58)	98 (3.52)	10 (8.00)
Headache	0	0	0	54 (1.44)	163 (5.86)	6 (4.80)
Convulsion	0	0	1 (8.33)	60 (1.60)	40 (1.44)	10 (8.00)
Abdominal pain	0	0	1 (8.33)	47 (1.26)	63 (2.26)	6 (4.80)

\* The version of the MedDRA used in searching the database is not specified.

# Serious adverse events include deaths, life threatening, hospitalization, and disabilities.

\$ The term "drug abuser" was not on the list of terms in PSE report.

(Source: Volume 5.9, Section 5.3.1.2, page 128-134, 157-162)

### 7.1.1 Deaths

There was no death in the clinical pharmacology study S07-0441 in this application.

In searching AERS database covering the period from January 1, 2003 through December 31, 2007, there were 6,668 adverse event reports with 2,545 deaths (38.17%) for the search terms of hydrocodone plus pseudoephedrine plus guaifenesin HC+PSE+GU), hydrocodone plus pseudoephedrine (HC+PSE), hydrocodone plus guaifenesin (HC+GU), hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GU). The most death reports (2,327) came from searching with hydrocodone, accounting for 62.15% of the adverse event reports (3,744). The four most commonly reported adverse event terms were completed suicide (25.08%, 939/3,744),

multiple drug overdose (22.97%, 860/3,744), overdose (13.41%, 502/3,744), and cardiorespiratory arrest (8.87%, 332/3,744). Noticeably, the overall adverse events and death reports for hydrocodone did not differentiate if the hydrocodone was taken as antitussive doses or as much higher analgesic doses. Because the data reflect a large fraction of suicide and overdoses, the dosage forms of hydrocodone for the deaths and adverse events were most possibly higher than doses as an antitussive. There were 194 and 19 death reports for pseudoephedrine and guaifenesin, respectively. The data also reflect a large portion of suicide and overdoses.

*Reviewer comment:*

*The AERS database search shows the death rate is high in the AE reports for hydrocodone. The death reports reflects a large fraction of suicide and overdoses reported for hydrocodone use. Also, hydrocodone is known to be used in symptomatic treatment for many end stage diseases. Without the knowledge of dosage forms, diseases, co-administered medications, a simple search of AERS, a spontaneous post-marketing adverse event reporting database, does not provide meaningful safety information for hydrocodone use. The OSE consult has been requested to evaluate the AERS data regarding the high incidence of death reports related to hydrocodone use.*

#### 7.1.2 Other Serious Adverse Events

There was no serious adverse event in the clinical pharmacology study in this application.

The search of the AERS database covering the period from January 1, 2003 through December 31, 2007 does not identify new safety signals for hydrocodone, pseudoephedrine and guaifenesin.

#### 7.1.3 Dropouts and Other Significant Adverse Events

There was no dropout or withdrawal from the clinical pharmacology study S07-0441 due to adverse events. There was no significant adverse event in the clinical pharmacology study in this application.

#### 7.1.4 Other Search Strategies

No other search strategies were used in this application.

*Reviewer comment:*

*In 74-day letter, the Applicant was informed to provide safety information from WHO adverse event database and international regulatory actions for the proposed drug. The Applicant has not provided the information requested.*

### 7.1.5 Common Adverse Events

In the clinical pharmacology study S07-0441, there were 5 subjects reported 8 adverse events (3 dizziness, 2 nauseas, 2 headaches, and 1 fatigue). These adverse events were mild in nature and spontaneously resolved without special treatment.

The case report review revealed that all 5 subjects reported adverse events were females aged 27 to 42 years old. There were 3 white, one was an African American, and one was an Asian.

*Reviewer comment:*

*These data do not identify a safety signal. Because of the small number of the subjects, there was no meaningful information in differences in adverse events in gender, age, and race/ethnicity.*

### 7.1.6 Less Common Adverse Events

Adverse events occurring in the clinical pharmacology study in adults are reviewed in Section 7.1.5. Less common adverse events did not suggest a safety signal.

### 7.1.7 Laboratory Findings

Laboratory examinations were not safety endpoints in the clinical pharmacology study of this application.

### 7.1.8 Vital Signs

Vital sign assessments were conducted before and the end of the clinical pharmacology study. No clinically significant changes from baseline data were reported.

### 7.1.9 Electrocardiograms (ECGs)

ECGs were not safety endpoints in the clinical pharmacology study of this application.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. Adams EH, Breiner S, Cicero TJ, et al. reported a 12-month study in chronic pain patients that showed an abuse rate of 1.2% for hydrocodone<sup>1</sup>. The applicant provided data regarding the drug-related ED visits in 2005, collected by the Drug Abuse Warning Network (DAWN). The data show that hydrocodone/combinations accounted for 51,225 (6.27%) of the 816,696 total illicit drug-related ED visits in 2005<sup>2</sup>. Although hydrocodone dosages as an antitussive is much lower than that of analgesics and illicit drugs, hydrocodone-containing medications should be prescribed and administered with caution.

