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APPLICATION NUMBER:

205474Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name	Xu Wang, M.D., Ph.D.
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Established Name	Guaifenesin and Hydrocodone Bitartrate Oral Solution
(Proposed) Trade Name	None
Therapeutic Class	Antitussive/expectorant
Applicant	Sovereign Pharmaceuticals, LLC
Priority Designation	S
Formulation	Oral solution
Dosing Regimen	For patients 18 years and older: 10 mL every 4 to 6 hours, no to exceed 6 doses (60 mL) in 24 hours
Indication	Symptomatic relief of cough and to loosen mucus associated with common cold
Intended Population	Adults 18 years and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend an “Approval” action for this NDA application for symptomatic relief of cough and to loosen mucus associated with 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 guaifenesin and hydrocodone bitartrate (200 and 2.5 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 Pharmalac (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 and uses an OTC guaifenesin product as the RLD for guaifenesin component 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. The clinical pharmacology study demonstrated the bioequivalence between the proposed drug product Guaifenesin and Hydrocodone Bitartrate Oral Solution and the reference drugs, showing that the 90% CI of ratios of AUC and C_{max} for the two components in Guaifenesin and Hydrocodone Bitartrate Oral Solution vs. reference drugs are within the 80 - 125% goal post for bioequivalence.

The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. The agreement has been reached between the Applicant and the Division for a pediatric study plan, in which a partial waiver for pediatric studies is granted below 6 years of age because hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. However, pediatric studies in the population from 6 to less than 18 years of age for pharmacokinetics (PK) and safety data in this age group are required. The Pediatric Review Committee (PeRC) agreed with the Division to grant a partial waiver for pediatric studies below 6 years of age and to grant a deferral for the PK and safety studies in the pediatric population from 6 to under 18 years of age to a post-approval phase because adult studies are completed and the product is ready for approval in adults.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Applicant did not submit a risk management plan for the proposed drug product. Routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of Guaifenesin and Hydrocodone Bitartrate Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

1.2.2 Required Phase 4 Commitments

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. (b) (4)

[REDACTED]

[REDACTED]. In an Agency regulatory briefing regarding the abuse potential safety testing for hydrocodone cough and cold combination products on June 12, 2009, the consensus was that abuse liability studies were not required prior to approval of these drug products but that studies may be necessary on a case-by-case basis if a signal is detected post-marketing.

No special Phase 4 commitments are recommended at this time. A routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of Guaifenesin and Hydrocodone Bitartrate Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

1.2.3 Other Phase 4 Requests

The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. The Applicant requested a partial waiver for pediatric studies below 6 years of age because hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. Pediatric studies in population from 6 to less than 18 years of age for pharmacokinetics and safety data in this age group are required.

The proposed dose for guaifenesin is the same as the dose in the Agency's approved OTC Monograph. Since the dose proposed in the combination product is within the doses that were declared by the Agency to be safe and effective for OTC use, no additional PK data is necessary to support the guaifenesin dose. However, hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age. Safety concerns of dose-related respiratory depression over the last few years raises the issue of the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression, including fatalities due to respiratory failure has been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children less than 6 years of age, and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require that the Applicant establish the appropriate dose of hydrocodone for the pediatric (less than 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population.

The Division discussed with the Applicant regarding the concerns of lacking PK and safety data of hydrocodone in the pediatric population. The Applicant agreed to conduct PK and safety studies in the pediatric population from 6 to less than 18 years of age to a post-approval phase. The Applicant submitted a pediatric study plan that was discussed at the Pediatric Review Committee (PeRC) PREA Subcommittee meeting on May 7, 2014. The PeRC agreed the Division to grant a partial waiver for pediatric studies below 6 years of age and to grant a deferral for the PK and safety studies in the pediatric population from 6 to less than 18 years of age to a post-approval phase because adult

studies are completed and the product is ready for approval in adults. The agreed on post-approval pediatric studies are listed below:

- a. Conduct a study to assess the pharmacokinetics of each active component in proposed drug product in (b) (4) children ages 6-17 years with symptoms of (b) (4)

The timelines for protocol submission, study initiation, and final report submission dates for the study are set to be March 2015, September 2015, and March 2017, respectively.

- b. Conduct a study to assess the safety of the proposed drug product in (b) (4) children 6 -17 years of age with symptoms of (b) (4)

Although this study is primarily a safety study, the effectiveness of the proposed drug will be assessed. (b) (4)

The timelines for protocol submission, study initiation, and final report submission dates for the study are set to be September 2018, March 2019, and September 2022.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is a clinical pharmacology program. The application relies on the Agency's findings of safety and efficacy of Hycodan (NDA 5-213) and subsequent DESI review to support the efficacy and safety of the hydrocodone component, and relies on the OTC Monograph to support the safety and efficacy of the guaifenesin component in the proposed drug product. The Applicant's drug development program for is based on establishing that their combination product produces exposures that are equivalent to that of approved and marketed products for hydrocodone and to that of OTC Monograph dose of guaifenesin. The bioequivalent data come from one single dose clinical pharmacology Study 11244403, and the food effect data come from a single dose food effect Study 92001. There were no clinical efficacy or safety studies in this application.

The Applicant submitted a Summary of Clinical Safety including the safety data from the clinical pharmacology studies and a literature survey to provide support for the safety of the proposed drug product.

1.3.2 Efficacy

No clinical efficacy studies were submitted to support this application. This is a 505(b)(2) application using bioequivalence approach to support the approval. The Agency's previous findings of efficacy and safety of the approved hydrocodone NDA (Hycodan) and the OTC Monograph for guaifenesin are used to substantiate the efficacy and safety of this combination product.

1.3.3 Safety

The safety of the proposed product is based on establishing bioequivalence of the product compared to the approved reference product for hydrocodone and the OTC Monograph for guaifenesin. In addition, the Applicant provided a Summary of Clinical Safety including the safety data from the clinical pharmacology studies and a literature survey. In 3 clinical pharmacology studies a total of 146 subjects received single dose of the test drug Guaifenesin and Hydrocodone Bitartrate Oral Solution. There were no death or serious adverse event occurred in the clinical pharmacology studies. The most common adverse events were headache, somnolence, dizziness, and nausea. There were no significant difference in adverse events between the test drug and reference hydrocodone and guaifenesin. The adverse events occurred in the clinical pharmacology studies did not reveal a new safety signal.

The post-marketing adverse events from the AERS database covered the period from October, 2007 through March, 2008. The AERS database search used terms of hydrocodone (HC), hydrocodone plus chlorpheniramine (HC/CPM), and hydrocodone plus acetaminophen (HC/ACT). There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The proposed drug product was marketed as an unapproved drug product under the name of (b) (4) in the United States from February 2006 through October 2007. During the period (b) (4) size were distributed. There have been no adverse event reports received by the Applicant from any source for the proposed drug product.

The Applicant compiled nine literature references for information relevant to safety of hydrocodone and guaifenesin in general. The references included the product labeling of the reference drug Hycodan, and articles published in peer reviewed journals. The literature survey revealed no new safety signals for hydrocodone and guaifenesin. The result of the literature review is provided in the Section 8.6 of this review.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 120-day safety update for the proposed drug product on April 10, 2014. Since the submission of the NDA, the Applicant has conducted no clinical studies, received no adverse event reports regarding safety of hydrocodone and guaifenesin. A search of published literature yielded no additional safety information for active ingredients hydrocodone and guaifenesin.

1.3.4 Dosing Regimen and Administration

The proposed drug 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: "Symptomatic relief of cough and to loosen mucus associated with common cold." The dose regimen is 10 mL every 4 to 6 hours for patients 18 years of age and older, not to exceed 6 doses (60 mL) in 24 hours.

1.3.5 Drug-Drug Interactions

There is no drug-drug interaction study conducted in this NDA submission. The result of a clinical pharmacology study (11244403) showed that for hydrocodone, the geometric mean ratios (combination/reference) of AUC 0-t, AUC 0-∞ and Cmax were 1.03 (90% CI = 1.00, 1.07), 1.03 (90% CI = 1.00, 1.07), and 1.17 (90% CI = 0.96, 1.05), respectively, and for guaifenesin, the least

square geometric mean ratios (combination/reference) of AUC 0–t, AUC 0–∞ and C_{max} were 1.08 (90% CI = 1.02, 1.13), 1.08 (90% CI = 1.02, 1.13), and 1.11 (90% CI = 1.01, 1.21), respectively. These data suggest that no apparent drug-drug interaction between hydrocodone and guaifenesin in proposed drug, because there are no differences in hydrocodone and guaifenesin exposure between the proposed drug product Guaifenesin and Hydrocodone Bitartrate Oral Solution and the reference hydrocodone solution and guaifenesin solution. More information regarding possible drug-drug interaction in the Guaifenesin and Hydrocodone Bitartrate Oral Solution may be found in the Clinical Pharmacology Review [NDA 205-474, Clinical Pharmacology Review, Yunzhao Ren, Ph. D.].

