

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022424Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

|                        |   |
|------------------------|---|
| Application Type       | NDA   |
| Submission Number      | 22-424  |
| Submission Code        | N-018   |
| Letter Date            | 11/18/2014  |
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| PDUFA Goal Date        | 05/18/2015  |
| Reviewer Name          | Xu Wang, M.D., Ph.D.  |
| Review Completion Date | 04/21/2015  |
| Established Name       | hydrocodone and guaifenesin   |
| (Proposed) Trade Name  | Flowtuss Oral Solution  |
| Therapeutic Class      | antitussive/expectorant   |
| Applicant              | Mikart, Inc.  |
| Priority Designation   | S   |
| Formulation            | Oral solution   |
| Dosing Regimen         | 10 mL every 4 to 6 hours, not to exceed 6 doses (60 mL) in 24 hours                 |
| Indication             | For symptomatic relief of cough and to loosen mucus associated with the common cold |
| Intended Population    | Adults and adolescents 18 years of age and older                                    |

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## 1 Executive Summary

### 1.1 Recommendation on Regulatory Action

This reviewer recommends an “Approval” action for the hydrocodone bitartrate and guaifenesin oral solution (proposed trade name Flowtuss) for symptomatic relief of cough 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 and guaifenesin (2.5 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 cites OTC Monograph 21 CFR 341.18 to support guaifenesin component of the combination drug 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 a complete response submission. In previous review cycle, the clinical pharmacology studies demonstrated the bioequivalence between the hydrocodone component of the proposed drug product and the reference drug. However, the guaifenesin component of the proposed drug product was not bioequivalent to the reference drug (b) (4)

In this submission, the pivotal clinical pharmacology study (11467601) 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 component in the previous submission, supports the approval for the proposed drug product.

The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. (b) (4)

### 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

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. (b) (4)

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(b) (4)

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### 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 341.18 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 component of the proposed drug product and the reference drug. However, the guaifenesin component of the proposed drug product was not bioequivalent to the reference drug (b) (4)

In this submission, the bioequivalent data for guaifenesin component of the proposed drug product come from the clinical pharmacology studies 11467601. There were 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 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 drug for guaifenesin. In addition, the Applicant provided clinical summary for the safety data from the clinical pharmacology study, post-marketing adverse event searches, and a literature survey. In the pivotal clinical pharmacology 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 new safety signal. Also, the clinical pharmacology studies submitted and reviewed in previous review cycle did not reveal new 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 Flowtuss Oral Solution. The proposed drug product contains 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive and expectorant. The indication is "for symptomatic relief of cough and to help loosen mucus associated with the common cold". The dosage is 10 mL every 4 to 6 hours, not to exceed 6 doses (60 mL) in 24 hours for adults and adolescents 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 combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone 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 Flowtuss 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 Flowtuss Oral Solution is administered to nursing mothers.

*Reviewer's comments:*

(b) (4)

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## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The Applicant has developed an immediate release oral solution formulation of hydrocodone and guaifenesin. The drug product contains 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin per 5 mL. It is proposed as a prescription fixed dose combination of antitussive and expectorant. The labeled indication is for symptomatic relief of cough and to help loosen mucus associated with the common cold. The sponsor's proposed name, Flowtuss Oral Solution, is accepted. [Proprietary Name Request Conditionally Acceptable Letter, Division of Medical Error Prevention and Analysis, OSE, 03/13/2015] The dosage is 10 mL every 4 to 6 hours, not to exceed (NTE) 6 doses (60 mL) in 24 hours for adults and children 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). 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.

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].

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 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 also 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 (Guaifenesin and Hydrocodone Bitartrate Oral Solution, 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), Tussion (ANDA 88506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40613, ANDA 88008). Guaifenesin is a readily available immediate release OTC monograph drug, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph doses 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).

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), hydrocodone bitartrate (NDA 205-474), and pseudoephedrine HCl (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 advise on the abuse potential for the related 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 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.

## 2.5 Presubmission Regulatory Activity

- 3/26/2007: The Applicant (Propharma, Inc.) 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: (1) hydrocodone and guaifenesin and (2) hydrocodone, pseudoephedrine, and guaifenesin. The formulations for the proposed drugs were exactly the same for the double and triple combination products except for an addition of pseudoephedrine component 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.
- 9/25/2007: 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, 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) 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. A Complete Response Letter was issued to the submission on 6/22/ 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 bitartrate 2.5 mg/pseudoephedrine HCl 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) including PK data obtained from two clinical pharmacology studies. A Complete Response Letter was issued on 1/25/2011, stating that the pharmacology studies submitted in the NDA cannot be relied upon to support the clinical pharmacology of hydrocodone bitartrate, pseudoephedrine HCl, 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.

- 11/29/2010: The Applicant filed the current NDA 22-424, using the same 2 clinical pharmacology studies, which had been determined unacceptable, to support the proposed hydrocodone and guaifenesin oral solution.
- 2/11/2011: In a filing communication for the NDA 22-424, the Agency conveyed to the Applicant that “these studies may not be used to support this NDA submission”. Subsequently, the Applicant performed 2 new clinical pharmacology studies (S11-0028 and S11-0029) and submitted the study reports on June 23 (received on June 27), 2011 to support the NDA 22-424. The Applicant would also use these 2 clinical pharmacology studies to support their complete response resubmission of the NDA 22-279 for the triple combination product hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin oral solution. (The Applicant resubmitted the NDA 22-279, N030 complete response submission on 07/18/2011.)
- 9/28/2011: 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.”
- 10/07/2011: Notice received that the NDA 22-424 was transferred ownership from Tiber Laboratories to Teresina Holdings, LLC
- 10/24/2011: Notice received that the NDA was transferred ownership from Teresina Holdings, LLC to the present owner of the NDA, Mikart, Inc.
- 11/18/2014: The present complete response resubmission (NDA 22-424, N018) 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 BE for hydrocodone in the previous submission, is considered acceptable by the Agency’s clinical pharmacology review team. [NDA 22-424 N018, 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 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 (as colorants), and (b) (4) black raspberry flavor. The proposed combination drug is manufactured and supplied by Mikart, Inc.

Hydrocodone bitartrate USP used in the test formulation was manufactured (b) (4)  
Guaifenesin USP used in the test formulation (b) (4)  
was manufactured (b) (4) The  
excipients in the test formulation include (b) (4)

A detailed review of the CMC portion of the application may be found in the ONDQA review [NDA 22-424, ONDQA Review, Xiaobin Shen, Ph.D., 4/27/2011].

