

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22279Orig1s000

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

TABLE OF CONTENTS

Item	Page number
1. EXECUTIVE SUMMARY	2
1.1 Recommendation	4
1.2 Phase 4 Commitments	4
1.3 Summary of Clinical Pharmacology Findings	4
2. QUESTION-BASED REVIEW	10
2.1 List of Clinical Pharmacology Studies	10
2.2 General Attributes of the Drug	10
2.3 General Clinical Pharmacology	N/A
2.4 Exposure Response	N/A
2.5 PK characteristics of the drug	N/A
2.6 Intrinsic Factors	
2.6.2 Pediatrics	11
2.7 Extrinsic Factors	N/A
2.8 General Biopharmaceutics	N/A
2.9 Analytical Section	12
3. Detailed Labeling Recommendations	14
4. APPENDIX	15
4.1 Individual Study Reviews	15

1. EXECUTIVE SUMMARY

Mikart, Inc. has submitted the current amendment to NDA 022279 in response to the 01/11/2012 Complete Response Action Letter. The Clinical Pharmacology deficiency and path forward cited in this letter are as follows:

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

This deficiency may be addressed by doing the following:

- a. Assess the design of your relative bioavailability (BA) study and, if appropriate, correct design deficiencies and repeat the single-dose clinical pharmacology study to evaluate the bioavailability of your proposed hydrocodone 2.5 mg/guaifenesin 200 mg per 5 mL oral solution combination product compared to the individual reference products, using the bioequivalence goal post of 80–125%.*

OR

- b. Evaluate whether there is a formulation effect with your proposed combination product and reformulate the product if necessary. If you reformulate the product you must repeat*

the clinical pharmacology program to evaluate the bioavailability of the reformulated combination product compared to the individual reference products, using the bioequivalence goal post of 80-125%. You may also need to repeat the food effect study if the product is reformulated.

OR

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

Sponsor chose the option *a.* in this submission, and provided data from five new BA/BE studies, including a pivotal guaifenesin BA/BE study (study 11467601), demonstrating the bioequivalence of the guaifenesin component in the test product to the Reference product.

Study 11467601 was an open-label, randomized, single-center, single-dose, two-treatment, two-period, two-sequence, crossover study under fasted conditions comparing equal doses of guaifenesin (400 mg/10 mL) from the test product and the Reference product. A washout period of 24 hours was selected for this study. A total of 36 healthy adults completed the study. A total of 18 PK samples per subject per period were collected within 5-hour post-dose. 4 mL venous blood was collected for each PK sample. Guaifenesin plasma concentration was quantified via HPLC with MS/MS detection.

The guaifenesin geometric mean ratios (test/reference, N=36) of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.969 (90% CI = 0.920, 1.020), 0.967 (90% CI = 0.919, 1.019), and 0.925 (90% CI= 0.850, 1.007), respectively (Table 1). The 90% confidence interval of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} ratios (test/reference) is within the range of 0.80-1.25. Therefore, the guaifenesin component from the test product is bioequivalent to the guaifenesin component from the reference product.

Table 1 Comparison of PK Parameters of Guaifenesin between the Test product (A) and the Reference Product (B) in Study 11467601 (N=36)

Parameter	Test product (A)*	Reference product (B)*	Ratio (A/B)	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC_{0-t} (ng·h/mL)	2519	2601	0.9687	0.9203	1.0197
AUC_{0-inf} (ng·h/mL)	2603	2690	0.9674	0.9188	1.0186
C_{max} (ng/mL)	2015	2178	0.9253	0.8500	1.0072
T_{max} (hour)	0.42 (0.17 – 1.5)	0.42 (0.25 – 0.83)	-	-	-

* Least-squares geometric means for areas and peak concentrations. T_{max} reported as median (range). Means were adjusted by treatment, sequence and period in a general linear model. (Source: adapted from CSR report-body-11467601, page 7, Table 2.1)

Office of Study Integrity and Surveillance (OSIS) in their Bioequivalence Establishment Inspection Report Review recommended (Review dated 02/04/2015) accepting data without an on-site inspection because OSIS inspected the relevant site within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Bioequivalence of hydrocodone and pseudoephedrine components was previously demonstrated and the effect of food on this product was previously assessed. As such, overall, adequate clinical pharmacology information in support of the product was submitted.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the NDA 022279 resubmitted on December 02, 2014 and has found the application Acceptable from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

NDA 022279 (Hydrocodone Bitartrate/Guaifenesin/Pseudoephedrine Hydrochloride) and NDA 022424 (Hydrocodone Bitartrate/Guaifenesin) are related products with the same solution formulation composition except for the pseudoephedrine component. The data acquired in support of NDA 022279 are also applicable to NDA 022424. NDA 022279 was first submitted to the FDA on 8/22/2008 by (b) (4). The application was given a complete response (CR) on 06/22/2009 and the clinical pharmacology deficiency and the remedy recommended are as following:

The single-dose, single arm, clinical pharmacology study #S07-0441 is not adequate to support this application because this study does not fulfill the bioavailability criteria for combination products as described in 21 CFR 320.25 (g). The study, as designed did not allow for comparison of the rate and extent of absorption of each active drug ingredient in your proposed hydrocodone, pseudoephedrine, guaifenesin oral solution to the rate and extent of absorption of each active drug ingredient administered concurrently in separate single-ingredient preparations.

Your proposed product contains sorbitol. Sorbitol has been found to affect the bioavailability of some compounds with low permeability in a dose-proportional manner. The permeability of hydrocodone, pseudoephedrine, and guaifenesin are not known and therefore, an assessment of food effect on your proposed product is necessary to support approval.

These deficiencies may be addressed by doing the following:

- a. Conduct a single-dose clinical pharmacology study to establish the bioequivalence of your proposed product to the reference products.*
- b. Conduct a food effect study of your proposed product under fed and fasted conditions.*

(b) (4) (new sponsor) resubmitted NDA 022279 on 07/26/2010 and included data from a drug-drug interaction and relative bioavailability study (S09-0009) and a food effect study (S09-0010). A CR was issued on 1/25/2011. The Clinical Pharmacology deficiency and path forward cited in this letter are as follows:

An audit performed by the Agency for studies S09-0009 and S09-0010 identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies cannot be relied upon to support the clinical pharmacology of hydrocodone, pseudoephedrine, and guaifenesin oral solution.

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

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

OR

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

OR

- c. Conduct clinical efficacy and safety studies to support your combination product.*

(b) (4) chose option *b.* and resubmitted NDA 022279 on 07/18/2011 and included data from a bioavailability study (S11-0028) and food effect study (S11-0029). The BE of hydrocodone and pseudoephedrine were established between the test product and the reference products in study S011-0028. However, BE could not be demonstrated for guaifenesin. A CR was issued on 01/11/2012 with the following Clinical Pharmacology deficiency and recommendations for addressing this deficiency (For details, refer to Clinical Pharmacology review by Dr. Arun Agrawal, review dated 11/03/2011).

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

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

- a. Assess the design of your relative bioavailability study and, if appropriate, correct design deficiencies and repeat the single-dose clinical pharmacology study to evaluate the bioavailability of your proposed hydrocodone 2.5 mg/pseudoephedrine 30*

mg/guaifenesin 200 mg per 5 mL oral solution combination product compared to the individual reference products, using the bioequivalence goal post of 80-125%.

OR

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

OR

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

A type C meeting was held on December 16, 2011 between the FDA and the current Sponsor, Mikart, Inc. under NDA 022424. FDA's position of requiring demonstration of bioequivalence of their product to the reference products was reiterated as follows:

Even though the Sponsor's statement that the guaifenesin dosage of the proposed drug is within the dose range of the OTC monograph for guaifenesin is correct, the Sponsor needs to understand that they are not developing a monograph product but a fixed combination drug with the other component (hydrocodone) of the proposed combination drug which is a prescription drug, and which impacts the application of the OTC monograph. as the guaifenesin component in the proposed product was not bioequivalent to the reference product. Bioequivalence to reference drug is a standard in providing a clinical bridge for product quality, safety and efficacy, and the bioequivalence criteria have been applied to all similar cough and cold prescription combination products DPARP reviews.

Mikart has submitted Amendment 0014 on 01/31/2012 under NDA 022424 to provide a study design outline for a new guaifenesin bioequivalence study. The study was proposed to be an open-label, single-dose, randomized, 2-period and 2-treatment crossover study under fasting conditions assessing the bioequivalence of guaifenesin component only as hydrocodone and pseudoephedrine bioequivalence was previously demonstrated. Agency agreed with Mikart's proposal as follows (Clinical Pharmacology review by Dr. Arun Agrawal, review dated 02/22/2012):

Your proposal to characterize the pharmacokinetic profile of guaifenesin only and determine if guaifenesin bioequivalence can be determined for the test product (hydrocodone, pseudoephedrine and guaifenesin oral solution) when compared to the reference drug is acceptable.

Subsequently, sponsor conducted five BA/BE studies with the pivotal PK study 11467601 demonstrating the bioequivalence of guaifenesin from the test product and the reference product. Summary of the results supporting the establishment of guaifenesin BE is provided below.

1.3.2 Bioequivalence

Study 11467601 was the pivotal study addressing the guaifenesin BE deficiency. This was an open-label, single-dose, randomized, two-treatment, two-period, two-sequence, two-way crossover trial in 36 healthy volunteers under fasted conditions. The washout period was 24 hours.

Test product (A): Hydrocodone Bitartrate, Guaifenesin, and Pseudoephedrine HCl Oral Solution 2.5 mg/200 mg/30 mg per 5 mL from ^{(b) (4)} Mikart Inc.

Reference product (B): Refenesen™ Mucus Relief Expectorant (guaifenesin), 200 mg/5 mL distributed by Reese Pharmaceutical

Following oral administration of single-dose of the test product or the reference product, the guaifenesin geometric mean ratios (test/reference, N=36) of AUC_{0-t}, AUC_{0-∞}, and C_{max} were 0.969 (90% CI = 0.920, 1.020), 0.967 (90% CI = 0.919, 1.019), and 0.925 (90% CI= 0.850, 1.007), respectively (Table 2 and Fig.1). The 90% confidence interval of AUC_{0-t}, AUC_{0-∞}, and C_{max} ratios (test/reference) is within the range of 0.80-1.25. Therefore, the guaifenesin component from the test product is bioequivalent to the guaifenesin component from the reference product. The median T_{max} (range) of guaifenesin in the test product and the reference product were both 0.42 hour (Table 2).

Table 2 Comparison of PK Parameters of Guaifenesin between the Test product (A) and the Reference product (B) in Study 11467601 (N=36)

Parameter	Test product (A)*	Reference product (B)*	Ratio (A/B)	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC _{0-t} (ng·h/mL)	2519	2601	0.9687	0.9203	1.0197
AUC _{0-inf} (ng·h/mL)	2603	2690	0.9674	0.9188	1.0186
C _{max} (ng/mL)	2015	2178	0.9253	0.8500	1.0072
T _{max} (hour)	0.42 (0.17 – 1.5)	0.42 (0.25 – 0.83)	-	-	-

* Least-squares geometric means for areas and peak concentrations. T_{max} reported as median (range). Means were adjusted by treatment, sequence and period in a general linear model. (Source: adapted from CSR report-body-11467601, page 7, Table 2.1)

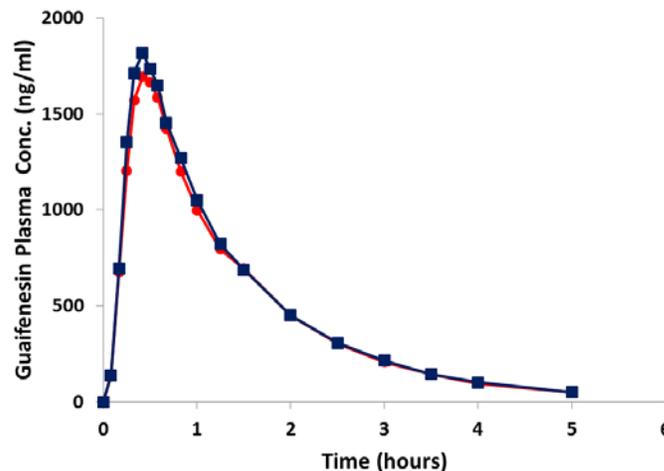


Figure 1 Guaifenesin plasma concentration-time profile following single dose administration of the test product (red) and the reference product (blue) from study 11467601 (N=36); observations represent the geometric mean for each time point. (Source: adapted from CSR report-body-11467601, page 50, figure 14.2.1)

A visual display of establishment of BE for hydrocodone, pseudoephedrine, and guaifenesin on different PK parameters is shown in Fig.2.