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 addressed these potential drug-drug interactions.

1.3.6 Specific Populations

There were no studies in specific populations for Guaifenesin and Hydrocodone Bitartrate 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 Guaifenesin and Hydrocodone Bitartrate Oral Solution is administered to nursing mothers. The information about the hydrocodone excreted in breast milk and the potential risks of hydrocodone use in nursing women should be added to the proposed labeling.

Reviewer's comment:

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

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

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

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The Applicant has developed an immediate release oral solution formulation of guaifenesin and hydrocodone bitartrate. 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 indication is: "Symptomatic relief of cough and to loosen mucus associated with common cold." The dosing regimen is 10 mL every 4 to 6 hours, not to exceed 6 doses (60 mL) in 24 hours for patients 18 years of age and older. This is a 505(b)(2) application and the Applicant has provided an electronic submission.

As a basis for the 505(b)(2) submission route, the Applicant cited the following reference listed drugs (RLDs) and OTC Monograph in their original NDA submission: 1) Hycodan (Hydrocodone Bitartrate /Homatropine Methylbromide Syrup (5 mg/1.5 mg per 5 mL), NDA 05-213, and 2) 21 CFR 341.18 for guaifenesin. Because the Hycodan syrup manufactured by Endo Pharmaceuticals was discontinued from the market (not for reasons of safety or efficacy), the Applicant conducted the clinical pharmacology study using the hydrocodone bitartrate/homatropine methylbromide syrup developed by HI-TECH Pharma as the reference drug for hydrocodone. HI-TECH Pharma's product is a generic drug (ANDA 40-613).

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

Hydrocodone Syrup (HC 5 mg plus homatropine methylbromide (HTM) 1.5 mg) was classified in the DESI review as safe and effective for prescription drug for symptomatic relief of cough (DESI Notice #5123). Hycodan has the following approved dosage (Hycodan product labeling):

- Adults: One teaspoonful of the syrup (5 mg HC) every 4 to 6 hours as needed; not to exceed (NTE) 6 teaspoonfuls (30 mg HC) in 24 hours
- Children 6 to 12 years of age: One-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 teaspoonfuls (15 mg HC) in 24 hours

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 341.72]:

- 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

The OTC Monograph considers the combination of any single Monograph oral antitussive drug (such as codeine phosphate) with single expectorant to be a permitted combination [21 CFR 341.40].

The Applicant does not have an agreed trade name for the proposed drug product at this time.

Reviewer's comment:

Hydrocodone, a schedule II controlled substance and a prescription drug, is not an OTC Monograph antitussive. Therefore, the proposed combinations of HC/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 program 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, provided that bioequivalence can be established with the reference products.

Although Hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age, safety concerns of dose-related respiratory depression over the last few years raise the issue of the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression cases, including fatalities due to respiratory failure have been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children less than 6 years of age, and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require that the sponsor establish the appropriate dose of hydrocodone for the pediatric (≤ 17 years old) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population. The Applicant will need to conduct PK and safety studies in the pediatric population from 6 to 17 years of age.

2.2 Currently Available Treatment for Indications

Hydrocodone is currently approved in the United States in tablet and syrup as an immediate release antitussive drug (Hycodan, NDA 5-213, approved on March 23, 1943). On February 4, 2009, Endo Pharmaceuticals (the maker of Hycodan) informed FDA that manufacture of Hycodan syrup was discontinued on May 14, 2008 and Hycodan tablet manufacture was discontinued on January 4, 2008. The discontinuation of Hycodan manufacture was not because of reasons of safety or efficacy. The last lot of drug expired on December 31, 2008 (syrup) and January 31, 2009 (tablets). Endo Pharmaceuticals did not withdraw the NDAs for Hycodan products and therefore, can resume marketing the products again in the future. Hydrocodone is also approved in combination with chlorpheniramine in an extended release suspension for cough (Tussionex Pennkinetic, NDA 19-111). Hydrocodone is also available in immediate release solutions in combination with pseudoephedrine (NDA 22-442) and with chlorpheniramine and pseudoephedrine (NDA 22-439). There are other generic Hydrocodone products as antitussive drugs on the market. These are Hydrocodone Compound (ANDA 88-017), Tussicaps (ANDA 77-273), Tussigon (ANDA 88-506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40295, ANDA 40-613, ANDA 88-008).

Guaifenesin is a readily available non-prescription Monograph drug, being considered to be generally recognized as safe and effective (GRASE) at OTC Monograph dose 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 (Tussionex Pennkinetic, NDA 19-111), with pseudoephedrine in immediate release solution (Rezira, NDA 22-442) and with chlorpheniramine and pseudoephedrine immediate release solution (Zutripro, NDA 22-439), and generic antitussive drugs Hydrocodone Compound (ANDA 88-017), Tussicaps (ANDA 77-273), Tussigon (ANDA 88-506), and Homatropine Methylbromide and Hydrocodone Bitartrate Tablet and Syrup (ANDA 40-295, ANDA 40-613, ANDA 88-008). 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 20-716), Vicodin and Vicodin HP (ANDA 88-058, ANDA 40-117), Lortab (ANDA 40100, ANDA 87-722), and Anexsia (ANDA 40-405, ANDA 40-409, ANDA 89-729, ANDA 40-686, ANDA 89-160). 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].

Guaifenesin is a readily available non-prescription Monograph drug in the United States in immediate-release and extended-release formulations.

The proposed drug product has been marketed as an unapproved drug product under the name of (b)(4) in the United States from February 2006 through October 2007. During the period (b)(4) size were distributed. The Applicant ceased the distribution of the proposed drug product following the FDA's announcement intending 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].

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), and, according to 21 CFR 1308 published on February 27, 2014 in Federal Register Volume 79, Number 39, all HC combination products (analgesic and antitussive) are placed into schedule II controlled substance as well.

2.5 Presubmission Regulatory Activity

The Applicant had a pre-IND meeting on April 14, 2008 with the Division to discuss the plan to conduct a clinical pharmacology program in order to file an NDA for their unapproved drug product (b)(4). The Division's comments in the pre-IND meeting are summarized as follows [Pre-IND 101,683 Meeting Minutes, April 30, 2008]:

- A 505(b)(2) pathway would be an acceptable approach for the planned combination drug products;
- No additional pre-clinical studies are required for the IND/NDA submission based on the approved NDA products and OTC Monograph;

- The bioequivalence should be demonstrated between the proposed products and an approved hydrocodone antitussive drug product (e.g. Hycodan) and a solution of guaifenesin by conducting bioequivalent studies;
- In addition to the food effect on the proposed drug product, the potential drug-drug interaction between hydrocodone and guaifenesin should be addressed. This information may be provided from the literature or by conducting pharmacokinetic drug-drug interaction studies.

The Applicant submitted an opening IND on February 26, 2009, for the proposed Hydrocodone and Guaifenesin Oral Solution (IND 101,683). Subsequently at the pre-NDA meeting on November 9, 2011, the Applicant presented the data showing that the guaifenesin component of the proposed drug product had a significantly higher bioavailability than that of the reference guaifenesin solution. The Applicant contributed the higher relative bioavailability of the proposed drug product to the formulation effect of the reference guaifenesin solution prepared by the Applicant. The Division indicated that the proposed drug product should be bioequivalent to the reference drug, and advised the Applicant to also consider the possible issues with the formulation for their product, for example the (b)(4) propylene glycol and sorbitol. [IND 101,683, Pre-NDA Meeting Minutes, December 8, 2011]

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The drug product is an oral aqueous solution containing guaifenesin USP 200 mg and hydrocodone bitartrate USP 5 mg per 5 mL. This is an immediate release formulation. The excipients in the test formulation include glycerin, propylene glycol, methylparaben, propylparaben, citric acid, potassium citrate, potassium sorbate, sodium saccharin, and flavoring agents Raspberry (b)(4) Cherry (b)(4) (The oral solution is either raspberry flavored or cherry punch flavored.) The proposed combination drug product is manufactured by Sovereign Pharmaceuticals, LLC. At the manufacturing facility at 7590 Sand Street, Fort Worth, Texas. The Applicant certified that the facility, equipment, methods, and controls used in the manufacture, packaging, holding and testing of drug products and their components are in conformance with Current Good Manufacturing Practice as defined in 21 CFR 210 and 211 [m3, Section 3.2 P.3.1, page 1]. A detailed review of the CMC portion of the application may be found in the ONDQA review.