#### 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 Flowtuss 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 drug guaifenesin. This application refers to the pivotal clinical pharmacology studies 11467601 that provided support for the bioequivalence of the guaifenesin component between the test drug and the reference drug. There were no clinical efficacy or safety studies in this application.

The Applicant is also developing a triple combination product, hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin oral solution, which has exactly the same formulation, except for an additional component of pseudoephedrine HCl 0.6% (30 mg/5 mL), with the proposed double combination product Flowtuss Oral Solution. The Applicant conducted all pharmacologic studies using the triple combination in order to obtain data to support both NDAs, the present NDA 22-424 for the hydrocodone bitartrate and guaifenesin combination, and NDA 22-279 for the hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin triple combination product that is currently under review in the Division.

The Applicant also included in this submission 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 the triple combination hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin with marketed guaifenesin drugs. Because these studies were exploratory in nature and were not used to support the proposed drug product, the 4 studies were only briefly mentioned in this review.

In the previous review cycle, the bioequivalence of hydrocodone bitartrate component between the proposed drug product and reference drugs was demonstrated in clinical pharmacology studies. For detailed review of those studies, readers are referred to the medical officer review. [NDA 22-424 N000, Medical Officer Review, Xu Wang, M.D., Ph.D. 8/18/2011]

#### 4.2 Table of Clinical Studies

The Applicant included 5 clinical pharmacology studies in this submission (Table 1). 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 1 Summary of clinical pharmacology studies in the submission**

| Study No.                             | Study type | Treatment group   | Design                                   | Subject No. | Subjects                        | Guaifenesin BE Result  |
|---------------------------------------|------------|---|--|-------------|---------------------------------|--|
| 11267601                              | BA/BE      | A: Test drug*<br>B: Children's Mucinex (guaifenesin)200mg/10mL<br>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;<br><br>Cmax of reference B failed to meet BE criteria |
| 11267602                              | BA/BE      | A: Test drug*<br>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                              | BA/BE      | A: Test drug*<br>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                              | BA/BE      | A: Test drug*<br>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><br>(pivotal PK study) | BA/BE      | A: Test drug*<br>B: (b) (4) (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. Detailed review of the clinical pharmacology data can be found in the Clinical Pharmacology Review. [NDA 22-424, N018, Clinical Pharmacology Review by Yunzhao Ren, Ph. D.] It is also included in this review 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.

In the previous review cycle, the bioequivalence of hydrocodone component between the proposed drug product and reference drugs was demonstrated in clinical pharmacology studies. For detailed review of those studies, readers are referred to the medical officer review. [NDA 22-424 N000, Medical Officer Review, Xu Wang, M.D., Ph.D. 8/18/2011]

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

#### 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 studies 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. 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.

The formulation of Flowtuss Oral Solution is displayed in Table 2. The experimental formulation is supplied by Mikart, Inc.

**Table 2 Formulation of Flowtuss Oral Solution\***

| Ingredient                             | %       | mg/5 mL |
|--|---------|---------|
| Hydrocodone bitartrate USP             | 0.05    | 2.5     |
| Guaifenesin USP                        | 4.00    | 200     |
| Sorbitol (b) (4) USP                   | (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                     |         |         |

\* The Applicant is developing a triple combination product, hydrocodone bitartrate, pseudoephedrine HCl, and guaifenesin oral solution, which has exactly the same formulation, except for an additional component of pseudoephedrine HCl 0.6% (30 mg/5 mL), with the proposed product hydrocodone bitartrate and guaifenesin oral solution.

**Study 11467601** is a 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 formulations 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™ (b) (4) (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 hour), 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-∞</sub>, C<sub>max</sub>, T<sub>max</sub>, Kel 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 met the 90% CI criterion for bioequivalence compared to an equal dose of guaifenesin in reference product, Refenesen™ (b) (4) (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><br>(ng·hr/mL) | A   | 36         | 2519              | A vs B<br>(n=36)      | 96.87          | 92.03-101.97         |
|                                  | B   | 36         | 2601              |                       |                |                      |
| AUC <sub>0-∞</sub><br>(ng·hr/mL) | A   | 36         | 2603              | A vs B<br>(n=36)      | 96.74          | 91.88-101.86         |
|                                  | B   | 36         | 2690              |                       |                |                      |
| C <sub>max</sub><br>(ng/mL)      | A   | 36         | 2015              | A vs B<br>(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 (b) (4)

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)**

|                                      | Test    | Reference | % Ratio | 90% CI        |
|--------------------------------------|---------|-----------|---------|---------------|
| <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>Guaifenesin</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>       |         |           |         |               |

Source: NDA 22-279 S030, MO Review, page 18.

## 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

Flowtuss (hydrocodone bitartrate and guaifenesin) Oral Solution is indicated for symptomatic relief of cough 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 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 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 references. The adverse events reported in the 4 exploratory studies were rare and mild in nature, and did not show significant difference in subjects with the test drug and references.

In the 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 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 was no deaths in the clinical pharmacology study 11467601.

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'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 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<br>Study No. 11467601 |                      |
|---|--|----------------------|
|   | Test A<br>N (%)                            | Reference B<br>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™ (b) (4) (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:*

*These data did 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 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.

### 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>3</sup>. The infants of

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

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 Flowtuss 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's comment:*

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

#### 7.1.17 Postmarketing Experience

The proposed drug product Flowtuss 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 did not reveal a new safety signal.

**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 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 drug for 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. 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 a single-dose clinical pharmacology study 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 in previous submission 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. 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 Flowtuss Oral Solution. The proposed drug product contains 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin per 5 mL. It is proposed as a prescription fixed

dose combination of antitussive and expectorant. The indication is for symptomatic relief of cough and to loosen mucus associated with the common cold. The dosage is 10 mL every 4 to 6 hours, not to exceed (NTE) 6 doses (60 mL) in 24 hours for adults and adolescents 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 combination product and conclude that there was no evidence of drug-drug interaction when hydrocodone 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 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. 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 and Guaifenesin 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. In previous submission, 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.

(b) (4)

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(b) (4)

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## 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 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.

#### Reference

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#### 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 Flowtuss 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 Flowtuss, an immediate release oral solution of hydrocodone bitartrate and guaifenesin. The product contains 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin per 5 mL. It is proposed as a prescription combination drug of antitussive and expectorant. The indication is for symptomatic relief of cough 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) 6 doses (60 mL) in 24 hours for adults and adolescents 18 years of age and older.

