

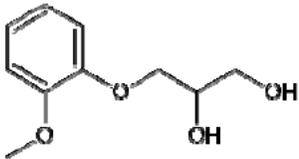
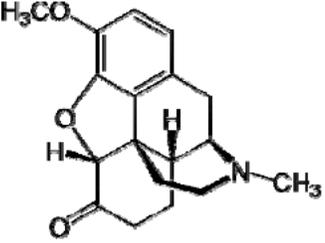
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205474Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	205474 (Related IND 101683)
Submissions Date:	01/14/2014
Submission Type:	505(b)(2)
Proposed Brand Name:	(b) (4)
Generic Name:	Guaifenesin/Hydrocodone Bitartrate
Sponsor:	Sovereign Pharmaceuticals, LLC.
Route of Administration:	Oral
Dosage Form:	Immediate Release Solution
Dosage Strength:	200 mg Guaifenesin/2.5 mg Hydrocodone Bitartrate per 5 ml
Proposed Dosing Regimen:	- Adults (b) (4) 10 mL every 4 hours. (b) (4)
Proposed Indication(s):	Symptomatic relief of (b) (4)
Proposed Population(s):	Adults (b) (4)
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader:	Satjit Brar, Pharm.D., Ph.D.
Molecular Structure of Guaifenesin	
Molecular Structure of Hydrocodone	

The intent of the study was to compare the rate and extent of absorption of 5 mg hydrocodone bitartrate/400 mg guaifenesin oral solution after single-dose administration under fasting and fed conditions.

Study 11244403 was a randomized, single-dose, four-treatment, four-period, four-sequence, four way-crossover study under fasted conditions comparing bioavailability from the proposed product [10 mL oral solution of hydrocodone (5 mg) and guaifenesin (400 mg)] and the reference product [10 mL hydrocodone bitartrate (5 mg) and homatropine methylbromide (3 mg) syrup from Hi-Tech Pharmcal and 10 mL Liquituss GG (400 mg guaifenesin) oral solution from Capellon Pharmaceuticals]. The treatment phases were separated by washout periods of at least 7 days. A total of 57 and 36 subjects' PK samples were collected for comparison of guaifenesin and hydrocodone, respectively. A total of 17 (within 20-hour) and 15 (within 10-hour) post-dose blood samples per subject per period were collected for measuring plasma concentrations of hydrocodone and guaifenesin, respectively. The intent of the study was 1) to compare the rate and extent of absorption of hydrocodone/guaifenesin from the proposed product and the reference product; 2) to determine if drug-drug interaction exists between hydrocodone and guaifenesin.

The following points are the major findings of the current review:

- 1) The bioequivalence of hydrocodone was established between the proposed product and the reference product. The geometric mean ratio (proposed/reference) of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.99 (90% CI = 0.96, 1.03), 0.99 (90% CI = 0.96, 1.03), and 0.94 (90% CI= 0.90, 0.98), respectively.
- 2) The bioequivalence of guaifenesin was established between the proposed product and the reference product. The geometric mean ratio (proposed/reference) of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 1.04 (90% CI = 0.99, 1.09), 1.04 (90% CI = 0.99, 1.09), and 1.03 (90% CI= 0.94, 1.13), respectively.
- 3) Food significantly reduces the bioavailability of guaifenesin. The geometric mean ratio (fed/fast) of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.52 (90% CI = 0.44, 0.60), 0.53 (90% CI = 0.45, 0.60), and 0.31 (90% CI= 0.16, 0.46), respectively. The bioavailability of hydrocodone is comparable with the geometric mean ratio (fed/fast) of AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} being 1.15 (90% CI = 1.12, 1.18), 1.16 (90% CI = 1.12, 1.19), and 0.88 (90% CI= 0.82, 0.94), respectively, between the fed and the fasted status. Hydrocodone median T_{max} was 30 minutes later under the fed condition than the fasted condition.
- 4) There is no apparent DDI between reference guaifenesin and reference hydrocodone. For hydrocodone, the geometric mean ratios (combination/reference) of AUC_{0-t} , $AUC_{0-\infty}$ 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. For guaifenesin, the least square geometric mean ratios (combination/reference) of AUC_{0-t} , $AUC_{0-\infty}$ 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.

According to the inspection report from Office of Scientific Investigations (OSI) (DARRTS date 7/30/2014), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of the bioanalytical portion of the *in vivo* bioequivalence study 11244403 from (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.

The DBGLPC scientists concluded that the bioanalytical data from study 11244403 are acceptable for further Agency review.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 has reviewed the original NDA 205474 submitted on January 14, 2014 and has found the application approvable from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

Guaifenesin, an expectorant, was approved by the FDA in 1952 and currently is the only drug available under 21 CFR 341 final monograph of expectorant.

On March 1, 2007, the FDA received a petition asking the FDA to notify the public that some antitussives, expectorants, decongestants, antihistamines, and cough/cold combinations are not known to be safe and effective in children under the age of 6 years. After the negotiation between FDA and major manufacturers, a voluntary transition of labels for not using guaifenesin in children under the age of 4 years was endorsed by FDA in 2008.

Hydrocodone, a semi-synthetic opioid derived from codeine, was first approved by the FDA in 1943. Due to its narcotic effect, hydrocodone was only approved as component in combination product (except NDA 202880 Zohydro ER) for prescription purpose. Currently, approved combination products containing hydrocodone are classified as Schedule III controlled substances. Before 2007, many hydrocodone-containing products were illegally marketed as unapproved products, including this proposed product from Sovereign Pharmaceuticals. The product was withdrawn from the market based on the Federal Registered notice published on October 1, 2007. In accordance with the notice, manufacturers who wish to market these drug products containing hydrocodone must obtain FDA approval through the NDA or ANDA process. In response to this FDA action, Sovereign submitted IND101683 on February 26, 2009 for a fixed-dose combination product of hydrocodone and guaifenesin.

During pre-IND and pre-NDA meetings, the FDA commented that 1) the bioequivalence of both guaifenesin and hydrocodone, and 2) the potential drug-drug interaction (DDI) between guaifenesin and hydrocodone should be addressed before NDA submission.

The sponsor conducted total four bioavailability/bioequivalence pharmacokinetic (PK) studies to measure the relative bioavailability of guaifenesin and/or hydrocodone for evaluating bioequivalence, food effect and DDI. Study 11244403 is the pivotal PK study to support the bioequivalence between the proposed product and the reference listed drugs (RLD). Summary of the results supporting approval of this 505(b)(2) NDA is provided below:

1.3.2 Bioequivalence

Study 11244403:

Test product: guaifenesin and hydrocodone bitartrate 200 mg/2.5 mg per 5 ml from Sovereign Pharmaceuticals, LLC.

Reference HB: Hydrocodone Bitartrate and Homatropine Methylbromide syrup 5 mg/1.5 mg per 5 ml from Hi-Tech Pharmacal Co., Inc.

Reference G: Liquituss GG Expectorant Liquid (guaifenesin oral solution 200 mg/5 ml) from Capellon Pharmaceuticals, LLC.

Following oral administration of single-dose 5 mg hydrocodone bitartrate, the ratios (test drug/reference drug, N=36) of the least-squares geometric means for hydrocodone AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.99 (90% CI = 0.96, 1.03), 0.99 (90% CI = 0.96, 1.03), and 0.94 (90% CI= 0.90, 0.98), respectively (Fig.1). Hydrocodone median T_{max} of the test drug was 15 minutes later than the reference drug (Table 16), indicating that the absorption profiles of hydrocodone from two products were similar.

Following oral administration of single-dose 400 mg guaifenesin, the ratios (test drug/reference drug, N=57) of the least-squares geometric means for guaifenesin AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 1.04 (90% CI = 0.99, 1.09), 1.04 (90% CI = 0.99, 1.09), and 1.03 (90% CI= 0.94, 1.13), respectively (Fig.1). Guaifenesin median T_{max} was the same between two products (Table 17, 20 minutes post-dose), indicating that the absorption profiles of guaifenesin from two products were similar.

Both guaifenesin and hydrocodone from the test product are considered to be bioequivalent to the RLD; the 90% confidence interval of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} ratios (test drug/reference drug) are all within the range of 0.80-1.25.

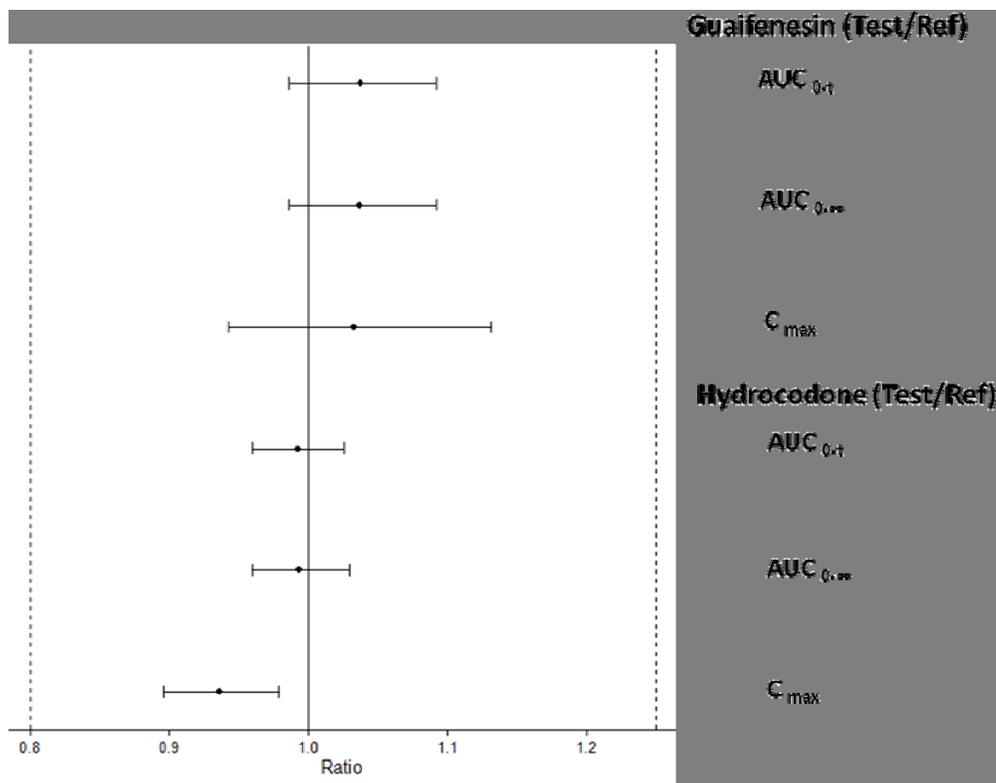


Fig.1 Forest-plot display of results from bioequivalence study 11244403. Test, test drug; Ref, reference drug. (Source: Table 16 and 17)

1.3.3 Food Effect

Study 92001:

Test product: guaifenesin and hydrocodone bitartrate 200 mg/2.5 mg per 5 ml from Sovereign Pharmaceuticals, LLC.

Test conditions: Fast and fed

Following oral administration of a single-dose of test product (400 mg guaifenesin and 5 mg hydrocodone bitartrate), the ratios (fed/fasted, N=25) of least-squares geometric means for hydrocodone AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were 1.15 (90% CI = 1.12, 1.18), 1.16 (90% CI = 1.12, 1.19), and 0.88 (90% CI= 0.82, 0.94), respectively (Table 9). Hydrocodone median T_{max} was 25 minutes later under the fed condition than the fasted condition (4.1.2).

Following oral administration of a single-dose of test product (400 mg guaifenesin and 5 mg hydrocodone bitartrate), the ratios (fed/fasted, N=25) of least-squares geometric means for guaifenesin AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.52 (90% CI = 0.44, 0.60), 0.53 (90% CI = 0.45, 0.60), and 0.31 (90% CI= 0.16, 0.46), respectively (Table 10). Guaifenesin median T_{max} was 20 minutes under both fed and fasted conditions (4.1.2).

Based on the results from study 92001, food significantly reduces the bioavailability of guaifenesin (AUC and C_{max} of fed status are a half and one-third of those of fasted status, respectively). The bioavailability of hydrocodone is comparable between the fed and the fasted status, though hydrocodone median T_{max} was 30 minutes later under the fed condition than the fasted condition.

1.3.4 Drug-drug Interaction

Study 11244403:

Reference HB: Hydrocodone Bitartrate and Homatropine Methylbromide syrup 5 mg/1.5 mg per 5 ml from Hi-Tech Pharmacal Co., Inc.

Reference G: Liquituss GG Expectorant Liquid (guaifenesin oral solution 200 mg/5 ml) from Capellon Pharmaceuticals, LLC.

Combination: Co-administration of reference HB and reference G

Following oral administration of a single-dose of hydrocodone bitartrate (5 mg), the ratios (combination/reference drug, N=36) of least-squares geometric means for hydrocodone AUC_{0-t} , $AUC_{0-\infty}$ 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 (Table 18). Hydrocodone median T_{max} was the same between two products (1 hour post-dose), indicating that the absorption profiles of hydrocodone were similar between the combination and the reference drug.