The Applicant (Sovereign Pharmaceuticals, LLC) obtains guaifenesin from (b)(4) and reference DMF (b)(4). This DMF has been reviewed in the recent past and has been found acceptable for support of approved solid oral dosage form (SODF) drug products. Hydrocodone bitartrate drug substance is obtained from (b)(4) and the application references DMF (b)(4). This DMF was recently reviewed to support a solid oral dosage form and was found to be inadequate.

The proposed drug product Guaifenesin and Hydrocodone Bitartrate Oral Solution is a non-sterile oral solution. The drug product contains methylparaben (b)(4) and propylparaben (b)(4). As part of product development, testing was performed on product containing (b)(4)

(b) (4)

The product quality microbiology reviewer recommends an approval from a quality microbiology standpoint [NDA 205-474, Product Quality Microbiology Review, Erika Pfeiler, Ph. D., Microbiologist].

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 the Agency's previous findings of efficacy and safety of the proposed drug product to the reference drug Hycodan and the OTC Monograph product guaifenesin. The Applicant's drug development program for Guaifenesin and Hydrocodone Bitartrate Oral Solution is based on establishing that their combination product produces exposures that are equivalent to that of approved and marketed products for hydrocodone and to that of OTC Monograph dose of guaifenesin. The bioequivalence data come from one clinical pharmacology, Study 11244403, and the food effect data come from Study 92001. There were no clinical efficacy or safety studies in this application.

4.2 Table of Clinical Studies

The Applicant has submitted 4 clinical pharmacology study reports as listed in Table 1 below.

Table 1. Summary of Clinical Pharmacology Studies in the application

Type of study	Study ID	n	Objective of the study	Reference listed drug (RLD)
Relative BA	R08-0467	20	Comparison of sponsor's hydrocodone with RLD	Hycodan®
Food effect	92001	27	Food effect of proposed product	Proposed product (fed/fasted)
Relative BA and DDI	92002	36	Comparison of proposed product with RLD	Hydrocodone + Homatropine (HiTech); Guaifenesin
Relative BA and DDI	11244403	56	Comparison of proposed product with RLD	Hydrocodone + Homatropine (HiTech); Guaifenesin

Study R08-0467 was a randomized, single-dose, open-label, two-way crossover study in healthy volunteers to compare the relative bioavailability of the Applicant's hydrocodone bitartrate solution (5 mg/5 mL) with Hycodan Syrup under fasting conditions. This was a pilot study in the Applicant's drug development program to assess the bioavailability of their hydrocodone bitartrate solution in comparison with that of the reference drug Hycodan Syrup. Note that the test drug hydrocodone bitartrate solution is not the proposed drug product in this NDA submission. Therefore, the data from this study is not included in this review.

Study 92001 was a randomized, single-dose, open-label, 2-way crossover food effect study in healthy volunteers to assess the bioavailability of the proposed drug product Hydrocodone Bitartrate and Guaifenesin Oral Solution under fasting and fed conditions.

Study 92002 was a randomized, single-dose, open-label, 4-way crossover, comparative bioavailability study in healthy volunteers to compare the relative bioavailability of the proposed drug product Hydrocodone Bitartrate and Guaifenesin Oral Solution with reference drugs hydrocodone bitartrate solution, guaifenesin solution, and hydrocodone bitartrate solution plus guaifenesin solution. The results of this study showed that the guaifenesin component of the proposed drug product had a significant higher bioavailability than that of the reference guaifenesin solution. The Applicant contributed the higher relative bioavailability of the proposed drug product to the formulation effect of the reference guaifenesin solution prepared by the Applicant. The Applicant then re-conducted the study with another commercially available guaifenesin solution as the reference drug for guaifenesin component of the proposed drug product. Only safety data are included in this review.

Study 11244403 was basically a duplicate study of the Study 92002 with a new reference guaifenesin solution. The results of this study, together with the data obtained from the food effect study, formed the base of this NDA submission.

4.3 Review Strategy

This is mainly a review of the safety data of clinical pharmacology studies in which the proposed drug product was administered. It is also reviewed the literatures for hydrocodone and guaifenesin safety data and the data for post-marketing and spontaneous adverse event reports.

4.4 Data Quality and Integrity

This is a clinical pharmacology program. The clinical pharmacology team requested the Division of Scientific Investigation (DSI) audit for the bioanalytics of Study 11244403. FDA investigators conducted the inspection at (b) (4)

(b) (4) The audit included a thorough review of the study records, examinations of facilities and equipment, and interviews and discussions with the firm's management and staff. During the audit, FDA investigators did not observe any objectionable conditions, identified no deficiencies, and did not issue Form FDA-483 at the conclusion of the inspection. The inspection concluded that “the bioanalytical data from study 11244403 are acceptable for further Agency review”. [Memorandum, DSI Report on an Audit of Study 11244403, Hansong Chen, Ph. D., July 29, 2014]

4.5 Compliance with Good Clinical Practices

The clinical pharmacology studies in this application were conducted in accordance with the U.S. Code of Federal Regulations Guidelines for Good Clinical Practice (Code of Federal Regulations (21 CFR), Parts 50, 54, 56, 312 and 314), the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (ICH Guideline E6), the Declaration of Helsinki on the ethical conduct of medical research, and the Belmont Report [m5, Section 5.2, page 17].

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 investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant stated that the clinical investigators of the clinical pharmacology studies in this application certified that they did not disclose any proprietary interest in the proposed product. The clinical investigators certified that he was not a recipient of significant payments defined in 21 CFR 54.2(f) [m1, FDA Form 3454, page 1].

5 CLINICAL PHARMACOLOGY

There are 4 clinical pharmacology studies in this NDA. A summary of data of the clinical pharmacology studies are presented in Section 5.1 Discussion of Individual Studies/Clinical Trials below. Detailed information can be found in the Clinical Pharmacology Review [NDA 205-474, Clinical Pharmacology Review, Yunzhao Ren, Ph. D.].

The formulation of the proposed drug product Hydrocodone Bitartrate and Guaifenesin Oral Solution is displayed in Table 2. The experimental formulation is manufactured and supplied by Sovereign Pharmaceuticals, LLC.

Table 2 Formulation of Guaifenesin and Hydrocodone Bitartrate Oral Solution

Ingredient	% w/v	mg/5 mL	Function
Hydrocodone bitartrate, USP	0.044	2.50	Active ingredient
Guaifenesin, USP	3.518	200.00	Active ingredient
Glycerin, NF			(b) (4)
Polylene glycol, NF			(b) (4)
Methylparaben, NF			(b) (4)
Propylparaben, NF			(b) (4)
Citric acid (b) (4), NF			(b) (4)
Potassium citrate, NF			(b) (4)
Potassium sorbate, NF			(b) (4)
(b) (4) *			(b) (4)
Cherry (b) (4) *			(b) (4)
Saccharin sodium, NF			(b) (4)
Purified water, USP			(b) (4)
Total weight, 5 mL dose	100.00		(b) (4) -----

NF = National Formulary (Source: m2, Section 2.3.P.1, page 2)

* Raspberry (b) (4) is the flavoring agent in some batches of formulation to give a flavoring choice for the proposed drug product.

5.1 Discussion of Individual Studies/Clinical Trials

Study 11244403 was a randomized, single-dose, open-label, 4-way crossover, comparative bioavailability study in 56 healthy volunteers 18 years of age and older to compare the relative bioavailability of the proposed drug product Hydrocodone Bitartrate and Guaifenesin Oral Solution with reference drugs hydrocodone bitartrate solution, guaifenesin solution, and hydrocodone bitartrate solution plus guaifenesin solution. The study subjects were randomized to receive a single dose of the following 4 treatments after an overnight fasting: A. Proposed drug product Hydrocodone Bitartrate and Guaifenesin Oral Solution (10 mL, 2.5/200 mg per 5 mL); B. Hi-Tech Pharma’s Hydrocodone Bitartrate /Homatropine Methylbromide Syrup (5 mL, 5 mg/1.5 mg, ANDA

40-613); C. Capellon Pharmaceuticals Guaifenesin Solution (10 mL, 200 mg per 5 mL); and D. Hydrocodone Bitartrate /Homatropine Methylbromide Syrup plus Capellon Pharmaceuticals Guaifenesin Solution (B + C). After a 7-day washout period the study subject would then cross over to receive another treatment until each subject received all 4 treatments. The following pharmacokinetic variables were calculated for each treatment: AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , and $t_{1/2}$.