Guaifenesin is OTC monograph drugs, being considered to be generally recognized as safe and effective (GRASE) in specified doses as an expectorant. The monograph considers the combination of any single monograph oral antitussive drug (such as codeine phosphate) with 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 the previous review cycle, the clinical pharmacology studies demonstrated the bioequivalence between the hydrocodone component 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 (b) (4)

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 BE plus the demonstrated BE for hydrocodone component in the previous submission, supports the approval for the proposed drug product.

### 9.2 Recommendation on Regulatory Action

This reviewer recommends an "Approval" action for Flowtuss (hydrocodone bitartrate and guaifenesin) Oral Solution for symptomatic relief of cough 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 combination drug product containing hydrocodone bitartrate and guaifenesin (2.5 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 341.18 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 a complete response submission. In the previous review cycle, the clinical pharmacology studies demonstrated the bioequivalence between the hydrocodone component 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 (b) (4)

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 BE plus the demonstrated BE for hydrocodone component in the previous submission, supports the approval for the proposed drug product.

The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. (b) (4)

### 9.3 Recommendation on Postmarketing Actions

(b) (4)

#### 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.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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XU WANG  
04/24/2015

ANTHONY G DURMOWICZ  
04/24/2015

## SUMMARY REVIEW OF REGULATORY ACTION

|  |   |
|--|---|
| <b>Date</b>                                      | September 28, 2011  |
| <b>From</b>                                      | Lydia Gilbert-McClain, MD, FCCP   |
| <b>Subject</b>                                   | Summary Review of Regulatory Action   |
| <b>NDA/BLA#</b>                                  | NDA 22-424  |
| <b>Applicant</b>                                 | Tiber Laboratories, LLC   |
| <b>Date of Submission</b>                        | November 29, 2010   |
| <b>PDUFA Goal Date</b>                           | September 29, 2011  |
| <b>Proprietary Name/Established (USAN) Names</b> | FLOWTUSS/hydrocodone bitartrate and guaifenesin                                   |
| <b>Dosage forms/strengths</b>                    | Oral solution/hydrocodone bitartrate 2.5 mg /guaifenesin 200 mg/5 mL              |
| <b>Proposed indication (s)</b>                   | <div style="background-color: #cccccc; height: 20px; width: 100%;"></div> (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, Suresh Doddapaneni, PhD  |
| CMC review                                       | Xiaobin Shen, PhD, Prasad Peri, PhD   |
| CDTL   | Anthony Durmowicz, MD   |
| DMEPA consult                                    | Nichelle, Rashid  |
| Microbiology Consult                             | John Metcalfe, Ph.D   |

### 1. Introduction

This is a 505 (b) (2) new drug application submitted on November 29, 2010 by Tiber Laboratories, LLC. The application is for a fixed dose combination oral solution containing hydrocodone bitartrate, and guaifenesin (b) (4)

The original NDA submission relies on clinical pharmacology data submitted to NDA 22-279 for a triple combination solution containing hydrocodone, *pseudoephedrine*, and guaifenesin. That application (originally submitted on August 22, 2008, and given a first complete response on June 22, 2009, followed by another complete response on January 26, 2011) contained the results of the clinical pharmacology program intended to be used to support NDA 22-424. NDA 22-279 was given a complete response on January 26, 2011, because the data from the two clinical pharmacology studies [S-09-009 a single-dose crossover bioavailability study and S09-0010 a single dose food effect study]

could not be used to support the NDA because of data irregularities discovered upon DSI inspection of the study analytical sites. Knowing this beforehand, the Division already knew that this new NDA 22-424 could not rely on the clinical pharmacology data from NDA 22-729, but did not have a legal mechanism to refuse to file the application. The Division communicated the deficiency to the applicant in the filing communication letter issued on February 11, 2011, stating that the data from studies S-09-009 and S-09-0010 could not be used to support NDA 22-424. Therefore, the applicant conducted 2 new clinical pharmacology studies during the review cycle and submitted the results as an amendment to the NDA on June 23, 2011. These new studies failed to demonstrate bioequivalence for one of the components (guaifenesin) of the combination product to the reference product and also showed a significant food effect. Since the applicant did not conduct a clinical program and is relying on the Agency's finding of safety and efficacy of previously approved ingredients, establishing bioequivalence is essential to support approval of this product. Therefore, this application cannot be approved at this time. This review will summarize the salient findings that 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. Tiber's hydrocodone guaifenesin combination product is one of these products under development to support FDA approval in response to the Agency's compliance efforts regarding illegally marketed cough/cold products.

## **3. CMC/Device**

The proposed product in this NDA is for an aqueous non-sterile oral solution containing hydrocodone bitartrate (HC) 2.5 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. Both drug substances comply with their respective USP monographs and have been previously assessed to support other NDA applications in the past. There are no unresolved DMF issues. The applicant has provided adequate stability data to support a 24 month expiry for the product, and there are no outstanding facilities inspection issues. However from a CMC standpoint the application cannot be approved because of outstanding quality microbiology issues. Although this is a non-sterile solution, acceptable microbial limits are still required. There is no testing and acceptance criterion established for the absence of *Burkholderia cepacia*. This deficiency will be communicated to the applicant 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

As noted in the introduction, the two studies initially submitted to support the application were cross referenced from NDA 22-279: 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. Data irregularities discovered during the DSI audit make these data unsuitable for use for regulatory decision making. The DSI findings notwithstanding, the guaifenesin component of the combination product was not bioequivalent to the reference product (b) (4)

On June 24<sup>th</sup>, 2011, the applicant submitted 2 new studies: studies S11-0028 and S11-029 a single dose BE study and a food effect study respectively. The results of these new studies also show that the guaifenesin component of the combination product was not bioequivalent (b) (4). The results are depicted in the tables below taken from Dr. Anthony Durmowicz's CDTL review.

**Table 1. Results for guaifenesin test/reference (Study S11-0028) Single dose BA study** (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 (Study S11-0029)** (b) (4)

## 6. Clinical Microbiology

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 for 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. There were no serious adverse reactions reported in the clinical pharmacology studies. 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 two 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)



(b) (4)



(b) (4)



## 11. Other Relevant Regulatory Issues

### Data Quality, Integrity, and Financial Disclosure

As noted in the Introduction, 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) that were initially intended to support the NDA cross-referenced to NDA 22-279. The clinical portions of the studies were conducted at Cetero Research, St Charles, MO and the analytical portions were conducted (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 (b) (4)

In view of these findings, the data from studies S09-0009 and S09-0010 could not be used to support the NDA and this was conveyed to the sponsor in the filing communication letter for this NDA. The two new

studies that the applicant conducted and submitted on June 23, 2011, failed to establish bioequivalence for the guaifenesin component of the combination product. Therefore, a DSI audit of those studies was not requested.