---

1 Adams EH, Breiner S, Cicero TJ, et al. J Pain Symptom Manage. May 2006;31(5):465-476

2 Manchikanti L. Pain Physician 2007;10:399-424

Pseudoephedrine is a sympathomimetic amine used as an oral nasal decongestant. It can be unlawfully used to make illicit drug methamphetamine<sup>3</sup>. The Combat Methamphetamine Act, signed into law by President Bush on March 9, 2005, restricts the access of pseudoephedrine by requiring retailers to place drug products with pseudoephedrine behind the counter, limiting a person's daily and monthly purchases, and requiring buyers' identification and signature for each purchase. The potential of unlawfully using pseudoephedrine in the proposed drug to make methamphetamine is addressed by the access restriction required in the Combat Methamphetamine Act. The proposed Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution is a prescription drug, which provides limitation to its accessibility for the unlawful use.

Controlled Substance Staff (CSS) reviewed this NDA submission. CSS concludes that the proposed drug, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution meets the statutory definition for Schedule III of the Controlled Substances Act. CSS indicates that currently available information in the public domain shows that the products containing hydrocodone alone and in combination with other substances each have an abuse potential, and the Applicant has not provided specific data in the NDA to evaluate the abuse potential of the proposed combination drug. CSS recommends that the Applicant conduct well designed animal and human studies to characterize the abuse potential of the proposed combination drug. More details can be found in the Memorandum, Consult on NDA 22-279, Controlled Substance Staff, March 27, 2009. At the time of finalization of this primary review, it has not been decided whether this recommendation will be an approvability issue or the abuse potential studies could be completed as a post-marketing commitment.

#### 7.1.14 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected in the clinical pharmacological study. The Applicant has not observed or reported adverse events associated with drug exposure during pregnancy in the post-marketing surveillance. The Applicant's proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. The Applicant searched MEDLINE database for hydrocodone and human reproduction. A report revealed 2 cases of hydrocodone excretion in breast milk<sup>4</sup>. The infants of the mothers who were taking hydrocodone received an estimated 3.1% and 3.7% of the maternal weight-adjusted dosage. The absolute hydrocodone doses the infants received were 8.58 mcg/kg and 3.07 mcg/kg per day. One infant (18-day-old) became groggy and slept for most of the day while the mother was taking 20 mg hydrocodone every 4 hours. The infant's symptoms improved when mother decrease her hydrocodone dose by half. Another infant (5-week-old) became cyanotic and required intubation while the mother was taking hydrocodone and methadone for migraine headache. The infant was positive for opioids in urinary test and responded well to naloxone treatment. There are no reports of hydrocodone in breast milk while a mother takes hydrocodone at a much lower antitussive dosage. The prescribers and patients should be aware of the potential hydrocodone excretion into breast milk and use Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution with caution.

---

<sup>3</sup> [www.streetdrugs.org](http://www.streetdrugs.org), accessed on March 5, 2009

<sup>4</sup> Anderson PO, Sauberan JB, Lane JR, et al. Breastfeeding Med March 2007;2(1):10-14

### 7.1.16 Overdose Experience

There is no overdose experience reported in the clinical pharmacological study. The applicant searched the AERS database and the result shows that 36.38% of the reported adverse events associated with hydrocodone were overdose or multiple drug overdose. In the literature review, the Applicant summarized that hydrocodone had the potential of being overdosed by self-medication and abuse, like other opioids. The AERS database search and literature review did not differentiate whether the hydrocodone was taken as antitussives or at much higher dosages as analgesics. The Applicant identified no new pattern of overdose for the ingredients of the proposed drug.

*Reviewer comment:*

*The reviewer concurs with the Applicant that there are no new concerns regarding overdose with the ingredients of their proposed drug product. The potential for abuse including overdose with hydrocodone is well recognized. The Applicant has not provided specific data in the NDA to evaluate the abuse potential of the proposed combination drug. CSS recommends that the Applicant conduct well designed animal and human studies to characterize the abuse potential of the proposed combination drug. More details can be found in the Memorandum, Consult on NDA 22-279, Controlled Substance Staff, March 27, 2009. At the time of finalization of this primary review, it has not been decided whether this recommendation will be an approvability issue or the abuse potential studies could be completed as a post-marketing commitment.*

### 7.1.17 Postmarketing Experience

The proposed drug product Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution has not been marketed. But there have been multiple illegally marketed hydrocodone-containing products in the U.S. market. The FDA has announced its intention to take enforcement actions against unapproved drug products containing hydrocodone bitartrate if such drug products are manufactured and marketed on or after October 31, 2007 [Federal Register Vol. 72, No 189, October 1, 2007]. The post-marketing experiences were obtained from AERS database search covering pseudoephedrine, guaifenesin and hydrocodone drug products, including approved and unapproved drug products containing hydrocodone as antitussives and analgesics.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

In the clinical pharmacology study S07-0441, a total of 18 healthy, adult subjects aged 19 to 55 years receive a single dose of 10 mL of an immediate release oral solution of 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin under fasting condition. There were 5 subjects who reported 8 adverse events (3 dizziness, 2 nauseas, 2 headaches, and 1 fatigue). These adverse events were mild in nature and spontaneously resolved without special treatment.