Blood samples were collected from each subject pre-dose (0 hour) and at 0.083, 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 7, 10, 15, and 20 hours post-dose during each period of the study. The total volume of blood collected during the study from each subjects was approximately 554 mL, including pharmacokinetic samplings and samples for clinical laboratory tests.

Table 3 shows the PK measurements of the Study 11244403. The Applicant compared the PK of hydrocodone and guaifenesin between the proposed drug product and the reference drugs. The comparison shows that the 90% confidence intervals of ratios of AUC and C_{max} for two components in Guaifenesin and Hydrocodone Bitartrate Oral Solution and reference drugs are within the 80 - 125% goal post for bioequivalence. The 90% confidence intervals of the geometric mean $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} for the co-administration of the guaifenesin and hydrocodone Reference Products compared to each Reference product administered separately were contained within the bioequivalence interval 0.80 to 1.25. There was no evidence of significant drug interaction between the immediate-release guaifenesin and hydrocodone doses administered in this study.

Table 3 Pharmacokinetics results, Study 11244403

PK Parameters	AUC_{0-inf} (pg.hr/mL) Geometric Mean	AUC_{0-t} (pg.hr/mL) Geometric Mean	C_{max} (pg/mL) Geometric Mean	T_{max} (hr) Mean	$t_{1/2}$ (hr) Mean
A. Test Drug					
Hydrocodone	80186	75373	12501	1.25	4.81
Guaifenesin	4222	4202	3711	0.333	0.855
B. Reference					
Hi-Tech's Hydrocodone	80630	75922	13351	1.00	4.78
C. Reference					
Guaifenesin	4070	4050	3593	0.333	0.865
D. Reference					
Hydrocodone plus Guaifenesin	83272	78402	13415	1.00	4.78
	4373	4352	3593	0.333	0.865
Ratio of Test Drug vs ref. (90% CI)					
Hydrocodone (A vs B)	0.99 (0.96 -1.03)	0.99 (0.96- 1.03)	0.94 (0.90 -0.98)	---	---
Guaifenesin (A vs C)	1.04 (0.99 -1.09)	1.04 (0.99 -1.09)	1.03 (0.94- 1.13)	---	---

(Source: NDA 205-474 N-000, m5, Section 5.3.1.2, #403, pages 36-38)

Study 92001 was a randomized, single-dose, open-label, 2-way crossover study in 25 healthy volunteers 18 years of age and older to compare the rate and extent of absorption of the proposed drug product Hydrocodone Bitartrate and Guaifenesin Oral Solution under fed and fasted conditions. The study subjects were randomized to receive a single dose of the proposed drug product Hydrocodone Bitartrate and Guaifenesin Oral Solution (10 mL, 2.5/200 mg per 5 mL) under fed or fasted condition (fasted for at least 11 hours). After a 7-day washout period the study subject would then cross over to receive another treatment. The following pharmacokinetic variables were calculated for each treatment: AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , and $t_{1/2}$.

For hydrocodone, a total of 19 blood samples were drawn from each subject for PK analyses: at pre-dose (0), and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 20, and 24 hours post-dose. For guaifenesin, a total of 17 blood samples were drawn from each subject for pharmacokinetic analyses: at pre-dose (0), and 0.167, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, and 24 hours post-dose. The total volume of blood collected during the study from each subject was approximately 366 mL, including pharmacokinetic samplings and samples for clinical laboratory tests.

The PK measurements of the Study 92001 are listed in Table 4 below. For hydrocodone the 90% confidence intervals of ratios of AUC and C_{max} for fed-to-fasted are within the bioequivalence interval 0.80-1.25. For guaifenesin, however, the 90% confidence intervals of ratios of AUC and C_{max} for fed-to-fasted are below the bioequivalence lower limit of 0.80.

Table 4 Pharmacokinetics results, Study 92001

PK Parameters	AUC _{0-inf} (pg.hr/mL) Geometric Mean	AUC _{0-t} (pg.hr/mL) Geometric Mean	C _{max} (pg/mL) Geometric Mean	T _{max} (hr) Mean	t _{1/2} (hr) Mean
Test Drug, fed					
Hydrocodone	81158	77609	10958	1.43	5.17
Guaifenesin	2529	2495	1658	0.364	0.953
Test Drug, fasted					
Hydrocodone	70109	67323	12450	0.94	5.19
Guaifenesin	4821	4789	5295	0.330	0.901
Fed/fasted, ratio (90% CI)					
Hydrocodone	1.158 (1.12– 1.19)	1.153 (1.12–1.18)	0.880 (0.82 – 0.94)	---	---
Guaifenesin	0.525 (0.45– 0.60)	0.521 (0.44–0.60)	0.313 (0.16 – 0.46)	---	---

(Source: NDA 205-474 N-000, m5, Section 5.3.1.2, #92001, page 43)

Table 4 shows that the amount of guaifenesin absorption appears to be reduced by almost 50% when the Test drug is administered with food. However, this food effect on guaifenesin absorption has no significant impact on the efficacy and safety of the proposed drug product. The efficacy of guaifenesin is supported by OTC Monograph, and the OTC Monograph [21 CFR 341.72] specified guaifenesin dose is ranged from 200 to 400 mg every 4 to 6 hours. So as the proposed drug product being administered with food at the proposed dose (i.e., 400 mg every 4 to 6 hours), a decreased absorption of 50% would still result in an exposure that is effective per OTC Monograph. With regard to safety, a lower absorption of guaifenesin is not a safety concern.

Study R08-0467 was a randomized, single-dose, open-label, two-way crossover study in healthy volunteers to compare the relative bioavailability of the Applicant's hydrocodone bitartrate solution (5 mg/5 mL) with Hycodan Syrup under fasting conditions in 20 healthy volunteers. This is a pilot study in the Applicant's drug development program to assess the bioavailability of their hydrocodone bitartrate solution in comparison with that of the reference drug Hycodan Syrup. Because the test drug hydrocodone bitartrate solution in this study is not the proposed drug product in this NDA submission, the data obtained from this study are not included in this review.

Study 92002 was a randomized, single-dose, open-label, 4-way crossover, comparative bioavailability study in 34 healthy volunteers to compare the relative bioavailability of the proposed drug product Hydrocodone Bitartrate and Guaifenesin Oral Solution with reference drugs hydrocodone bitartrate solution, guaifenesin solution, and hydrocodone bitartrate solution plus guaifenesin solution. The results of this study showed that the guaifenesin component of the

proposed drug product was not bioequivalent to the reference guaifenesin solution prepared by the sponsor. The guaifenesin of the test drug had a significantly higher bioavailability (189% in C_{max} and 162% in AUC) than that of the reference guaifenesin solution. The Applicant concluded that the formulation effect of their own guaifenesin solution reference resulted in the higher C_{max} and AUC of guaifenesin in the proposed drug product. The Applicant then re-conducted the study (i.e. Study 11244403) with a commercially available Guaifenesin Solution (manufactured by Capellon Pharmaceuticals) as the reference drug for guaifenesin component of the proposed drug product. The pharmacokinetic data obtained from study 92002 are not presented in this review. However, safety data are included because the subjects in the study who were exposed to the proposed drug product.

6 INTEGRATED REVIEW OF EFFICACY

This application is supported by the bioequivalence of the proposed drug product and the approved hydrocodone product (Hi-Tech Pharma's Hydrocodone Bitartrate /Homatropine Methylbromide Syrup, ANDA 40-613) and OTC Monograph drug guaifenesin. No clinical efficacy studies were conducted to support this application.

6.1 Indication

The indication for Guaifenesin and Hydrocodone Bitartrate Oral Solution is: "Symptomatic relief of cough and to loosen mucus associated with common cold."

7 INTEGRATED REVIEW OF SAFETY

The Applicant provided a Summary of Clinical Safety including the safety data from the clinical pharmacology studies and a literature survey. In 3 clinical pharmacology studies a total of 146 subjects received single dose of the test drug Guaifenesin and Hydrocodone Bitartrate Oral Solution. There were no death or serious adverse event occurred in the clinical pharmacology studies. The most common adverse events were headache, somnolence, dizziness, and nausea. There were no significant difference in adverse events between the test drug and reference hydrocodone and guaifenesin. The adverse events occurred in the clinical pharmacology studies did not reveal a new safety signal.