## 12. Labeling

Given that the clinical pharmacology data are not acceptable to support the application; a labeling review of the proposed package insert was not conducted during this review cycle. The applicant submitted a tradename for their product "FLOWTUSS" that was found to be provisionally acceptable.

## 13. Action and Risk Benefit Assessment

### Regulatory action

The regulatory action on the application will be a complete response. Tiber Laboratories LLC has not submitted adequate data to support approval of their hydrocodone, guaifenesin oral solution combination product for use as an antitussive and expectorant (b) (4)

The studies conducted failed to show bioequivalence for the guaifenesin component. Furthermore, an inspection of the first 2 studies conducted by the Department of Scientific Investigations (DSI) in the Office of Compliance found significant violations in the analytical portions of the studies which render those data unacceptable for use in the NDA to make regulatory decisions. A DSI audit was not requested of the 2 new studies submitted June 2011 because these new studies also failed to establish bioequivalence.

### 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 and guaifenesin oral solution. The additional clinical pharmacology studies that you submitted on June 23, 2011, 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:

- 1) 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%.

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, using the bioequivalence goal post of 80 – 125%. 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.

- 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 III 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.

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/s/  
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LYDIA I GILBERT MCCLAIN  
09/28/2011

## Cross-Discipline Team Leader Review

|  |   |
|--|---|
| <b>Date</b>  | September 8, 2011   |
| <b>From</b>  | Anthony G. Durmowicz, M.D.                                  |
| <b>Subject</b>                                     | Cross-Discipline Team Leader Review                         |
| <b>NDA/BLA #</b>                                   | 22-424  |
| <b>Supplement#</b>                                 |   |
| <b>Applicant</b>                                   | Tiber Laboratories, LLC                                     |
| <b>Date of Submission</b>                          | November 29, 2010   |
| <b>PDUFA Goal Date</b>                             | September 29, 2011  |
|  |   |
| <b>Proprietary Name / Established (USAN) names</b> | Flowtuss/hydrocodone bitartrate and guaifenesin             |
| <b>Dosage forms / Strength</b>                     | Oral Solution/2.5 mg and 200 mg, respectively, in each 5 ml |
| <b>Proposed Indication(s)</b>                      | (b) (4)   |
| <b>Recommended Action:</b>                         | Complete Response   |

### 1. Introduction

This current submission by the Applicant, received November 29, 2010, is a 505(b)(2) new drug application based on a clinical pharmacology program for a hydrocodone bitartrate and guaifenesin combination immediate release oral solution (proposed name Flowtuss) with a proposed indication (b) (4)

Because the application is based on clinical pharmacology studies, in order to support the safety and efficacy (and therefore approval) of the proposed hydrocodone and guaifenesin combination product, the Applicant must rely on demonstrating bioequivalence to the approved product for hydrocodone and OTC monograph for guaifenesin to support the efficacy and safety of the proposed drug product.

For this NDA submission the Applicant originally submitted data from 2 clinical pharmacology studies (S09-0009 and S09-0010) that had been previously submitted to support approval of a related NDA application (22-279) by Tiber, a triple combination cough and cold drug which contained the same hydrocodone and guaifenesin components as the current submission with the addition of the decongestant pseudoephedrine. However, in the review cycle of NDA 22-279, an audit performed by the Division of Scientific Investigations identified deficiencies related to documentation irregularities and the integrity of bioanalytical data and, as a result, the studies could not be used to support the clinical pharmacology program and the Division took a Complete Response for the application. The issue that the Division had already determined that the studies were inadequate to support an NDA was communicated to the Applicant in a filing communication for this NDA (22-424) on February 11, 2011. Subsequently, the Applicant performed two new clinical pharmacology studies (S11-

Anthony Durmowicz M.D.  
Cross Discipline Team Leader Review  
NDA 22-424, Flowtuss (hydrocodone bitartrate and guaifenesin oral solution)  
0028 and S11-0029) and submitted the study reports on June 23 (received on June 27), 2011,  
to support this NDA.

This CDTL review will provide an overview of the application, with a focus on the two newly conducted clinical pharmacology studies submitted during the review cycle. The PDUFA date for this application is September 29, 2011.

## 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 and guaifenesin, as an immediate release oral solution containing 2.5 mg and 200 mg of hydrocodone and guaifenesin, per 5 mL respectively. Guaifenesin is a well known expectorant found in many cough and cold products and is listed in the OTC monograph (21 CFR 341.40). The proposed dosage is (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 22-424 (hydrocodone and guaifenesin) and the already mentioned related NDA 22-279 in which pseudoephedrine was added to the hydrocodone and guaifenesin combination. The formulations for the proposed drugs were exactly the same for the double and triple combination products except for an addition of pseudoephedrine component 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). To date, the Applicant has received two complete responses for the proposed triple combination product (June 22, 2009 and January 25, 2011) citing inadequacies in their clinical pharmacology program and deficiencies found upon inspection of the analytical site related to documentation irregularities and the integrity of bioanalytical data, respectively, for the first and second submission. This is the first submission specifically for the hydrocodone and guaifenesin double combination product.

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 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 hydrocodone bitartrate USP product manufactured (b) (4) 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 and guaifenesin USP 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 (as colorants), and (b) (4) black raspberry flavor.

Hydrocodone bitartrate USP used in the test formulation was manufactured (b) (4) (b) (4) Guaifenesin USP used in the test formulation was manufactured (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, assay, assay for (b) (4) 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. The proposed product is a non-sterile solution for oral ingestion (b) (4) 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. 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

There were four clinical pharmacology studies in the submission (Table 1). Because two of the studies (S11-0009 and S11-0010) were reviewed in the previously submitted related NDA 22-279 and determined unacceptable due to the deficiencies found in the Agency's inspection of the analytical site, this review will focus on data submitted for studies S11-0028 and S11-0029. Note that the Applicant is developing a triple combination product, hydrocodone, pseudoephedrine and guaifenesin oral solution, which has the same formulation, except for an additional component of pseudoephedrine. As the pharmacology studies were performed to support the 2 combination products (NDAs 22-424 and 22-279), they include pseudoephedrine.

**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<br>B: HC 5 mg<br>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<br>B: HC 5 mg<br>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 Tiber'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): Tiber'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

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

### Results

The hydrocodone component of the combination product was bioequivalent to the reference product, in that the 90% CI for the ratio 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 2).