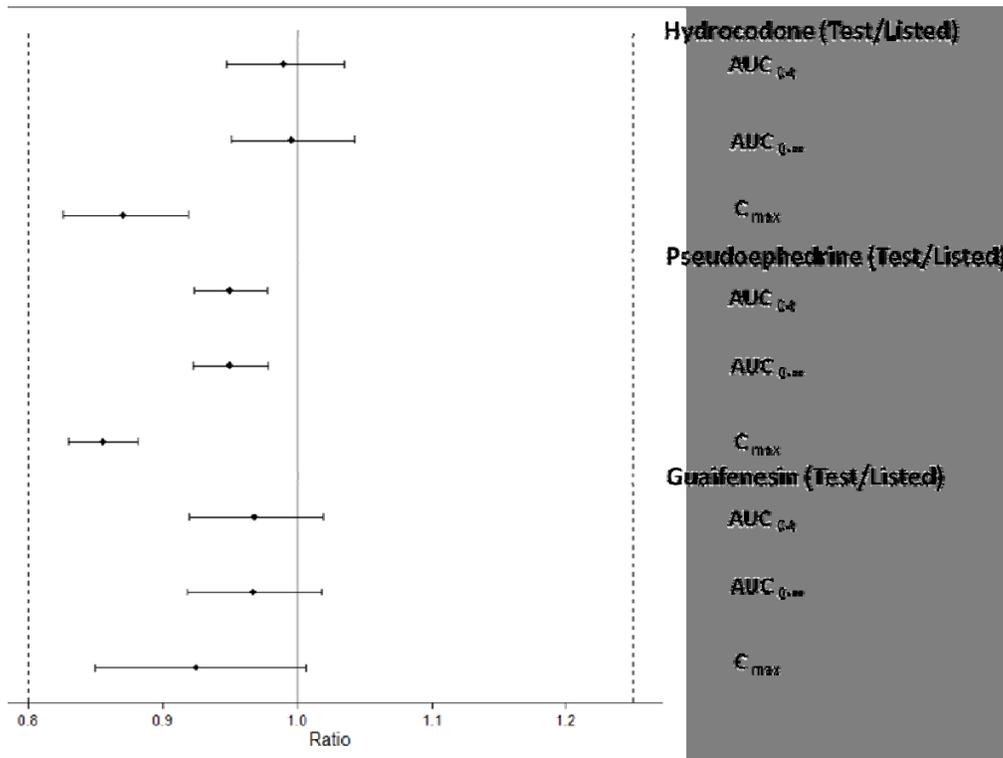


Figure 2 Forest-plot display of guaifenesin BE results of study 11467601 from the current submission, hydrocodone and pseudoephedrine BE results of study S11-0028 from the prior submission. (Source: Table 2 and CSR study-report-s11-0028-ich-sections-1-15.pdf, page 53-54, Table 11.4.7.1)

1.3.3 Food Effect

As stated, the food effect study S011-0029 of the test product was previously submitted and reviewed (review by Dr. Arun Agrawal dated 11/03/2011). Here the results from this study are recapped and compared with the results of the food effect study in NDA 205474, another hydrocodone/guaifenesin product approved on 11/14/2014 (for additional details, see clinical pharmacology review by Dr. Yunzhao Ren dated 09/19/2014).



(b) (4)

(b) (4)

(b) (4)

(b) (4)

T_{\max} of guaifenesin for both products.

As such, similar labeling language related to the food effect is appropriate for this product as well.

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

To be noted, only the studies from the current submission were listed as below:

Table 2.1 List of Five Phase 1 BE Single-Dose Studies in Healthy Volunteers

Study ID	Study Design*	# of subjects	Reference Product
11267601	3-way crossover	17	Children's Mucinex® Chest Congestion Guaifenesin Syrup manufactured (b) (4)
11267602	2-way crossover	30	Guaifenesin Syrup manufactured (b) (4)
11267603	2-way crossover	29	Children's Mucinex® Chest Congestion
11267604	2-way crossover	36	Children's Mucinex® Chest Congestion
11467601	2-way crossover	36	Refenesen® Mucus Relief Expectorant

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

Among five submitted BE studies, study 11267601 was a pilot study with 17 healthy subjects. The BE was demonstrated between the test product and the guaifenesin product from (b) (4) but not between the test product and Children's Mucinex®. Studies 11267602, 11267603, and 11267604 failed to demonstrate the BE between the test product and reference products. Study 11467601 was the designated pivotal BE study that demonstrated the BE between the test product and the reference guaifenesin product Refenesen®.

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?

Table 2.2 Qualitative and Quantitative Composition of the To-Be-Marketed Product

Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution		
% w/v	mg/5mL	Ingredient
0.050	2.5	Hydrocodone Bitartrate USP
4.000	200.0	Guaifenesin USP
0.600	30.0	Pseudoephedrine Hydrochloride USP
(b) (4)		Sorbitol (b) (4) USP
		Glycerin USP
		Polyethylene Glycol (b) (4) NF
		Methylparaben NF
		Propylparaben NF
		Citric Acid (b) (4) USP
		Sodium Citrate (b) (4) USP
		Saccharin Sodium
		D & C Red #33
		FD & C Blue #1
		(b) (4) Black Raspberry Flavor (b) (4)
		Purified Water USP

Source: NDA22279 paper submission, page 31

2.6.2 Pediatrics

This product was not studied in pediatric population.

(b) (4)
(b) (4)

2.9 Analytical Section

To be noted, only the guaifenesin analytical method from this submission will be reviewed here. For details of analytical methods of hydrocodone and pseudoephedrine, refer to Clinical Pharmacology review by Dr. Arun Agrawal (Review date 11/03/2011).

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) was measured in the BE studies. Human plasma containing guaifenesin were analyzed by HPLC ESI+MS/MS.

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

Total amount of guaifenesin 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?

For the pivotal BE study 11467601, the range of the standard curve is from 8.00 to 4000 ng/mL. The limit of quantitation (LOQ) is 8.00 ng/mL. The accuracy and precision at different range of concentration were listed in Table 2.3. The coefficient of variation of precision and the bias of accuracy were all within $\pm 15\%$ of the nominal value. Guaifenesin solution was stable for 546 day at $2 - 8$ °C. The frozen matrix storage was stable for 6 days at -20 and -70 °C. The matrix could sustain five cycles thawed at room temperature. The thawed matrix was stable for 23 hours at room temperature.

Table 2.3 Precision and Accuracy of Method Validation at Different Range

Concentration (ng/mL)	Precision	Accuracy
8.00	3.85 to 4.80%	-0.458 to 3.84%
20.0	3.51 to 5.75%	-0.780 to 9.16%
50.0	3.25 to 3.59%	4.36 to 7.78%
175	2.77 to 4.51%	6.07 to 8.38%
600	1.13 to 4.02%	5.05 to 8.07%
3000	2.15 to 5.39%	-3.99 to -1.83%

Source: adapted from [analyt-validation-11467601.pdf](#), page 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 total 1293 blood samples were collected for PK analysis in study 11467601, the lowest guaifenesin post-dose concentration among these samples was 10.2 ng/mL, which was above the LOQ (8.00 ng/mL). Guaifenesin post-dose concentrations from 9 PK samples (0.7%) were higher than the upper limit of quantitation (4000 ng/mL). The ability to dilute samples originally above the upper limit of the calibration range was validated by analyzing six replicate QCs, containing 10000 ng/mL guaifenesin, as ten-fold dilutions in Run 3AGVT2. Quantitation is performed using analyte to IS area ratio and a $1/\text{concentration}^2$ weighted linear regression.

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

Reinjection reproducibility was evaluated by analyzing calibration standards and quality controls that were extracted and injected as part of Run 2AGVT2 and stored at 5 °C prior to and during reanalysis as Run 2AGVT2-RR. The reinjection reproducibility results were within $\pm 10\%$ of theoretical concentrations.

3. DETAILED LABELING RECOMMENDATIONS

Reviewer recommended changes are shown by additions and deletions to the sponsor proposed text.

12.3 pharmacokinetics

Systemic exposure (in terms of peak plasma concentrations and area under plasma concentration versus time curve) of hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin (b) (4) respective reference solutions of 5 mL hydrocodone bitartrate (5 mg/5 mL), 5 mL pseudoephedrine hydrochloride (30 mg/5 mL), and 10 mL guaifenesin (200 mg/5 mL).

Hydrocodone: following a single 10 ml oral dose of (b) (4) administered to 37 healthy adults, the geometric mean c_{max} and auc_{0-inf} for hydrocodone were 9.0 ng/(b) (4) ml and 61.2 ng·hr^{(b) (4)} ml, respectively. The median time to maximum concentration for hydrocodone was about 1 (b) (4) 67 hours. Food has no significant effect on the extent of absorption of hydrocodone. The mean plasma half-life of hydrocodone is approximately 4 (b) (4) hours.

Pseudoephedrine: following a single 10 ml oral dose of (b) (4) administered to 37 healthy adults, the geometric mean c_{max} and auc_{0-inf} for pseudoephedrine were 0.19 mcg/(b) (4) ml and 1.9 mcg·hr^{(b) (4)} ml, respectively. The median time to maximum concentration for pseudoephedrine is about 2.5 hours. Food has no significant effect on the extent of absorption of pseudoephedrine. The mean plasma half-life of pseudoephedrine is approximately (b) (4) 6 hours.

Guaifenesin: following a single 10 ml oral dose of (b) (4) administered to 36 healthy adults, the geometric mean c_{max} and auc_{0-inf} for guaifenesin were 2.0 mcg/(b) (4) ml and 2.6 mcg·hr^{(b) (4)} ml, respectively. The median time to maximum concentration is about (b) (4) 25 minutes. The effect of food on guaifenesin systemic exposure is not considered to be clinically meaningful. The mean plasma half-life of guaifenesin is approximately 1 hour.

Drug interactions

When guaifenesin, pseudoephedrine, and hydrocodone were administered in combination, the pharmacokinetics for each component (b) (4) was similar to those observed when each component was administered separately.

4. Appendix

4.1 Appendix – Individual Study Review

4.1.1 Study 11267601

Study Type: Phase 1 BA/BE PK study in healthy volunteers

Title:

A Study to Evaluate the Relative Bioavailability of Guaifenesin from a Formulation of Hydrocodone Bitartrate/Guaifenesin/Pseudoephedrine HCl 2.5 mg/200 mg/30 mg/5 mL Oral Solution (b) (4) Compared to Two Marketed Formulations of Guaifenesin 100 mg/5 mL Oral Solution in Healthy Volunteers under Fasted Conditions

Objective:

The purpose of this study was to evaluate the relative bioavailability of equal 400 mg dose of guaifenesin from a test formulation of hydrocodone bitartrate/guaifenesin/pseudoephedrine HCl 2.5 mg/200 mg/30 mg per 5 mL oral solution (b) (4) compared with that of two already marketed reference formulations: Children’s Mucinex® Chest Congestion Guaifenesin Oral Solution, USP, 100 mg/5 mL (distributed by Reckitt Benckiser) and Guaifenesin Syrup, USP; 100 mg/5 mL (manufactured by (b) (4) under fasted conditions in healthy adults subjects.

The two reference formulations were also compared with each other for informational purposes. The results of this study will be used in the design of a pivotal bioequivalence study.

Study Design and Method:

This investigation was a randomized, open-label, single-dose, three-treatment, three-period, crossover study conducted in 18 (17 completed all three study periods) healthy adults under fasting conditions. The washout period was at least one day. The treatments in each period were:

- Period 1 (test product A):
Single dose of 10 mL hydrocodone bitartrate, guaifenesin, and pseudoephedrine HCl 2.5 mg/200 mg/30 mg per 5 mL Oral Solution from (b) (4)
- Period 2 (Reference product B):
Single dose of 20 mL Children’s Mucinex® Chest Congestion Guaifenesin Oral Solution, USP 100 mg/5 mL Solution distributed by Reckitt Benckiser
- Period 3 (Reference product C):
Single dose of 20 mL Guaifenesin Syrup, USP 100 mg/5 mL manufactured by (b) (4)

16 blood samples were collected pre-dose (0 hour) and 5, 10, 15, 20, 30, 40, 50 minutes and 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5 and 4.0 hours post-dose. The total volume of blood collected for PK sampling will be approximately 192 mL. The analytical data were used to calculate the pharmacokinetic parameters: 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 guaifenesin concentrations. Samples were analyzed by HPLC ESI+MS/MS with LOQ at 2.00 pg/mL. The assay was validated from 2.00 pg/mL to 2000 pg/mL in plasma. The coefficient of variation of the precision and the bias of accuracy were 1.08% to 9.84% (CV) and -7.42% to +5.27% (bias), respectively.

Results:

18 subjects were dosed in Period 1, and 17 subjects completed all three study periods. Subject 10 (G-M) did not complete the Period 2 and Period 3 of the study and therefore did not have samples sent for analysis. There are 17 sets of data for guaifenesin for this study.

Following single-dose (400 mg guaifenesin) oral administration, the ratios (test drug/reference product B, N=17) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were (b)(4). The median T_{max} of the test drug and reference product B were the same (0.5 hour).

Table 4.1 Comparison of PK Parameters of Guaifenesin between the Tested Product and the Reference product B (Children’s Mucinex® Chest Congestion) in Study 11267601

Parameter	Test A (N = 17)	Reference B (N = 17)	Ratio	CI*
AUC_{0-t} (ng·hr/mL)	(b)(4)			
AUC_{0-inf} (ng·hr/mL)				
C_{max} (ng/mL)				

Analyses of Variance were performed using the General Linear Model containing main effects of treatment and period.

Source: CSR 11267601, page 11

Following single-dose (400 mg guaifenesin) oral administration, the ratios (test drug/reference product C, N=17) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.952 (90% CI = 0.884, 1.026), 0.956 (90% CI = 0.888, 1.031), and 0.934 (90% CI = 0.824, 1.058), respectively (Table 4.2 and Fig.4.1). The median T_{max} of reference product C was 0.5 hour.

Table 4.2 Comparison of PK Parameters of Guaifenesin between the Tested Product and the Reference product C (Guaifenesin Syrup from (b)(4) in Study 11267601 (N=17)

Parameter	Test A (N = 17)	Reference C (N = 17)	Ratio	CI*
AUC_{0-t} (ng·hr/mL)	2487.50	2612.63	0.9521	0.8836 – 1.0260
AUC_{0-inf} (ng·hr/mL)	2698.35	2821.28	0.9564	0.8877 – 1.0305
C_{max} (ng/mL)	1845.50	1976.24	0.9338	0.8239 – 1.0584

Analyses of Variance were performed using the General Linear Model containing main effects of treatment and period.

Source: CSR 11267601, page 11

The comparison between two reference products (B and C) showed that the 90% CI of the ratios of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were all within the 80% to 125% boundary.

Table 4.3 Comparison of PK Parameters of Guaifenesin between the Reference product B (Children’s Mucinex® Chest Congestion) and the Reference product C (Guaifenesin Syrup from (b) (4))

Parameter	Reference B (N = 17)	Reference C (N = 17)	Ratio	CI*
AUC_{0-t} (ng·hr/mL)	2755.43	2612.63	1.0547	0.9787 – 1.1365
AUC_{0-inf} (ng·hr/mL)	3015.08	2821.28	1.0687	0.9919 – 1.1514
C_{max} (ng/mL)	2035.93	1976.24	1.0302	0.9089 – 1.1677

Analyses of Variance were performed using the General Linear Model containing main effects of treatment and period.