The review of the case reports revealed that all 5 subjects who reported adverse events were females aged 27 to 42 years old. Three of the subjects were white, one was an African American, and one was an Asian.

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable

### 7.2.2.3 Literature

The Applicant performed a search of the medical literature for information relevant to safety of hydrocodone, pseudoephedrine, and guaifenesin in general. The search covered three individual active ingredient hydrocodone, pseudoephedrine, guaifenesin) for two years (2006 – 2008) and the products containing all three ingredients for 10 years (1998 – 2008). The search was conducted with the MEDLINE and EMBASE database. There were no studies related to safety of products containing all three ingredients. The literature search revealed no new safety signals for hydrocodone, pseudoephedrine and guaifenesin. The result of the literature search is provided in the Section 8.6 of this review.

#### *Reviewer comment:*

*The Applicant's search strategies and search terms are acceptable and provide an acceptable approach to identify relevant safety information on the use of hydrocodone, pseudoephedrine and guaifenesin.*

## 7.2.3 Adequacy of Overall Clinical Experience

This submission includes a single-dose clinical pharmacology study in 18 healthy subjects. The study was small in size and provides a fairly limited amount of safety information. The efficacy and safety of the proposed drug is supported by DESI review for hydrocodone and by OTC monograph for pseudoephedrine and guaifenesin. The AERS database and literature search revealed no new safety signals for hydrocodone, pseudoephedrine and guaifenesin at proposed doses. Given the extensive experience with use of hydrocodone as an antitussive, pseudoephedrine as a nasal decongestant, and guaifenesin as an expectorant, this reviewer concludes that the overall clinical exposure to the proposed drug is adequate.

## 7.2.9 Additional Submissions, Including Safety Update

As noted in the Section 5 CLINICAL PHARMACOLOGY, the results of clinical pharmacology studies to establish BE of the proposed drug to the reference and to evaluate the potential DDI and food effect are to be submitted for clinical pharmacology review.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required for a NDA submission. However, there are no animal studies and clinical safety studies conducted for the proposed drug and the proposed drug has not been manufactured and marketed. The Applicant did not submit a safety update. This reviewer does not expect new safety information for the proposed drug.

### 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the clinical pharmacology study, the number of subjects treated was small and AEs were infrequent. No new safety concerns have become apparent in the clinical study.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The application is for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only). The proposed drug product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed indications are “for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4).

### 8.2 Drug-Drug Interactions

The Applicant submitted literature references to address the drug-drug interaction potential of the triple combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone, pseudoephedrine and guaifenesin are administered together. In the 74-day letter, the Applicant was informed that the claim of lack of DDI based on the literature information will be a review issue. The primary clinical pharmacology review recommends an *in vivo* clinical pharmacology study to address the potential of DDI of the three active ingredients HC, PSE, and GU and the formulation effect because the test drug formulation contains a significant amount (b) (4) % w/v) of sorbitol that has been found to affect the bioavailability of some compounds with low permeability in a dose-proportional manner [74-day Letter, November 3, 2008]. The Applicant subsequently submitted a DDI study protocol for the proposed drug. More information regarding the recommended clinical pharmacology studies can be found in the Clinical Pharmacology Review, IND 76365, Sandra Suarez-Sharp, Ph. D., January 18, 2009. The Applicant has not yet submitted the result of the proposed DDI study for review.

Use of MAO inhibitors or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or codeine. Concurrent use of opioids, antihistamines, anti-psychotics, anti-anxiety agents or other CNS depressants including alcohol concomitantly with hydrocodone may result in additive CNS depression. The applicant’s proposed labeling appropriately addresses the potential these drug-drug interactions.

### 8.3 Special Populations

There were no studies in special populations for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution in this submission to review. The applicant's proposed labeling indicates that the product is a pregnancy category C drug for the lack of adequate and well-controlled studies in pregnant women. As with other opioids, use of hydrocodone during labor can produce respiratory depression in the neonate. (b) (4)

A literature search shows a report that two infants exposed to hydrocodone through breast milk while mothers were taking hydrocodone as an analgesic. Caution should be exercised when Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution is administered to nursing mothers. The information about the hydrocodone excreted in breast milk and the potential risks of hydrocodone use in nursing women should be added to the proposed labeling when it is considered for approval.

### 8.4 Pediatrics

The Clinical pharmacology study S07-0441 included no pediatric subjects. The Applicant conducted the post-marketing adverse event search in AERS for age groups of 0 to under 18, 18 to under 35, 35 to under 50, 50 to under 65, 65 to under 80, and above 80 years. The adverse events in the 0 to 18 age groups were less than most other age groups, accounting for 2.4%, 9.6%, and 8.8% of all adverse events for hydrocodone, pseudoephedrine and guaifenesin, respectively. No pediatric subgroup analyses were conducted for the post-market adverse events for the proposed drug. The Applicant conducted the literature review that revealed no new pediatric safety concerns for hydrocodone, pseudoephedrine and guaifenesin when used for approved indications at approved doses.