The post-marketing adverse events from the AERS database covered the period from October, 2007 through March, 2008. The AERS database search used terms of hydrocodone (HC), hydrocodone plus chlorpheniramine (HC/CPM), and hydrocodone plus acetaminophen (HC/ACT). There were no new safety signals revealed through the search of AERS database for post-marketing adverse events.

The proposed drug product was marketed as an unapproved drug product under the name of (b) (4) in the United States from February 2006 through October 2007. During the period (b) (4) size were distributed. There have been no adverse event reports received by the Applicant from any source for the proposed drug product.

The Applicant compiled nine literature references for information relevant to safety of hydrocodone and guaifenesin in general. The references included the product labeling of the reference drug Hycodan, and articles published in peer reviewed journals. The literature survey revealed no new safety signals for hydrocodone and guaifenesin. The result of the literature review is provided in the Section 8.6 of this review.

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 120-day safety update for the proposed drug product on April 10, 2014. Since the submission of the NDA, the Applicant has conducted no clinical studies, received no adverse event reports regarding safety of hydrocodone and guaifenesin. A search of published literature yielded no additional safety information for active ingredients hydrocodone and guaifenesin.

7.1 Methods and Findings

7.1.1 Deaths

There was no death in the clinical pharmacology studies in this application.

7.1.2 Other Serious Adverse Events

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

7.1.3 Dropouts and Other Significant Adverse Events

A total of 60 healthy volunteers were enrolled into the clinical pharmacology Study 11244403. There were 10 subjects who did not take all 4 treatments (test drug and 3 references) by not returning to the study site at different stage of the study. No subject dropped off the study due to adverse reactions.

A total of 28 healthy volunteers were enrolled into the food effect Study 92001. There were 2 subjects were withdrawn from the study due to adverse events, including vasodilat, nausea, headache, and dizziness.

In the clinical pharmacology Study 92002, a total of 36 healthy volunteers were enrolled. There were 2 subjects who did not take all 4 treatments (test drug and 3 references) by missing a dosing at different stage of the study. No subject dropped off the study due to adverse reactions.

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 3 clinical pharmacology studies (bioavailability/bioequivalent studies 11244403 and 92002, and food effect study 92001), a total of 146 subjects received single dose of the test drug Guaifenesin and Hydrocodone Bitartrate Oral Solution. There were 54 subjects (36.98%) reported adverse events during the study. The most common adverse events were headache (16, 11%), somnolence (16, 11%), dizziness (15, 10.3%), and nausea (14, 9.6%). There were no significant difference in adverse events between the test drug and reference hydrocodone and guaifenesin (Reference C). Table 5

below lists the common adverse events occurred in 3 clinical pharmacology studies. The adverse events occurred in the clinical pharmacology studies did not reveal a new safety signal.

Table 5 Common adverse events in PK studies

Adverse event*	Number (%) of subjects			
	Test drug N=146	Reference A N=94	Reference B N=93	Reference C N=92
Subject with any AE	54 (36.98)	26 (27.66)	18 (19.35)	33 (35.87)
Nervous system disorders				
Dizziness	15 (10.3)	5 (5.3)	1 (1.1)	14 (15.2)
Headache	16 (11.0)	7 (7.4)	3 (3.2)	6 (6.5)
Somnolence	16 (11.0)	9 (9.6)	8 (8.6)	13 (14.1)
Pre-syncope	2 (1.4)	3 (3.2)	0	1 (1.1)
Syncope	0	1 (1.1)	1 (1.1)	0
GI disorders				
Diarrhea	4 (2.7)	0	0	0
Nausea	14 (9.6)	7 (7.4)	0	4 (4.3)
Cardiovascular system disorders				
Bradycardia	1 (0.7)	2 (2.1)	0	0
Hypotension	3 (2.1)	3 (3.2)	0	0

Reference A: 5 mL of Hydrocodone Bitartrate and Homatropine Methylbromide Syrup, 5 mg/1.5 mg per 5 mL (manufactured by Hi-Tech Pharmacal Co., Inc.)

Reference B: 5 mL of Guaifenesin Oral Solution, 200 mg per 5 mL (manufactured by Capellon Pharmaceuticals, LLC)

Reference C: Reference A plus B

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 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 signs (respiratory rate, pulse rate, and blood pressure) were measured before-dosing, 3 hours post-dosing, and before the subjects leave the study center. No clinically significant changes were reported in the clinical pharmacology studies of this application.

7.1.9 Electrocardiograms (ECGs)

ECGs were not performed 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 hydrocodone¹. Manchikanti reported 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 2005². Although hydrocodone dosages as an antitussive are much lower than that of analgesics, hydrocodone-containing medications should be prescribed and administered with caution.

The proposed drug Guaifenesin and Hydrocodone Bitartrate Oral Solution is a schedule II controlled substance, which provides limitation to its accessibility for the unlawful use.

7.1.14 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were collected in the clinical pharmacological program. 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. A report revealed 2 cases of hydrocodone excretion in breast milk³. The infants of the mothers who were taking hydrocodone received an estimated 3.1% and 3.7% of the maternal weight-adjusted dosage. The absolute hydrocodone doses the infants received were 8.58 mcg/kg and 3.07 mcg/kg per day. One infant (18-day-old) became groggy and slept for most of the day while the mother was taking 20 mg hydrocodone every 4 hours. The infant's symptoms improved when mother decrease her hydrocodone dose by half. Another infant (5-week-old) became cyanotic and required intubation while the mother was taking hydrocodone and methadone for migraine headache. The infant was positive for opioids in urinary test and responded well to naloxone treatment. There are no reports of hydrocodone in breast milk while a mother takes hydrocodone at a much lower antitussive dosage. The prescribers and patients should be aware of the potential hydrocodone excretion into breast milk and use the proposed drug Hydrocodone Bitartrate and Guaifenesin Oral Solution with caution.

7.1.16 Overdose Experience

There is no overdose experience reported in the clinical pharmacological studies in this application. An AERS database search covering the period from October 2007 through March 2008 showed that overdose/misuse/error were frequently reported as adverse events associated with hydrocodone drug products. The reports in the AERS database did not differentiate whether the hydrocodone was taken as antitussives or at much higher dosages as analgesics.

Reviewer's comment:

The potential for abuse including overdose with hydrocodone is well recognized. However, the Applicant has not provided specific data in the NDA to evaluate the abuse potential of the proposed

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

combination drug.

(b) (4)

In an Agency regulatory briefing regarding the abuse potential safety testing for hydrocodone cough cold combination products on June 12, 2009, the consensus was not to require these studies for approval. If there are safety signals post-marketing the issue of the need for these types of studies can be revisited.

7.1.17 Postmarketing Experience

The proposed drug product had been distributed in the U.S. market as an unapproved drug product under the name of (b) (4) from February 2006 to October 2007. The Applicant ceased the distribution of the proposed drug product following the FDA's announcement intending 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]. A total of approximately (b) (4) size were distributed during the period. The proposed drug product has not been marketed in any foreign market.

There have been no adverse event reports received by the Applicant from any source for the proposed drug product. Previously the Agency conducted a database search in adverse events reporting system (AERS) for hydrocodone and hydrocodone-containing drug products (hydrocodone/chlorpheniramine and hydrocodone/acetaminophen). Table 6 summarizes the results of the AERS database search for the period from October 2007 through March 2008.

Table 6 Post-marketing adverse events (AERS database, Oct. 2007 to March, 2008)

Adverse event	Hydrocodone	Hydrocodone / chlorpheniramine	Hydrocodone / acetaminophen
Total adverse events	37	2	160
<6 years	1	0	1
6-<12 years	0	1	0
≥12 years	28	1	88
Age unknown	8	0	71
Misuse/overdose/error	8	0	11
Death	29	0	123
Suicide	12	0	94

In searching AERS database covering the period from October, 2007 through March, 2008, the most death cases were from hydrocodone/acetaminophen drugs (123 deaths), accounting for 76.88% of the adverse events reported for hydrocodone/acetaminophen drugs. There were 29 deaths reported for hydrocodone alone, accounting for 78.39% of the adverse events reported for hydrocodone drugs. The overall adverse events and death reports for hydrocodone alone did not differentiate if the hydrocodone was taken as antitussive doses or as much higher analgesic doses. Hydrocodone and hydrocodone/acetaminophen are common analgesic drugs being used in symptomatic treatment for many end stage diseases. Without the knowledge of dosage forms, diseases, co-administered medications, a search of AERS, a spontaneous post-marketing adverse event reporting database, does not provide meaningful safety information for hydrocodone use. Also, the data reflect a large fraction of suicide, the dosage forms of hydrocodone for the deaths and adverse events were most possibly higher analgesic doses rather than antitussives. Noticeably, hydrocodone/chlorpheniramine,

which is a fixed dose combination antitussive drug product (Tussionex, NDA 19-111 and Tussicaps, ANDA 77-273), had only two adverse events and no death reported. The data suggest that hydrocodone and hydrocodone-containing drug products, as antitussive formulations, are unlikely a safety concern.