Source: CSR 11267601, page 22

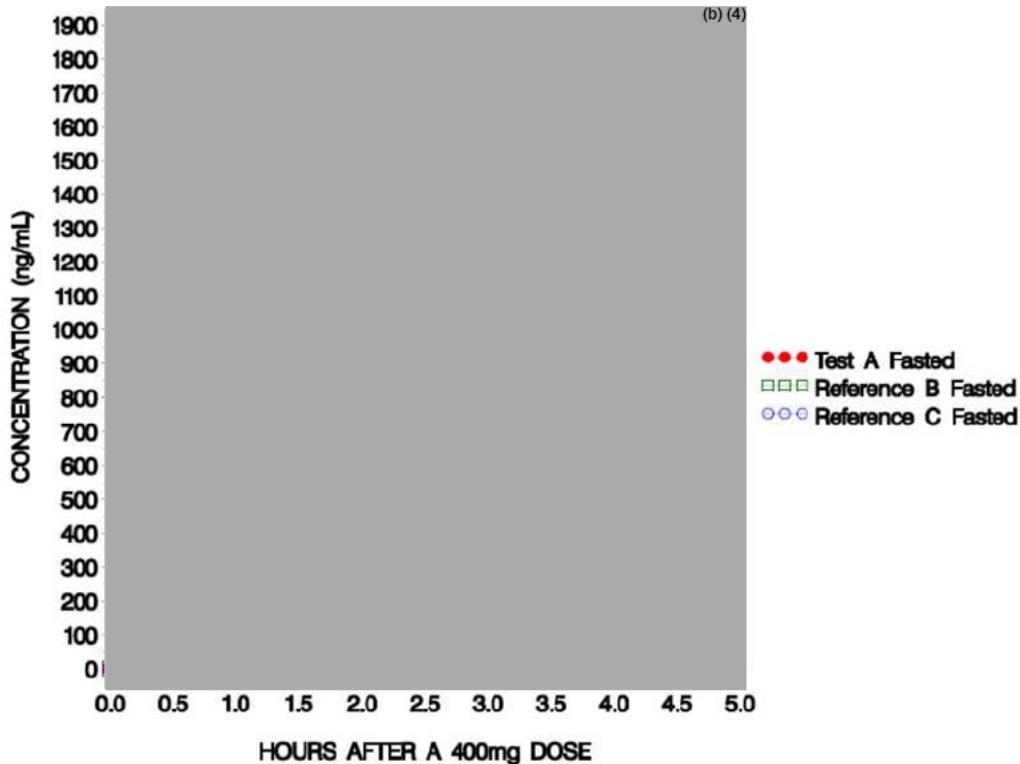


Figure 4.1 Guaifenesin plasma concentration-time profile following 400 mg single dose administration (n=17) in study 11267601, observations represent the least square geometric mean for each time point. (Source: CSR 11267601, page 9)

Conclusions:

The BE was established between the test product and the reference product C (manufactured by

(b) (4) The BE was not established between the test product and the reference product B (Children's Mucinex® Chest Congestion) (b) (4)

The two reference products (B and C) were shown to be BE. The results of this study appeared useful in the design of a pivotal bioequivalence study.

4.1.2 Study 11267602

Study Type: Phase 1 BA/BE PK study in healthy volunteers

Title:

A Study to Evaluate the Relative Bioavailability of Guaifenesin from a Formulation of Hydrocodone Bitartrate/Guaifenesin/ Pseudoephedrine HCl 2.5 mg/200 mg/30 mg/ 5 mL Oral Solution (b) (4) Compared to Guaifenesin Syrup USP, 100 mg/5 mL (b) (4) in Healthy Volunteers under Fasted Conditions

Objective:

The purpose of this study was to evaluate the relative bioavailability of guaifenesin from a test formulation of hydrocodone bitartrate/guaifenesin /pseudoephedrine HCl 2.5 mg/200 mg/30 mg/5 mL oral solution (b) (4) compared with that of the already marketed reference formulation; guaifenesin syrup USP, 100 mg/5 mL, (manufactured by (b) (4) under fasted conditions in healthy adult subjects.

Study Design and Method:

This investigation was a randomized, open-label, single-dose, two-treatment, two-period, crossover study conducted in 30 healthy adults under fasting conditions. The washout period was at least one day. The treatments in different period were listed as following:

- Period 1(test product A):
Single dose of 10 mL hydrocodone bitartrate, guaifenesin, and pseudoephedrine HCl 2.5 mg/200 mg/30 mg per 5 mL Oral Solution from (b) (4)
- Period 2 (Reference product B):
Single dose of 20 mL Guaifenesin Syrup, USP 100 mg/5 mL manufactured by (b) (4)

17 blood samples were collected pre-dose (0 hour) and 5, 10, 15, 20, 30, 40, 50 minutes and 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 5.0 hours post-dose. 4 mL of venous blood was collected for PK sampling at each time point per subject. The analytical data were used to calculate the pharmacokinetic parameters: AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , T_{max} , K_{el} , and $T_{1/2}$.

Analytical Method:

The plasma samples were sent to (b) (4) for determination of guaifenesin concentrations. Samples were analyzed by HPLC ESI+MS/MS with LOQ at 2.00 pg/mL. The assay was validated from 2.00 pg/mL to 2000 pg/mL in plasma. The coefficient of variation of the precision and the bias of accuracy were 1.08% to 9.84% (CV) and -7.42% to +5.27% (bias), respectively.

Results:

30 subjects entered into this study and all 30 subjects completed both periods of the study.

Following single-dose (400 mg guaifenesin) oral administration, the ratios (test drug/reference product B, N=30) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were (b) (4)

(b) (4)
 The median T_{max} of the test drug and reference product B were the same (0.5 hour).

Table 4.4 Comparison of PK Parameters of Guaifenesin between the Test Product and the Reference product B Guaifenesin Syrup from (b) (4) in Study 11267602 (N=30)

Parameter	Test A (N = 30)	Reference B (N = 30)	Ratio	CI*
AUC _{0-t} (ng·hr/mL)	(b) (4)			
AUC _{0-inf} (ng·hr/mL)				
C _{max} (ng/mL)				

Analyses of Variance were performed using the General Linear Model containing main effects of treatment and period.

Source: CSR 11267602, page 37

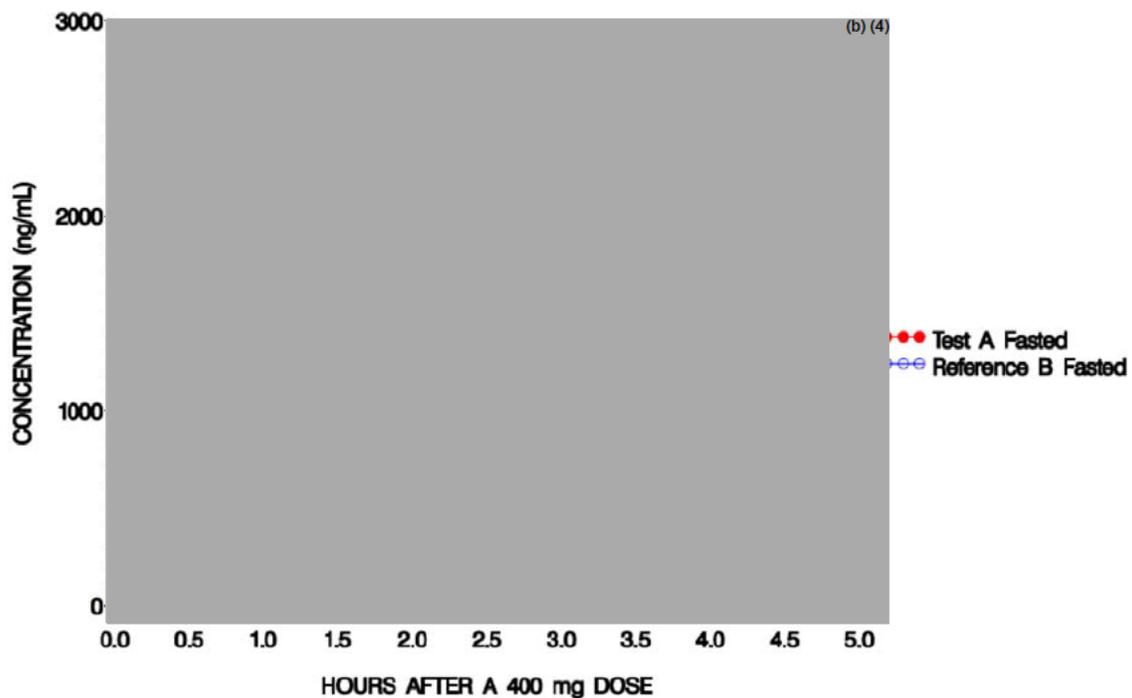


Figure 4.2 Guaifenesin plasma concentration-time profile following 400 mg single dose administration (n=30) in study 11267602, observations represent the least square geometric mean for each time point. (Source: CSR 11267602, page 6)

Conclusions:

The BE was not established between the test product and the reference product B in study 11267602.

4.1.3 Study 11267603

Study Type: Phase 1 BA/BE PK study in healthy volunteers

Title:

A Study to Evaluate the Relative Bioavailability of Guaifenesin from a Formulation of Hydrocodone Bitartrate/Guaifenesin/ Pseudoephedrine HCl 2.5 mg/200 mg/30 mg/ 5 mL Oral Solution (b) (4) Compared to Children's Mucinex® Chest Congestion Guaifenesin Oral Solution, USP 100 mg/5 mL (Distributed by: Reckitt Benckiser) in Healthy Volunteers under Fasted Conditions

Objective:

The purpose of this study was to evaluate the relative bioavailability of guaifenesin from a test formulation of hydrocodone bitartrate/guaifenesin/ pseudoephedrine HCl 2.5 mg/200 mg/30 mg/5 mL oral solution (b) (4) compared with that of the already marketed formulation; Children's Mucinex® Chest Congestion Guaifenesin Oral Solution, USP 100 mg/5 mL (distributed by Reckitt Benckiser) under fasted conditions in healthy adult subjects.

Study Design and Method:

This investigation was a randomized, open-label, single-dose, two-treatment, two-period, two-sequence, crossover study conducted in 30 (29 completed both periods) healthy adults under fasting conditions. The washout period was at least one day. Subjects received the treatment from one of the following product in each period:

- Test product A:
Single dose of 10 mL hydrocodone bitartrate, guaifenesin, and pseudoephedrine HCl 2.5 mg/200 mg/30 mg per 5 mL Oral Solution from (b) (4)
- Reference product B:
Single dose of 20 mL Children's Mucinex® Chest Congestion Guaifenesin Oral Solution, USP 100 mg/5 mL Solution distributed by Reckitt Benckiser

19 blood samples were collected pre-dose (0 hour) and 5, 10, 15, 20, 25, 30, 35, 40, 50 minutes and 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 5.0 hours post-dose. 4 mL of venous blood was collected for PK sampling at each time point per subject. The analytical data were used to calculate the pharmacokinetic parameters: 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 guaifenesin concentrations. Samples were analyzed by HPLC ESI+MS/MS with LOQ at 8.00 pg/mL. The assay was validated from 8.00 pg/mL to 4000 pg/mL in plasma. The coefficient of variation of the precision and the bias of accuracy were 1.13% to 6.10% (CV) and -3.99% to +9.16% (bias), respectively.

Results:

30 subjects entered into this study, and 29 subjects completed both periods of the study. There were 29 sets of data for guaifenesin for this study.

Following single-dose (400 mg guaifenesin) oral administration, the ratios (test drug/reference product B, N=30) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were (b) (4)

The median T_{max} of the test product A and the reference product B was 0.44 and 0.5 hour, respectively.

Table 4.5 Comparison of PK Parameters of Guaifenesin between the Test Product and The Reference product B (Children’s Mucinex® Chest Congestion) in Study 11267603 (N=29)

Parameter	Test A (N = 29)	Reference B (N = 29)	Ratio	CI*
AUC_{0-t} (ng·hr/mL)	(b) (4)			
AUC_{0-inf} (ng·hr/mL)				
C_{max} (ng/mL)				

Analyses of Variance were performed using the General Linear Model containing main effects of sequence, subject within sequence, treatment, and period.

Source: CSR 11267603, page 37, Table 11.4.1.4

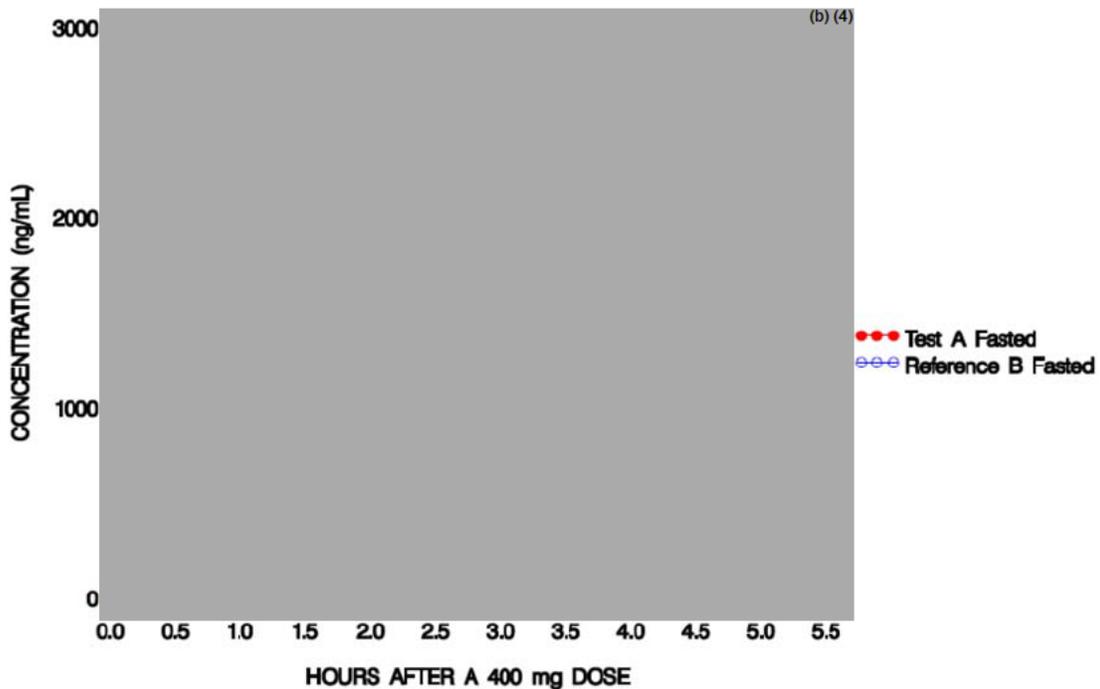


Figure 4.3 Guaifenesin plasma concentration-time profile following 400 mg single dose administration (n=29) in study 11267603, observations represent the least square geometric mean for each time point. (Source: CSR 11267603, page 3)

Conclusions:

The BE was not established between the test product and the reference product B in study 11267603.