On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received long-acting hydrocodone-containing cough product.

[<http://www.fda.gov/cder/drug/advisory/hydrocodone.htm>,  
<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>].

The Applicant is requesting a waiver for pediatric studies below 6 years of age, and provides the following justification for the waiver:

(b) (4)

This reviewer considers that the request for a waiver for pediatric studies below 6 years of age is appropriate.

## 8.6 Literature Review

The applicant performed a search of the medical literature for information relevant to hydrocodone, pseudoephedrine and guaifenesin in general. The search covered three individual active ingredient hydrocodone, pseudoephedrine, guaifenesin) for a period of two years (January 1, 2006 – June 24, 2008) and the products containing all three ingredients for a period of 10 years (January 1, 1998 – June 24, 2008). There was no new safety signal revealed through the literature search.

There were four case reports, two observational studies, five clinical trials, and one drug-drug interaction study involving hydrocodone adverse events. All four clinical trials were to study hydrocodone in different types of pain patients. All adverse events reported were consistent with what would be expected in use of any opiate (nausea, vomiting, dizziness, somnolence, constipation, etc.)<sup>1-5</sup> The drug-drug interaction study in chronic pain patients demonstrated that serum nicotine levels were negatively correlated with serum hydrocodone levels in smokers.<sup>6</sup> The observational studies and case reports were involved lethal hydrocodone intoxication cases,<sup>7</sup> traffic related deaths with hydrocodone and alcohol use,<sup>8</sup> multiple drug abuse including hydrocodone,<sup>9</sup> and breast milk hydrocodone excretion in mothers taking prescribed hydrocodone for pain.<sup>10</sup>

There were eight case reports, two observational studies and ten clinical trials involving pseudoephedrine adverse events. There were reported death cases related to multiple drug intoxication including pseudoephedrine.<sup>11</sup> A report of 15 deaths of children younger than 17 months involved OTC medications containing pseudoephedrine.<sup>12</sup> The reported adverse events related to pseudoephedrine use included insomnia, hypertension,<sup>13</sup> two case of myocardial infarction,<sup>14</sup> and a case of transient ischemic attack.<sup>15</sup> It appears that these serious adverse events involved serious diseases and other concomitant treatments.

There were no reported adverse events related to guaifenesin use. There were no studies related to safety of products containing all three ingredients. The literature search revealed no new safety signals for hydrocodone, pseudoephedrine and guaifenesin.

### Reference

1. Adams EH, Breiner S, Cicero TJ, et al. *J Pain Symptom Manage.* May 2006;31(5):465-476
2. Chelly JE, Nissen CW, Rodgers AJ, et al. *Curr Med Res Opin.* Jan 2007 ;23(1):195-206
3. Church CA, Stewart CT, et al. *Laryngoscope.* April 2006;116(4):602-606
4. Hewitt DJ, Todd KH, Xiang J, et al. *Am Emerg Med.* April 2007;49(4):468-480
5. Rodriguez RF, Bravol LE, Castro F, et al. *J Palliat Med.* Feb 2007 ;10(1) :56-60
6. Ackerman WE, Ahmad M. *J Ark Med Soc.* July 2007;104(1):19-21
7. Baker DD, Jenkins AJ. *J Anal Toxicol.* March 2008;32(2):165-171
8. Schwilke EW, Sampario MI. et al. *J Forensic Sci.* Sept 2006;51(5):1191-1198
9. Kyle PB, Daley WP. *J Anal Toxicol.* Sept 2007;31(7):415-418
10. Anderson PO, Sauberan JB, Lane JR, et al. *Breastfeeding Med* March 2007;2(1):10-14

11. Carson HJ. Legal Med. 2008;10(2):92-95
12. Wingert WE, Mundy LA, Collins GL, et al. J Forensic Sci. March 2007;52(2):487-490
13. Latte J, Taverner D. Am J Rhinol. 2007;21(4):452-455
14. Biyik I, Ergene O. Can J Cardiol. March 2006;22(3):254-256
15. Profice P, Pilato F, Michetti F, et al. Acta Neurol Scand. Nov 2006 ;114(5) :358-359

## 8.7 Postmarketing Risk Management Plan

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The risk associated with Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only) is expected being similar to the risks of other hydrocodone-containing antitussives. Controlled Substance Staff (CSS) indicates that currently available information in the public domain shows that the products containing hydrocodone alone and in combination with other substances each have an abuse potential, and the Applicant has not provided specific data in the NDA to evaluate the abuse potential of the proposed combination drug. CSS recommends that the Applicant conduct well designed animal and human studies to characterize the abuse potential of the proposed combination drug. More details can be found in the Memorandum, Consult on NDA 22-279, Controlled Substance Staff, March 27, 2009. At the time of finalization of this primary review, it has not been decided whether this recommendation will be an approvability issue or the abuse potential studies could be completed as a post-marketing commitment.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The Applicant seeks the approval of an immediate release oral solution formulation of hydrocodone, pseudoephedrine, and guaifenesin. The product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4)

Guaifenesin and pseudoephedrine are OTC monograph drugs, being considered to be generally recognized as safe and effective (GRASE) in specified doses as an expectorant and an oral nasal decongestant, respectively. The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single nasal decongestant (such as pseudoephedrine) and any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

Hydrocodone, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50). However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product. The FDA has previously determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. Based on this policy, the Division has approved drug development programs for HC and OTC monograph product combinations, concluding that a drug development plan does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the efficacy and safety of the combination product.