Following oral administration of a single-dose of 400 mg guaifenesin, the ratios (combination/reference drug, N=57) of least-squares geometric means for guaifenesin AUC_{0-t} , $AUC_{0-\infty}$, 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 (Table 19). Guaifenesin median T_{max} was the same between two products (20 minutes post-dose), indicating that the absorption profiles of guaifenesin were similar between the combination and the reference drug.

Based on study 11244403, no apparent DDI was observed between reference guaifenesin and reference hydrocodone. This indicates that no meaningful clinical differences would be expected when hydrocodone and guaifenesin are co-administered at the studied dosage.

2. QUESTION BASED REVIEW

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

Table 1 List of Four Phase 1 Single-dose Studies in Healthy Volunteers in NDA 205474

Study ID	Objectives of the study	Study Design*	Fasted	# of subjects	Reference listed drug
R08-0467	Comparison of sponsor's hydrocodone with RLD	R, OL, 2-way Crossover	Fasted	20	HYCODAN®
92001	Food effect of proposed product	R, OL, 2-way Crossover	Fasted or fed	25	Proposed product
92002	Comparison of proposed product with 3 RLDs	R, OL, 4-way Crossover	Fasted	34	Hydrocodon + Homatropine (Hi Tech), extemporaneous Guaifenesin
11244403	Comparison of proposed product with 3 RLDs	R, OL, 4-way Crossover	Fasted	60 (56 completed all periods)	Hydrocodon + Homatropine (Hi Tech), Liquituss GG®

* R: Randomized; OL, Open-Labeled. (Source: reviewer's summary based on 5.2 Tabular listing of clinical reports)

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Guaifenesin is a racemic mixture of (2R)-3-(2-Methoxyphenoxy)-propoane-1,2-diol and (2S)-3-(2-Methoxyphenoxy)-propoane-1,2-diol. Hydrocodone is 4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one hydrogen (2R,3R)-2,3-dihydroxybutnedioate, 2.5 hydrate. The proposed product has an appearance as a clear, colorless to light yellow liquid. Every 5 ml of the liquid formulation contains 200 mg guaifenesin and 2.5 mg hydrocodone bitartrate.

Although guaifenesin is a highly water-soluble drug with the solubility of 40.4 mg/ml in pure water at 25 °C (the solubility reduces when temperature drops)¹, a 200 mg/ 5 ml dosing strength will result in near-saturation in the pure water solution. Therefore, additional organic solutions such as propylene glycol are needed in the formulation to improve guaifenesin solubility (Table 2). The proposed product contains (b) (4) % of propylene glycol (w/w). Propylene glycol sometimes is used to enhance the absorption and oral bioavailability for some drugs².

Table 2 Qualitative and Quantitative Composition of the Proposed Product

Ingredient	Weight (mg) per 5 mL	% (w/w)	Function			
Hydrocodone Bitartrate, USP	2.500	0.044	Active ingredient			
Guaifenesin, USP	200.00	3.518	Active ingredient			
Propylene Glycol, NF	(b) (4)	(b) (4)	(b) (4)			
Methylparaben, NF						
Propylparaben, NF						
Cherry (b) (4)						
(b) (4)						
Potassium Sorbate, NF						
Potassium Citrate, NF						
Saccharin Sodium, NF						
Citric Acid, (b) (4) NF						
Glycerin, NF						
Purified Water, USP						
Total Weight, 5 mL dose				5685.0 mg	100%	---

Listed is the composition of the original Cherry Punch flavor; for the alternative Raspberry flavor, (b) (4) are replaced by raspberry (b) (4) (Source: section 3.2.P.1 Description and composition of the drug product)

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Guaifenesin is thought to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi. In turn, this may increase the efficiency of the cough reflex and facilitate removal of the secretions. The indication of guaifenesin is to help loosen phlegm (mucus) (b) (4)

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. Hydrocodone suppresses cough through binding to the μ -opioid receptor of the cough center located in the brain stem. The indication of hydrocodone is for the symptomatic relief of (b) (4).

2.2.3 What are the proposed dosage(s) and route(s) of administration?

Adults (b) (4) take 10 mL (400 mg guaifenesin and 5 mg hydrocodone bitartrate) solution orally every 4 hours.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

After the removal of illegally marketed hydrocodone combination products in 2007/2008 (see 1.3.1), there are currently no guaifenesin/hydrocodone combination product on the US market. The guaifenesin reference drug Liquituss GG (guaifenesin 200 mg/5 ml) is an over-the-counter (OTC) product provided by Capellon Pharmaceuticals, LLC. The hydrocodone reference drug hydrocodone bitartrate and homatropine methylbromide (5 mg/ 1.5 mg per 5 ml) is provided by Hi-Tech Pharmal Co., Inc.

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The intent of this 505(b)(2) NDA is to establish the bioequivalence of the proposed product (200 mg guaifenesin and 2.5 mg hydrocodone bitartrate per 5 ml) with the reference guaifenesin (Liquituss GG with guaifenesin 200 mg/5 ml) and the reference hydrocodone (hydrocodone bitartrate and homatropine methylbromide syrup 5 mg/1.5 mg per 5 ml). The Sponsor is relying on the previous approval of hydrocodone bitartrate as a previously approved active and guaifenesin as an OTC monograph active as listed in 21 CFR 341.18 for safety and efficacy.

As listed in Table 1, the pivotal bioavailability/bioequivalence PK study 11244403 was a randomized, single-dose, four-treatment, four-period, four-sequence, crossover study under fasted conditions comparing equal doses of hydrocodone and equal doses of guaifenesin from the test and reference products. A total of 60 healthy adults were enrolled with 56 subjects completed all four periods of the study. The results of 57 subjects were analyzed for guaifenesin and 36 for hydrocodone.

2.3.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, both guaifenesin and hydrocodone, the active moieties in the plasma, were measured by high performance liquid chromatography – positive electrospray ionization – tandem mass spectrometry (HPLC ESI+MS/MS) to evaluate their PK parameters.

2.4 Exposure Response

Due to the nature of 505(b)(2) submission, no dose-response or exposure-response relationship was evaluated. The Sponsor is relying on the previous approval of hydrocodone bitartrate as a previously approved active and guaifenesin as an OTC monograph active as listed in 21 CFR 341.18 for safety and efficacy. There are no literature reports indicating that guaifenesin or hydrocodone is associated with prolongation of QT/QTc interval.

2.5 PK Characteristics of the Drug

2.5.1 What are the single and multiple dose PK parameters of parent drug in healthy adults?

The sponsor only conducted single-dose PK studies. The single-dose PK information of the proposed product is summarized from pivotal study 11244403 (Table 3).

Non-compartmental analysis was used to calculate primary PK parameters. Any sample concentration reported less than the assay limit of quantitation was set to zero for use in the pharmacokinetic and statistical analyses. Pharmacokinetic and statistical analyses were conducted on reported values. No concentration estimates were calculated for missing values. Primary pharmacokinetic variables included area under the concentration-time curve calculated by the linear trapezoidal rule from time 0 to the time of last sample with a quantifiable concentration AUC_{0-t} , area under the concentration time curve from time 0 extrapolated to infinity $AUC_{0-\infty}$, and peak concentration (C_{max}).

Table 3 Descriptive Statistics of PK Parameters for Guaifenesin and Hydrocodone of the Proposed Product from Study 11244403

PK parameter	Unit	Guaifenesin (n=57)	Hydrocodone (n=36)
AUC_{0-t}	hr· μ g/mL	4.20 (51.6%)	0.0756 (29.7%)
AUC_{0-inf}	hr· μ g/mL	4.22 (51.4%)	0.0805 (31.5%)
C_{max}	μ g/mL	3.71 (58.5%)	0.0126 (25.7%)
T_{max}^*	hr	0.333 (0.167 - 1.25)	1.25 (0.333 - 3)
Kel	1/hr	0.819 (13.5%)	0.146 (17.9%)
$T_{1/2}$	hr	0.847 (13.5%)	4.74 (17.9%)
CL/F	L/hr	94.8 (51.4%)	62.1 (31.5%)
V/F	L	116 (45.7%)	425 (26.5%)

* geometric mean (geometric CV) is listed in the table except for T_{max} , which the median value (range) was listed. (Source: Reviewer's analysis)

Geometric mean plasma concentration-time profile of guaifenesin from proposed product is shown in Fig. 2. Geometric mean plasma concentration-time profile of hydrocodone from proposed product is shown in Fig. 3.

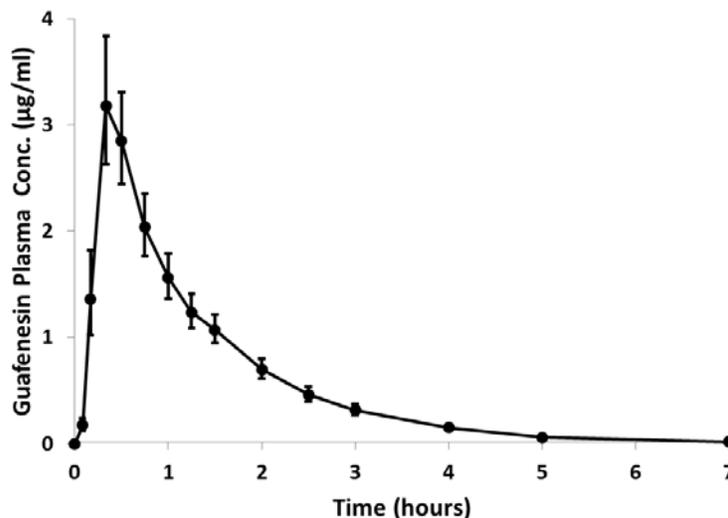


Fig.2 Guaifenesin plasma concentration-time profile following single dose administration of the proposed product from study 11244403; observations represent the geometric mean (\pm 95% CI) for each time point. (Source: reviewer’s analysis)

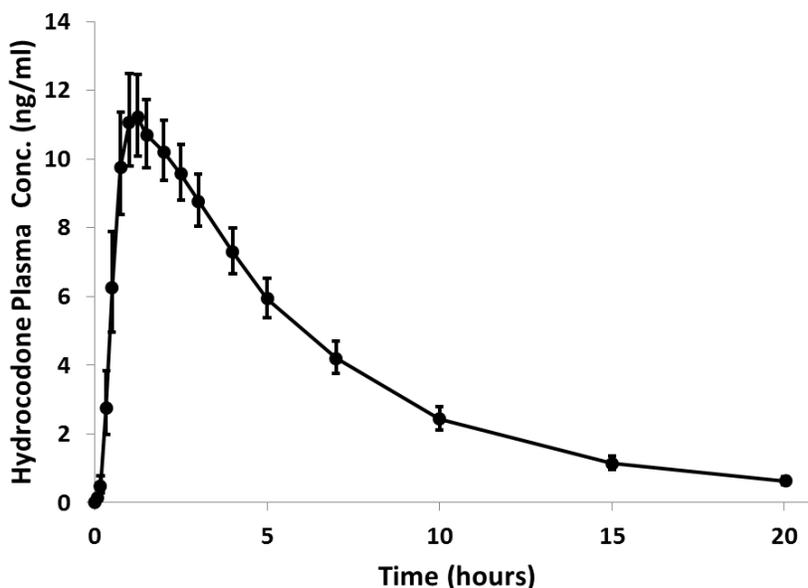


Fig.3 Hydrocodone plasma concentration-time profile following single dose administration of the proposed product from study 11244403; observations represent the geometric mean (\pm 95% CI) for each time point. (Source: reviewer’s analysis)

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

All four PK studies were conducted in healthy volunteers.

2.5.3. What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

The inter-subject geometric coefficient of variation for guaifenesin AUC_{0-t} , AUC_{0-inf} , and C_{max} were 51.6%, 51.4% and 58.5%, respectively (Table 3). The inter-subject geometric coefficient of variation for hydrocodone AUC_{0-t} , AUC_{0-inf} , and C_{max} were 29.7%, 31.5% and 25.7%, respectively.

2.5.4 What are the characteristics of drug absorption?

Following single dose administration of the proposed product from study 11244403, guaifenesin median T_{max} was reached at 20 minutes (ranging from 10 min to 75 min); guaifenesin geometric mean C_{max} was 3.71 (CV=58.5%) μ g/mL. Hydrocodone median T_{max} was reached at 75 minutes (ranging from 20 min to 3 hours); hydrocodone geometric mean C_{max} was 12.6 (CV=25.7%) ng/mL.

2.5.5 What are the characteristics of drug distribution?

Following single dose administration of the proposed product from study 11244403, guaifenesin geometric mean apparent volume of distribution (V/F) was 116 (CV=45.7%) L; hydrocodone geometric mean apparent volume of distribution was 425 (CV=26.5%) L.

2.5.6 What are the characteristics of drug metabolism?

Metabolism information of guaifenesin in human is limited. The major urinary metabolite of guaifenesin in human is β -(2-methoxyphenoxy) lactic acid³.