4.1.4 Study 11267604

Study Type: Phase 1 BA/BE PK study in healthy volunteers

Title:

A Study to Evaluate the Relative Bioavailability of Guaifenesin from a Combination Formulation of Hydrocodone Bitartrate/ Guaifenesin/ Pseudoephedrine HCl 2.5 mg/200 mg/30 mg/5 mL Oral Solution (b) (4) Compared to Children's MUCINEX® Chest Congestion Liquid (Guaifenesin 100 mg/5 mL) (Reckitt Benckiser) when given in Combination with Hydrocodone Bitartrate and Pseudoephedrine HCl in Healthy Volunteers under Fasted Conditions

Objective:

The purpose of this study was to evaluate the relative bioavailability of guaifenesin from a test formulation of hydrocodone bitartrate, guaifenesin, and pseudoephedrine HCl oral solution 2.5 mg/200 mg/30 mg per 5 mL (b) (4) compared with that of the marketed Reference formulation; Children's Mucinex® chest congestion oral solution (guaifenesin 100 mg/5 mL) (distributed by Reckitt Benckiser) when given together with 5 mL of hydrocodone bitartrate and homatropine methylbromide syrup 5 mg/1.5 mg per 5 mL CIII (Hi-Tech Pharmacal Co.) and 10 mL of pseudoephedrine HCl 30 mg per 5 mL oral solution nasal decongestant (mfd for: (b) (4)) under fasted conditions in healthy adult subjects.

Study Design and Method:

This investigation was a randomized, open-label, single-dose, two-treatment, two-period, two-sequence, crossover study conducted in 36 (36 completed both periods) healthy adults under fasting conditions. The washout period was at least one day. Subjects received the treatment from one of the following product in each period:

- Test product A:
Single dose of 10 mL hydrocodone bitartrate, guaifenesin, and pseudoephedrine HCl 2.5 mg/200 mg/30 mg per 5 mL Oral Solution from (b) (4)
- Reference product B:
Single dose of 20 mL Children's Mucinex® Chest Congestion Guaifenesin Oral Solution, USP 100 mg/5 mL Solution distributed by Reckitt Benckiser
And
5 mL Hydrocodone Bitartrate and Homatropine Methylbromide Syrup 5 mg/1.5 mg per 5 mL CIII Hi-Tech Pharmacal Co.

19 blood samples were collected pre-dose (0 hour) and 5, 10, 15, 20, 25, 30, 35, 40, 50 minutes and 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 5.0 hours post-dose. 4 mL of venous blood was collected for PK sampling at each time point per subject. The analytical data were used to calculate the pharmacokinetic parameters: 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 guaifenesin concentrations. Samples were analyzed by HPLC ESI+MS/MS with LOQ at 8.00 pg/mL. The assay was validated from 8.00 pg/mL to 4000 pg/mL in plasma. The coefficient of variation of the precision and the bias of accuracy were 1.13% to 6.10% (CV) and -3.99% to +9.16% (bias), respectively.

Results:

36 subjects entered into this study and all 36 subjects completed both periods of the study. Following single-dose (400 mg guaifenesin) oral administration, the ratios (test drug/reference product B, N=30) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were (b)(4). The median T_{max} of the test product and the reference product B was 0.42 and 0.5 hour, respectively.

Table 4.6 Comparison of PK Parameters of Guaifenesin between the Test Product and The Reference product B (Children’s Mucinex® Chest Congestion and Hydrocodone Bitartrate and Homatropine Methylbromide from Hi-Tech) in Study 11267603 (N=29)

Parameter	Test A (N = 36)	Reference B (N = 36)	Ratio	CI*
AUC_{0-t} (ng·hr/mL)	(b)(4)			
AUC_{0-inf} (ng·hr/mL)				
C_{max} (ng/mL)				

Analyses of Variance were performed using the General Linear Model containing main effects of sequence, subject within sequence, treatment, and period.
 Source: CSR 11267604, page 40, Table 11.4.1.4

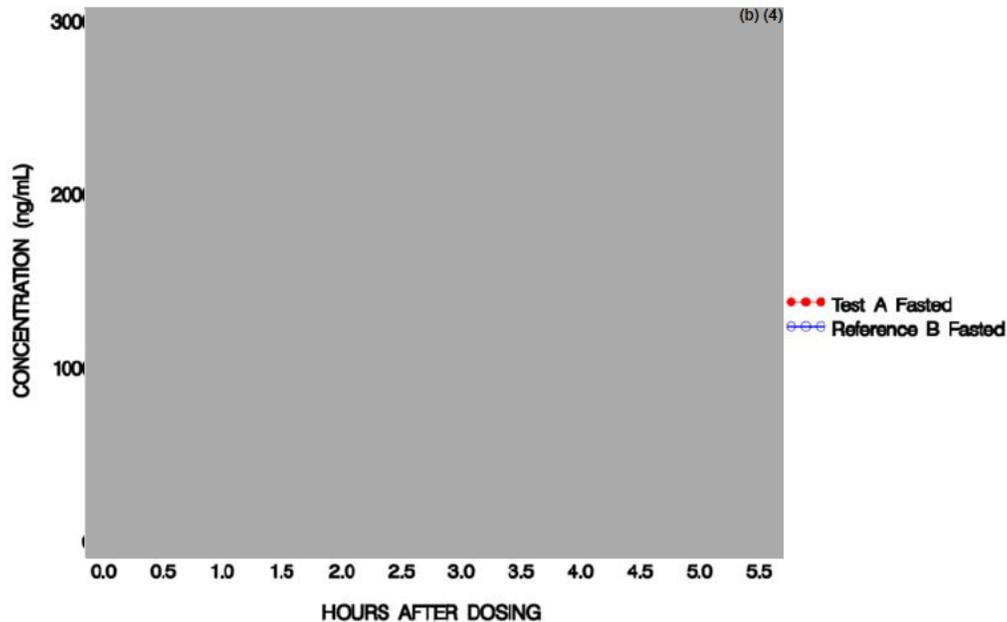


Figure 4.4 Guaifenesin plasma concentration-time profile following 400 mg single dose administration (n=36) in study 11267604, observations represent the least square geometric mean for each time point. (Source: CSR 11267604, page 6)

Conclusions:

The BE was not established between the test product and the reference product B in study 11267604.

4.1.5 Study 11467601

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

Title:

A Study to Evaluate the Relative Bioavailability of Guaifenesin from a Test Formulation of Hydrocodone Bitartrate/ Guaifenesin/ Pseudoephedrine HCl 2.5 mg/200 mg/30 mg/5 mL Oral Solution (Mikart, Inc.) Compared to Refenesen™ Mucus Relief Expectorant (Guaifenesin) 200 mg/5 mL Oral Solution (Distributed by Reese Pharmaceutical) in Healthy Adult Subjects under Fasted Conditions

Objective:

The objective of this study was to evaluate the relative bioavailability of guaifenesin from a test formulation of hydrocodone bitartrate, guaifenesin, and pseudoephedrine HCl oral solution 2.5 mg/200 mg/30 mg per 5 mL (b) (4) Mikart, Inc.) compared to the listed formulation, Refenesen™ Mucus Relief Expectorant (guaifenesin), 200 mg/5 mL (distributed by Reese Pharmaceutical) under fasted conditions in healthy adults subjects.

Method:

This investigation was a randomized, open-label, single-dose, two-treatment, two-period, two-sequence, crossover study conducted in 36 healthy adults under fasting conditions. The washout period was 24 hours. Subjects received the treatment from one of the following product in each period:

- Test product A:
Single dose of 10 mL hydrocodone bitartrate, guaifenesin, and pseudoephedrine HCl 2.5 mg/200 mg/30 mg per 5 mL Oral Solution from (b) (4) (Lot No.: E140392A)
- Reference product B:
Single dose of Refenesen™ Mucus Relief Expectorant (guaifenesin), 200 mg/5 mL distributed by Reese Pharmaceutical (Lot No.: K130682B)

19 blood samples were collected pre-dose (0 hour) and 0.08, 0.17, 0.25, 0.33, 0.42, 0.50, 0.58, 0.67, 0.83, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 5.0 hours post-dose. 4 mL of venous blood was collected for PK sampling at each time point per subject. The analytical data were used to calculate the pharmacokinetic parameters: 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 guaifenesin concentrations. Samples were analyzed by HPLC ESI+MS/MS with LOQ at 8.00 pg/mL. The assay was validated from 8.00 pg/mL to 4000 pg/mL in plasma. The coefficient of variation of the precision and the bias of accuracy were 1.13% to 5.75% (CV) and -3.99% to +9.16% (bias), respectively.

Results:

36 subjects entered into this study and all 36 subjects completed both periods of the study. The summary of demographics was listed in Table 4.7. Subject 27 missed the first three post-dose sample collections in Period 1 on the test product.

Bioequivalence

Following single-dose (400 mg guaifenesin) oral administration, the ratios (test drug/reference product B, N=36) of least-squares geometric means for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.969 (90% CI = 0.920, 1.020), 0.967 (90% CI = 0.919, 1.020), and 0.925 (90% CI= 0.850, 1.007), respectively (Table 4.8 and Fig.4.5). The median T_{max} of the test product and the reference product B were the same (0.42 hour).

Table 4.7 Summary of Demographics in Study 11467601

SUBJECTS INCLUDED IN BIOEQUIVALENCE ANALYSIS (N = 36)	
Gender	
Males	30 (83.33%)
Females	6 (16.67%)
Race	
Asian	0 (0.00%)
Black	15 (41.67%)
Caucasian	14 (38.89%)
Hispanic	4 (11.11%)
Other	3 (8.33%)
Age (years)	
Mean ± SD	42.75 ± 13.50
Median	44.00
Range	18 - 64
Age Groups	
< 18	0 (0.00%)
18 – 40	17 (47.22%)
41 – 64	19 (52.78%)
65 – 75	0 (0.00%)
> 75	0 (0.00%)
Weight (lbs)	
Mean ± SD	172.03 ± 30.54
Median	166.50
Range	93 - 235
BMI (Kg/m²)	
Mean ± SD	25.62 ± 2.90
Median	25.55
Range	18.0 - 29.9
Tobacco User²	
Yes	16 (44.44%)
No	20 (55.56%)

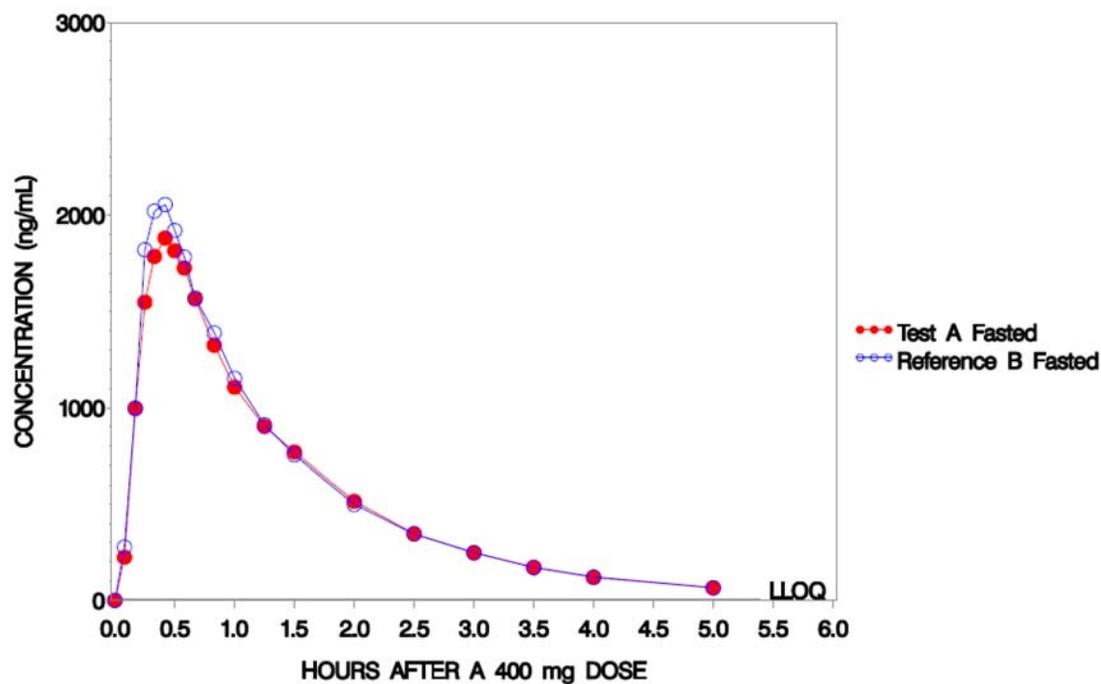
Source: CSR 11467601, page 34, Table 11.2.1

Table 4.8 Comparison of PK Parameters of Guaifenesin between the Test Product and The Reference product B (Refenesen™ Mucus Relief Expectorant) in Study 11467601 (N=36)

Parameter	Test product (A)	Reference product (B)	Ratio (A/B)	90% of CI
AUC _{0-t} (ng·h/mL)	2519	2601	0.9687	0.9203 – 1.0197
AUC _{0-inf} (ng·h/mL)	2603	2690	0.9674	0.9188 – 1.0186
C _{max} (ng/mL)	2015	2178	0.9253	0.8500 – 1.0072
T _{max} (hour)	0.42 (0.17 – 1.5)	0.42 (0.25 – 0.83)	-	

Analyses of Variance were performed using the General Linear Model containing main effects of sequence, subject within sequence, treatment, and period.