The application is supported by a clinical pharmacology program. No clinical efficacy studies were submitted to support this application. The clinical pharmacology study submitted in this application is not adequate to support approval of this application. The formulation of the proposed drug contains sorbitol that affects the bioavailability of the active ingredients, and clinical pharmacology studies are required to establish the bioequivalence (BE) of the proposed drug to the reference.

The safety data from the clinical pharmacology study in adult subjects did not identify a safety signal. Because of the small number of the subjects, there was no meaningful information in differences of adverse events in gender, age, and race/ethnicity. The Applicant's search of the medical literature for safety information related to hydrocodone, pseudoephedrine and guaifenesin identified no new safety signal for adverse events.

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The Controlled substances Staff noted in their recommendation that the applicant needs to fully characterize the abuse potential of the combination product specifically to evaluate how the addition of the non-narcotic 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 Controlled Substances Act (CSA). At the time of finalization of this primary review, it has not been decided if this recommendation will be an approvability issue of whether this assessment could be completed as a post marketing commitment.

## **9.2 Recommendation on Regulatory Action**

The Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only) is not ready for approval in the present NDA submission and I recommend that the application be given a Complete Response Action.

This drug development program is a clinical pharmacology program. The formulation of the proposed drug contains sorbitol that affects the bioavailability of the active ingredients, and clinical pharmacology studies are required to establish the bioequivalence (BE) of the proposed drug to the reference products. The present NDA submission only includes a small bioavailability study to characterize the exposure of hydrocodone, pseudoephedrine and

guaifenesin in the proposed drug product compared to literature references. In the 74-day Letter issued on November 3, 2008, the Applicant was informed of the clinical pharmacology studies needed to support the new drug product. During this review cycle, the Applicant submitted study protocols to start the clinical pharmacology studies. The clinical pharmacology approvability requirements for this NDA will depend on the review of the new clinical pharmacology data that have not been submitted yet.

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The Controlled substances Staff noted in their recommendation that the applicant needs to fully characterize the abuse potential of the combination product specifically to evaluate how the addition of the non-narcotic 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 Controlled Substances Act (CSA). At the time of finalization of this primary review, it has not been decided if this recommendation will be an approvability issue of whether this assessment could be completed as a post marketing commitment.

### 9.3 Recommendation on Postmarketing Actions

No special post-marketing risk management activities are recommended at this time. It is unclear if the recommendation from the CSS of the need to assess the abuse potential of this combination product will ultimately result in special post-marketing risk management activities.

### 9.4 Labeling Review

Proposed labeling was submitted in Physician's Labeling Rule (PLR) format. Brief labeling review revealed the following sections need to be revised. Additions are shown underlined, and deletions are shown in strikethrough. These will need to be addressed at the time the application is considered for approval.

- Revise the DOSAGE AND ADMINISTRATION – Recommended Dosing section as follows:

Adults and <sup>(b) (4)</sup> Years of Age and Older:  
10 mL <sup>(b) (4)</sup> every 4 hours, not to exceed 40 mL <sup>(b) (4)</sup> in 24 hours.

<sup>(b) (4)</sup>

- Revise the CONTRAINDICATIONS section as follows:

<sup>(b) (4)</sup>

- Revise the INDICATIONS AND USAGE section as follows:

[Redacted] (b) (4)

- Revise the WARNINGS AND PRECAUTIONS – [Redacted] (b) (4)

[Redacted] (b) (4)

- Revise the USE IN SPECIFIC POPULATIONS – Nursing Mothers section as follows:

[Redacted] (b) (4)

- Revise the USE IN SPECIFIC POPULATIONS – Pediatric Use section as follows:

Safety and effectiveness of [Redacted] (b) (4) in pediatric patients under [Redacted] (b) (4) not been established. The use of Hydrocodone in children less than 6 years of age [Redacted] (b) (4) associated with [Redacted] (b) (4) fatal respiratory depression. [Redacted] (b) (4)

## 9.5 Comments to Applicant

Deficiency comments will be sent to the applicant in the complete response letter.