Referring to the approved label of hydrocodone bitartrate (NDA 202880, Zohydro ER), hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α and 6- β -hydroxymetabolites. *In vitro* studies showed that CYP3A4 mediated N-demethylation to norhydrocodone is the primary metabolic pathway of hydrocodone with a lower contribution from CYP2D6 mediated O-demethylation to hydromorphone.

2.5.7 What are the characteristics of drug elimination?

Following single dose administration of the proposed product from study 11244403, guaifenesin mean clearance (CL/F) was 94.8 (CV=51.4%) L/hr; hydrocodone mean clearance (CL/F) was 62.1 (CV=31.5%) L/hr. The mean terminal half-life of guaifenesin and hydrocodone was 0.85 hr and 4.7 hr, respectively (Table 3). Hydrocodone and its metabolites are eliminated primarily in the kidneys.

2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Due to the nature of 505(b)(2) submission, only one dose in adults was studied.

2.5.9 How do the PK parameters change with time following chronic dosing?

Due to the nature of 505(b)(2) submission for product with immediate release formulation, all studies were conducted as single-dose studies.

2.6 Intrinsic Factors

2.6.1 Does body weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

Due to the nature of 505(b)(2) submission, the above intrinsic factors were not evaluated in the PK studies.

2.6.2 Pediatrics

Since the proposed product is a novel drug combination, PREA was triggered. In Sponsor's initial pediatric study plan (iPSP):

- 1) The Sponsor requests a partial pediatric waiver to exempt from the requirement to perform pediatric studies using children under the age of 6 years old with the proposed drug product. The request is consistent with the currently approved label of hydrocodone bitartrate, which the use of hydrocodone in children under the age of 6 has been associated with fatal respiratory depression.
- 2) The Sponsor has proposed a pediatric PK study. It will be a Phase 4, open-label, single arm, single dose PK study in symptomatic children between the ages of 6 and 17. A pediatric-specific

formulation will not be developed. The dose adjustment in children is described in 2.2.3. The sample size will be (b) (4) children. AUC_{0-inf} , C_{max} , t_{max} and apparent volume of distribution, clearance and elimination half-life will be estimated for both guaifenesin and hydrocodone. Refer to Table 4 for the timeline of this study.

- 3) The Sponsor proposed a pediatric safety study. It will be a Phase 4, open-label, multi-center, multiple dose, single arm study in symptomatic children between the ages of 6 and 17. The adverse event profile of the patient, as recorded by a parent or guardian, will be the primary endpoint. The sample size will be (b) (4) children. Refer to Table 4 for the timeline of this study.

Table 4 Timeline of the Pediatric Development Plans

	PK Study	Safety Study
Protocol submission date	March 2015	September 2019
Study initiation date	September 2015	March 2020
Final report submission date	March 2019	September 2025

(Source: Reviewer’s summary based on section 1.9.4 Initial Pediatric Study Plan)

2.6.3 Renal Impairment

Due to the nature of 505(b)(2) submission, the effect of renal impairment on guaifenesin and hydrocodone systemic exposure was not evaluated in NDA 205474.

Referring to the approved label of hydrocodone bitartrate extended release capsule (NDA 202880 Zohydro ER), “hydrocodone C_{max} values were 15%, 48%, and 41% higher and AUC values were 15%, 57% and 44% higher in patients with mild, moderate and severe renal impairment, respectively”. The label of hydrocodone bitartrate (NDA005213 HYCODAN, the hydrocodone reference product in study R08-0467) describes “HYCODAN should be given with caution to certain patients such as those with severe impairment of renal functions”. Therefore, as the Sponsor suggests, it is reasonable to include the following information in the drug label: “Use with caution in patients with severe renal impairment.”

Literature reports on renal impairment effects on guaifenesin exposure are limited. However, it’s not reasonable to include the renal adverse events of guaifenesin (urinary calculi)⁴ in the clinical pharmacology section of the label: (b) (4)

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2.6.4 Hepatic Impairment

Due to the nature of 505(b)(2) submission, the effect of renal impairment on guaifenesin and hydrocodone systemic exposure was not evaluated in NDA 205474.

Referring to the approved label of hydrocodone bitartrate (NDA 202880 Zohydro ER), “hydrocodone C_{max} values were 8-10% higher in patients with hepatic impairment while AUC values were 10% and 26% higher in patients with mild and moderate hepatic impairment, respectively. Severely impaired

subjects were not studied”. The label of hydrocodone bitartrate (NDA005213 HYCODAN, the hydrocodone reference product in study R08-0467) describes “HYCODAN should be given with caution to certain patients such as those with severe impairment of hepatic functions”. Therefore, as the Sponsor suggests, it is appropriate to include the following information in the drug label: “Use with caution in patients with severe hepatic impairment.”

Literature reports on hepatic impairment effects on guaifenesin exposure are limited.

2.6.5 Does genetic variation impact exposure and/or response?

Due to the nature of 505(b)(2) submission, no genetic variation impact was evaluated.

2.7 Extrinsic Factors

2.7.1 What extrinsic factors (drugs herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Due to the nature of 505(b)(2) submission, the above extrinsic factors were not evaluated in the PK studies. However, since hydrocodone may produce marked drowsiness and impair the mental and/or physical abilities, as suggested by the proposed label, patients should be advised to avoid the use of alcohol and other central nervous system depressants while taking the proposed product because additional reduction in mental alertness may occur.

2.7.2 Drug-drug interactions (DDI)

2.7.2.1 Is the drug a substrate, an inhibitor and/or an inducer of CYP enzymes or transporter processes?

Referring to the approved label of hydrocodone bitartrate (NDA 202880 Zohydro ER), hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6- α and 6- β -hydroxymetabolites. *In vitro* studies showed that CYP3A4 mediated N-demethylation to norhydrocodone is the primary metabolic pathway of hydrocodone with a lower contribution from CYP2D6 mediated O-demethylation to hydromorphone. Therefore, if co-administration is necessary, monitor patients closely who are currently taking, or discontinuing, CYP3A4 inhibitors or CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved.

The metabolism pathway for guaifenesin in human is not clear. Studies are lacking to show if hydrocodone or guaifenesin is an inhibitor and/or an inducer of enzymes or transporters.

NDA 202880 Zohydro ER is indicated for long-term pain management which the daily dose of hydrocodone could be much higher than functioning as an antitussive. The efficacy and addiction are the major concerns for the high dose of hydrocodone, thus dose adjustment may be needed when co-administration of CYP3A4 inhibitors/inducers are necessary. The similar DDI language did not appear on NDA 005213 HYCODA, which is a fixed dose (5 mg hydrocodone every 4 hours as antitussive). Therefore, it's reasonable not to include CYP3A4 inhibitors/inducers DDI language in the label of the proposed product.

2.7.2.2 Is there a DDI between the components of the combination product?

No. For details, refer to discussion under section 1.3.4.

2.7.2.3 What co-medications are likely to be administered to the target population?

It's obvious that the targeted population of the proposed product overlaps with population having common cold. Therefore, the targeted population are likely to take OTC products containing antipyretic and analgesic components (such as acetaminophen and ibuprofen), antihistamines (such as diphenhydramine and loratadine), and nasal decongestants (such as phenylephrine and oxymetazoline).

2.7.2.4 Does the label specify co-administration of the above medicines or other drugs have the interaction potential with the proposed product?

Yes, since hydrocodone may produce marked drowsiness and impair the mental and/or physical abilities, co-administration of the following drugs, as suggested by the proposed label, may aggravate the symptoms:

- 1) The use of opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (b) (4) concomitantly with the proposed product may cause an additive CNS depressant effect and should be avoided.
- 2) Hydrocodone should be administered cautiously to persons receiving anticholinergic drugs in order to avoid paralytic ileus and excessive anticholinergic effects.

MAOI (monoamine-oxidase inhibitor) DDI statement was listed in NDA 005213 HYCODA label, therefore the following statement should be included in the label of this product: "The use of MAOI (b) (4) or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone."

2.7.2.5 Is there a known mechanistic basis for pharmacodynamics drug-drug interactions?

Refer to 2.7.1 and 2.7.2.3.

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation?

The sponsor claims that both guaifenesin and hydrocodone are BCS class I drugs. The solubility profile of both drugs is listed in Table 5:

Table 5 Solubility Profile of Guaifenesin and Hydrocodone

pH	Solubility (mg/ml)	
	Guaifenesin	Hydrocodone
1.2	94	113.4
4.5	95	228.9
6.8	94	109.4

(Source: reviewer’s summary based on section 2.3.P. Quality overall summary for the drug product, page 8 and page 9)

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical development formulation?

The formulation in study 92001, 92002 and pivotal study 11244403 (b) (4) to the proposed commercial to-be-marketed formulation.

2.8.3 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

In pivotal study 11244403, AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} of both guaifenesin and hydrocodone meet the 90% CI using equivalence limits of 80-125%. There was no serious adverse event reported in the study. The efficacy was not evaluated in the study.

2.8.4 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Study 92001 was the dedicated food effect study. For fasted group, no food was allowed from at least 10 hours before dosing until at least 4 hours after dosing. For fed group, a standard high-fat, high-caloric breakfast (800 – 1000 calories) was required to complete to consume prior to drug administration.

Referring to 1.3.3, the bioavailability of hydrocodone is comparable between the fed and the fasted status, though hydrocodone median T_{max} was 25 minutes later under the fed condition than the fasted condition. However food has significant effect on guaifenesin bioavailability. Guaifenesin AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} of fed group were 52.1% (90% CI = 44.3%, 59.8%), 52.5% (90% CI = 44.7%, 60.2%), 31.3 (90% CI = 16.2%, 46.4%) of that of fasted group, respectively.

This food effect on guaifenesin was observed from another guaifenesin immediate release (IR) solution (NDA (b) (4), Table 6). However this food effect is less significant in IR/extended release (ER) guaifenesin product (NDA 21585, NDA 21620). The pivotal study 11244403 was conducted under fasted status.

Table 6 Food Effect on Guaifenesin

	NDA 205474	NDA (b) (4)	NDA 21585	NDA 21620
Product	Guaifenesin/ Hydrocodone	Guaifenesin/Hydrocodone /pseudoephedrine	Guaifenesin/ Pseudoephedrine	Guaifenesin/ Dextromethophan
Formulation	IR solution	IR solution	IR/ER tablet	IR/ER tablet
AUC_{0-t} Ratio	0.521 (0.443 - 0.598)	0.737 (0.665 - 0.817)	0.900 (0.846 - 0.955)	0.896 (0.850 - 0.946)
AUC_{0-inf} Ratio	0.525 (0.447 - 0.602)	0.815 (0.756 - 0.878)	0.902 (0.847 - 0.960)	0.896 (0.850 - 0.945)
C_{max} Ratio	0.313 (0.162 - 0.464)	0.458 (0.372 - 0.565)	0.735 (0.659 - 0.832)	0.910 (0.822 - 1.00)

Source: Table 10, (b) (4) Dr. Sandra Suarez-Sharp’s review for NDA 21585 (DARRT date 10/24/2003, Dr. Shinja Kim’s review for NDA 21620 (DARRT date 3/10/2004)

2.8.5 Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so were they bioequivalent or not?

No other strength of the to-be-marketed formulation was tested. However another hydrocodone solution with different strength (5 mg hydrocodone bitartrate per 5 ml solution, which doubled the strength of the to-be-marketed product) was tested in study R08-0467. The results showed that this hydrocodone solution was bioequivalent to the reference hydrocodone (HYCODAN[®]).

2.8.6 If unapproved products or altered approved products were used as active controls, how is BE to the to-be-marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

All the RLDs used in the pivotal study 11244403 were approved product or legally marketed product. When an extemporaneously prepared guaifenesin was used as a reference drug in study 92002, the proposed to-be-marketed product was not bioequivalent to this extemporaneously prepared guaifenesin with AUC_{0-t}, AUC_{0-∞}, and C_{max} ratios (proposed product/EP guaifenesin) of 1.63 (90% CI = 1.52, 1.74), 1.62 (90% CI = 1.51, 1.72), and 1.89 (90% CI= 1.70, 2.08), respectively.

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Only parent drugs (guaifenesin and hydrocodone) were measured in all four studies. Human plasma containing guaifenesin and hydrocodone were analyzed by the technique of (b) (4) followed by HPLC ESI+MS/MS.

2.9.2 For all moieties measured, is free, bound, or total measured?

Due to the nature of the measuring method, it's the total amount of (b) (4) was measured.

2.9.3 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?

Parameters of bioanalytical method validation are listed in Table 7. The coefficient of variation of the precision and the bias of accuracy were all within (b) (4) % of the nominal value.