Source: adapted from CSR 11467601, page 36, Table 11.4.1.1 and 11.4.1.2



Mean concentration values below LLOQ (<8.0) in the terminal phase are not plotted

Figure 4.5 Guaifenesin plasma concentration-time profile following 400 mg single dose administration (n=36) in study 11467601, observations represent the least square geometric mean for each time point. (Source: CSR 11467601, page 5, Figure 2.1)

The PK parameters of the test product and the reference product were summarized in Table 4.9.

Table 4.9 Summary of PK Parameters of the Test Product and the Reference product in Study 11467601 (N=36)

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)	
	Test A (N = 36 datasets)	Reference B (N = 36 datasets)
AUC _{0-t} (ng·hr/mL)	2752.1321 \pm 1200.7658 (43.6304)	2841.8861 \pm 1244.5619 (43.7935)
AUC _{0-inf} (ng·hr/mL)	2849.3941 \pm 1263.9448 (44.3584)	2949.7700 \pm 1320.7932 (44.7761)
AUC _{0-t} / AUC _{0-inf} ratio	0.9681 \pm 0.0215 (2.2227)	0.9668 \pm 0.0194 (2.0068)
C _{max} (ng/mL)	2198.1389 \pm 897.0113 (40.8078)	2408.8333 \pm 1176.8301 (48.8548)
T _{max} (hr)	0.4631 \pm 0.2404 (51.9242)	0.4331 \pm 0.1635 (37.7494)
Median T _{max} (hr) (min – max)	0.42 (0.17 – 1.50)	0.42 (0.25 – 0.83)
K _{el} (1/hr)	0.7405 \pm 0.1266 (17.0957)	0.7057 \pm 0.1366 (19.3547)
T _½ (hr)	0.9619 \pm 0.1582 (16.4425)	1.0203 \pm 0.2107 (20.6476)

Source: CSR 11467601, page 36, Table 11.4.1.1

Conclusion:

The BE was established between the test product (hydrocodone bitartrate, guaifenesin, and pseudoephedrine HCl 2.5 mg/200 mg/30 mg per 5 mL Oral Solution from [REDACTED]^{(b) (4)} and the reference product B (Refenesen™ Mucus Relief Expectorant, 200 mg/5 mL guaifenesin distributed by Reese Pharmaceutical). The 90% confidence interval of AUC_{0-t}, AUC_{0-∞}, and C_{max} ratios (test/reference) was within the range of 0.80-1.25

Reviewer’s comments:

Reviewer’s independent analysis (Table 4.10) showed similar results that guaifenesin from the test product is bioequivalent to the reference product, which is in agreement with the Sponsor’s conclusions.

Table 4.10 Comparison of PK Parameters of Guaifenesin between Tested Product (A) and the Reference product (B) in Study 11244403 (N=36)

Parameter	Test product (A)	Reference product (B)	Ratio (A/B)	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC _{0-t} (ng·h/mL)	2519	2601	0.9688	0.9204	1.0197
AUC _{0-inf} (ng·h/mL)	2603	2690	0.9676	0.9189	1.0187
C _{max} (ng/mL)	2015	2178	0.9253	0.8500	1.0071
T _{max} (hour)	0.42 (0.17 – 1.5)	0.42 (0.25 – 0.83)	-	-	-

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

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

/s/

YUNZHAO REN
04/24/2015

SURESH DODDAPANENI
04/24/2015

(b) (4) submitted data from two new clinical pharmacology studies (Study S11-028: a single-dose drug-drug interaction study, and Study S11-0029: a single-dose food effect study) on 07/19/2011 in their Resubmission. Data from study S11-028 indicated that the guaifenesin component of the proposed product is not bioequivalent to the reference guaifenesin product (b) (4)

Test Product A vs. Reference Product C				
Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)				
Ln-Transformed data				
Guaifenesin				
N = 38				
Parameter	Test A	Reference C	% Ratio	90% CI
AUC _{0-t} (ng-hr/mL)	(b) (4)			
AUC _{0-inf} (ng-hr/mL)	(b) (4)			
C _{max} (ng/mL)	(b) (4)			

Test A: HC bitartrate/PSE HCl/GUA, 2.5/30/200 mg per 5 mL oral solution
 Reference C: Combination of GUA and PSE HCl, 30/200 mg per 5 mL oral solution

Since this is a significant review issue, sponsor should be sent the following comment:

The clinical pharmacology studies submitted to support this application (studies S11-028 a single-dose bioavailability study and S11-0029 a single-dose crossover food effect study) have been reviewed under NDA 22-424 and show that the guaifenesin component of your oral solution product is not bioequivalent to the reference guaifenesin product (b) (4)

As such, their acceptability to support the approval of your proposed hydrocodone, pseudoephedrine, and guaifenesin product is in question and will be a review issue.

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

/s/

ARUN K AGRAWAL
09/30/2011

SURESH DODDAPANENI
10/03/2011

Addendum to Clinical Pharmacology Review for NDA 22-279 on December 28, 2010

Date: January 20, 2011

NDA: 22-279

Drug name: Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution

The following information reflects update on the bioequivalence (BE) study S09-0009 and food effect study S09-0010 in the clinical pharmacology review for NDA 22-279, which was finalized in DARRTs on December 28, 2010.

On September 01, 2010, the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) sent a request to the Division of Scientific Investigations (DSI) to audit both the clinical and bioanalytical portions of the following bioequivalence studies:

1. Study #1: S09-0009: Single Dose Bioequivalence Study - A relative bioavailability study of hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution
2. Study #2: S09-0010: Food Effect PK Study - A food effect study of hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution

The DSI inspection report was not available on January 03, 2011, the primary due date for clinical pharmacology review. Therefore, in the original clinical pharmacology review, the pharmacokinetic (PK) results for both the above studies were discussed and summarized without DSI audit results. The PK analyses from Study #1 showed that the PK for hydrocodone and pseudoephedrine met the BE criteria, however, guaifenesin did not meet the BE criteria (b) (4)

The PK analyses from Study #2 showed that a high-fat breakfast does not impact the relative bioavailability of hydrocodone and pseudoephedrine, but (b) (4)

On January 20, 2011, the DSI inspection memorandum for the above two studies was issued. Following the inspection, DSI has found the following issues:

1. An audit performed by the Agency of studies S09-0009 (a drug-drug interaction and relative bioavailability study) and S09-0010 (a food effect study) identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies cannot be relied upon to support the clinical pharmacology of NDA 22-279 (b) (4)

Conclusions

In conclusion, the results of the bioequivalence studies from S09-0009 and S S09-0010 are *not* acceptable based on the DSI audit outcome from clinical pharmacology perspective. The following conclusions from DSI audit memorandum should be conveyed to the sponsor:

1. An audit performed by the Agency of studies S09-0009 (a drug-drug interaction and relative bioavailability study) and S09-0010 (a food effect study) identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies cannot be relied upon to support the clinical pharmacology of NDA 22-279 (b) (4)

This deficiency may be addressed by doing the following:

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

OR

- b. Repeat the clinical pharmacology program to demonstrate BE between the proposed product and the reference product under fasted state, and repeat the food effect study. To establish bioequivalence to the reference product, the 90% CIs of the geometric mean ratio of both AUC and Cmax should be within the 80 - 125% goal post for bioequivalence.

OR

- c. Conduct a clinical development program with clinical studies to support your combination product

Readers are referred to the full DSI report below:

MEMORANDUM

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

DATE: January 20, 2011

TO: Badrul A. Chowdhury, M.D.
Director
Division of Pulmonary and Allergy Products (DPAP)

Chandrasah Sahajwalla, Ph.D.
Director
Division of Clinical Pharmacology-2
Office of Clinical Pharmacology (HFD-870)

FROM: Martin K. Yau, Ph.D.
Acting Team Leader (Bioequivalence)
Division of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph. _____
Chief, GLP and Bioequivalence Branch
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-279, Hydrocodone
Bitartrate/Pseudoephedrine HCl/Guaifenesin Oral
Solution, Sponsored by _____ (b) (4)

At the request of DPAP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following phase I studies supporting NDA 22-279:

Study Number: S09-0009

Study Title: "A drug-drug interaction and relative bioavailability study of hydrocodone bitartrate 5 mg/guaifenesin 400 mg/pseudoephedrine HCl 60 mg oral solution"

Study Number: S09-0010

Study Title: "A food effect study of hydrocodone bitartrate 5 mg/guaifenesin 400 mg/pseudoephedrine HCl 60 mg oral solution"

The clinical portions of Studies S09-0009 and S09-0010 were conducted at Cetero Research, St. Charles, MO (Cetero - St. Charles). The analytical portions (b) (4)

Following inspection of the clinical (December 28 - 30, 2010) and analytical sites (b) (4) Form FDA 483 was issued at each site (Attachments 1 and 2).

In addition to the studies mentioned above, the inspection at the analytical site also included a follow-up investigation of a complaint received by the Agency in June of 2009, in which an ex-employee of (b) (4) alleged misconduct in a number of bioanalytical studies. As of this writing, Cetero-St Charles's response to the Form FDA-483 has not been received by DSI. The (b) (4) response to the Form FDA-483 was received on (b) (4) electronically via an e-mail. The 483 observations, (b) (4) written response, and our evaluations follow:

Clinical Site: Cetero Research, St. Charles, MO

1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, you failed to follow the exclusion criteria in protocols S09-0009 and S09-0010. Both protocols state an exclusion criteria of: "Reports a history of clinically significant allergies including food or drug allergies." One subject (009, (b) (6)) from protocol S09-0009, and three subjects (015 (b) (6); 007 (b) (6); 001 (b) (6)) from protocol S09-0010 reported clinically significant drug allergies.

As the four subjects cited in the above 483 observation failed to meet the inclusion/exclusion criteria, data generated from these subjects should be excluded from data analysis.

2. You failed to follow your Standard Operating Procedures regarding transferring subjects from a different study.

Specifically, for protocol S09-0009 an alternate subject (b) (6) was used to replace subject number 015 in the study. This alternate signed the informed consent form on the day of dosing, and exact time was not documented as required by Cetero Research's Standard Operating Procedures (SOP) STL_WI_03_SCT_007, Version 2, "Conducting Inter-study Subject Transfer". This SOP states "If informed consent is obtained on the study day, ensure to document the exact time the informed consent was obtained."

In addition, you failed to follow SOP STL_WI_03_SCT_007, Version 2, "Conducting Inter-study Subject Transfer" regarding the obtaining of the investigator's signature when transferring a subject into a different study. The SOP states "obtain investigator dated signature confirming subject eligibility for study participation in instances when inter-study transfer involves two unrelated studies. In instances when inter-study transfer involves two related studies (e.g., fast / fed), enter N/A in the space provided." This space on subject SAP's Subject Transfer form for the Investigator's signature was left blank.

3. Not all changes in research activity or documentation were approved by the Institutional Review Board prior to implementation.

Specifically, revisions to the informed consent forms for protocol numbers S09-0009 and S09-0010 were only reviewed by the Institutional Review Board Chairman and not by the entire Institutional Review Board before implementation.

Although the observations cited in Items 2 and 3 above are objectionable, these observations should not affect the study outcomes. However, Cetero-St. Charles should correct these objectionable practices in their current and future studies.

4. You failed to retain an adequate quantity of the investigational drug, Hydrocodone Bitartrate 5 mg/Guaifenesin 400 mg/Pseudoephedrine HCl 60 mg oral solution, for protocols S09-0009 and S09-0010, in order to permit FDA to perform five times all relevant tests required in the application.

Although the study reserves retained at the clinical site are less the 'five times' quantity, the volumes of test and reference oral solutions collected by the ORA field investigator during the FDA inspection should be sufficient to allow the FDA lab in St. Louis to carry out the necessary testing.

Analytical Site: [REDACTED] (b) (4)

1. Failure to identify and document procedures for "prep" run injections as described in the Form FDA-483 issued to [REDACTED] (b) (4). Specifically, in studies S09-009 and S09-0010, analytical runs were 'prep' for one to several times using run samples (i.e., samples could be uninjected subject samples, calibration standard and/or quality control samples (QCs)), and the number of samples in the 'prep' runs varied greatly. No explanation, rationale, or justification of how the 'prep' runs were carried out was provided by [REDACTED] (b) (4). Analysts that conducted the 'prep' runs did not follow any written procedure and did not document any of the actions they completed during the performance of the "prep" runs.

In their written response (Attachment 3), [REDACTED] (b) (4) stated that 'prep' runs were performed to equilibrate and to ensure optimal performance of the LC/MS/MS system before being used for study sample analysis. However, they also acknowledged that study samples not yet analyzed should not be used to equilibrate the LC/MS/MS system. They said that the practice of using study samples not yet analyzed in the 'prep' runs was stopped in May 2009 shortly after the bioanalytical work of studies S09-0009 and S09-0010 was completed.