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

/s/

-----  
Xu Wang  
4/22/2009 03:19:25 PM  
MEDICAL OFFICER

Lydia McClain  
4/23/2009 12:20:05 PM  
MEDICAL OFFICER

I concur that this application be given a complete response

**MEDICAL OFFICER REVIEW**  
**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

<b>APPLICATION:</b> NDA 22-279	<b>TRADE NAME:</b> None
<b>APPLICANT/SPONSOR:</b> (b) (4)	<b>USAN NAME:</b> Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution (Rx Only)
<b>MEDICAL OFFICER:</b> Xu Wang, M.D., Ph.D.	
<b>TEAM LEADER:</b> Lydia I Gilbert-McClain, M.D., F.C.C.P.	<b>CATEGORY:</b> Antitussive /Decongestant /Expectorant
<b>DATE:</b> 10/2/08	<b>ROUTE:</b> Oral

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
8/22/08	8/22/08	NDA 22-279, N-000	11 volumes

**RELATED APPLICATIONS**

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
9/25/07	IND 76,365	Opening IND
2/06/07	Pre-IND 76,365	Pre-IND meeting package

**REVIEW SUMMARY:**

This NDA is a 505(b)(2) application for an immediate release oral solution formulation of hydrocodone, pseudoephedrine, and guaifenesin. The product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed labeled indications are "for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)". The sponsor's proposed product name is Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4).

This is a clinical pharmacology program. The sponsor's drug development program is based on establishing that their combination product produces equivalent exposures (blood levels) to the published (package insert or Summary Basis of Approval) blood levels of the reference products. There is one clinical pharmacology study submitted in support of this application. From clinical perspective, the study is appropriately indexed and organized to allow review. However, the clinical pharmacology review team considers the data submitted inadequate to establish the required clinical pharmacology information necessary to support approval of the product.

**OUTSTANDING ISSUES:** The submission is fileable from clinical perspective. Additional clinical pharmacology information is necessary to assess the full pharmacokinetic profile of this combination product.

**RECOMMENDED REGULATORY ACTION**

<b>IND/NEW STUDIES:</b>	<input type="checkbox"/> SAFE TO PROCEED	<input type="checkbox"/> CLINICAL HOLD
<b>NDA/SUPPLEMENTS:</b>	<input checked="" type="checkbox"/> FILEABLE	<input checked="" type="checkbox"/> NOT FILEABLE
	<input type="checkbox"/> APPROVAL	<input type="checkbox"/> APPROVABLE
<b>OTHER ACTION:</b>	<input type="checkbox"/>	<input type="checkbox"/>

## 1. GENERAL INFORMATION AND BACKGROUND

This NDA is a 505(b)(2) application for an immediate release oral solution formulation of hydrocodone, pseudoephedrine, and guaifenesin. The product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed labeled indications are “for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4). The sponsor’s proposed name is Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4). (b) (4) The sponsor has provided a paper submission.

Hydrocodone (HC) is a commonly used antitussive. The safety and effectiveness of HC as a prescription drug for the symptomatic relief of cough are supported by DESI review and by the FDA approved product Hycodan (NDA 5-213). HC is an opioid, a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in combination with active nonnarcotic ingredients and if the product contains not more than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15).

Hycodan Tablets and Syrup (HC 5 mg plus homatropine methylbromide (HTM) 1.5 mg, and HC 5 mg plus HTM 1.5 mg per 5 mL, NDA 5-213) was classified in the DESI review as safe and effective for prescription drug for the symptomatic relief of cough. The approved dosages are:

- Adults: One tablet or one teaspoonful of the syrup (5 mg HC) every 4 to 6 hours as needed; not to exceed (NTE) 6 tablets or 6 teaspoonfuls (30 mg HC) in 24 hours
- Children 6 to 12 years of age: One-half (1/2) tablet or one-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 tablets or 3 teaspoonfuls (15 mg HC) in 24 hours
- Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic labeling].

Pseudoephedrine (PSE) is an OTC monograph oral nasal decongestant [21 CFR 341.20]. The dosages specified in OTC monograph for products containing PSE are [21 CFR 341.80(d)]:

- Adults and children 12 years of age and over: 60 mg every 4 to 6 hours NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 to 6 hours NTE 120 mg in 24 hours
- Children 2 to under 6 years of age: 15 mg every 4 to 6 hours NTE 60 mg in 24 hours
- Children under 2 years of age: consult a doctor

Guaifenesin (GU) is an OTC monograph oral expectorant [21 CFR 341.18]. The dosages specified in OTC monograph for products containing PSE are [21 CFR 341.78]:

- Adults and children 12 years of age and older: 200 to 400 mg every 4 hours, not to exceed (NTE) 2400 mg in 24 hours
- Children 6 to under 12 years of age: 100 to 200 mg every 4 hours, NTE 1200 mg in 24 hours
- Children 2 to under 6 years of age: 50 to 100 mg every 4 hours, NTE 600 mg in 24 hours
- Children under 2 years of age: consult a doctor

The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with any single nasal decongestant (such as pseudoephedrine) and any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

HC, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50).

However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product, which can be found in detail in Medical Officer Review, IND (b) (4) M-001, MR, Charles E. Lee, M.D., 9/25/2006. Briefly, the FDA has previously determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. Based on this policy, the Division has approved drug development programs for HC and OTC monograph product combinations, concluding that a drug development plan does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the efficacy and safety of the combination product. However, the sponsor will need to demonstrate that there are no drug-drug or formulation interactions for the ingredients in the product.