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

(b) (4)



### **Study S11-0029:**

#### Design

This was a single-dose food effect cross-over study to assess the impact of food on the bioavailability of Tiber's hydrocodone 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 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

(b) (4)



## 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 hydrocodone 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 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 studies #S09-0009 and #S09-0010 which were previously reviewed under NDA 22-279) 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, 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



## 11. Other Relevant Regulatory Issues

### **Withdrawal and Abuse Potential**

Previously, for the related NDA (22-279), the Controlled Substances Staff (CSS) was consulted to give their opinion on the abuse potential for the Applicant's other hydrocodone containing triple combination product during its 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 proposed trade name Flowtuss was reviewed and deemed to be provisionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

### **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. A memo which stated that program deficiencies preclude labeling discussions was sent to the Applicant on August 8, 2011.

### **13. Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

The recommended regulatory action is for a Complete Response as Tiber Laboratories LLC has not submitted adequate data to support approval of hydrocodone and guaifenesin oral solution for use as an antitussive and expectorant (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 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 III 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 (b) (4)

To address this deficiency you should do the following:

- If 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 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.
3.  (b) (4)

Anthony Durmowicz M.D.  
Cross Discipline Team Leader Review  
NDA 22-424, Flowtuss (hydrocodone bitartrate and guaifenesin oral solution)

(b) (4)



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ANTHONY G DURMOWICZ  
09/08/2011

## CLINICAL REVIEW

|                        |                             |
|------------------------|-----------------------------|
| Application Type       | NDA                         |
| Submission Number      | 22-424                      |
| Submission Code        | N-000                       |
| Letter Date            | 11/24/2010                  |
| Stamp Date             | 11/29/2010                  |
| PDUFA Goal Date        | 09/29/2011                  |
| Reviewer Name          | Xu Wang, M.D., Ph.D.        |
| Review Completion Date | 08/16/2011                  |
| Established Name       | Hydrocodone and Guaifenesin |
| (Proposed) Trade Name  | (b) (4)                     |
| Therapeutic Class      | Antitussive/Expectorant     |
| Applicant              | Tiber Laboratories, LLC     |
| Priority Designation   | S                           |
| Formulation            | Oral solution               |
| Dosing Regimen         | (b) (4)                     |
| Indication             | (b) (4)                     |
| Intended Population    | (b) (4)                     |

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

The (b) (4) is not ready for approval in the present NDA submission 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 OTC monograph for 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 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 (b) (4)

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 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 505(b)(2) new drug application based on a clinical pharmacology program to demonstrate the bioequivalence of the proposed combination drug product to the individual

reference drugs and therefore be able to rely on the Agency's previous determination of efficacy and safety for hydrocodone and guaifenesin as a cough suppressant and expectorant, respectively. Originally, the Applicant submitted data from 2 clinical pharmacology studies (S09-0009 and S09-0010) that had been submitted in another NDA (22-279). In the review cycle of the NDA 22-279, an audit performed by the Agency identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site of 2 studies. The Agency concluded that "these studies cannot be relied upon to support" the proposed drug product in NDA 22-279 [NDA 22-279, CR Letter, January 25, 2011]. In a filing communication on February 11, 2011 regarding the present NDA (22-424), the Agency conveyed to the Applicant that "these studies may not be used to support this NDA submission". Subsequently, the Applicant has performed 2 new clinical pharmacology studies (S11-0028 and S11-0029) and submitted the study reports on June 23 (received on June 27), 2011, to support the NDA 22-424.

Study S11-0028 was a single-dose, randomized, three-treatment crossover study under fasting condition to assess the relative bioavailability and bioequivalence of the test drug, Tiber's hydrocodone bitartrate 2.5 mg/guaifenesin 200 mg per 5 mL solution, and reference solutions. The results of this study demonstrated that hydrocodone met the bioequivalence criteria. However, the guaifenesin component of the proposed product was not bioequivalent to the reference drug

(b) (4)

Study S11-0029 was a food effect study to assess the impact of food on the bioavailability of Tiber's triple combination solution. This is a single-dose, randomized, open-label, two-treatment crossover study under fed and fasting conditions.

(b) (4)

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 based on 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 guaifenesin were used to substantiate the efficacy and safety of this 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 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 also 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. However, because of the failure to demonstrate bioequivalency to approved marketed guaifenesin-containing products, the above AERS database and literature searches are of limited value in supporting the safety of the proposed HC and GA 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 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 (b) (4) The proposed drug product contains 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive and expectorant. The proposed

(b) (4)

The proposed dosage is (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 (b) (4) 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 (b) (4) administered to nursing mothers.

#### *Reviewer's comments:*

(b) (4)

(b) (4)

(b) (4)

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The Applicant has developed an immediate release oral solution formulation of hydrocodone and guaifenesin. The drug product contains 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive and expectorant. The proposed

(b) (4)

The sponsor's proposed name is  
. The proposed dosage is

(b) (4)

(b) (4)

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].

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 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.*

(b) (4)



## 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). Guaifenesin is a readily available immediate release OTC monograph drug, being considered to be generally recognized as safe and effective (GRASE) at OTC monograph doses 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 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 Agency has encouraged manufacturers of these and other unapproved products to submit NDAs to obtain approval for marketing these products in the United States.

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 (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.

## 2.5 Presubmission Regulatory Activity

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: (1) hydrocodone and guaifenesin and (2) hydrocodone, pseudoephedrine and guaifenesin. The formulations for the proposed drugs were exactly the same for the double and triple combination products except for an addition of pseudoephedrine component 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. 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.” Before the action date for the NDA 22-279 (1/25/2011), the Applicant filed the current NDA 22-424, using the same 2 clinical pharmacology studies (S09-0009 and S09-0010), which had been determined unacceptable, to support the proposed hydrocodone and guaifenesin oral solution. In a filing communication on February 11, 2011 for the NDA 22-424, the Agency conveyed to the Applicant that “these studies may not be used to support this NDA submission”. Subsequently, the Applicant performed 2 new clinical pharmacology studies (S11-0028 and S11-0029) and submitted the study reports on June 23 (received on June 27), 2011 to support the NDA 22-424. The Applicant will also use these 2 clinical pharmacology studies to support their complete response resubmission of the NDA 22-279 for the triple combination product hydrocodone, pseudoephedrine, and guaifenesin oral solution on a later date.

### 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 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 (as colorants), and (b) (4) black raspberry flavor. The proposed combination drug is manufactured and supplied by Mikart, Inc. 2090 Marietta Blvd, Atlanta, GA 30318 [m3, Section 3.2.P.3.1, page 1].

Hydrocodone bitartrate USP used in the rest 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)

A detailed review of the CMC portion of the application may be found in the ONDQA review [NDA 22-424, ONDQA Review, Xiaobin Shen, Ph.D., 4/27/2011].