7.2 Adequacy of Patient Exposure and Safety Assessments

This is a clinical pharmacology program. The subject number of the studies for safety assessment is relatively small. The efficacy and safety of the proposed drug is supported by DESI review for hydrocodone and by OTC Monograph for guaifenesin.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable.

7.2.2.3 Literature

The Applicant compiled six literature references for information relevant to safety of hydrocodone and guaifenesin in general [NDA 205-474 N-000, m3, Section 3.3]. The reference included articles published on the peer reviewed journals. The literature survey revealed no new safety signals for hydrocodone and guaifenesin.

7.2.3 Adequacy of Overall Clinical Experience

This submission includes 4 single-dose clinical pharmacology studies that provided a fairly limited amount of safety information. The efficacy and safety of the proposed drug are supported by DESI review for hydrocodone and by OTC Monograph for guaifenesin. Given the extensive experience with use of hydrocodone as an antitussive 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), the Applicant submitted a safety update for the proposed drug product on April 10, 2014. There are no new safety data included in the 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 proposed drug 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 “Symptomatic relief of cough and to loosen mucus associated with common cold”. The dosing

regimen is 10 mL every 4 to 6 hours for patients 18 years of age and older, not to exceed 6 doses (60 mL) in 24 hours.

8.2 Drug-Drug Interactions

There is no drug-drug interaction study conducted in this NDA submission. The result of a clinical pharmacology study (11244403) showed that for hydrocodone, the geometric mean ratios (combination/reference) of AUC 0–t, AUC 0–∞ and C_{max} were 1.03 (90% CI = 1.00, 1.07), 1.03 (90% CI = 1.00, 1.07), and 1.17 (90% CI = 0.96, 1.05), respectively, and for guaifenesin, the least square geometric mean ratios (combination/reference) of AUC 0–t, AUC 0–∞ and C_{max} were 1.08 (90% CI = 1.02, 1.13), 1.08 (90% CI = 1.02, 1.13), and 1.11 (90% CI = 1.01, 1.21), respectively. These data suggest that no apparent drug-drug interaction between hydrocodone and guaifenesin in proposed drug, because there are no differences in hydrocodone and guaifenesin exposure between the proposed drug product Guaifenesin and Hydrocodone Bitartrate Oral Solution and the reference hydrocodone solution and guaifenesin solution.

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 addressed these potential drug-drug interactions.

More information regarding possible drug-drug interaction in the proposed Guaifenesin and Hydrocodone Bitartrate Oral Solution may be found in the Clinical Pharmacology Review [NDA 205-474, Clinical Pharmacology Review, Yunzhao Ren, Ph. D.].

8.3 Specific Populations

There were no studies in special populations 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 the proposed drug is administered to nursing mothers.

8.4 Pediatrics

The clinical pharmacology studies in this NDA included no pediatric subjects. The post-marketing adverse event search in AERS for hydrocodone and hydrocodone containing drugs covered the period from October, 2007 through March, 2008 for age groups of under 6, 6 to less than 12, and 12 years and above. The most adverse events for hydrocodone were in the age group of 12 years and above. The post-marketing adverse event data revealed no new pediatric safety concerns for hydrocodone when used for approved indications at approved doses.

On March 11, 2008, FDA published a Public Health Advisory and a Healthcare Professionals Information sheet addressing the risk of a long-acting hydrocodone-containing cough product in patients younger than the approved age group of 6 years and older.

[\[http://www.fda.gov/cder/drug/advisory/hydrocodone.htm\]](http://www.fda.gov/cder/drug/advisory/hydrocodone.htm),

<http://www.fda.gov/cder/drug/InfoSheets/HCP/hydrocodoneHCP.htm>]. FDA has received reports of life-threatening adverse events and death in patients, including children, who have received long-acting hydrocodone-containing cough product. The product labels of marketed hydrocodone products (Hycodan, Tussionex) have indicated that hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression.

The Applicant requested a partial waiver for pediatric studies below 6 years of age because hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. Pediatric studies in population from 6 to under 18 years of age for pharmacokinetics and safety data in this age group are required.

The proposed dose for guaifenesin is within the dose range in the Agency's approved OTC Monograph. Since the dose proposed in the combination product is within the doses that were declared by the Agency to be safe and effective for OTC use, no additional PK data is necessary to support the guaifenesin dose. However, hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age. Safety concerns of dose-related respiratory depression over the last few years raises the issue of the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression, including fatalities due to respiratory failure has been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children under 6 years of age, and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require that the sponsor establish the appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population.

The Division discussed with the Applicant regarding the concerns of lacking PK and safety data of hydrocodone in the pediatric population. The Applicant agreed to conduct PK and safety studies in the pediatric population from 6 to under 18 years of age to a post-approval phase. The Applicant submitted a pediatric study plan that was discussed at the Pediatric Review Committee (PeRC) PREA Subcommittee meeting on May 7, 2014. The PeRC agreed the Division to grant a partial waiver for pediatric studies below 6 years of age and to grant a deferral for the PK and safety studies in the pediatric population from 6 to under 18 years of age to a post-approval phase because adult studies are completed and the product is ready for approval in adults. The agreed on post-approval pediatric studies are listed below:

- a. Conduct a study to assess the pharmacokinetics of each active component in proposed drug product in (b) (4) children ages 6-17 years with symptoms of (b) (4)
The timelines of protocol submission, study initiation, and final report submission dates for the study are set to be March 2015, September 2015, and March 2017, respectively.
- b. Conduct a study to assess the safety of the proposed drug product in (b) (4) children 6 -17 years of age with symptoms of (b) (4)

(b) (4) Although this study is primarily a safety study, the effectiveness of the proposed drug will be assessed. (b) (4) The timelines of protocol submission, study initiation, and final report submission dates for the study are set to be September 2018, March 2019, and September 2022, respectively.

8.6 Literature Review

Hydrocodone has been approved as an antitussive for more than 50 years. The proposed drug product is relying on the Agency's finding of safety and efficacy of Hycodan (NDA 5-213, approved on March 23, 1943)^{1,2} and subsequent DESI review, to support the efficacy and safety of the hydrocodone in the proposed product. Clinical studies have demonstrated the effectiveness and safety of hydrocodone in treatment of cough symptom in cancer patients³.

Guaifenesin is considered to be generally recognized as safe and effective (GRASE) as an expectorant in the OTC Monograph [21 CFR 341.78]. A literature search using guaifenesin provided citations only tangentially related to the interest of safety.

Reference

1. Endo Pharmaceuticals. HYCODAN (Hydrocodone Bitartrate and Homatropine Methylbromide) Tablet and Syrup Prescribing Information. 2003.
2. Eddy NB, Halbach H, Braenden OJ. Synthetic substances with morphine-like effect: clinical experience; potency, side-effects, addiction liability. Bull World Health Organ 1957; 17(4-5):569-863.
3. Homsy J, Walsh D, Nelson KA, Sarhill N, Rybicki L, Legrand SB et al. A phase II study of hydrocodone for cough in advanced cancer. Am J Hosp Palliat Care 2002; 19(1):49-56.

8.7 Postmarketing Risk Management Plan

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. The risk associated with Guaifenesin and Hydrocodone Bitartrate Oral Solution is expected being similar to the risks of other hydrocodone-containing antitussives. (b) (4)

(b) (4) In an Agency regulatory briefing regarding the abuse potential safety testing for hydrocodone cough cold combination products on June 12, 2009, the consensus was that abuse liability studies were not required prior to approval of these drug products but that studies may be necessary on a case-by case basis if a signal is detected.

No special post-marketing risk management plan is recommended at this time. A routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of the proposed drug. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Applicant seeks the approval of Guaifenesin and Hydrocodone Bitartrate Oral Solution based on a clinical pharmacology program to demonstrate the bioequivalence to the reference drugs. No clinical efficacy and safety studies were submitted to support this application. The results of bioequivalent study show that the proposed combination drug product is bioequivalent to the reference drug for hydrocodone and OTC Monograph for guaifenesin.

The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. The Applicant requested a partial waiver for pediatric studies below 6 years of age because hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. Pediatric studies in population from 6 to less than 18 years of age for pharmacokinetics and safety data in this age group are required.