The sponsor's application was submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of the approved reference products and a comparison of the bioavailability and bioequivalence of the proposed new drug to those reference products. The sponsor's drug development program for Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only) is based on establishing that their combination

product produces equivalent exposures (blood levels) to the published (package insert or Summary Basis of Approval) blood levels of the reference products.

The sponsor's application includes report of one bioavailability study [Volume 5.1 – 5.4]:

Study S07-0441 is an open-label study to characterize the exposure of hydrocodone, guaifenesin, and pseudoephedrine from a single dose of an oral antitussive, expectorant and decongestant immediate release solution in fasted, healthy, adult subjects.

The study is described in greater depth in a later section of this filing and planning review.

## 2. FOREIGN MARKETING AND REGULATORY HISTORY

There is no information on whether Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only) is marketed in any country.

*Reviewer comment:*

*The sponsor will be asked to submit a foreign marketing history for the product.*

## 3. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [Volume 1.1, Section 1.1.2]
- Debarment certification [Volume 1.1, Section 1.3.3]
- Financial disclosure statement: From FDA 3454 [Volume 1.1, Section 1.3.4]
- Statements of Good Clinical Practice [Volume 5.1, Section 5.3.1.1, page 7]. The Applicant states that the clinical contractor shall comply with all applicable federal, state and local laws, codes, regulations, and orders, including, but not limited to, the Federal Food, Drug, and Cosmetic Act and regulations promulgated thereunder, and Institutional Review Board requirements relative to clinical studies.
- There is no Integrated Summary of Efficacy in the submission. The Applicant submitted an Overview of Efficacy that cites parts of the OTC monograph and the DESI Notice #5213 [Volume 2.1, Section 2.5.4, page 19 – 23].
  - This application relies on the support of a clinical pharmacology study to demonstrate the equivalent exposures (blood levels) to the published (package insert or Summary Basis of Approval) blood levels of the reference products. No clinical studies of the efficacy of the product are required. The Applicant submitted 2 volumes of compiled published literatures and package inserts related to their product [Volume 5.6 – 5.7, Section 5.4.1].
- There is no Integrated Summary of Safety (ISS) in the submission. The Applicant submitted an Overview of Safety including the safety data from the clinical pharmacology study, the search result of AERS data base from January 1, 2003

until December 31, 2007, and a brief literature review for safety of hydrocodone, pseudoephedrine, and guaifenesin [Volume 2.1, Section 2.5.4, page 24 – 42]. The Applicant also submitted 2 volumes of compiled published literatures related to their product [Volume 5.6 – 5.7, Section 5.4.1].

- Proposed labeling and annotated labeling [Volume 1.1, Section 1.14.1.2, Section 1.14.1.3]
- Case report forms for all 18 subjects of the study [Volume 5.4, Section 5.3.1.1, Appendix VI, pages 1367-1619]
- List of referenced DMFs [Volume 1.1, Section 1.4.1]
- Environmental assessment [Volume 1.1, Section 1.12.14]
  - The Applicant has requested a categorical exclusion from this requirement because approval of this NDA would not increase the amount of the active moieties because they are in current use at the same total daily levels for hydrocodone, pseudoephedrine, and guaifenesin. [Volume 1.1, Section 1.12.14]
- Request for waiver of pediatric studies [Volume 1.1, Section 1.9.1]
  - The Applicant states that the prescription only status and the labeling indication of this drug will limit the exposure of the product in the pediatric population. The Applicant certifies that this drug product is not likely to be used in a substantial number of pediatric patients. The Applicant hereby requests a full waiver of the requirements of 21 CFR 314.55(a) Pediatric Use Information. The Applicant states that this NDA addresses the adolescent segment of the pediatric population ( $\geq 12$  years). It is unclear that for which age group the Applicant requests the pediatric waiver.

*Reviewer comments:*

*It is not acceptable to only search AERS data base from January 1, 2003 until December 31, 2007. The Applicant will be asked to submit additional safety information from other sources such as, a summary of the clinical safety from the literature, the World Health Organization (WHO) adverse event database, and International regulatory actions. The safety data should be presented by gender, age, and racial subgroups as available. A 120-day safety update is required as per 21 CFR 314.50.*

*The Agency has approved antitussive drugs containing hydrocodone to the patients 6 years of age and older. Hydrocodone is not appropriate for children less than 6 years of age due to the risk of respiratory depression. It is appropriate to waive pediatric studies in children less than 6 years of age.*

#### **4. CLINICAL PHARMACOLOGY STUDY**

This submission refers to one clinical pharmacology study. The study is appropriately indexed to allow review. The study is summarized in Table 1. More detailed description of the study follow below.

#### 4.1. Study S07-0441

Study S07-0441 is an open-label study to characterize the exposure of hydrocodone, guaifenesin, and pseudoephedrine from a single dose of an oral antitussive, expectorant and decongestant immediate release solution in fasted, healthy, adult subjects.