Table 7 Parameters of Bioanalytical Method Validation

Study ID	R08-0467	92001		92002		11244403	
Analyte	Hydrocodone	Guaifenesin	Hydrocodone	Guaifenesin	Hydrocodone	Guaifenesin	Hydrocodone
Limit of Quantitation	150 pg/ml	9.97 ng/ml	150 pg/ml	9.97 ng/ml	150 pg/ml	5 ng/ml	100 pg/ml
Range of Standard Curve	150 - 15000 pg/ml	10.04 - 5019 ng/ml	150 - 30000 pg/ml	10.04 - 5019 ng/ml	150 - 30000 pg/ml	5 - 2000 ng/ml	100 - 20000 pg/ml
Intraday Precision (CV%)	0.45% - 6.44%	1.66% - 3.88%	0.45% - 6.44%	1.66% - 3.88%	0.45% - 6.44%	1.2% - 6.3%	1.3% - 3.1%
Intraday Accuracy (RE%)	96.83% - 104.60%	-7.32% - 2.52%	96.83% - 104.60%	-7.32% - 2.52%	96.83% - 104.60%	101.7% - 106.7%	98.5% - 100.6%
Interday Precision (CV%)	2.30% - 4.39%	2.91% - 9.09%	2.30% - 4.39%	2.91% - 9.09%	2.30% - 4.39%	1.5% - 4.5%	1.9% - 3.1%
Interday Accuracy (RE%)	96.77% - 99.56%	-4.69% - 0.94%	96.77% - 99.56%	-4.69% - 0.94%	96.77% - 99.56%	101.4% - 102.5%	96.0% - 98.9%
Room Temperature Stability	25 hr in matrix	22 hr in matrix	25 hr in matrix	22 hr in matrix	25 hr in matrix	25.5 hr	24 hr in plasma
Processed Stability	N/A	N/A	N/A	N/A	N/A	117 hr at 10 °C	24 hr at 10°C
Freeze-thaw Stability	4 cycles at -20 °C	4 cycles at -20 °C	4 cycles at -20 °C	4 cycles at -20 °C	4 cycles at -20 °C	3 cycles	3 cycles
-20 oC Storage Stability	137 days in K2 plasma	308 days in solution	137 days in K2 plasma	308 days in solution	137 days in K2 plasma	23 days	173 days
Interference by Matrices	No	No in 9/10 matrices	No	No in 9/10 matrices	No	No	No

Source: reviewer’s summary based on section 2.7.1 Summary of biopharmaceutical studies and associated methods, page 8 to page 20, Table 4.1 to Table 4.7

2.9.4 How does the range of standard curve relate to the requirements for clinical studies? What curve fitting techniques were used?

In study 11244403, the range of the standard curves for measuring guaifenesin and hydrocodone were 5.00 – 2,000.00 ng/ml and 100 – 20,000 pg/mL, respectively. For sample concentrations greater than upper limit of linear range, the samples were diluted for re-analysis. None of the sample concentrations were below the lower limit of linear range at the first sampling time point passing three mean elimination half-lives (2.5 hour for guaifenesin and 15 hour for hydrocodone). Quantitation is performed using analyte to IS area ratio and a 1/x weighted linear regression.

2.9.5 What is the result for the re-analysis of the incurred samples?

In study 11244403, 99.3% (151/152) of hydrocodone incurred sample re-analysis (ISR) results were within ±20% of their mean results. 98.5% (196/199) of ISR results were within ±20% of their mean results.

2.10 Reference

1. Mani N, Jun HW, Beach JW, Nerurkar J. Solubility of guaifenesin in the presence of common pharmaceutical additives. *Pharm Dev Technol.* 2003;8(4):385-96.
2. Nanjwade BK, Patel DJ, Udhani RA, Manvi FV. Functions of lipids for enhancement of oral bioavailability of poorly water-soluble drugs. *Sci Pharm.* 2011;79(4):705-27
3. Vandenneuvel WJ, Smith JL, Silber RH. β -(2-Methoxyphenoxy)lactic acid, the major urinary metabolite of glyceryl guaiacolate in man. *J Pharm Sci.* 1972 Dec;61(12):1997-8.
4. Pickens CL1, Milliron AR, Fussner AL, Dversdall BC, Langenstroer P, Ferguson S, Fu X, Schmitz FJ, Poole EC. Abuse of guaifenesin-containing medications generates an excess of a carboxylate salt of beta-(2-methoxyphenoxy)-lactic acid, a guaifenesin metabolite, and results in urolithiasis. *Urology.* 1999 Jul;54(1):23-7.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4. Appendix

4.1 Appendix – Individual Study Review

4.1.1 Study R08-0467

Study Type: Phase 1 single dose bioavailability/bioequivalence PK study in healthy volunteers

Title:

A Relative Bioavailability Study of 5 mg/5 mL Hydrocodone Bitartrate Solution Versus 5 mL HYCODAN® Syrup Under Fasting Conditions

Objective:

The objective of this study was to assess the relative bioavailability of 5 mL hydrocodone bitartrate solution (5 mg/5mL, prepared by (b)(4)) compared to that of 5 mL HYCODAN® syrup (5 mg hydrocodone bitartrate and 1.5 mg homatropine methylbromide per 5 mL) following a single oral dose in healthy adult subjects when administered under fasting conditions.

Study Design and Method:

This investigation was a randomized, single-dose, open-label, two-period, two-sequence, two-way crossover study conducted in 20 healthy adults. In each study period, a single 5 mg dose (5 mg/5 mL solution or syrup) was administered to all subjects following an overnight fast of at least 10 hours. The test formulation was hydrocodone Bitartrate Solution (5 mg/5 mL) and the reference formulation was HYCODAN® syrup. The subjects received the test product in one study period and the reference product in the other study period. Drug administration occurred according to the dosing randomization schedule. There was a 7-day washout interval between treatments.

Blood samples were collected within 90 minutes prior to dosing (0 hour) and post-dose at study hours 0.17, 0.33, 0.5, 0.67, 1, 1.25, 1.5, 2, 3, 4, 5, 7, 10, 14, 18, and 24. The analytical data were used to calculate the pharmacokinetic parameters: AUC_{0-t} , AUC_{0-inf} , AUC_{0-t}/AUC_{0-inf} , C_{max} , T_{max} , K_{el} , and $T_{1/2}$.

Analytical Method:

The plasma samples were sent to (b)(4) for determination of hydrocodone plasma concentrations. Samples were analyzed by HPLC ESI+MS/MS with LLOQ at 150 pg/mL. The assay was validated from 150 pg/mL to 15000 pg/mL in plasma. The coefficient of variation of the precision and the bias of accuracy were 0.45% to 6.44% (CV) and -3.23% to +4.60% (bias), respectively.

Results:

Following single-dose (5 mg hydrocodone bitartrate) oral administration, the ratios (test drug/reference drug, N=20) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.97 (90% CI = 0.93, 1.01), 0.97 (90% CI = 0.93, 1.01), and 0.92 (90% CI= 0.85, 0.98), respectively (Table 8 and Fig.4). Hydrocodone mean T_{max} of the test drug was approximately 10 minutes later than the reference drug.

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Conclusions:

The hydrocodone solution provided by the sponsor in this study was bioequivalent to the reference hydrocodone (HYCODAN®).

Table 8 Comparison of PK Parameters of Hydrocodone between Tested Product and HYCODAN® in Study R08-0467 (N=20)

Parameter	Least-Squares Means ¹		Ratio ²	CV% ³	90% Confidence Interval ⁴	
	Test	Reference			Lower	Upper
AUC 0-t (ng-hr/mL)	73.2	75.7	0.966	-	0.925	1.008
AUCinf (ng-hr/mL)	75.1	77.5	0.969	-	0.927	1.010
Cmax (ng/mL)	12.3	13.4	0.918*	-	0.853	0.984
Tmax (hour)	1.26	1.09	1.147	-	-	-
λ_z (1/hour)	0.1604	0.1564	1.025	-	-	-
T½ (hour)	4.43	4.52	0.980	-	-	-

1. Least-squares geometric means for ln-transformed data.
 2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean.
- (Source: (b) (4) R08-0467, page 49, Table 14.1)

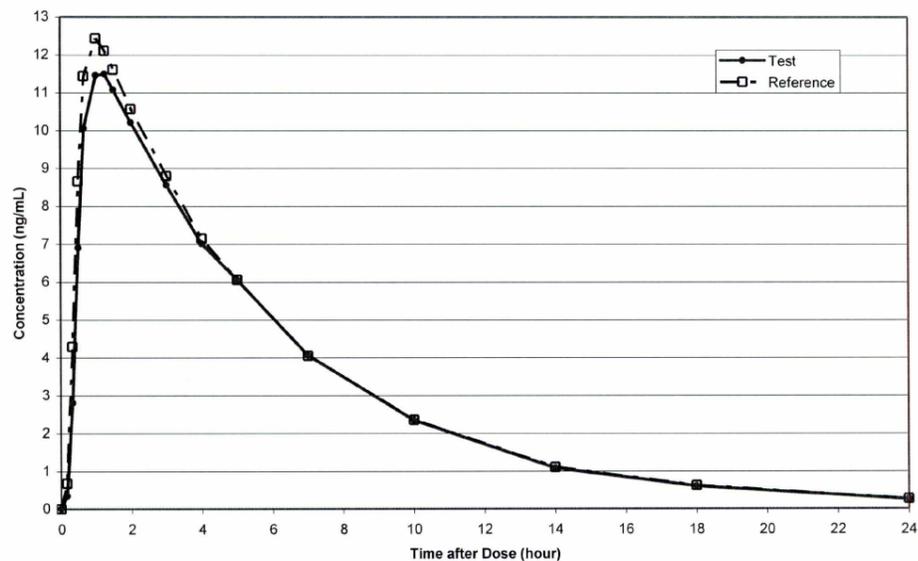


Fig.4 Hydrocodone plasma concentration-time profile following 5 mg single dose administration (n=20) in study R08-0467, observations represent the least square geometric mean for each time point. (Source: (b) (4) R08-0467, page 51, Figure 14.1)

Reviewer’s comments:

Median T_{max} , but not geometric mean T_{max} should be compared between two products .However T_{max} appears similar between two products by visual check.

4.1.2 Study 92001

Study Type: Phase 1 single dose food effect PK study in healthy volunteers

Title:

Phase I, Randomized, Open-Label, 2-Way Crossover, Comparative Bioavailability, Food Effect Study of a hydrocodone-Guaifenesin 2.5 mg-200 mg/5 mL Solution Following a 5 mg-400 mg Dose in Healthy Subjects under Fasting and Fed Conditions

Objective:

The objective of this study was to compare the rate and extent of absorption of hydrocodone bitartrate-guaifenesin 2.5 mg-200 mg/5 mL solution (manufactured by Sovereign Pharmaceuticals LLC), administered as 1 x 10 mL (5 mg-400 mg) solution under fasting and fed conditions.

Method:

This was a single center, randomized, open-label, two-period, two-sequence, 2-way crossover, Phase I, comparative bioavailability, food effect study with 25 healthy adults completed 2 periods. A single oral dose of hydrocodone-guaifenesin 2.5 mg-200 mg/5 mL as a 1 x 10 mL solution (total dose of 5 mg-400 mg) either under fasting or fed conditions was administered in each study period. For fasted group, no food was allowed from at least 10 hours before dosing until at least 4 hours after dosing. For fed group, a standard high-fat, high-caloric critical breakfast (800 – 1000 calories) was required to complete to consume prior to drug administration. The treatment phases were separated by a washout period of 7 days.

For hydrocodone, blood samples were collected prior to drug administration and 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.0, 16.0, 20.0, and 24.0 hours post-dose in each period.

For guaifenesin, blood samples were collected prior to drug administration and 0.167, 0.333, 0.50, 0.75, 1.00, 1.25, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.0, 16.0, 20.0, and 24.0 hours post-dose in each period.

Analytical Method:

The plasma samples were sent to (b)(4) for determination of hydrocodone and guaifenesin plasma concentrations. Samples were analyzed by HPLC ESI+MS/MS. For hydrocodone, the LLOQ was 150 pg/mL, the range of standard curve was from 150 pg/mL to 30000 pg/mL in plasma. The coefficient of variation of the precision and the bias of accuracy ranges were 0.45% to 6.44% (CV) and -3.23% to +4.60% (bias), respectively. For guaifenesin, the LLOQ was 9.97 ng/mL, the range of standard curve was from 10.04 ng/mL to 5019 ng/mL in plasma. The coefficient of variation of the precision and the bias of accuracy were 1.66% to 9.09% (CV) and -7.32% to +2.52% (bias), respectively.

Results:

For hydrocodone, the ratios (fed/fasted, N=25) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 1.15 (90% CI = 1.12, 1.18), 1.16 (90% CI = 1.12, 1.19), and 0.88 (90% CI= 0.82, 0.94), respectively (Table 9 and Fig.5). Hydrocodone mean T_{max} under fed condition was approximately 30 minutes later than under fasted condition.

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For guaifenesin, the ratios (fed/fasted, N=25) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.52 (90% CI = 0.44, 0.60), 0.53 (90% CI = 0.45, 0.60), and 0.31 (90% CI= 0.16, 0.46), respectively (Table 10 and Fig.6). Guaifenesin mean T_{max} of the test drug was similar between fed and fasted status, all about 20 minutes post-dose.