The proposed dose for guaifenesin is within the dose range in the Agency's approved OTC Monograph. Since the dose proposed in the combination product is within the doses that were declared by the Agency to be safe and effective for OTC use, no additional PK data is necessary to support the guaifenesin dose. However, hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age. Safety concerns of dose-related respiratory depression over the last few years raises the issue of the need to be assured of the most appropriate dose for the pediatric population. Dose-related respiratory depression, including fatalities due to respiratory failure, has been reported with the use of hydrocodone in children. Several of these cases were associated with overdose, and led to the revised labeling currently in the single-ingredient and combination hydrocodone products; i.e. that hydrocodone is contraindicated in children under 6 years of age, and that the dose should be administered with an accurate measuring device. In view of this dose-related safety concern, it is appropriate to require that the sponsor establish the appropriate dose of hydrocodone for the pediatric (under 18) population. Therefore, pharmacokinetic data for proper dose selection, and safety data are needed in the pediatric population.

The Division discussed with the Applicant regarding the concerns of lacking PK and safety data of hydrocodone in the pediatric population. The Applicant agreed to conduct PK and safety studies in the pediatric population from 6 to less than 18 years of age to a post-approval phase. The Applicant submitted a pediatric study plan that was discussed at the Pediatric Review Committee (PeRC) PREA Subcommittee meeting on May 7, 2014. The PeRC agreed the Division to grant a partial waiver for pediatric studies below 6 years of age and to grant a deferral for the PK and safety studies in the pediatric population from 6 to under 18 years of age to a post-approval phase because adult studies are completed and the product is ready for approval in adults.

9.2 Recommendation on Regulatory Action

I recommend an "Approval" action for this NDA application. The development program for the proposed drug product is a clinical pharmacology program. The proposed drug product Guaifenesin and Hydrocodone Bitartrate Oral Solution depends on the bioequivalence to the reference drug Hycodan (hydrocodone bitartrate and homatropine methylbromide, NDA 5-213) and Hydrocodone Bitartrate and Homatropine Methylbromide Oral Syrup by Hi-Tech Pharmacal (ANDA 40-613) for

hydrocodone and to OTC Monograph ingredient guaifenesin to support its efficacy and safety. No clinical efficacy studies were submitted to support this application. The clinical pharmacology study demonstrated that the bioequivalence between the proposed drug product Guaifenesin and Hydrocodone Bitartrate Oral Solution and the reference drugs, showing that the 90% CI of ratios of AUC and C_{max} for the active components in Guaifenesin and Hydrocodone Bitartrate Oral Solution vs. reference drugs are within the 80 - 125% goal post for bioequivalence.

9.3 Recommendation on Postmarketing Actions

Hydrocodone is a controlled substance that is known to have a certain level of abuse potential. (b) (4)

In an Agency regulatory briefing regarding the abuse potential safety testing for hydrocodone cough and cold combination products on June 12, 2009, the consensus was that abuse liability studies were not required prior to approval of these drug products but that studies may be necessary on a case-by case basis if a signal is detected.

Routine post-marketing surveillance is recommended to monitor the adverse events associated with the use of Guaifenesin and Hydrocodone Bitartrate Oral Solution. If a signal of abuse, misuse, overdose and addiction is identified, further abuse liability assessment may need to be conducted.

The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. The clinical pharmacology studies to support this NDA were conducted in adults 18 years of age and older. The Applicant requested a partial waiver for pediatric studies below 6 years of age because hydrocodone is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression. To meet the PREA requirement, the Applicant will be requested to conduct pediatric studies in population from 6 to less than 18 years of age for pharmacokinetics and safety data in this age group for the proposed drug product in post-approval phase.

9.4 Labeling Review

The proposed labeling is reference to the approved product labeling of NDA 19111 Tussionex (hydrocodone polistirex and chlorpheniramine polistirex) Extended-Release Suspension and NDA 22-439 Zutripro (hydrocodone bitartrate, pseudoephedrine hydrochloride and chlorpheniramine maleate) Oral Solution, with the components of pseudoephedrine and chlorpheniramine being taken out, and to the guaifenesin Monograph. The proposed package insert was submitted in Physician's Labeling Rule (PLR) format.

The Division of Professional Drug Promotion (DPDP), Office of Prescription Drug Promotion (OPDP), and the Division of Medication Error Prevention & Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) have been consulted regarding the product labeling and the consultation comments have been incorporated into the labeling revision. The final labeling discussion is ongoing at the time of this review.

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

/s/

XU WANG
10/09/2014

ANTHONY G DURMOWICZ
10/09/2014
I concur with Dr. Wang's review

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION: NDA 205-474	TRADE NAME: (b)(4) (proposed)
APPLICANT/SPONSOR: Sovereign Pharmaceuticals	USAN NAME: Guaifenesin and Hydrocodone Bitartrate Oral Solution
MEDICAL OFFICER: Xu Wang, M.D., Ph.D.	
TEAM LEADER: Anthony G. Durmowicz, M.D.	CATEGORY: Cough suppressant and expectorant
DATE: 3/26/2014	ROUTE: Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
01/13/2014	01/14/2014	NDA 205-474	NDA

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
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REVIEW SUMMARY:

This is a 505(b)(2) application for an immediate release oral solution combination product containing guaifenesin and hydrocodone bitartrate (200 and 2.5 mg, respectively, per 5 ml). The drug product has been marketed as an unapproved drug product under the name of "(b)(4)" in the US since 2006. In response to the Agency's request to cease manufacturing unapproved hydrocodone products, the Applicant filed this NDA to seek approval of their unapproved drug product.

As a basis for the 505(b)(2) application, the Applicant cites Hycodan (hydrocodone bitartrate and homatropine methylbromide, NDA 5-213) and Hydrocodone Bitartrate and Homatropine Methylbromide Oral Syrup by Hi-Tech Pharmalac (ANDA 40-613) as the reference drug (RLD) for hydrocodone of the combination product. The Applicant also cites OTC Monograph (21 CFR 341.18) to support guaifenesin and uses OTC guaifenesin product as RLD for guaifenesin of the combination product. The drug development program is a clinical pharmacology program to determine the bioequivalence of the proposed drug to the reference drugs.

The submission includes 4 single dose bioavailability (BA)/bioequivalence (BE) studies to address the BE, food effect and drug-drug interaction (DDI) for the proposed drug product. A total of 135 healthy volunteers were enrolled in the 4 studies. The following pharmacokinetic variables were calculated for each treatment: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, Kel, and T_{1/2}. Dizziness, headache, and somnolence were the most common adverse events reported in the studies. There was no significant difference in adverse events between the proposed drug product and RLDs. There is no death or serious adverse event reported during the studies. The proposed product labeling is based on the approved product labeling for RLDs. There are no major labeling issues identified.

The NDA did not include a pediatric study plan (PSP) to assess the safety and effectiveness for the claimed indication in pediatric patients as required by the Pediatric Research Equity Act (PREA). In response to the Division's information requests, the Applicant submitted an initial PSP including a partial waiver request for pediatric studies in patients <6 years of age, and a plan with timelines to conduct 2 studies to assess the pharmacokinetics and safety of the proposed drug in pediatric patients 6 to 17 years of age.

This application contains items required for filing and data that are organized adequately to allow reviewing. The NDA is filable.

OUTSTANDING ISSUES: none

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	FILABLE <input checked="" type="checkbox"/>	NOT FILABLE _____
	APPROVAL _____	APPROVABLE _____ NOT APPROVABLE _____

OTHER ACTION: **COMMENTS FOR SPONSOR**

1. GENERAL INFORMATION

This is a 505(b)(2) application for an immediate release oral solution combination product containing guaifenesin and hydrocodone bitartrate (200 and 2.5 mg, respectively, per 5 ml). The sponsor is Sovereign Pharmaceuticals. The proposed name for the product is (b) (4). The proposed indication is for the symptomatic relief of (b) (4) cough (b) (4).

(b) (4). The application is submitted electronically.

As a basis for the 505(b)(2) submission route, the applicant uses Hycodan (hydrocodone bitartrate and homatropine methylbromide, NDA 5-213) and Hydrocodone Bitartrate and Homatropine Methylbromide Oral Syrup by Hi-Tech Pharmcal (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 and uses OTC Guaifenesin product as RLD for guaifenesin component of the combination product.

1. CLINICAL DEVELOPMENT PROGRAM

The clinical pharmacology program for this combination product is a 505(b)(2) program, including 4 single dose bioavailability (BA)/bioequivalent (BE) studies to address the BE, food effect and drug-drug interaction (DDI) for the proposed product (Table 1).