The above 483 observation was issued to [REDACTED] (b) (4) because the sample analyses of studies S09-009 and S09-0010 were conducted at the time period when study samples not yet analyzed were used in the 'prep' run. DSI has concerns regarding the integrity of the bioanalytical data generated in these two studies due to the following reasons:

- A. In a letter dated [REDACTED] (b) (4) a former employee alleged that laboratory staff of [REDACTED] (b) (4) altered the outcome of analytical runs (i.e., runs were 'fixed' through 'prep' runs injected prior to the actual subject sample batch). An evaluation of the

allegations by a third party (b) (4)
(b) (4)
for the audit report) as well as by DSI during the (b) (4)
(b) (4) inspections raised concerns regarding the integrity of the bioanalytical work generated by (b) (4). Specifically, the basic elements of the analytical process are in questions due to documentation irregularities. For example:

(a) In studies S09-0009 and S09-0010, there is no SOP nor any Analytical Procedure (AP) sheets to document what samples was injected to condition the LC/MS/MS system or what was done afterwards. Many prep runs were repeated several times and the number of samples in the 'prep' runs varied greatly, but the rationale behind these variations, what if anything was altered between the prep runs, and the outcome of the prep run injections were not documented. For example, DSI found during the inspection that samples in pseudoephedrine run 16 in study S09-0009 were injected multiple times. Specifically, the 'prep' run for pseudoephedrine run 16 contained 20 samples listed as standards, QC, and blanks. After the official injections on LC/MS/MS system 92, all samples in run 16 were re-injected officially as run 17 on LC/MS/MS system 75 with a 'prep' run for run 17 containing 51 samples. The type of samples in 'prep' run 17 was not listed and only vial number was assigned to each of these prep samples. The pseudoephedrine QCs results of runs 16 and 17 were similar (mean difference = 1.5%) but the pseudoephedrine concentrations of the subjects samples in runs 16 and 17 were very different (about 14%), suggesting possible manipulation of standard and QC samples to impact the results. After the official runs 16 and 17, all samples in these two runs were re-injected again, but these re-injections were not recorded on the AP sheets and pseudoephedrine concentration of these re-injections were not included in the run study binders. The above example of documentation and procedural irregularities makes it difficult to dismiss allegations of improper procedures and possible data manipulation.

According to the complainant's allegations, certain chemist in the laboratory would 'prep' the calibration standards and quality control samples in an attempt to review the results and make correction (i.e., by

substituting or spiking standard and QC samples) to the standard curve and quality control samples prior to injecting the run into the pertinent project folder; blank & blank/blank were fixed to assure they were clean. No direct evidence was uncovered during the inspection to confirm these allegations. Overall, due to documentation irregularities, it is difficult to dismiss allegations of improper procedures and possible data manipulation to cause official runs to pass, when in fact they would have failed.

(b) During the (b)(4) inspections, DSI scientists only looked at prep runs that were provided in the electronic study folder (i.e., official prep runs). It is possible that there were other prep runs injected but were not put in the electronic study folders, as alleged by the complainant. DSI found that it is impossible to determine this during the inspection.

(c) There were notes found written by laboratory staff suggesting improper conduct. Specifically, a note written by (b)(6) the MS supervisor was found and it stated *"Please correct AP sheets to read guard column - Onyx C18. We may not have had them for this study but always refer to what's on the AP sheet"* This was cited in the third party audit report as clearly a directive to falsify data. In addition, the third party auditor also reported there are notes to the instrument operators that said *"if the 'prep' does not pass, save the run for the supervisor to inject the following days"*. This practice by staff in the laboratory raised questions on the integrity of their work.

Formatted: Indent: Left: 36 pt,
First line: 0 pt

B. In agreement with the (b)(4) DSI inspectional findings, the present DSI inspection also concludes that the firm's investigation was insufficient to thoroughly address the allegation of "fixing" runs. As stated in the (b)(4) EIR cover memo, (b)(4) lacked adequate documentation and written procedures to verify the identity of samples in the 'prep' runs. Instead, (b)(4) made assumptions about the identity of such samples for the conduct of their investigation. Given the lack of confirmatory information, it is not possible to determine if the

firms's investigation could identify runs affected by "fixing" versus those without such manipulation.

C. As reported in the previous EIR cover memo to DPAP and OCP2 on (b) (4) internal investigations of (b) (4) (b) (4) found unexplained discrepancies between the initial system equilibration result ('prep' run) and the actual rerun results in four runs from three studies. Specifically, "prep' run calibration standards had no drug or internal standard peak present yet the actual subject sample run had these peaks. In the (b) (4) FDA inspection, (b) (4) (b) (4) still could not explain the discrepancy. Thus falsification of analytical batches can not be ruled out for studies conducted by (b) (4) before June 2009.

2. Review of the records for the extraction of subject samples for the determination of guaifenesin and pseudoephedrine concentrations in plasma verified that the records were falsified as described in the Form FDA-483 issued to (b) (4). Examples include analytical Run 5 and Run 6 for guaifenesin and analytical Run 4 for pseudoephedrine in Study S09-0010.

As cited above, extraction records of some analytical runs in Study S09-0010 were falsified. Moreover, during the (b) (4) inspection, DSI inquired and learned that falsification occurred during weekday extractions as well, although it was not as frequent as on weekends. (b) (4) confirmed that some analysts that falsified extraction records on the weekends also committed falsifications on weekdays as well. In the written response, (b) (4) stated that the falsification was limited to the date/time of extraction. However, from DSI viewpoint, the falsification itself along with the concerns stated in Item 1 above, question the integrity of the activities carried out at (b) (4)

3. Stability was not demonstrated under the same conditions as in the study samples. Specifically, samples in stability experiments contained either hydrocodone/chlorpheniramine, fexofenadine/pseudoephedrine, or guaifenesin, whereas study samples in Study S09-0010 contained hydrocodone, pseudoephedrine, and guaifenesin; study samples in Study S09-0009 contained combinations of

hydrocodone, pseudoephedrine, and guaifenesin or hydrocodone and homatropine.

(b) (4) acknowledged this observation and agreed to establish storage stability for all analytes (hydrocodone, guaifenesin, pseudoephedrine, and homatropine) in the presence of each other. In the written response, (b) (4) stated these stability experiments should be completed in May 2011.

4. Documentation for re-injections of analytical runs was not contemporaneous. For example, samples in Study S09-0009 Run 5 were analyzed for guaifenesin on April 4, 2009. Majority of samples in Run 5 were re-injected on April 7, 2009. However, there was no documentation at that time to explain or justify these re-injections. Explanation was later provided, during the course of an investigation of allegations of improprieties, in a LC/MS/MS supervisor memo

(b) (4)

(b) (4) acknowledged the lack of contemporaneous documentation in their written response and said their practices now mandate documenting all sample re-injections with an appropriate reason for the activity. This observation added to DSI's concerns for documentation irregularities found at this firm

Conclusions

Following DSI's evaluation of the inspectional findings, DSI recommends the following:

- Study S09-0009 and S09-0010 should not be accepted for review at this time due to concerns raised by DSI and the incomplete investigation of complaint allegations by (b) (4) (see analytical 483 items 1 and 2 above).
- Appropriate freeze/thaw and long term frozen storage stability to demonstrate analyte stability under the same conditions as the subject samples (i.e., hydrocodone, guaifenesin, pseudoephedrine, and/or homatropine combinations) are needed to confirm samples integrity during sample processing and storage.

Page 9 - NDA 22-279, Hydrocodone Bitartrate/Pseudoephedrine
HCl/Guaifenesin Oral Solution

After you have reviewed this transmittal memo, please
append it to the original NDA submission.

Martin K. Yau, Ph.D.

Final Classification:

Cetero Research, St. Charles, MO - VAI

(b) (4)

cc:

CDER DSI PM TRACK (e-mail)

OC DSI/Ball/Viswanathan/Haidar/Yau/CF

OND/ODE/DPAP/Bowen

OTS/OCP/DCPII/Agrawal/Wang/Xu

HFR-SW1580/Peacock

HFR-SW400/Bous

Draft: MKY 1/20/11

Edit: XC 1/20/11

DSI: 6114; O:\BE\EIRCover\22279hydr.tib.doc

FACTS _____

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

/s/

ARUN K AGRAWAL
01/21/2011

YUN XU
01/21/2011

CLINICAL PHARMACOLOGY REVIEW

NDA Number: 22-279
Type: 505(b)(2)
Brand Name: TRADENAME
Generic Name: Hydrocodone (HC), Pseudoephedrine (PSE), and Guaifenesin (GUA) Oral Solution
Indication: Symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) mucus (b) (4)
Dosage Form: Solution
Dosage Strength: 2.5 mg HC/30 mg PSE/200 mg GUA per 5 mL
Dosage Administration: Adults (b) (4): Two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours (b) (4)
Route of Administration: Oral
Sponsor: (b) (4)
Submission Type: NDA Resubmission
Submissions Date: July 26, 2010
OCP Division: Division of Clinical Pharmacology 2
OND Division: Pulmonary, Allergy, and Rheumatology Products
Reviewer: Arun Agrawal, Ph.D.
Team Leader (Acting): Yun Xu, Ph.D.

TABLE OF CONTENTS

Item	Page number
1. Executive Summary	2
1.1 Recommendation	2
1.2 Phase IV Commitments	3
1.3 Summary of Clinical Pharmacology Findings	3
2. Question-Based Review	10
2.1 General Attributes	10
2.2 General Clinical Pharmacology	15
2.3 Analytical Section	16
3. Labeling Comments	16
4. Appendices	16

1. EXECUTIVE SUMMARY

This NDA review is for hydrocodone (HC), pseudoephedrine (PSE), and guaifenesin (GUA) oral solution submitted under 505(b)(2) of the FDC Act. This triple combination product is an immediate release solution that contains hydrocodone bitartrate (antitussive), pseudoephedrine hydrochloride (nasal decongestant), and guaifenesin (expectorant) at the concentration of 2.5 mg, 30 mg, and 200 mg per 5 mL, respectively.

(b) (4) purchased rights to this NDA from (b) (4) on March 25, 2009. (b) (4) is seeking approval of this cough/cold product (b) (4)

The proposed dose in adults (b) (4) is two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)

This product was submitted on August 22, 2008 as an NDA but was issued a CR on June 22, 2009. On July 26, 2010 (b) (4) submitted results of the following 2 PK studies and is seeking market approval for their HC, PSE, and GUA oral solution:

1. Single Dose Bioequivalence Study (Study #S09-0009)

2. Food Effect PK Study (Study #S09-0010)

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP 2) has reviewed the Clinical Pharmacology information for NDA 22-279 submitted on July 26, 2010 and found this NDA is NOT acceptable from an OCP standpoint. The guaifenesin component of the proposed product is not bioequivalent to the reference drug Robitussin Chest Congestion (guaifenesin) oral solution at 400 mg dose. The following information should be conveyed to the sponsor.

The clinical pharmacology program submitted to support this application shows that the guaifenesin component in your oral solution product is not bioequivalent to the reference product (b) (4)

This deficiency may be addressed by doing the following:

- Conduct single dose bioavailability trial(s) between your proposed product and the reference products under fasted state. Include sufficient number of subjects in the bioavailability trial(s). To gain approval, BE must be established between your proposed product and the reference products under fasted state, or
- Conduct a clinical development program with clinical trials to support your proposed product, or

- Reformulate the product and repeat the clinical pharmacology program to demonstrate BE between the reformulated product and the reference products under fasted state, and repeat the food effect study if necessary.

1.2 Phase IV Commitments

Not applicable

1.3 Summary of Clinical Pharmacology Findings

The clinical pharmacology program included in this submission to support the approval of HC, PSE, and GUA oral solution for the relief of symptoms due to the cold and cough contained 2 clinical pharmacology studies (Study #S09-0009 and Study #S09-0010).

Study #S09-0009: Single Dose Bioequivalence Study - A relative bioavailability study of hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution

This was an open-label, single-dose, randomized, three-period, three-treatment crossover study under fasting conditions. At least 7-day washout period was observed between the doses. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12,16, 24 and 36 hours post-dose. Blood samples were collected only up to 16 hours for hydrocodone bitartate/homatropine methylbromide arm (Treatment B).