#### 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 (b) (4) 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 dose for guaifenesin. 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 developing a triple combination product, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution, which has exactly the same formulation, except for an additional component of pseudoephedrine HCl 0.6% (30 mg/5 mL), with the proposed double combination product (b) (4). The Applicant has conducted all pharmacologic studies using the triple combination in order to obtain data to support the present NDA and an NDA for the triple combination product that will be submitted on a later date.

### 4.2 Table of Clinical Studies

The Applicant has submitted the results from 4 clinical pharmacology studies. 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<br>B: HC 5 mg<br>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<br>B: HC 5 mg<br>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        |

\* Studies S11-0009 and S11-0010 have been reviewed in the previously submitted NDA 22-279. 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 submitted NDA 22-279. The 2 studies 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 22-424, N-000, 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 studies 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 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 22-424, N-000, Clinical Pharmacology Review, Arun Agrawal, Ph.D.].

The formulation (b) (4) is displayed in Table 2 [m3, Section 3.2.P.1.2, page 2].

**Table 2. Formulation** (b) (4) \*

| Ingredient                             | %       | mg/5 mL |
|--|---------|---------|
| Hydrocodone bitartrate USP             | 0.05    | 2.5     |
| Guaifenesin USP                        | 4.00    | 200     |
| Sorbitol (b) (4) USP                   | (b) (4) | (b) (4) |
| Glycerine USP                          | (b) (4) | (b) (4) |
| Polyethylene glycol (b) (4) NF         | (b) (4) | (b) (4) |
| Methylparaben NF                       | (b) (4) | (b) (4) |
| Propylparaben NF                       | (b) (4) | (b) (4) |
| Citric acid (b) (4) USP                | (b) (4) | (b) (4) |
| Sodium citrate (b) (4) USP             | (b) (4) | (b) (4) |
| Saccharin sodium                       | (b) (4) | (b) (4) |
| D & C red #33                          | (b) (4) | (b) (4) |
| FD & C blue #1                         | (b) (4) | (b) (4) |
| (b) (4) black raspberry flavor (b) (4) | (b) (4) | (b) (4) |
| Purified water USP                     | (b) (4) | (b) (4) |

\* The Applicant is developing a triple combination product, Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution, which has exactly the same formulation, except for an additional component of pseudoephedrine HCl 0.6% (30 mg/5 mL), with the proposed product (b) (4)

**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 Tiber's triple combination solution.

Treatment A (Test): Tiber's 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 ratios of geometric means were 99.01% (90% CI 94.73% - 103.49%) for  $AUC_{0-t}$ , 99.60% (90% CI 95.10% - 104.30%) for  $AUC_{0-inf}$ , and 87.12% (90% CI 82.54% - 91.96%) 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): (b) (4)

**Study S11-0029** is a food effect study to assess the impact of food on the bioavailability of Tiber's (b) (4) (5/400 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 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: (b) (4)

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:

(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 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). In addition, the Applicant searched MEDLINE and EMBASE for the medical literature relevant to safety of hydrocodone, pseudoephedrine and guaifenesin. However, because of the failure to demonstrate bioequivalency to approved marketed guaifenesin-containing products, the above AERS database and literature searches are of limited value in supporting the safety of the proposed HC and GA 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 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 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             | 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 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 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 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 4 summarizes the adverse events occurred in study S11-0028.

**Table 4. 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's 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 (b) (4) 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.

### 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>3</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

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

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 (b) (4) 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's comment:*

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

### 7.1.17 Postmarketing Experience

The proposed drug product (b) (4) 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.

## 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 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, 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 HC and GA 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 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 (b) (4) The proposed drug product contains 2.5 mg hydrocodone bitartrate and 200 mg guaifenesin per 5 mL. It is proposed as a prescription drug combination of antitussive and expectorant. The proposed

(b) (4)  
The proposed dosage is (b) (4)

(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 (b) (4) 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. 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 (b) (4) administered to nursing mothers.

#### 8.4 Pediatrics

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

#### 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.

#### Reference

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#### 8.7 Postmarketing Risk Management Plan

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

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

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 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 (b) (4)

. The clinical experience 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 safety and efficacy.

### 9.2 Recommendation on Regulatory Action

The (b) (4) is not ready for approval in the present NDA submission 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 OTC monograph for 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 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 (b) (4)

To support the registration 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 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 (b) (4). 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 and guaifenesin or conduct clinical studies to support its efficacy and safety.

- (2) (b) (4)

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/s/  
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XU WANG  
08/18/2011

ANTHONY G DURMOWICZ  
08/18/2011  
I concur.

| <b>MEDICAL OFFICER REVIEW</b>  |   |   |  |
|--|---|---|--|
| <b>Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)</b>   |   |   |  |
| <b>APPLICATION:</b> NDA 22-424   | <b>TRADE NAME:</b> (b) (4)                                      |   |  |
| <b>APPLICANT/SPONSOR:</b> Tiber Laboratories, LLC  | <b>USAN NAME:</b> hydrocodone and guaifenesin oral solution     |   |  |
| <b>MEDICAL OFFICER:</b> Xu Wang, M.D., Ph.D.   |   |   |  |
| <b>TEAM LEADER:</b> Anthony G. Durmowicz, M.D.   | <b>CATEGORY:</b> antitussive and expectorant                    |   |  |
| <b>DATE:</b> January 28, 2011  | <b>ROUTE:</b> oral  |   |  |
| <b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>   |   |   |  |
| <u>Document Date</u>   | <u>CDER Stamp Date</u>  | <u>Submission</u>   | <u>Comments</u>                                |
| Nov 29, 2010   | Nov 29, 2010  | NDA 22-424  | Original NDA submission                        |
| <b>RELATED APPLICATIONS</b>  |   |   |  |
| <u>Document Date</u>   | <u>Application Type</u>   | <u>Comments</u>   |  |
| July 26, 2010  | NDA 22-279  | Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution (Rx Only) |  |
| <b>REVIEW SUMMARY:</b>   |   |   |  |
| <p>This is a 505(b)(2) application. The Applicant, Tiber Laboratories LLC, submitted the application to support this immediate release oral solution combination product containing hydrocodone bitartrate 2.5 mg and guaifenesin 200 mg per 5 ml). The proposed indication (b) (4)</p>  |   |   |  |
| <p>This is a clinical pharmacology program. The Applicant conducted two clinical pharmacology studies S09-0009 and S09-0010. 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. Study S09-0010 was a food effect study to compare the rate and extent of absorption of the combination product in the fasted vs. fed state. There are no clinical efficacy and safety studies included in the submission. In addition to the present submission (NDA 22-424) the 2 studies have previously been submitted to support NDA 22-279 (Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution Rx Only). For that submission, the clinical pharmacology studies submitted failed to show bioequivalence for the guaifenesin component of the combination product. Furthermore, an inspection conducted by the Division of Scientific Investigations (DSI) in the office of compliance identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. The deficiencies render the data unacceptable for use in the NDA to make regulatory decisions. A CR letter was issued for NDA 22-279 on January 26, 2011. Because the present submission (NDA 22-424) is supported by the same clinical pharmacology data that have been determined unacceptable for use in the NDA to make regulatory decisions, the approvability of the present NDA 22-424 submission has been preempted. However, from a regulatory perspective, the Division has decided that NDA 22-424 is fileable because the submission meets the requirement for submission of an NDA (21 CFR 314.54).</p> |   |   |  |
| There is one comment to be conveyed to the Applicant.  |   |   |  |
| <b>OUTSTANDING ISSUES:</b> none  |   |   |  |
| <b>RECOMMENDED REGULATORY ACTION</b>   |   |   |  |
| <b>NDA/SUPPLEMENTS:</b>  | <b>FILABLE</b> <input checked="" type="checkbox"/>              | <b>NOT FILABLE</b> <input type="checkbox"/>                           |  |
|  | <b>APPROVAL</b> <input type="checkbox"/>                        | <b>APPROVABLE</b> <input type="checkbox"/>                            | <b>NOT APPROVABLE</b> <input type="checkbox"/> |
| <b>OTHER ACTION:</b>   | <b>COMMENTS FOR SPONSOR</b> <input checked="" type="checkbox"/> |   |  |