Table 1. Clinical studies in the NDA application

Type of study	Study ID	n	Objectives of the study	Reference listed drug (RLD)
Relative BA	R08-0467	20	Comparison of sponsor's hydrocodone with RLD	Hycodan®
Food effect	92001	25	Food effect of proposed product	Proposed product
Relative BA and DDI	92002	34	Comparison of proposed product with RLD	Hydrocodon + Homatropine (HiTech); Guaifenesin
Relative BA and DDI	11244403	56	Comparison of proposed product with RLD	Hydrocodon + Homatropine (HiTech); Guaifenesin

2. FOREIGN MARKETING AND REGULATORY HISTORY

A pre-IND meeting was held with the Division on April 4, 2008. The Agency recommended that the sponsor needed to address the potential for drug-drug interaction (DDI) between hydrocodone and guaifenesin. IND101,683 was submitted on February 26, 2009 for a single dose clinical pharmacology study to determine the BA of the proposed drug product in comparison with RLD.

At a pre-NDA meeting on November 9, 2011, the Applicant presented data from a BA/BE study (92002). The data showed that the BE criteria was not met for the guaifenesin component between the proposed drug product and RLD. The Agency commented that BE should be demonstrated for hydrocodone and guaifenesin between the proposed drug product and RLD. The sponsor later conducted another BE study (11244403).

The Applicant stated that the proposed drug product has been marketed as an unapproved drug product under the name of “(b) (4)” in the US since 2006. The proposed drug product is not marked in foreign markets.

Reviewer’s comment:

The Agency’s DESI review determined that hydrocodone is safe and effective for symptomatic relief of cough. There is regulatory precedent regarding the combination of hydrocodone with a monograph cold, cough, allergy, bronchodilator, and antiasthmatic drug. The precedent was established in response to the NDA for Tussionex Pennkinetic Extended-Release Suspension (NDA 19-111), equivalent to 10 mg hydrocodone plus 8 mg chlorpheniramine maleate/5 ml. The NDA, which included three bioavailability studies and no clinical studies, was approved on December 31, 1987. The decision was made at the Center level. Given this regulatory background, and recognizing that the Agency has determined that both single ingredients are safe and effective for their respective indications, the pK program as the Division recommended is sufficient to support the proposed combination drug products, provided bioequivalence and no drug-drug interactions are demonstrated.

3. 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\11-forms\112-fda-form-356h]
- Index [index.xml]
- Summary [m2\27-clinical summary]
- Clinical technical section
 - Clinical study reports
 - Study 11244403 [m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-BA-BE-stud-rep]
 - Study 92001 [m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-food-effect-stud-rep]
 - Other pertinent data
 - none
 - Good clinical practice certification [m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-BA-BE-stud-rep\study-report-11244403\report-body.pdf, Section 5 Ethics]
 - Risk/benefit analysis:

- not provided
- Debarment certification [m1\13-administrative-information\133-debarment-certification]
- Pediatric use [m1\19-pediatric-administrative-information\191-request-waiver-pediatric-studies]
- Labeling [m1\us\114-labeling\1141-draft-labeling]
- Case report forms [m5\531-rep-biopharm-stud\5312-compar-BA-BE-stud-rep\study report 11244403\crfs]
- Financial disclosure [m1\13-administrative-information\134-financial-certification-disclosure]

The NDA did not include a pediatric study plan (PSP) to assess the safety and effectiveness for the claimed indication in pediatric patients as required by the Pediatric Research Equity Act (PREA). In response to the Division's information requests, the Applicant submitted an initial PSP including a partial waiver request for pediatric studies in patients <6 years of age, and a plan with timelines to conduct 2 studies to assess the pharmacokinetics and safety of the proposed drug in pediatric patients 6 to 17 years of age.

4. CLINICAL STUDIES

There are 4 single dose clinical pharmacology studies in the application to address the BE, food effect and drug-drug interaction (DDI) for the proposed product (Table 1). A total of 135 healthy volunteers were enrolled in the 4 studies. The following pharmacokinetic variables were calculated for each treatment: AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , K_{el} , and $T_{1/2}$.

Dizziness, headache, and somnolence were the most common adverse events reported in the studies. There was no significant difference in adverse events between the proposed drug product and RLDs. There were no death or serious adverse events reported during the studies.

5. BRIEF REVIEW OF PROPOSED LABELING

The proposed product labeling is based on the approved product labeling for RLDs. There are no major labeling issues identified.

6. DSI REVIEW AND AUDIT

The clinical pharmacology review team has requested DSI audit for this NDA application. Study 11244403 is the major clinical pharmacology study providing BE data to support the proposed drug product. The study center for clinical pharmacology study 11244403 is requested for DSI audit:

Novum Pharmaceutical Research Services
Mavis N. Matsumoto, M.D., Principal Investigator

3760 Pecos McLeod
Las Vegas, NV 89121

7. SUMMARY

This is a 505(b)(2) application for an immediate release oral solution combination drug product containing guaifenesin and hydrocodone bitartrate (200 and 2.5 mg, respectively, per 5 ml). The proposed drug product has been marketed as an unapproved drug product under the name of (b) (4) in the US since 2006. In response to the Agency's request to cease manufacturing unapproved hydrocodone products, the Applicant filed this NDA to seek approval of their proposed drug product. The proposed indication is for the symptomatic relief of (b) (4)

As a basis for the 505(b)(2) submission route, the applicant cites Hycodan (hydrocodone bitartrate and homatropine methylbromide, NDA 5-213) and Hydrocodone Bitartrate and Homatropine Methylbromide Oral Syrup by Hi-Tech Pharmcal (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 and uses OTC Guaifenesin product as RLD for guaifenesin component of the combination product.

The clinical pharmacology program for this combination product includes 4 single dose bioavailability (BA)/bioequivalent (BE) studies to address the BE, food effect and drug-drug interaction (DDI) for the proposed drug product. A total of 135 healthy volunteers were enrolled in the 4 studies. The following pharmacokinetic variables were calculated for each treatment: AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , Kel , and $T_{1/2}$. Dizziness, headache, and somnolence were the most common adverse events reported in the studies. There was no significant difference in adverse events between the proposed drug product and RLDs. There were no death or serious adverse events reported during the studies. The proposed product labeling is based on the approved product labeling for RLDs. There are no major labeling issues identified.

This application contains items required for filing and data that are organized adequately to allow reviewing. The NDA is fileable.

8. REVIEW TIMELINE

The PDUFA action date is November 14, 2014. The schedule for review is provided in Table 1. Write-up will be concomitant with the review process. The review will culminate with the proposed label, which will include comparison to the referenced listed products and monographs. The final draft review will be completed by October 10, 2014.

Table 1: Review timeline for NDA 205-474

Milestone	Target date for completion
Filing and planning meeting	February 24, 2014
MCR Meeting	May 30, 2014
Label Meeting	September 16, 2014
Wrap-up meeting	October 8, 2014
Final draft review complete	October 10, 2014
PDUFA Action date (10 months)	November 14, 2014

9. COMMENTS FOR THE SPONSOR

One comment will be included in 74-day letter:

Submit a 120-day safety update as required per 21 CFR 314.50(d)(5)(vi)(b).

Reviewed by:

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

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

cc: NDA 205-474
HFD-570/Division File
HFD-570/ Durmowicz /Medical Team Leader
HFD-570/Gilbert-McClain/Deputy Division Director
HFD-570/Wang/Medical Reviewer
HFD-715/Abugov/Biometrics Reviewer
HFD-570/Patel/Pharmacology-Toxicology Reviewer
ONDQA/Bertha/CMC Reviewer
OCP/Ren/Clinical Pharmacology Reviewer
HFD-570/Musse/CSO

Clinical Filing Checklist

NDA/BLA Number: 205-474 **Applicant: Sovereign** **Stamp Date: January 14, 2014**
Drug Name: (b) (4) **NDA/BLA Type: 505(b)(2)**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
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			
LABELING					
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			
SUMMARIES					
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	Active 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; Hydrocodone Bitartrate and Homatropine Methylbromide Syrup
DOSE					
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)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Indication:				
	Pivotal Study #2 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	
SAFETY					
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 (e.g., 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 ¹) 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 ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA Version 15.1
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
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission		X		

¹ 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.

² 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).

	Content Parameter	Yes	No	NA	Comment
	discussions?				
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	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
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
DATASETS					
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			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			CRFs submitted for all patients in the study
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			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
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.

None

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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

/s/

XU WANG
03/27/2014

ANTHONY G DURMOWICZ
03/27/2014