Table 9 Food Effect on Hydrocodone in Study 92001 (N=25)

PARAMETER	TEST FED (B)	TEST FASTED (A)	RATIO (B/A)	CV%	90% CI Lower Limit	90% CI Upper Limit	Significance (p<0.05)
AUC _(0-t)	77609	67323	1.153	-	1.122	1.183	<0.0001
AUC _(0-inf)	81158	70109	1.158	-	1.124	1.191	<0.0001
C _{max}	10958	12450	0.880	-	0.816	0.944	0.0040
T _{max}	1.43	0.941	1.517	-	-	-	0.0010
λ _z	0.1380	0.1379	1.001	-	-	-	None
t _{1/2}	5.17	5.19	0.996	-	-	-	None

(Source: (b) (4) 92001, page 7)

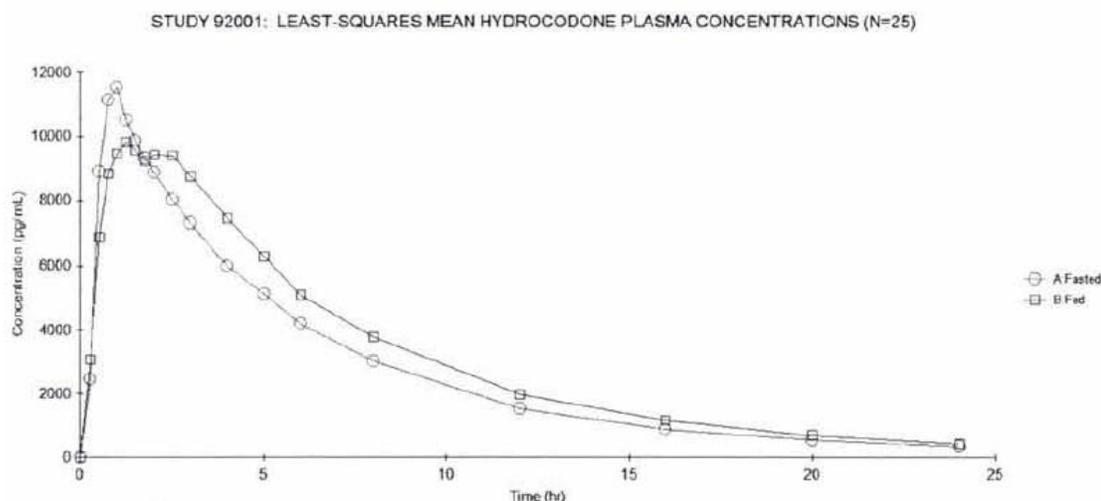


Fig.5 Hydrocodone plasma concentration-time profile following 5 mg hydrocodone/400 mg guaifenesin single dose administration (n=25) in study 92001, observations represent the least square geometric mean for each time point. (Source: (b) (4) 92001, page 8)

Table 10 Food Effect on Guaifenesin in Study 92001 (N=25)

PARAMETER	TEST FED (B)	TEST FASTED (A)	RATIO (B/A)	CV%	90% CI Lower Limit	90% CI Upper Limit	Significance (p<0.05)
AUC _(0-t)	2494	4789	0.521	-	0.443	0.598	<0.0001
AUC _(0-inf)	2529	4821	0.525	-	0.447	0.602	<0.0001
C _{max}	1658	5295	0.313	-	0.162	0.464	<0.0001
T _{max}	0.364	0.330	1.104	-	-	-	None
λ _z	0.7460	0.7827	0.953	-	-	-	None
t _{1/2}	0.953	0.901	1.058	-	-	-	None

(Source: (b) (4) 92001, page 7)

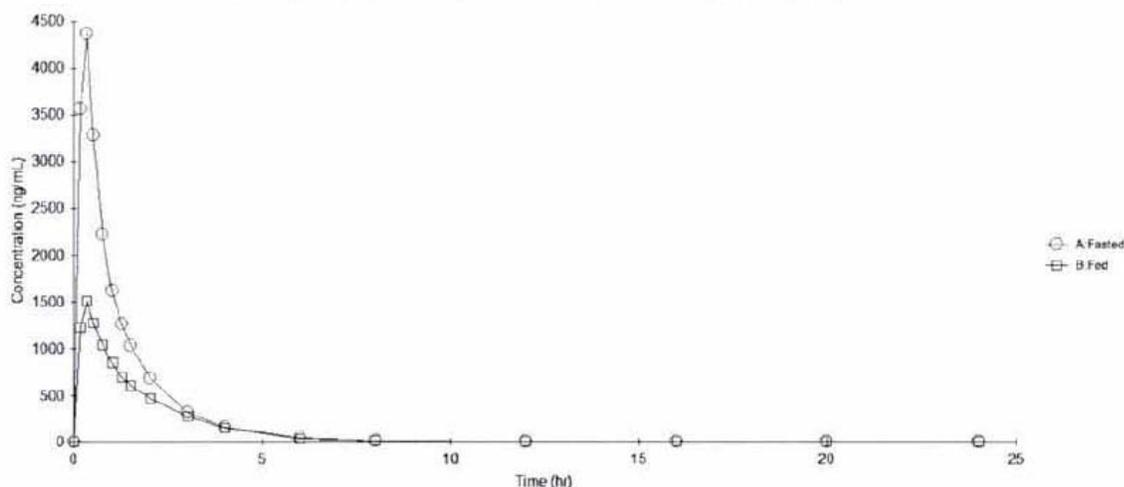


Fig.6 Guaifenesin plasma concentration-time profile following 5 mg hydrocodone/400 mg guaifenesin single dose administration (n=25) in study 92001, observations represent the least square geometric mean for each time point. (Source: (b)(4) 92001, page 9)

Conclusion:

Food significantly reduces the bioavailability of guaifenesin (AUC reduced to about a half, C_{max} reduced to about a third). Food delays hydrocodone absorption (peak plasma concentration delayed about half an hour).

Reviewer's comments:

Median T_{max} , but not geometric mean T_{max} should be compared between two products. Median T_{max} of hydrocodone was 1.25 hr and 1 hr under fed and fasted conditions, respectively, indicating a 25-minute delay of the absorption. Median T_{max} of guaifenesin was 20 minutes under both fed and fasted conditions, indicating a similar absorption rate.

Reviewer's independent analysis showed that the ratios (fed/fasted, N=25) of least-squares geometric means for guaifenesin AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.50 (90% CI = 0.47, 0.55), 0.51 (90% CI = 0.47, 0.55), and 0.31 (90% CI = 0.27, 0.35), respectively (Table 20). The results are in agreement with the Sponsor's conclusion.

Table 20 Food Effect on Guaifenesin in Study 92001 (N=25)

Parameter	Test Fed (B) ¹	Test Fasted (A) ¹	Ratio (B/A) ²	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC _{0-t} (ng·h/mL)	2209	4387	0.503	0.465	0.545
AUC _{0-inf} (ng·h/mL)	2247	4425	0.508	0.469	0.550
C _{max} (ng/mL)	1436	4647	0.309	0.272	0.351
T _{max} (hour)	0.333 (0.167 - 0.750)	0.333 (0.167 - 0.767)	-	-	-

1. Least-squares geometric means for areas and peak concentrations. T_{max} reported as median (range).

2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean.

Estimated means, standard errors, and confidence intervals derived from a linear mixed effects model with fixed effects sequence, treatment, period, and a random effect for subject.

(Source: reviewer's analysis)

Reviewer's independent analysis showed that the ratios (fed/fasted, N=25) of least-squares geometric means for hydrocodone AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 1.16 (90% CI = 1.12, 1.19), 1.16 (90% CI = 1.12, 1.20), and 0.89 (90% CI= 0.83, 0.94), respectively (Table 21). The results are in agreement with the Sponsor's conclusion.

Table 21 Food Effect on Hydrocodone in Study 92001 (N=25)

Parameter	Test Fed (B) ¹	Test Fasted (A) ¹	Ratio (B/A) ²	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC_{0-t} (pg·h/mL)	76101	65805	1.156	1.123	1.191
AUC_{0-inf} (pg·h/mL)	79382	68414	1.160	1.124	1.197
C_{max} (pg/mL)	10772	12150	0.887	0.834	0.943
T_{max} (hour)	1.25 (0.5 - 3)	1 (0.5 – 2)	-	-	-

1. Least-squares geometric means for areas and peak concentrations. Tmax reported as median (range).

2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean.

Estimated means, standard errors, and confidence intervals derived from a linear mixed effects model with fixed effects sequence, treatment, period, and a random effect for subject.

(Source: reviewer's analysis)

Study 92002

Study Type: Phase 1 single dose bioavailability/bioequivalence PK study in healthy volunteers

Title:

Phase I, Randomized, Open-Label, 4-Way Crossover, Relative Bioavailability and Drug Interaction Study Comparing the Pharmacokinetics of a Hydrocodone-Guaifenesin Combination Solution, Hydrocodone Bitartrate and Homatropine Methylbromide Syrup (Hi Tech Pharmacal), a Guaifenesin Solution and Co - Administration of Hydrocodone Bitartrate and Homatropine Methylbromide Syrup (Hi Tech Pharmacal) and Guaifenesin Solution in Healthy Subjects Under Fasting Conditions.

Objective:

The objectives of this study were:

- 1) To compare the rate and extent of hydrocodone absorption from a combination hydrocodone bitartrate-guaifenesin solution (2.5 mg-200mg/5mL from Sovereign Pharmaceuticals, LLC) with hydrocodone bitartrate and homatropine methylbromide syrup (5 mg-1.5 mg/5mL from Hi Tech Pharmacal).
- 2) To compare the rate and extent of guaifenesin absorption from a combination hydrocodone bitartrate-guaifenesin solution (2.5 mg-200mg/5mL from Sovereign Pharmaceuticals, LLC) with those from an extemporaneously prepared guaifenesin solution.
- 3) To determine if drug-drug interaction exists by comparing the rates and extents of hydrocodone and guaifenesin absorption from the co-administration of hydrocodone bitartrate and homatropine methylbromide syrup (5 mg-1.5 mg/5mL from Hi Tech Pharmacal) and an extemporaneously prepared guaifenesin solution with those obtained after separate administration of each.

Method:

This was a single center, randomized, open-label, 4-period, 4-sequence, 4-way crossover, Phase I, comparative bioavailability, and drug interaction study in 36 healthy volunteers (34 completed all 4

periods). In each period, subjects were administered a single oral dose of the following treatments in accordance with the randomization scheme:

Treatment A: 1 x 10 ml of hydrocodone bitartrate-guaifenesin 2.5 mg-200 mg/5 ml solution (Sovereign Pharmaceuticals, LLC., U.S.A.)

Treatment B: 1 x 5 ml of hydrocodone bitartrate and homatropine methylbromide syrup (5 mg-1.5 mg/5 ml, Hi Tech Pharmal, U.S.A.)

Treatment C: 1 x 10 ml of guaifenesin 200 mg/5 mL extemporaneously prepared solution (Sovereign Pharmaceuticals, LLC., U.S.A.). The solution was made by dissolving 6 grams of guaifenesin into 150 ml sterile water.

Treatment D: 1 x 5 ml of hydrocodone bitartrate and homatropine methylbromide syrup (5 mg- 1.5 mg/5 ml, Hi Tech Phannacal, U.S.A.) + 1 x 10 ml of guaifenesin 200 mg/5 ml extemporaneously prepared solution (Sovereign Pharmaceuticals, LLC., U.S.A.)

The treatment phases were separated by washout periods of at least 7 days.

For hydrocodone, blood samples were collected prior to drug administration and 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.0, 16.0, 20.0, and 24.0 hours post-dose in each period.

For guaifenesin, blood samples were collected prior to drug administration and 0.167, 0.333, 0.50, 0.75, 1.00, 1.25, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 12.0, 16.0, 20.0, and 24.0 hours post-dose in each period.

Analytical Method:

The plasma samples were sent to (b) (4) for determination of hydrocodone and guaifenesin plasma concentrations. Samples were analyzed by HPLC ESI+MS/MS. For hydrocodone, the LLOQ was 150 pg/mL, the range of standard curve was from 150 pg/mL to 30000 pg/mL in plasma. The coefficient of variation of the precision and the bias of accuracy ranges were 0.45% to 6.44% (CV) and -3.23% to +4.60% (bias), respectively. For guaifenesin, the LLOQ was 9.97 ng/mL, the range of standard curve was from 10.04 ng/mL to 5019 ng/mL in plasma. The coefficient of variation of the precision and the bias of accuracy were 1.66% to 9.09% (CV) and -7.32% to +2.52% (bias), respectively.

Results:

Bioequivalence

For hydrocodone, the ratios (treatment A/treatment B, N=35) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.93 (90% CI = 0.90, 0.96), 0.93 (90% CI = 0.90, 0.96), and 0.94 (90% CI = 0.87, 1.00), respectively (Table 11 and Fig.7). Hydrocodone mean T_{max} of the test product (treatment A) and the reference drug (treatment B) were similar, all about 1 hour post-dose.