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

Treatment A (Test) (b) (4) hydrocodone bitartrate/pseudoephedrine HCl/guaifenesin oral solution

Treatment B (References 1) Hydrocodone bitartate/homatropine methylbromide oral solution

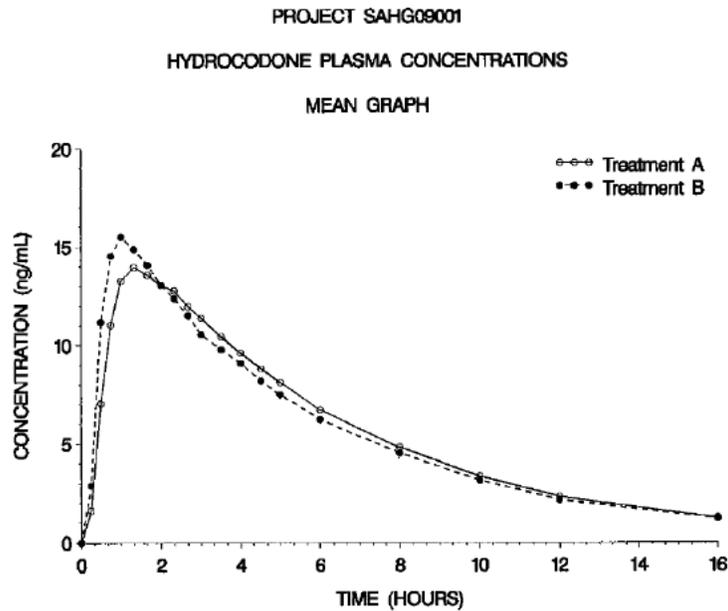
Treatment C (References 2) the combination of both pseudoephedrine HCl and Robitussin Chest Congestion (guaifenesin) oral solution

Total Dose = hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg in healthy adult subjects when administered under fasting conditions. The comparisons of interest are Treatment A versus Treatment B, and Treatment A versus Treatment C. Results are summarized below:

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

(b) (4) Ln-Transformed Data - Hydrocodone combination solution (Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg oral solution) vs. Hydrocodone Bitartrate / Homatropine Methylbromide 5 / 1.5 mg per 5 mL oral solution (Treatment A vs. Treatment B) N = 39				
Parameter	Treatment A	Treatment B	% Ratio	90% CI
AUC_{0-t} (ng.h/mL)	88.8591	88.0935	100.87	(98.21, 103.60)
AUC_{0-inf} (ng.h/mL)	96.2371	95.1725	101.12	(98.28, 104.04)
C_{max} (ng/mL)	14.3853	16.0187	89.80	(85.81, 93.98)

Treatment A: Hydrocodone Bitartrate/Pseudoephedrine HCl/Guaifenesin oral solution
Treatment B: Hydrocodone Bitartrate/Homatropine Methylbromide oral solution

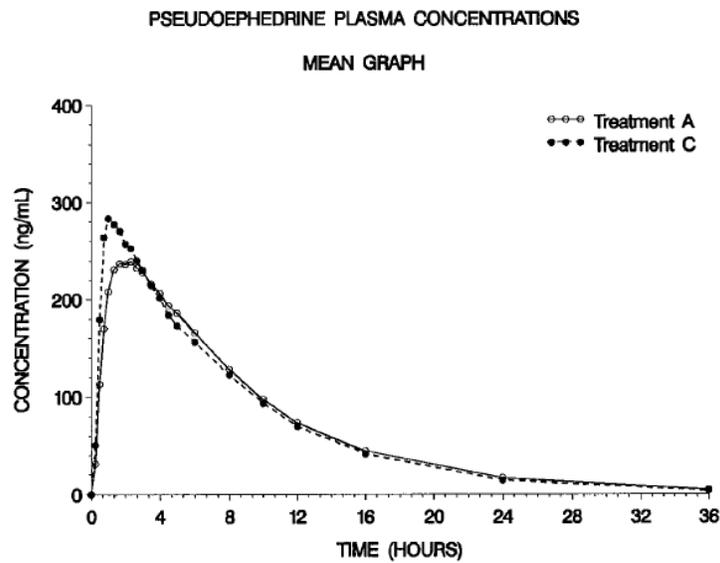


Pseudoephedrine (Treatment A versus Treatment C): The test ratios of geometric means were 100.48% (90% CI 96.54% - 104.57%) for AUC_{0-t} , 100.75% (90% CI 96.92% - 104.73%) for AUC_{0-inf} , and 85.68% (90% CI 82.08% - 89.44%) for C_{max} . The point estimates and their 90% CIs were all contained within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

Ln-Transformed Data - Pseudoephedrine				
Tiber's combination solution (Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg oral solution) vs. Robitussin® Chest Congestion oral solution (Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg) (Treatment A vs. Treatment C)				
N = 36				
Parameter	Treatment A	Treatment C	% Ratio	90% CI
AUC_{0-t} (ng.h/mL)	2394.6948	2383.3305	100.48	(96.54, 104.57)
AUC_{0-inf} (ng.h/mL)	2454.5881	2436.3557	100.75	(96.92, 104.73)
C_{max} (ng/mL)	253.6698	296.0544	85.68	(82.08, 89.44)

Treatment A: Hydrocodone Bitartrate/Pseudoephedrine HCl/Guaifenesin oral solution

Treatment C: Combination of both Robitussin Chest Congestion and Pseudoephedrine HCl oral solution



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

(b) (4)



Ln-Transformed Data - Guaifenesin				
Tiber's combination solution (Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg oral solution) vs. Robitussin [®] Chest Congestion oral solution (Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg) (Treatment A vs. Treatment C)				
N = 38				
Parameter	Treatment A	Treatment C	% Ratio	90% CI
AUC _{0-t} (ng.h/mL)				
AUC _{0-inf} (ng.h/mL)				
C _{max} (ng/mL)				

(b) (4)

Treatment A: Hydrocodone Bitartrate/Pseudoephedrine HCl/Guaifenesin oral solution
Treatment C: Combination of both Robitussin Chest Congestion and Pseudoephedrine HCl oral solution



(b) (4)

Conclusion for Study #S09-0009:

(b) (4)

however, guaifenesin did not meet the BE criteria

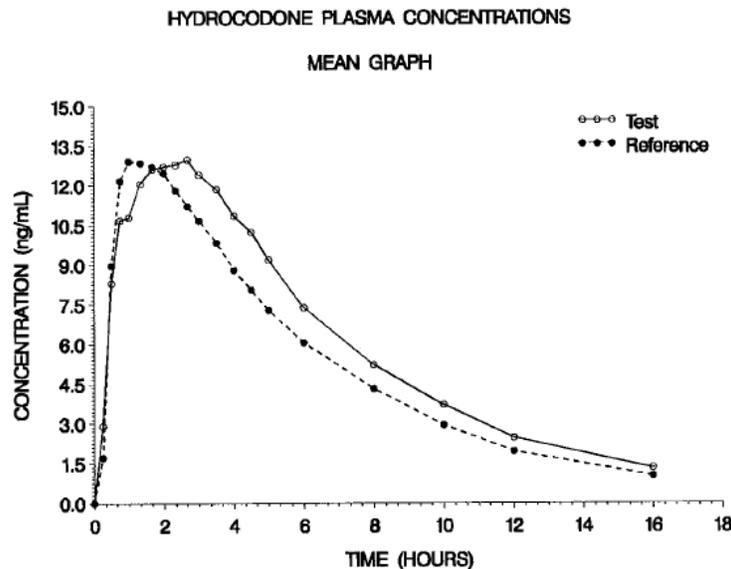
(b) (4)

Study #S09-0010: Food Effect PK Study - A food effect study of hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg oral solution

The food effect study assessed the impact of food on the bioavailability of hydrocodone bitartrate 2.5 mg/pseudoephedrine HCl 30 mg/guaifenesin 200 mg, per 5 mL oral solution, by comparing the pharmacokinetic parameters under fed and fasted conditions. This was an open-label, single-dose, randomized, two-period, two-treatment crossover study under fasting and fed conditions. At least a 7-day washout period was observed between the doses. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24 and 36 hours post-dose. Twenty two (22) blood samples were collected per period x 2 study periods (total of 44 samples, 424 mL total volume). Results are summarized below:

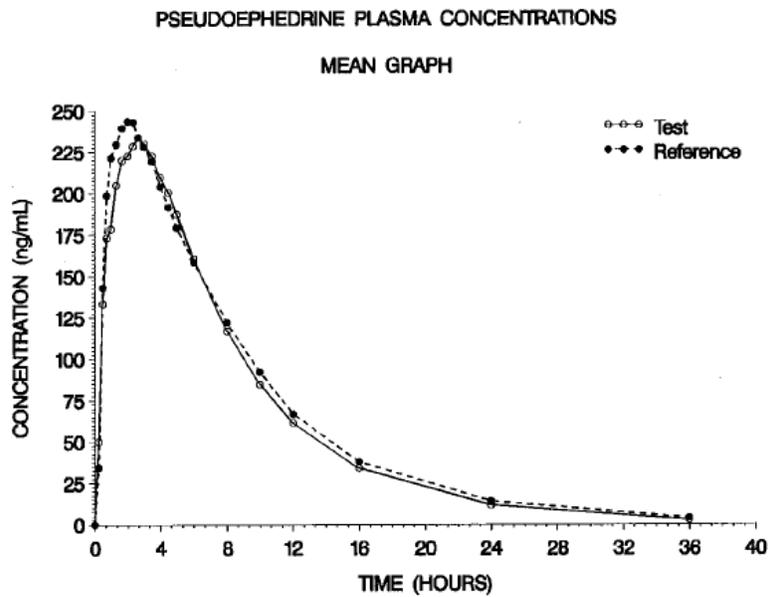
Hydrocodone: The test ratios of geometric least squares means (LSM) and 90% CI were 115.7% (90% CI 111.86% - 119.66%) for AUC_{0-t} , 117.0% (90% CI 112.94% - 121.0%) for $AUC_{0-\infty}$, and 102.6% (90% CI 97.17% - 108.28%) for C_{max} . The point estimates and their 90% CIs were all contained within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

Hydrocodone bitartrate under fed conditions vs. Hydrocodone bitartrate under fasted conditions Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI) Ln-Transformed data N = 18				
Parameter	Hydrocodone bitartrate (Fed) N = 18	Hydrocodone bitartrate (Fasted) N = 18	% Ratio	90% CI
AUC_{0-t} (ng-hr/mL)	95.0655	82.1693	115.7	111.86 – 119.66
$AUC_{0-\infty}$ (ng-hr/mL)	102.6032	87.7356	117.0	112.94 – 121.10
C_{max} (ng/mL)	13.8950	13.5463	102.6	97.17 – 108.28



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

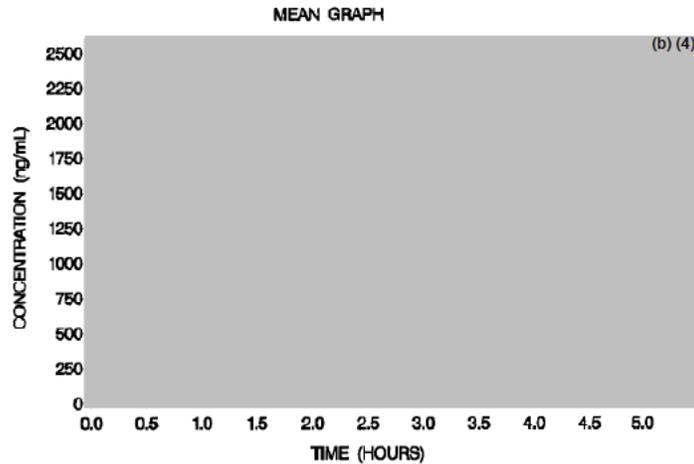
Pseudoephedrine HCl under fed conditions vs. Pseudoephedrine HCl under fasted conditions Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI) Ln-Transformed data N = 18				
Parameter	Pseudoephedrine HCl (Fed) N = 18	Pseudoephedrine HCl (Fasted) N = 18	% Ratio	90% CI
AUC_{0-t} (ng-hr/mL)	2169.5639	2286.4121	94.9	87.68 - 102.70
$AUC_{0-\infty}$ (ng-hr/mL)	2214.6118	2336.3734	94.8	87.37 - 102.83
C_{max} (ng/mL)	242.8839	249.6607	97.3	92.70 - 102.10



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

Guaifenesin under fed conditions vs. Guaifenesin under fasted conditions Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI) Ln-Transformed data N = 18				
Parameter	Guaifenesin (Fed) N = 18	Guaifenesin (Fasted) N = 18	% Ratio	90% CI
AUC _{0-t} (ng-hr/mL)	(b) (4)			
AUC _{0-∞} (ng-hr/mL)	(b) (4)			
C _{max} (ng/mL)	(b) (4)			

GUAIFENESIN PLASMA CONCENTRATIONS



The administration of guaifenesin in a combination formulation to healthy volunteers with a high-fat meal indicated that (b) (4)

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

Conclusion for Study #S09-0010:

The results of this food-effect study in healthy volunteers indicated that (b) (4) combination formulation containing a 10 mL single dose of hydrocodone bitartrate 5 mg/pseudoephedrine HCl 60 mg/guaifenesin 400 mg did not meet all the bioequivalence criteria when administered under fasted versus fed conditions. The results indicate that a high-fat breakfast does not impact the relative bioavailability of hydrocodone and pseudoephedrine, bu (b) (4)

For conservative purposes, it may be suitable to recommend that this solution be administered on an empty stomach.

2. QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Introduction

Hydrocodone is approved in various forms and in combinations with other drugs as a narcotic analgesic and as an antitussive agent. HC was not included in the OTC Monograph process and is available on a prescription only basis (Rx Only). The safety and effectiveness of HC as a prescription drug for the relief of cough are supported by DESI review and by the FDA approval of Hycodan (NDA 5213) (recently discontinued). HC is an opioid, a schedule controlled substance, a prescription drug and is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GUA is not in compliance with the OTC monograph (21CFR §341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed product as the regulation requires (21CFR§300.50). However, there is a regulatory precedence regarding the combination of HC with an OTC monograph product (refer to Medical Officer Review, IND (b) (4), Charles E. Lee, M.D., 9/25/2006). Based on Dr. Lee's review, the FDA has previously determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. Considering this policy, the Division has approved drug development programs for HC and OTC monograph product combinations, concluding that a drug development plan does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the efficacy and safety of the combination product.

Pseudoephedrine is generally recognized as safe and effective by monograph in OTC allergy products at doses of: 60 mg every 4 to 6 hours not to exceed 240 mg in 24 hours for adults and children 12 years of age and older. For children 6 to under 12 years of age: 30 mg every 4 to 6 hours not to exceed 120 mg in 24 hours.

Guaifenesin is an OTC monograph drug. Directions for products containing guaifenesin identified in 21CFR§341.18 are as follows: adults and children 12 years of age and over: oral dosage is 200 to 400 mg every 4 hours not to exceed 2,400 mg in 24 hours. Children 6 to under 12 years of age: oral dosage is 100 to 200 mg every 4 hours not to exceed 1,200 mg in 24 hours."

History of Previous Submission

The Division agreed during a face-to-face meeting held on March 26, 2007 (preIND 76,365 meeting) that the sponsor could perform a small single arm bioavailability study in fasted normal subjects on the test product as the basis of approval along with supporting published information on DDI and food effect to establish a clinical link. The DPAP stated that Tussionex (NDA 19-111, approved 12/31/1987, a polistirex extended release suspension containing 10 mg hydrocodone polistirex per 5 mL) would be the most recently approved NDA, and would contain the most appropriate hydrocodone information to reference in a 505(b)(2) NDA. In addition, the NDA for Hycodan (NDA 05-213, approved 7/26/1988, immediate release tablets and syrup containing

hydrocodone bitartrate 5 mg per tablet or 5 mL, homatropine methylbromide 1.5 mg, per tablet or 5 mL) would also be an appropriate reference product.