Eighteen male and female healthy volunteers aged 18 years and older were recruited. Subjects were screened 4 weeks prior to study start. At screening each subject had medical history, complete physical examination, laboratory tests including blood counts, serum electrolytes, liver and renal functions, drugs of abuse, pregnancy test for females, and ECG. Exclusion criteria included alcoholism and drug abuse, malignancy or other serious medical problems, history of asthma treatment within past 5 years, history of body piercing or tattoos within past 30 days, history of hypersensitivity to test drugs, received any prescription drug (except contraceptives for females) within 14 days, received any OTC medications (except multivitamins) within 7 days, females who were pregnant or lactating. After an over night fast for at least 10 hours, each subject received 10 mL Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only). Blood samples for PK determination were taken immediately before dosing (0 hours), and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours and analyzed for plasma hydrocodone, pseudoephedrine and guaifenesin (up to 4 hrs only). Subjects were confined to the clinic until after the hour 24 sample was obtained, and returned to the clinic for the hour 36 blood collection. Safety evaluation includes adverse events and vital signs monitoring during the study.

**Table 1 Summary of study S07-0441**

Study number	Study type	Treatment group	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects	Materials submitted
S07-0441	Bioavailability	HC 5mg/ PSE60mg/ GU400mg	Single dose	Open label, single dose	18	Healthy males and females, 19-55 yrs	Study report

#### 5. BRIEF REVIEW OF PROPOSED LABELING

Proposed labeling and annotated labeling has been included in this submission [Volume 1.1, Section 1.14.1.2, Section 1.14.1.3]. A brief review of proposed labeling was performed.

#### 6. DSI REVIEW/AUDIT

DSI will not be requested at this time by clinical pharmacology to audit the studies S07-0441.

## 7. SUMMARY AND RECOMMENDATION

This NDA is a 505(b)(2) application for an immediate release oral solution formulation of hydrocodone, pseudoephedrine, and guaifenesin. The product contains 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive, decongestant and expectorant. The proposed labeled indications are “for symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4).” The sponsor’s proposed product name is Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution (Rx Only). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed (NTE) 4 doses (8 teaspoonfuls) in 24 hours for adults (b) (4).

This is a clinical pharmacology program. The sponsor’s drug development program is based on establishing that their combination product produces equivalent exposures (blood levels) to the published (package insert or Summary Basis of Approval) blood levels of the reference products. There is one clinical pharmacology study submitted in support of this application. From clinical perspective, the study is appropriately indexed and organized to allow review. However, the clinical pharmacology review team considers the submitted clinical pharmacology data inadequate. Additional clinical pharmacology information is necessary to assess the full pharmacokinetic profile and to support the approval of this combination product [NDA 22-279, Clinical Pharmacology Filing Planning Review, Sandra Suarez, Ph. D. 10/06/2008].

The regulatory action recommended from clinical perspective “fileable.”

## 8. TIME LINE FOR REVIEW

Write-up will be concomitant with the review process. The schedule for review is displayed in Table 2. Clinical review will focus primarily on safety. The review of the safety review and ISS will take place next and will be complete by 1/10/09. Label review will be complete by 1/21/09. Mid cycle review meeting is 1/27/09. Draft review will be complete by 4/29/09. The PDUFA goal day is 6/22/09.

**Table 2. Proposed schedule for review of NDA 22-279**

Milestone	Target Date for Completion
Study S07-0441	10/16/08
Safety review and ISS	01/10/09
Label Review	01/21/09
Mid cycle review meeting	01/27/09
Full labeling meeting	03/23/09
Wrap-up meeting	04/22/09
Draft Review Complete	04/29/09
Action Date, 10 months	06/22/09

## 9. COMMENTS FOR THE SPONSOR

The following comments from clinical perspective are to be communicated to the sponsor:

1. *Submit a foreign marketing and regulatory history for your product.*
2. *Your safety summary includes only safety information from the AERS database covering the period 1/1/2003 to 12/31/2007. Submit additional safety information from other sources such as, a summary of the clinical safety from the literature, the World Health Organization (WHO) adverse event database, and International regulatory actions. Present the safety data by gender, age, and racial subgroups as available.*
3. *Submit a 120-day safety update as per 21 CFR 314.50.*

Reviewed by:

---

Xu Wang, M.D., Ph.D.  
Medical Officer, Division of Pulmonary and Allergy Products

---

Lydia I Gilbert-McClain, M.D., F.C.C.P.  
Medical Team Leader, Division of Pulmonary and Allergy Products

cc: Original NDA  
HFD-570/Division File  
HFD-570/ Gilbert-McClain /Medical Team Leader  
HFD-570/Wang/Medical Reviewer  
HFD-870/Suarez/Clinical Pharmacology Reviewer  
HFD-580/Peri/CMC Team Leader  
HFD-570/Wu/Pharmacology/Toxicology Reviewer  
HFD-570/Hill/CSO

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

/s/

-----  
Xu Wang  
10/6/2008 02:19:13 PM  
MEDICAL OFFICER

Lydia McClain  
10/6/2008 02:32:22 PM  
MEDICAL OFFICER  
I concur