Table 11 Comparison of PK Parameters of Hydrocodone between Tested Product (A) and Reference (B) in Study R92002 (N=35)

PARAMETER	TEST COMBO (A)	HYDROCODONE SYRUP (B)	RATIO (A/B)	CV%	90% CI Lower Limit	90% CI Upper Limit	Significance (p<0.05)
AUC _(0-t)	70949	76374	0.929	-	0.899	0.959	0.0002
AUC _(0-inf)	74240	79814	0.930	-	0.899	0.961	0.0004
C _{max}	12924	13817	0.935	-	0.868	1.003	None
T _{max}	1.02	0.917	1.114	-	-	-	None
λ _z	0.1332	0.1381	0.964	-	-	-	None
t _{1/2}	5.35	5.24	1.021	-	-	-	None

(Source: (b) (4) 92002, page 8)

!
!

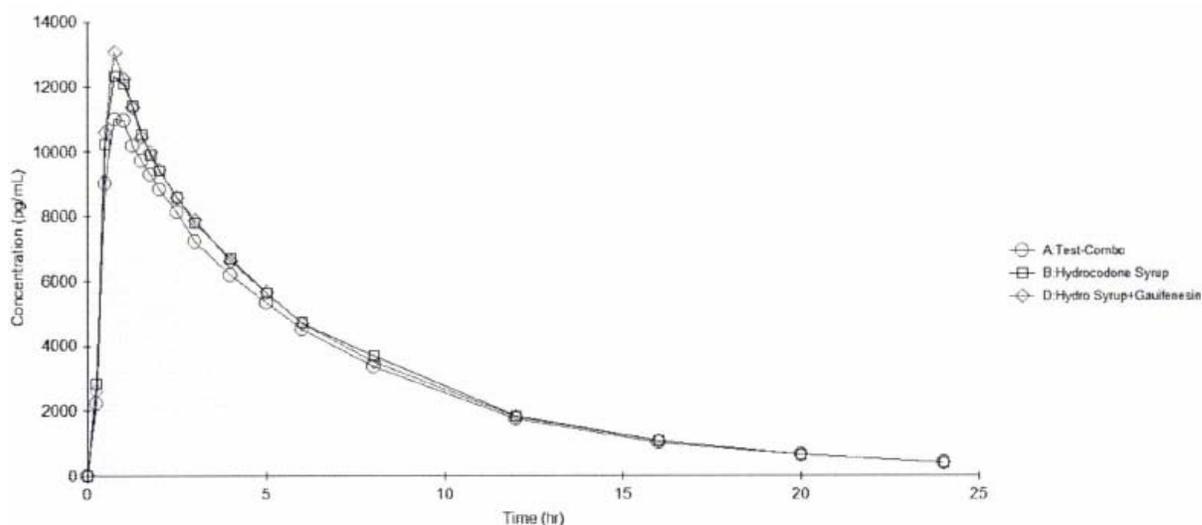


Fig.7 Hydrocodone plasma concentration-time profile of treatment A, B and D (n=35) in study 92002, observations represent the least square geometric mean for each time point. (Source: (b) (4) 92002, page 10)

!

For guaifenesin, the ratios (treatment A/treatment C, N=35) of least-squares geometric means for AUC_{0-t}, AUC_{0-∞}, and C_{max} were 1.63 (90% CI = 1.52, 1.74), 1.62 (90% CI = 1.51, 1.72), and 1.89 (90% CI= 1.70, 2.08), respectively (Table 12 and Fig.8). Guaifenesin mean T_{max} of the test product (treatment A) and the reference drug (treatment C) were similar, all about 25 minutes.

Table 12 Comparison of PK Parameters of Guaifenesin between Tested Product (A) and Reference (C) in Study R92002 (N=35)

PARAMETER	TEST COMBO (A)	GUAIFENESIN SOLUTION (C)	RATIO (A/C)	CV%	90% CI Lower Limit	90% CI Upper Limit	Significance (p<0.05)
AUC _(0-t)	4610	2834	1.627	-	1.519	1.735	<0.0001
AUC _(0-inf)	4641	2869	1.618	-	1.511	1.724	<0.0001
C _{max}	4577	2420	1.891	-	1.704	2.078	<0.0001
T _{max}	0.361	0.440	0.820	-	-	-	0.0182
λ _z	0.7660	0.7561	1.013	-	-	-	None
t _{1/2}	0.918	0.936	0.981	-	-	-	None

(Source: (b) (4) 92002, page 9)

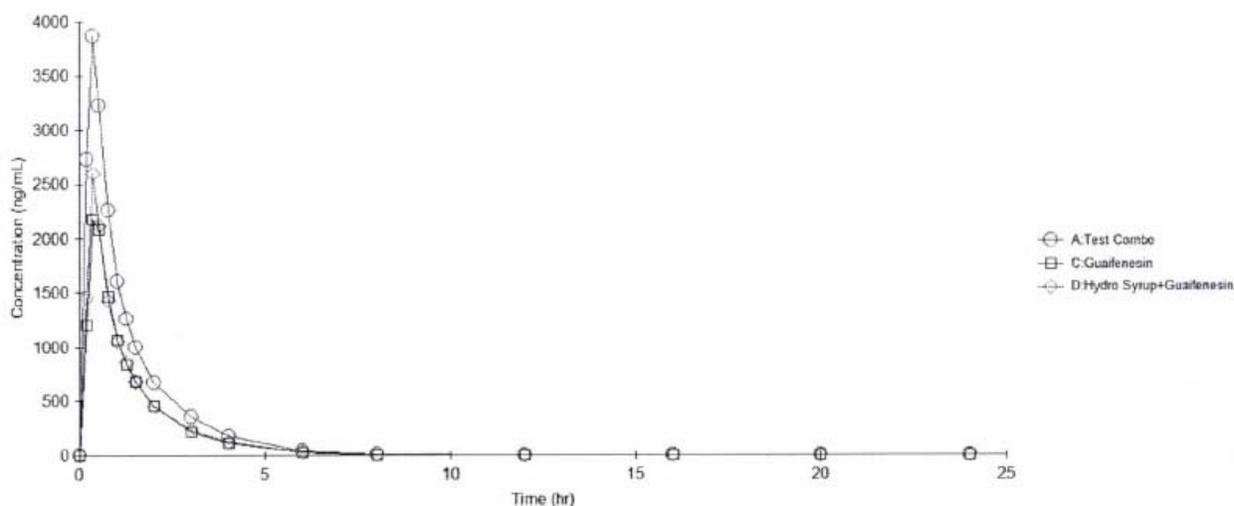


Fig.8 Guaifenesin plasma concentration-time profile of treatment A, C and D (n=35) in study 92002, observations represent the least square geometric mean for each time point. (Source: (b) (4) 92002, page 11)

DDI

For hydrocodone, the ratios (treatment D/treatment B, N=35) of least-squares geometric means for AUC_{0-t}, AUC_{0-∞}, and C_{max} were 0.99 (90% CI = 0.96, 1.02), 0.99 (90% CI = 0.96, 1.02), and 1.04 (90% CI= 0.97, 1.11), respectively (Table 13 and Fig.7). Hydrocodone T_{max} of combination product (treatment D) and reference product (treatment B) were similar, all about 55 minutes post-dose.

Table 13 Comparison of PK Parameters of Hydrocodone between Combined Product (D) and Reference (B) in Study R92002 (N=35)

PARAMETER	HYDRO+ GUAIF (D)	HYDROCODONE SYRUP (B)	RATIO (D/B)	CV%	90% CI Lower Limit	90% CI Upper Limit	Significance (p<0.05)
AUC _(0-t)	75805	76374	0.993	-	0.962	1.023	None
AUC _(0-inf)	78814	79814	0.987	-	0.956	1.019	None
C _{max}	14317	13817	1.036	-	0.967	1.106	None
T _{max}	0.907	0.917	0.990	-	-	-	None
λ _z	0.1407	0.1381	1.019	-	-	-	None
t _½	5.05	5.24	0.962	-	-	-	None

(Source: (b) (4) 92002, page 8)

!

For guaifenesin, the ratios (treatment D/treatment C, N=35) of least-squares geometric means for AUC_{0-t}, AUC_{0-∞}, and C_{max} were 1.05 (90% CI = 0.94, 1.16), 1.05 (90% CI = 0.94, 1.16), and 1.19 (90% CI = 1.00, 1.38), respectively (Table 14 and Fig.8). Guaifenesin T_{max} of combination product (treatment D) and reference product (treatment C) were similar, all about 25 minutes post-dose.

!

Table 14 Comparison of PK Parameters of Guaifenesin between Combined Product (D) and Reference (C) in Study R92002 (N=35)

PARAMETER	HYDRO+ GUAIF (D)	GUAIFENESIN SOLUTION (C)	RATIO (D/C)	CV%	90% CI Lower Limit	90% CI Upper Limit	Significance (p<0.05)
AUC _(0-t)	2979	2834	1.051	-	0.942	1.160	None
AUC _(0-inf)	3014	2869	1.051	-	0.943	1.158	None
C _{max}	2878	2420	1.189	-	1.001	1.378	None
T _{max}	0.366	0.440	0.832	-	-	-	None
λ _z	0.7629	0.7561	1.009	-	-	-	None
t _½	0.929	0.936	0.993	-	-	-	None

(Source: (b) (4) 92002, page 9)

Conclusion:

Bioequivalence:

Hydrocodone from the proposed product is bioequivalent to the reference hydrocodone (hydrocodone bitartrate and homatropine methylbromide syrup from Hi Tech).

Guaifenesin from the proposed product is not bioequivalent to the extemporaneously prepared guaifenesin from Sovereign Pharmaceuticals. The systemic exposure of guaifenesin from the test product is higher.

DDI:

There is no apparent DDI between the extemporaneously prepared guaifenesin (from Sovereign Pharmaceuticals) and the reference hydrocodone (hydrocodone bitartrate and homatropine methylbromide syrup from Hi Tech).

Discussion:

The sponsor held an audit after study 92002, probing the potential causes resulted in guaifenesin non-bioequivalence between the proposed product and the extemporaneously prepared guaifenesin. During the audit of (b) (4) documents, processes and procedures, it was noted that the retained material (extemporaneously prepared guaifenesin) from the clinical study had precipitated and that the remaining liquid appeared to be lower than expected. However, the drug dispensing/syringe filling record from this stud did not note precipitation of the drug (guaifenesin) in the syringes prior to dosing. The sponsor attributed the guaifenesin non-bioequivalence to a potential formulation effect of extemporaneously prepared guaifenesin.

Reviewers' comment:

Median T_{max} , but not geometric mean T_{max} should be compared between different treatments. As listed in Table 15, median T_{max} of hydrocodone appeared the same crossing all three treatments (A, B and D). Median T_{max} of guaifenesin were similar crossing all three treatments (A, C and D).

Table 15 List of Median T_{max} of Hydrocodone and Guaifenesin from Different Treatments

	Treatment A (N=36)	Treatment B (N=35)	Treatment C (N=34)	Treatment D (N=35)
Hydrocodone median T_{max} (hr)	0.75	0.75	-	0.75
Guaifenesin median T_{max} (hr)	0.333	-	0.5	0.333

(Source: Reviewer's analysis)

The sponsor's explanation for non-bioequivalence is acceptable.

- 1) The dedicated DDI investigation by comparing guaifenesin relative bioavailability between treatment C and treatment D did not show any significant DDI between guaifenesin and hydrocodone. Guaifenesin from treatment C and treatment D was bioequivalent to each other, but not bioequivalent to treatment A. The formulation of guaifenesin was the same between treatment C and treatment D, but different from treatment A. It's acceptable that it's the formulation difference causing the non-bioequivalence of guaifenesin.*
- 2) It's known that the solubility of guaifenesin in pure water at 25 °C is 40.4 mg/ml. The extemporaneously prepared guaifenesin provided by the sponsor (40 mg/ml) is at near-saturation status. Therefore the observation of in vitro precipitation is not a surprise¹. We don't know if precipitation could also happen in vivo, as the solubility of guaifenesin decreases dramatically with increase of pH and in the presence of different salt concentrations¹. Precipitation of drug in the digestive tract would reduce drug bioavailability, which may contribute to the observation that the extemporaneously prepared guaifenesin had much lower bioavailability than the proposed product.*

4.1.3 Study 11244403

Study Type: Phase 1 single dose bioavailability/bioequivalence PK study in healthy volunteers

Title:

A Relative Bioavailability and Drug Interaction Study of Test Formulation of Hydrocodone Bitartrate/Guaifenesin 2.5 mg / 200 mg per 5 mL Oral Solution (Sovereign Pharmaceuticals, LLC) compared to Two Marketed Products of Hydrocodone Bitartrate / Homatropine Methylbromide 5 mg / 1.5 mg per 5 mL Syrup (Hi-Tech Pharmacal Co., Inc.) and Guaifenesin 200 mg per 5 mL Oral Solution (Capellon Pharmaceuticals, LLC), in Healthy Volunteers under Fasted Conditions

Objective:

The objectives of this study were:

- 1) To compare the rate and extent of hydrocodone absorption from a combination hydrocodone bitartrate-guaifenesin solution (2.5 mg-200mg/5mL from Sovereign Pharmaceuticals, LLC) with hydrocodone bitartrate and homatropine methylbromide syrup (5 mg-1.5 mg/5mL from Hi Tech Pharmacal).
- 2) To compare the rate and extent of guaifenesin absorption from a combination hydrocodone bitartrate-guaifenesin solution (2.5 mg-200mg/5mL from Sovereign Pharmaceuticals, LLC) with Liquituss GG (200 mg guaifenesin /5 mL from Capellon Pharmaceuticals, LLC).
- 3) To determine if drug-drug interaction exists by comparing the rates and extents of hydrocodone and guaifenesin absorption from the co-administration of hydrocodone bitartrate and homatropine methylbromide syrup (2.5 mg-200mg/5mL from Sovereign Pharmaceuticals, LLC) and Liquituss GG (200 mg guaifenesin /5 mL from Capellon Pharmaceuticals, LLC) with those obtained after separate administration of each.