## 1. GENERAL INFORMATION

This is a 505(b)(2) application. The Applicant, Tiber Laboratories LLC, submitted the application to support this immediate release oral solution combination product containing hydrocodone bitartrate 2.5 mg and guaifenesin 200 mg per 5 ml). The proposed indication for [REDACTED] (b) (4). As a basis for the 505(b)(2) submission route, the Applicant cites the following reference listed drug (RLD) and OTC monograph: 1) Hycodan<sup>1</sup> (NDA 05-213, Endo Pharmaceuticals), 2) 21 CFR 341.18 for guaifenesin.

The application is provided electronically.

## 2. CLINICAL DEVELOPMENT PROGRAM

This is a clinical pharmacology program. The Applicant conducted two clinical pharmacology studies S09-0009 and S09-0010. 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. Study S09-0010 was a food effect study to compare the rate and extent of absorption of the combination product in the fasted vs. fed state. There are no clinical efficacy and safety studies included in the submission.

### Reviewer's comment:

The submitted clinical studies are to support the NDA 22-424 [REDACTED] (b) (4) and NDA 22-279 [REDACTED] (b) (4). NDA 22-279 was originally submitted August 22, 2008 but was given a complete response (CR) 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 study design. The Applicant resubmitted NDA 22-279 in the complete response on July 26, 2010, presenting reports for two clinical pharmacology studies S09-0009 and S09-0010. The clinical pharmacology studies submitted failed to show bioequivalence for the guaifenesin component of the combination product. Furthermore, an inspection conducted by the Division of Scientific Investigations (DSI) in the Office of Compliance identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. The deficiencies render the data unacceptable for use in the NDA to make regulatory decisions. A CR letter was issued for NDA 22-279 on January 26, 2011. Because the present submission (NDA 22-424) is supported by the same clinical pharmacology data that have been determined unacceptable for use in the NDA to make regulatory decisions, the approvability of the present NDA 22-424 submission has been preempted. However, from a regulatory perspective, the Division has decided that NDA 22-424 is fileable because the submission meets the requirement for submission of an NDA (21 CFR 314.54).

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<sup>1</sup> Hycodan is not available in the market because the manufacturer has discontinued its marketing. The Applicant used hydrocodone oral solution (the generic hydrocodone oral solution product from ANDA 88-008 (originally Morton Grove now owned by Wockhardt) as the reference drug for hydrocodone.

### 3. FOREIGN MARKETING AND REGULATORY HISTORY

It is unclear if Tiber's (b) (4) was ever marketed abroad and in the US as an unapproved product.

### 4. ITEMS REQUIRED FOR FILING (21 CFR 314.50)

The following items pertinent to a clinical review are included in the submission:

- Application form (FDA 356h) [m1.1.2-fda-form-356h]
- Summary [m2.2-introduction to m2.7-summary]
- Clinical technical section
  - Clinical study reports
    - #S09-0009 and #09-0010 [m5 clin-stud]
    - Good Clinical Practice certification [m5.3.1.2.3 clin-stud-rep, Section 5 Ethics]
  - Debarment certification [m1.3-administrative-information\1.3.3-debarment-certification]
  - Pediatric use [m1.9.1-request-waiver-pediatric-studies]
  - Safety update [m5.3.6.2\tiber-safety update]
- Labeling [m1.14-labeling]
- Financial disclosure [m1.3-administrative-information\1.3.4-financial-certification-disclosure]

### 5. CLINICAL STUDIES

The Applicant conducted two clinical pharmacology studies S09-0009 and S09-0010. The study reports are appropriately indexed to allow review. A summary of the studies follows below.

#### Study S09-0009

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 Tiber's 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 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)

### Study S09-0010

Study S09-0010 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)

## 6. BRIEF REVIEW OF PROPOSED LABELING

The Applicant submitted the proposed labeling in the PLR format. The labeling review is not conducted at this time because the approvability of this NDA submission has been preempted.

## 7. DSI REVIEW AND AUDIT

The submitted clinical studies were to support the present NDA submission and NDA 22-279 (Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution Rx Only). In the NDA 22-279 review cycle, the clinical pharmacology team requested a DSI audit of the sites for the clinical pharmacology studies. The DSI audit 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. For more details readers are referred to DSI report [MEMORANDUM Division of Scientific Investigation, Martin K. Yau, Ph.D., January 20, 2011].

## 8. REVIEW TIMELINE

The schedule for review is provided in Table 1. Write-up will be concomitant with the review process. The initial draft review will be complete by June 29, 2011, and the primary review will be finalized before July 29, 2011.