Method:

This was a randomized, single-dose, four-treatment, four-period, four-sequence, four way-crossover study under fasted conditions comparing equal doses of hydrocodone and equal doses of guaifenesin from the test and reference products. The study was conducted with 60 (56 completing all four periods) healthy adult subjects in accordance with Protocol No 11244403. Statistical analyses for guaifenesin results were performed using the results from the 57 evaluable subjects. The first 36 subjects from this population, with hydrocodone results for the test product (treatment A), the hydrocodone reference product (treatment B) and the co-administered reference products (treatment D), were used in the statistical evaluations for that analyte. Following an overnight fast of at least 10 hours in each study period, the subjects were dosed with one of the following four study treatments according to the four-treatment, four-sequence randomization:

Treatment A: Single 10 mL dose of guaifenesin 200 mg/ 5 mL, hydrocodone bitartrate 2.5 mg/5 mL, for a total dose of 400 mg guaifenesin and 5 mg hydrocodone bitartrate (Sovereign Pharmaceuticals, LLC)

Treatment B: Single 5 mL dose of hydrocodone bitartrate and homatropine methylbromide syrup 5 mg/ 1.5 mg per 5 mL, for a total dose of 5 mg hydrocodone bitartrate (Hi-Tech Pharmacal Co., Inc.)

Treatment C: Single 10 mL dose of Liquituss GG expectorant liquid (guaifenesin oral solution 200 mg/ 5 mL), for a total dose of 400 mg guaifenesin (Capellon Pharmaceuticals, LLC)

Treatment D: Co-administration of a single 5 mL dose of hydrocodone bitartrate and homatropine methylbromide syrup 5 mg/ 1.5 mg per 5 mL (Hi-Tech Pharmacal Co., Inc.), and a single 10 mL dose of Liquituss GG expectorant liquid (guaifenesin oral solution 200 mg/ 5 mL) (Capellon Pharmaceuticals, LLC), for a total dose of 5 mg hydrocodone bitartrate and 400 mg guaifenesin

The treatment phases were separated by washout periods of at least 7 days.

In each period, 7 mL venous blood was collected in sodium heparin vacutainers before dosing and at the following nominal times after dosing: 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.

Analytical Method:

The plasma samples were sent to (b) (4) for determination of hydrocodone concentrations (from all 18 time points) and guaifenesin concentrations (from all 18 time points except 15 and 20 hours post-dose). Samples were analyzed by HPLC ESI+MS/MS. For hydrocodone, the LLOQ was 100 pg/mL, the range of standard curve was from 100 pg/mL to 20000 pg/mL in plasma. The coefficient of variation of the precision and the bias of accuracy ranges were 1.3% to 3.1% (CV) and -4.0% to +0.60% (bias), respectively. For guaifenesin, the LLOQ was 5 ng/mL, the range of standard curve was from 5 ng/mL to 2000 ng/mL in plasma. The coefficient of variation of the precision and the bias of accuracy were 1.2% to 6.3% (CV) and +1.4% to +6.7% (bias), respectively.

Results:

Bioequivalence

For hydrocodone, the ratios (treatment A/treatment B, N=36) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.99 (90% CI = 0.96, 1.03), 0.99 (90% CI = 0.96, 1.03), and 0.94 (90% CI = 0.90, 0.98), respectively (Table 16 and Fig.9). Hydrocodone median T_{max} of treatment A was 15 minutes later than the treatment B, indicating that the absorption profiles of hydrocodone from two products were similar.

Table 16 Comparison of PK Parameters of Hydrocodone between Tested Product (A) and Reference (B) in Study 11244403 (N=36)

Parameter	Test Product ¹	Hydrocodone Reference ¹	Ratio ²	CV% ³	90% CI ⁴
$AUC_{(0-t)}$ (hr*pg/mL)	75375	75922	0.993	8.43	0.960 - 1.026
$AUC_{(0-\infty)}$ (hr*pg/mL)	80186	80630	0.994	8.86	0.960 - 1.030
C_{max} (pg/mL)	12501	13351	0.936*	11.2	0.896 - 0.979
T_{max} (hr)	1.25 (0.333 – 3.00)	1.00 (0.333 – 2.00)	1.133	-	-
K_{el} (1/hr)	0.1488	0.1508	0.986	-	-
$T_{1/2}$ (hr)	4.81	4.78	1.005	-	-

1. Least-squares geometric means for areas and peak concentrations. Least-squares arithmetic means for other parameters. T_{max} reported as median (range).
 2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean.
 3. Estimated intra-subject coefficient of variation, $CV\% = 100 * \text{SQRT}(e\text{MSE}-1)$, where MSE is the mean square error term from the analysis of variance (ANOVA).
 4. Confidence interval on the ratio.
- * Comparison was detected as statistically significant by ANOVA ($\alpha=0.05$ overall, 0.025 pair-wise).
 (Source: (b) (4) 11244403, page 9)

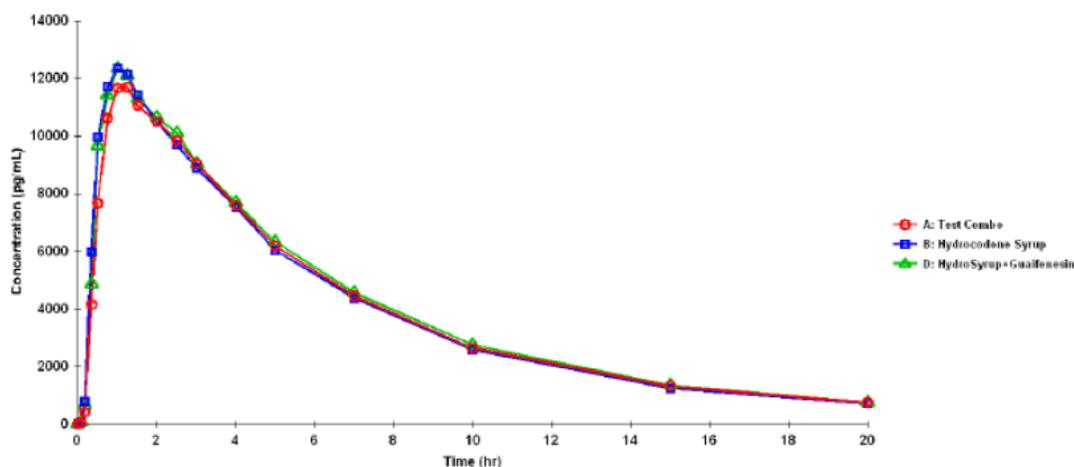


Fig.9 Hydrocodone plasma concentration-time profile of treatment A, B and D (n=36) in study 11244403, observations represent the least square geometric mean for each time point. (Source: (b) (4) 11244403, page 53, Figure 14.2.1.3)

! For guaifenesin, the ratios (treatment A/treatment C, N=57) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 1.04 (90% CI = 0.99, 1.09), 1.04 (90% CI = 0.99, 1.09), and 1.03 (90% CI= 0.94, 1.13), respectively (Table 17 and Fig. 10). Guaifenesin median T_{max} was the same (20 minutes post-dose) between the test product (treatment A) and the reference drug (treatment C).

Table 17 Comparison of PK Parameters of Guaifenesin between Tested Product (A) and Reference (C) in Study 11244403 (N=57)

Parameter	Test Product ¹	Guaifenesin Reference ¹	Ratio ²	CV% ³	90% CI ⁴
$AUC_{(0-t)}$ (hr*ng/mL)	4202	4050	1.038	16.5	0.986 - 1.092
$AUC_{(0-\infty)}$ (hr*ng/mL)	4222	4070	1.037	16.4	0.986 - 1.092
C_{max} (ng/mL)	3711	3593	1.033	29.7	0.943 - 1.131
T_{max} (hr)	0.333 (0.167 - 1.25)	0.333 (0.167 - 1.25)	1.068	-	-
K_{el} (1/hr)	0.8256	0.8188	1.008	-	-
$T_{1/2}$ (hr)	0.855	0.865	0.987	-	-

1. Least-squares geometric means for areas and peak concentrations. Least-squares arithmetic means for other parameters. T_{max} reported as median (range).

2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean.

3. Estimated intra-subject coefficient of variation, $CV\% = 100 * \text{SQRT}(eMSE - 1)$, where MSE is the mean square error term from the analysis of variance (ANOVA).

4. Confidence interval on the ratio

(Source: (b) (4) 11244403, page 7)

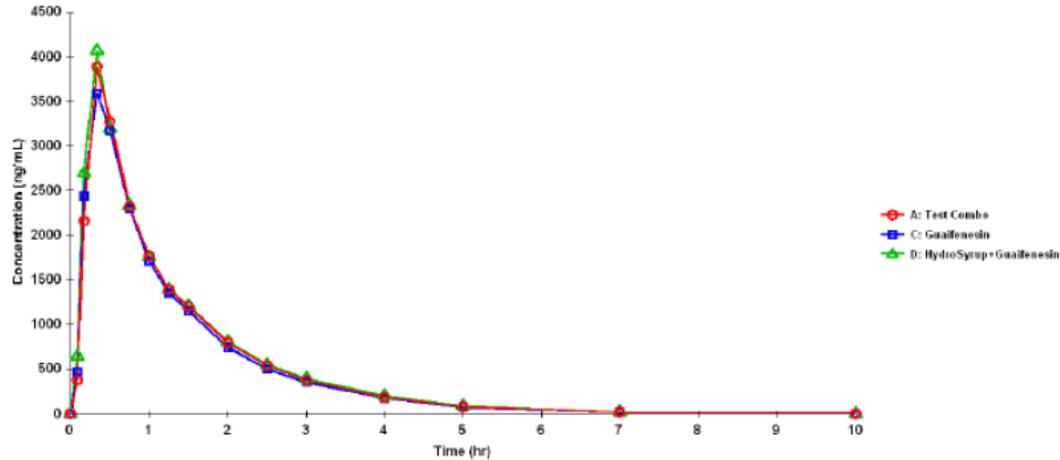


Fig.10 Guaifenesin plasma concentration-time profile of treatment A, C and D (n=57) in study 1244403, observations represent the least square geometric mean for each time point. (Source: (b) (4) 11244403, page 52, Figure 14.2.1.1)

!

DDI

For hydrocodone, the ratios (treatment D/treatment B, N=36) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 1.03 (90% CI = 1.00, 1.07), 1.03 (90% CI = 1.00, 1.07), and 1.01 (90% CI = 0.96, 1.05), respectively (Table 18 and Fig.9). Hydrocodone median T_{max} was the same between two products (1 hour post-dose), indicating that the absorption profiles of hydrocodone were similar between the combination (treatment D) and the reference drug (treatment B).

Table 18 Comparison of PK Parameters of Hydrocodone between Combined Product (D) and Reference (B) in Study 11244403 (N=36)

Parameter	Co-Administered References ¹	Hydrocodone Reference ¹	Ratio ²	CV% ³	90% CI ⁴
$AUC_{(0-t)}$ (hr*pg/mL)	78402	75922	1.033	8.43	0.999 - 1.067
$AUC_{(0-\infty)}$ (hr*pg/mL)	83272	80630	1.033	8.86	0.997 - 1.069
C_{max} (pg/mL)	13415	13351	1.005	11.2	0.961 - 1.050
T_{max} (hr)	1.00 (0.500 – 4.00)	1.00 (0.333 – 2.00)	1.173	-	-
K_{el} (1/hr)	0.1496	0.1508	0.992	-	-
$T_{1/2}$ (hr)	4.78	4.78	0.999	-	-

1. Least-squares geometric means for areas and peak concentrations. Least-squares arithmetic means for other parameters. Tmax reported as median (range).
2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean.
3. Estimated intra-subject coefficient of variation, $CV\% = 100 * \text{SQRT}(e\text{MSE}-1)$, where MSE is the mean square error term from the analysis of variance (ANOVA).
4. Confidence interval on the ratio
(Source: (b) (4) 11244403, page 10)

! For guaifenesin, the ratios (treatment D/treatment C, N=57) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, 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, 1.22), respectively (Table 19 and Fig.10). Guaifenesin median T_{max} was the same between two products (20 minutes post-dose), indicating that the absorption profiles of guaifenesin were similar between the combination (treatment D) and the reference drug (treatment C).