Table 1: Review timeline for NDA 22-424

| Milestone                     | Target date for completion |
|-------------------------------|----------------------------|
| Filing and planning meeting   | TBD                        |
| Wrap-up meeting               | TBD                        |
| Labeling T-con                | TBD                        |
| Primary review                | July 29, 2011              |
| PDUFA Action date (10 months) | September 29, 2011         |

## 9. COMMENTS FOR THE SPONSOR

*We refer you to the recent Complete Response letter for NDA 22-279. Note that the bioequivalence study you submitted to support NDA 22-279 was judged as unacceptable by the Division of Scientific Investigations based on documentation irregularities, and the integrity of the bioanalytical data. Since you have submitted the same bioequivalence study to support your present NDA (22-424), its acceptability to support the approval of NDA 22-424 is in question and will be a review issue.*

Reviewed by:

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Xu Wang, M.D., Ph.D.  
Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products

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Anthony G. Durmowicz, M.D.  
Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

cc: Original NDA  
HFD-570/Division File  
HFD-570/ Durmowicz/Medical Team Leader  
HFD-570/Wang/Medical Reviewer  
HFD-715/Abugov/Biometrics Reviewer  
HFD-570/Whitehurst/Pharmacology-Toxicology Reviewer  
ONDQA/Shen/CMC Reviewer  
OCP/Agrawal/Clinical Pharmacology Reviewer  
HFD-570/Nabavian/CSO

**Clinical Filing Checklist**

**NDA/BLA Number: 22-439/22-442 Applicant: Cypress Stamp Date: Dec. 08, 2010**  
**Drug Name: Rezira-CC/Rezira NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

|                                       | <b>Content Parameter</b>  | <b>Yes</b> | <b>No</b> | <b>NA</b> | <b>Comment</b>   |
|---------------------------------------|---|------------|-----------|-----------|--|
| <b>FORMAT/ORGANIZATION/LEGIBILITY</b> |   |            |           |           |  |
| 1.                                    | Identify the general format that has been used for this application, e.g. electronic CTD.   | X          |           |           |  |
| 2.                                    | On its face, is the clinical section organized in a manner to allow substantive review to begin?  | X          |           |           |  |
| 3.                                    | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?   | X          |           |           |  |
| 4.                                    | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?  | X          |           |           |  |
| 5.                                    | Are all documents submitted in English or are English translations provided when necessary?   | X          |           |           |  |
| 6.                                    | Is the clinical section legible so that substantive review can begin?   | X          |           |           |  |
| <b>LABELING</b>                       |   |            |           |           |  |
| 7.                                    | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?  | X          |           |           |  |
| <b>SUMMARIES</b>                      |   |            |           |           |  |
| 8.                                    | Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?   | X          |           |           |  |
| 9.                                    | Has the applicant submitted the integrated summary of safety (ISS)?   | X          |           |           |  |
| 10.                                   | Has the applicant submitted the integrated summary of efficacy (ISE)?   | X          |           |           |  |
| 11.                                   | Has the applicant submitted a benefit-risk analysis for the product?  |            |           | X         | All components of this combo product are DESI or GRASE |
| 12.                                   | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?  | X          |           |           | Hycodan; cough and cold monograph                      |
| <b>DOSE</b>                           |   |            |           |           |  |
| 13.                                   | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?<br>Study Number:<br>Study Title:<br>Sample Size: Arms:<br>Location in submission: |            |           | X         |  |
| <b>EFFICACY</b>                       |   |            |           |           |  |
| 14.                                   | Do there appear to be the requisite number of adequate and well-controlled studies in the application?<br><br>Pivotal Study #1<br><br>Indication:   |            |           | X         |  |

|               | <b>Content Parameter</b>  | <b>Yes</b> | <b>No</b> | <b>NA</b> | <b>Comment</b>                           |
|---------------|---|------------|-----------|-----------|--|
|               | Pivotal Study #2<br><br>Indication:   |            |           |           |  |
| 15.           | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? |            |           | X         |  |
| 16.           | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.   |            |           | X         |  |
| 17.           | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?   |            |           | X         |  |
| <b>SAFETY</b> |   |            |           |           |  |
| 18.           | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?  | X          |           |           |  |
| 19.           | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?   |            |           | X         |  |
| 20.           | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?  |            |           | X         |  |
| 21.           | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>2</sup> ) been exposed at the dose (or dose range) believed to be efficacious?   |            |           | X         |  |
| 22.           | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?   |            |           | X         |  |
| 23.           | Has the applicant submitted the coding dictionary <sup>3</sup> used for mapping investigator verbatim terms to preferred terms?   | X          |           |           | MedDRA Ver 11                            |
| 24.           | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?   | X          |           |           |  |
| 25.           | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?  |            |           | X         | No deaths or discontinuations due to AEs |

<sup>2</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>3</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

|                               | <b>Content Parameter</b>   | <b>Yes</b> | <b>No</b> | <b>NA</b> | <b>Comment</b>  |
|-------------------------------|--|------------|-----------|-----------|-----------------|
| <b>OTHER STUDIES</b>          |  |            |           |           |                 |
| 26.                           | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?  |            |           | X         |                 |
| 27.                           | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)? |            |           | X         |                 |
| <b>PEDIATRIC USE</b>          |  |            |           |           |                 |
| 28.                           | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?  | X          |           |           |                 |
| <b>ABUSE LIABILITY</b>        |  |            |           |           |                 |
| 29.                           | If relevant, has the applicant submitted information to assess the abuse liability of the product?   | X          |           |           |                 |
| <b>FOREIGN STUDIES</b>        |  |            |           |           |                 |
| 30.                           | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?   |            |           | X         | No foreign data |
| <b>DATASETS</b>               |  |            |           |           |                 |
| 31.                           | Has the applicant submitted datasets in a format to allow reasonable review of the patient data?   | X          |           |           |                 |
| 32.                           | Has the applicant submitted datasets in the format agreed to previously by the Division?   | X          |           |           |                 |
| 33.                           | Are all datasets for pivotal efficacy studies available and complete for all indications requested?  | X          |           |           |                 |
| 34.                           | Are all datasets to support the critical safety analyses available and complete?   | X          |           |           |                 |
| 35.                           | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?   | X          |           |           |                 |
| <b>CASE REPORT FORMS</b>      |  |            |           |           |                 |
| 36.                           | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?                                     | X          |           |           |                 |
| 37.                           | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?       |            |           | X         |                 |
| <b>FINANCIAL DISCLOSURE</b>   |  |            |           |           |                 |
| 38.                           | Has the applicant submitted the required Financial Disclosure information?   | X          |           |           |                 |
| <b>GOOD CLINICAL PRACTICE</b> |  |            |           |           |                 |
| 39.                           | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?    | X          |           |           |                 |

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ YES \_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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Reviewing Medical Officer Date

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Clinical Team Leader Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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XU WANG  
02/08/2011

ANTHONY G DURMOWICZ  
02/09/2011