! **Table 19 Comparison of PK Parameters of Guaifenesin between Combined Product (D) and Reference (C) in Study 11244403 (N=57)**

Parameter	Co-Administered References ¹	Guaifenesin Reference ¹	Ratio ²	CV% ³	90% CI ⁴
$AUC_{(0-t)}$ (hr*ng/mL)	4352	4050	1.075	16.5	1.021 - 1.131
$AUC_{(0-\infty)}$ (hr*ng/mL)	4373	4070	1.075	16.4	1.021 - 1.131
C_{max} (ng/mL)	3986	3593	1.110	29.7	1.013 - 1.216
T_{max} (hr)	0.333 (0.083 – 1.50)	0.333 (0.167 – 1.25)	0.969	-	-
K_{el} (1/hr)	0.8093	0.8188	0.988	-	-
$T_{1/2}$ (hr)	0.873	0.865	1.008	-	-

1. Least-squares geometric means for areas and peak concentrations. Least-squares arithmetic means for other parameters. Tmax reported as median (range).
2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean.
3. Estimated intra-subject coefficient of variation, $CV\% = 100 * \text{SQRT}(e\text{MSE}-1)$, where MSE is the mean square error term from the analysis of variance (ANOVA).
4. Confidence interval on the ratio
(Source: (b) (4) 11244403, page 8)

Conclusion:

Bioequivalence:

Hydrocodone from the proposed product is bioequivalent to the reference hydrocodone (hydrocodone bitartrate and homatropine methylbromide syrup from Hi Tech).

Guaifenesin from the proposed product is bioequivalent to the reference guaifenesin (Liquituss GG from Capellon Pharmaceuticals, LLC).

DDI:

There is no apparent DDI between Liquituss GG (from Capellon Pharmaceuticals, LLC) and the reference hydrocodone (hydrocodone bitartrate and homatropine methylbromide syrup from Hi Tech).

Reviewer's comments:

Reviewer's independent analysis showed similar results, which are in agreement with the Sponsor's conclusions:

1. Hydrocodone from the proposed product is bioequivalent to the reference hydrocodone (Table 22).
2. Guaifenesin from the proposed product is bioequivalent to the reference hydrocodone (Table 23).
3. Co-administration of guaifenesin does not affect bioavailability of hydrocodone (Table 24).
4. Co-administration of hydrocodone does not affect bioavailability of guaifenesin (Table 25).

Table 22 Comparison of PK Parameters of Hydrocodone between Tested Product (A) and Reference (B) in Study 11244403 (N=36)

Parameter	Test Product (A) ¹	Hydrocodone Reference (B) ¹	Ratio (B/A) ²	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC _{0-t} (pg·h/mL)	75374	75912	0.993	0.961	1.026
AUC _{0-inf} (pg·h/mL)	80190	80638	0.994	0.960	1.030
C _{max} (pg/mL)	12501	13351	0.936	0.896	0.979
T _{max} (hour)	1.25 (0.33 - 3.00)	1.00 (0.33 - 2.00)	-	-	-

1. Least-squares geometric means for areas and peak concentrations. Tmax reported as median (range).

2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean.

Estimated means, standard errors, and confidence intervals derived from a linear mixed effects model with fixed effects sequence, treatment, period, and a random effect for subject.

(Source: Reviewer's analysis)

Table 23 Comparison of PK Parameters of Guaifenesin between Tested Product (A) and Reference (C) in Study 11244403 (N=57)

Parameter	Test Product (A) ¹	Guaifenesin Reference (C) ¹	Ratio (B/A) ²	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC _{0-t} (ng·h/mL)	4202	4045	1.039	0.987	1.094
AUC _{0-inf} (ng·h/mL)	4222	4065	1.039	0.987	1.093
C _{max} (ng/mL)	3711	3589	1.034	0.944	1.133
T _{max} (hour)	0.33 (0.17 - 1.25)	0.33 (0.17 - 1.25)	-	-	-

1. Least-squares geometric means for areas and peak concentrations. Tmax reported as median (range).

2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean.

Estimated means, standard errors, and confidence intervals derived from a linear mixed effects model with fixed effects sequence, treatment, period, and a random effect for subject.

(Source: Reviewer's analysis)

Table 24 Comparison of PK Parameters of Hydrocodone between Combined Product (D) and Reference (B) in Study 11244403 (N=36)

Parameter	Co-Administration Reference (D) ¹	Hydrocodone Reference (B) ¹	Ratio (B/A) ²	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC _{0-t} (pg·h/mL)	78400	75912	1.033	0.999	1.068
AUC _{0-inf} (pg·h/mL)	83272	80638	1.033	0.997	1.069
C _{max} (pg/mL)	13415	13351	1.005	0.961	1.050
T _{max} (hour)	1.00 (0.50 - 4.00)	1.00 (0.33 - 2.00)	-	-	-

1. Least-squares geometric means for areas and peak concentrations. Tmax reported as median (range).

2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean. Estimated means, standard errors, and confidence intervals derived from a linear mixed effects model with fixed effects sequence, treatment, period, and a random effect for subject.
(Source: Reviewer's analysis)

Table 25 Comparison of PK Parameters of Guaifenesin between Combined Product (D) and Reference (C) in Study 11244403 (N=57)

Parameter	Co-Administration Reference (D) ¹	Guaifenesin Reference (C) ¹	Ratio (B/A) ²	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC _{0-t} (ng·h/mL)	4354	4045	1.076	1.022	1.133
AUC _{0-inf} (ng·h/mL)	4375	4065	1.076	1.023	1.133
C _{max} (ng/mL)	3986	3589	1.110	1.014	1.217
T _{max} (hour)	0.33 (0.083 - 1.50)	0.33 (0.17 - 1.25)	-	-	-

1. Least-squares geometric means for areas and peak concentrations. Tmax reported as median (range).
2. Ratio calculated as Test Product's least-squares mean divided by the Reference Product's least-squares mean. Estimated means, standard errors, and confidence intervals derived from a linear mixed effects model with fixed effects sequence, treatment, period, and a random effect for subject.
(Source: Reviewer's analysis)

4.2 Appendix – New Drug Application Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	205474	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Guaifenesin and Hydrocodone Bitartrate
Medical Division	Pulmonary, Allergy, and Rheumatology Products	Drug Class	Expectorant and antitussive
OCP Reviewer	Yunzhao Ren MD, Ph. D	Indication(s)	<ul style="list-style-type: none"> Symptomatic relief of irritating cough associated with upper and lower respiratory tract congestion by loosening phlegm (mucus) Thinning bronchial secretions and thereby helping to rid the bronchial passageways of bothersome mucus so as to make coughs more productive.
OCP Team Leader	Satjit Brar Pharm. D., Ph.D.	Dosage Form	Oral solution
Other discipline reviewers	-	Dosing Regimen	10 mL (400 mg Guaifenesin and 5 mg Hydrocodone Bitartrate) every 4 hours on an empty stomach
Date of Submission	1/14/2014	Route of Administration	Oral
Estimated Due Date of OCP Review	10/14/2014	Sponsor	Sovereign Pharmaceuticals, LLC
PDUFA Due Date	11/14/2014	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			IQMD!xjui!uboeffn!nbt! tqfduspfnfusz
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4	4	Study R08-0467, 92001, 92002, and 11244403
multiple dose:	X	4	4	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2	2	Study 92002, and 11244403

In-vivo effects of primary drug:	X	2	2	Study 92002, and 11244403
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	4	4	Study R08-0467, 92001, 92002, and 11244403
replicate design; single / multi dose:				
Food-drug interaction studies	X	1	1	Study 92001
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

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/s/

YUNZHAO REN
09/19/2014

SATJIT S BRAR
09/19/2014

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	205-474	Reviewer: Kareen Riviere, Ph.D.	
Submission Date:	1/14/2014		
Division:	DPARP	Team Leader: Tapash Ghosh, Ph.D.	
Applicant:	Sovereign Pharmaceuticals, LLC	Acting Supervisor: Richard Lostritto, Ph.D.	
Trade Name:	TBD	Date Assigned:	2/3/2014
Generic Name:	hydrocodone bitartrate/guaifensin oral solution	Date of Review:	3/5/2014
Indication:	- Symptomatic relief of (b) (4) (b) (4)	Type of Submission: 505(b)(2) NDA	
Formulation/strengths:	Oral Solution/ 200 mg; 2.5 mg/5mL		
Route of Administration:	Oral		

The Applicant conducted several BA/BE studies to support their proposed oral solution product. Per the current Memorandum of Understanding between Clinical Pharmacology and ONDQA Biopharmaceutics, and with the consent of Dr. Satjt Brar (OCP TL), these BA/BE studies will be reviewed by Clinical Pharmacology. Additionally, there are no biowaiver issues.

Thus, a Biopharmaceutics review is not needed for this NDA.

Kareen Riviere, Ph.D.
 Biopharmaceutics Reviewer
 Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
 Biopharmaceutics Team Leader
 Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

APPEARS THIS WAY ON ORIGINAL

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/s/

KAREEN RIVIERE
03/05/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	205474	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Guaifenesin and Hydrocodone Bitartrate
Medical Division	Pulmonary, Allergy, and Rheumatology Products	Drug Class	Expectorant and antitussive
OCP Reviewer	Yunzhao Ren MD, Ph. D	Indication(s)	<ul style="list-style-type: none"> Symptomatic relief (b) (4)
OCP Team Leader	Satjit Brar Pharm. D., Ph.D.	Dosage Form	Oral solution
Other discipline reviewers	-	Dosing Regimen	10 mL (400 mg Guaifenesin and 5 mg Hydrocodone Bitartrate) every 4 hours on an empty stomach
Date of Submission	1/14/2014	Route of Administration	Oral
Estimated Due Date of OCP Review	10/14/2014	Sponsor	Sovereign Pharmaceuticals, LLC
PDUFA Due Date	11/14/2014	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			HPLC with tandem mass spectrometry
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-	X	4	4	Study R08-0467, 92001, 92002, and 11244403
single dose:	X	4	4	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:	X	2	2	Study 92002, and 11244403
In-vivo effects of primary drug:	X	2	2	Study 92002, and 11244403
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	4	4	Study R08-0467, 92001, 92002, and 11244403
replicate design; single / multi dose:				
Food-drug interaction studies	X	1	1	Study 92001
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			DDI only
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____ Yes__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

- None

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

- None

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA OR SUPPLEMENT

Background

Sovereign Pharmaceuticals, LLC submitted NDA205474 under 505(b)(2) seeking approval of guaifenesin and hydrocodone bitartrate oral solution (200 mg; 2.5 mg/5 ml). The proposed indication is for the symptomatic relief (b) (4)

The proposed doses are 10ml every 4 hours for adults (b) (4)

Many of the hydrocodone combination products were illegally marketed as unapproved products and a Federal Registered notice was published on October 1, 2007, to remove these products from the market as of March 31, 2008. Manufacturers who wish to market these drug products containing hydrocodone must obtain FDA approval through the NDA or ANDA process. In response to this FDA action, Sovereign submitted IND101683 on February 26, 2009 for a fixed-dose combination product of hydrocodone and guaifenesin.

Clinical Pharmacology Regulatory History

A pre-IND meeting was held on April 4, 2008. The Agency recommended that the sponsor needed to address the potential for drug-drug interaction (DDI) between hydrocodone and guaifenesin. The sponsor later conducted DDI studies and submitted the results in this NDA.

A pre-NDA meeting was held on November 9, 2011. The Agency commented that BE criteria should also be met for guaifenesin. The sponsor later conducted another BE study for guaifenesin to address this problem.

Clinical Pharmacology Studies

The sponsor conducted 4 bioavailability (BA) / BE studies to address the BE, food effect and DDI for the proposed product:

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 3 RLDs	Hydrocodon + Homatropine (Hi Tech); extemporaneous Guaifenesin
Relative BA and DDI	11244403	56	Comparison of proposed product with 3 RLDs	Hydrocodon + Homatropine (Hi Tech); Liquituss GG

The sponsor stated following findings:

- 1) food appears to significantly decrease the extent of guaifenesin absorption from the proposed product;
- 2) BE criteria could not be met for guaifenesin when comparing the proposed product with the reference drug, an extemporaneously prepared guaifenesin. This is probably due to the instability of guaifenesin when dissolved in [REDACTED] (b) (4) were observed in the solution sometimes after the completion of the study 92002.
- 3) The BE criteria of guaifenesin was met in study 11244403 when the sponsor changed their guaifenesin reference drug to Liquituss GG.

Acceptance of these findings will be a review issue.

In accordance to FDA guidance for industry, handling and retention of BA and BE testing samples, an on-site inspection will be triggered as the BA/BE study is the pivotal study for the 505(b)(2) submission.

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/s/

YUNZHAO REN
02/28/2014

SATJIT S BRAR
02/28/2014