NDA 22-279 for hydrocodone, pseudoephedrine and guaifenesin oral solution was submitted to the Agency on Aug 22, 2008 through the 505(b)(2) route. A preliminary assessment on the pharmacokinetic data included in the NDA resulted in several issues which were conveyed to the sponsor during the 74-day letter (see filing letter dated 11/03/08) issues as follows:

- We have conducted a preliminary assessment on the pharmacokinetic data included in your NDA as supporting information to link the efficacy and safety of your product to related approved products and found the following limitations:
 - We notice that your product contains sorbitol. Sorbitol has been found to affect the bioavailability (BA) of some compounds with low permeability in a dose proportional manner. Therefore, we recommend that you conduct an in vivo study in which bioequivalence (BE) is established with respect to each active component of your product.
 - We also notice that your program does not address for a potential formulation effect. Section 21 (320.25)(g) of the CFR states that the purpose of an in vivo BA study involving a combination drug product is to determine if the rate and extent of absorption of each active ingredient in the combination product is equivalent to the rate and extend of absorption of each active drug ingredient administered concurrently in separate single ingredient preparations.
- In addition, you need to conduct an in vivo study to determine the effect of food on the bioavailability of [REDACTED]^{(b) (4)} oral solution's active ingredients for the same reason above stated. An equivalence approach is recommended for food-effect BA studies (refer to Guidance for industry: food-effect bioavailability and fed bioequivalence studies).

In response to the 74-day letter the sponsor submitted 3 study protocols (a BA/BE study, a DDI study and a food effect study) to DPAP on January 16, 2009 for comment as follows:

1. **Study Protocol S09-0008:** A relative bioavailability study of hydrocodone 5 mg/pseudoephedrine 60 mg/guaifenesin 400 mg oral solution under fasting conditions. This study is a randomized, single-dose, two-way open-label crossover study. Subjects (40 healthy volunteers) are to be randomized to the following treatments under fasting (over night) conditions:

A (Test Product): One 10 mL oral solution dose containing HC 2.5 mg/PSE 30 mg/GUA 200 mg per 5 mL [REDACTED]^{(b) (4)}

B (Reference Product): One 5 mL oral solution dose of Hycodan (Endo Pharmaceuticals) containing 5 mg of HC, one 10 mL oral solution dose of PSE containing 30 mg per 5 mL, and one 20 mL oral solution dose of Robitussin Chest Congestion (Wyeth Consumer Health Inc.) containing 100 mg GUA per 5 mL.

2. **Study Protocol S09-0009:** A drug-drug interaction study of hydrocodone 5 mg/pseudoephedrine 60 mg/guaifenesin 400 mg oral solution. This study is a randomized, single-dose, three-way open-label crossover study. Subjects are to be randomized to the following treatments under fasting (overnight) conditions:

Treatment A: One 5 mL oral solution dose of Hycodan (Endo Pharmaceuticals) containing 5 mg of HC, one 10 mL oral solution dose of PSE containing 30 mg per 5 mL (PSE 60 mg), and one 20 mL oral solution dose of Robitussin Chest Congestion (Wyeth Consumer Health Inc.) containing 100 mg GUA per 5 mL (GUA 400 mg) given as a single dose with approximately 240 mL of room temperature water after an overnight fast of at least 10 hours.

Treatment B: One 5 mL oral solution dose of Hycodan (Endo Pharmaceuticals) containing 5 mg of HC given as a single dose with approximately 240 mL of room temperature water after an overnight fast of at least 10 hours.

Treatment C: one 10 mL oral solution dose of PSE containing 30 mg per 5 mL (PSE 60 mg) and one 20 mL oral solution dose of Robitussin Chest Congestion (Wyeth Consumer Health Inc.) containing 100 mg GUA per 5 mL (GUA 400 mg) given as a single dose with approximately 240 mL of room temperature water after an overnight fast of at least 10 hours.

3. **Study Protocol S09-0010:** A food effect study of hydrocodone 5 mg/pseudoephedrine 60 mg/guaifenesin 400 mg oral solution under fasting conditions. This study is a randomized, single-dose, two-way open-label crossover study under fed and fasted conditions. Subjects are to be randomized to the following:

A (Test Product): One 10 mL oral solution dose containing HC 5 mg/PSE 60 mg/GUA 400 mg (b) (4) given as a single dose with approximately 240 mL of room temperature water 30 minutes after initiation of a standardized, high-fat and high-calorie meal preceded by an overnight fast of at least 10 hours.

B (Reference Product): One 10 mL oral solution dose containing HC 5 mg/PSE 60 mg/GUA 400 mg (b) (4) given as a single dose with approximately 240 mL of room temperature water after an overnight fast of at least 10 hours.

Upon review of these protocols the following comments were conveyed to the sponsor via Fax on January 27, 2009: “We recommend that you replace treatment A from study S09-0009 with an arm containing the product under investigation (hydrocodone, pseudoephedrine and guaifenesin oral solution, (b) (4)). The purpose of this substitution/inclusion is to allow a direct comparison of hydrocodone,

pseudoephedrine and guaifenesin oral solution (b) (4) to the approved product containing hydrocodone (Hycodan). Under these conditions, study S09-008 will no longer be necessary”.

During a teleconference meeting on February 2009, (b) (4) stated that it would take about 5 months to complete the studies and submit the reports. The Agency noted that the proposed timeline would extend far beyond the PDUFA date for completion of the review of the application. (b) (4) was reminded that any amendment submitted to the NDA must be received prior to the PDUFA due date, and depending on the time it is submitted, may not be reviewed in this cycle. (b) (4) purchased rights to this NDA from (b) (4) on March 25, 2009. (b) (4) was issued a CR on June 22, 2009 for not submitting the required amendments within the PDUFA time frame.

Present Submission:

On July 26, 2010 (b) (4) submitted results of the following 2 clinical studies and is seeking market approval for hydrocodone, pseudoephedrine, and guaifenesin oral solution. The sponsor did not use hycodan as the reference drug for hydrocodone in the study as it was withdrawn from the market by the manufacturer. Instead, sponsor used hydrocodone bitartrate/homatropine methylbromide solution as the reference drug for hydrocodone which is an approved generic product of hycodan (ANDA088008) and is AA rated. Therefore, it is reasonable to use this product as a reference for hydrocodone.

1. Single Dose Bioequivalence Study (Study #S09-0009)
2. Food Effect PK Study (Study #S09-0010)

2.1.2 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Hydrocodone Bitartrate is Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 α), (R- (R*,R*))-2,3-dihydroxybutanedioate (1:1), hydrate (2:5); also known as 4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5), and has a MW of 494.49. It is a fine white (b) (4) powder. (b) (4)

Pseudoephedrine Hydrochloride is Benzenemethanol, α -(1-(methylamino)ethyl)-, (S- (R*,R*))-, hydrochloride and has a MW of 201.69.

Guaifenesin is 1,2-Propanediol, 3-(2-methoxyphenoxy)-, (\pm)-; also known as (\pm)-3-(o-Methoxyphenoxy)-1,2-propanediol, and has a MW of 198.22.

(b) (4) is seeking a market approval for hydrocodone, pseudoephedrine and guaifenesin oral solution indicated (b) (4)

The components and composition for hydrocodone, pseudoephedrine, and guaifenesin oral solution is summarized in following Table.

Components and composition for hydrocodone, pseudoephedrine, and guaifenesin oral solution

% w/v	mg/5mL	Ingredient	Function	g per Liter
0.050	2.5	Hydrocodone Bitartrate USP	Active Ingredient	0.500
4.000	200.0	Guaifenesin USP	Active Ingredient	40.00
0.600	30.0	Pseudoephedrine Hydrochloride USP	Active Ingredient	6.00
(b) (4)		Sorbitol (b) (4) USP		(b) (4)
		Glycerin USP		
		Polyethylene Glycol (b) (4) NF		
		Methylparaben NF		
		Propylparaben NF		
		Citric Acid (b) (4) USP		
		Sodium Citrate (b) (4) USP		
		Saccharin Sodium		
		D & C Red #33		
		FD & C Blue #1		
		(b) (4) Black Raspberry Flavor (b) (4)		
		Purified Water USP		

**2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?
Mechanism of Action:**

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. The effects of hydrocodone at therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, and physical and psychological dependence. Hydrocodone bitartrate is available on a prescription only basis (Rx only). It is approved in various forms and in combinations with other drugs as a narcotic analgesic and as an antitussive.

Pseudoephedrine is a sympathomimetic amine commonly used as a decongestant. PSE acts directly on alpha-adrenergic receptors and to a lesser extent on beta-adrenergic receptors. Like ephedrine, PSE also has an indirect effect by releasing norepinephrine from its storage sites. PSE acts directly on alpha-adrenergic receptors in the mucosa of the respiratory tract producing vasoconstriction which results in shrinkage of swollen nasal mucous membranes, reduction of tissue hyperemia, edema, and nasal congestion, and an increase in nasal airway patency.

Guaifenesin is an OTC monograph drug. 21CFR§341.78(b) states that the labeling of a product containing guaifenesin must state, "under the heading "Indications" the

following: "Helps loosen phlegm (mucus) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive")."

2.1.4 What are the proposed dosage and route of administration?

The following tables provide a summary of the proposed and maximum doses permitted for HC, PSE and GUA.

(b) (4)			
Adults	Per Dose	Per 24 Hours	Maximum Amount Permitted
Hydrocodone Bitartrate	5 mg	20 mg	20-30 mg
Pseudoephedrine Hydrochloride	60 mg	240 mg	240 mg
Guaifenesin	400 mg	1600 mg	2400 mg



2.2 General Clinical Pharmacology

2.2.1 Was hydrocodone, pseudoephedrine and guaifenesin oral solution bioequivalent to the reference products?

Overall, the pharmacokinetic results of study S09-0009 demonstrated that (b) (4) combination oral solution containing hydrocodone bitartrate/pseudoephedrine (b) (4)



2.2.2 What is the effect of food on the BA of hydrocodone, pseudoephedrine and guaifenesin following administration of the proposed product?

Although the product is in solution, the product contains (b) (4) % (w/v) sorbitol, a substance known to affect the BA of some drugs by changing the gastric emptying time among other effects. For this reason, the sponsor was requested during the 74-day letter of the previous cycle of this NDA to address the effect of food on the BA of the proposed product.

The results of the food-effect study (S09-0010) in healthy volunteers indicated that (b) (4) combination oral solution containing a 10 mL single dose of hydrocodone bitartrate 2.5 mg/pseudoephedrine HCl 30 mg/guaifenesin 200 mg per 5 mL, oral

solution did not meet all the bioequivalence criteria when administered under fasted and fed conditions. The results indicate that a high-fat breakfast does not impact the relative bioavailability of hydrocodone and pseudoephedrine, *but* (b) (4)

. For conservative purposes, it may be suitable to recommend that this product be administered on an empty stomach.

2.2.3 Are there any drug-drug interactions between the components of the proposed hydrocodone, pseudoephedrine, and guaifenesin oral solution?

The pharmacokinetic results of study S09-0009 demonstrated that there was no significant interaction observed between the active drug components in (b) (4) combination oral solution containing hydrocodone bitartrate/pseudoephedrine HCl/guaifenesin when compared to reference drugs hydrocodone and pseudoephedrine, *however,* (b) (4)

2.3 Analytical Section

2.3.1 Was the suitability of the analytical method supported by the submitted information?

The drug plasma concentrations were measured using validated bioanalytical methods and according to the Bioanalytical Laboratory's Standard Operating Procedures and FDA Guidelines. The validated detection range was 0.1000 to 50.00 ng/mL for hydrocodone, 2.000 to 500.0 ng/mL for pseudoephedrine, and 5.000 to 1500 ng/mL for guaifenesin in human plasma. Plasma calibration curve standards and QC samples data demonstrated acceptable performance of the assay method during the analysis of the study samples. The accuracy and precision for calibration standards and QCs for HC, GUA, and PSE were acceptable.

3. Labeling Comments

Not applicable. The label is not being reviewed because this submission is considered NOT acceptable from the clinical pharmacology standpoint.

4. Appendices:

A DSI audit has been requested (on August 22, 2010) for the 2 clinical pharmacology studies and it is still pending now.

4.1 Proposed Label:

The proposed label is not being reviewed in this cycle since the agency does not plan to approve the product in this cycle.

4.2 NDA filing and review form:

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	22-279 (resubmission)	Brand Name	Hydrocodone, Pseudoephedrine, Guaifenesin Oral Solution
OCP Division (I, II, III, IV, V)	II	Generic Name	Hydrocodone, Pseudoephedrine, Guaifenesin Oral Solution
Medical Division	DPARP	Drug Class	Cough and cold medicine (b) (4)
OCP Reviewer	Arun Agrawal, Ph.D.	Indication(s)	
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	Oral solution
Pharmacometrics Reviewer		Dosing Regimen	Adults : two (2) teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)
Date of Submission	July 26, 2010	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	(b) (4)
Medical Division Due Date		Priority Classification	S
PDUFA Due Date	January 26, 2011		

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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		Single Dose Bioavailability Study (Study #S09-0009); and Single Dose Relative BA Study Under Fed and Fasted Conditions (Study #S09-0010)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	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:			
	In-vivo effects of primary drug:			
	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:			
	replicate design; single / multi dose:			
Food-drug interaction studies				
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	<input checked="" type="checkbox"/>	2		

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	
3	Has the sponsor submitted bioavailability data satisfying the CFR	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	requirements?				
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

This NDA resubmission filing review is for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution submitted under 505(b)(2) of the FDC Act. This triple combination product is an immediate release solution that contains hydrocodone bitartrate (antitussive), pseudoephedrine

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for

Reference ID: 2681702

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

hydrochloride (nasal decongestant) and guaifenesin (expectorant) at the concentration of 2.5 mg, 30 mg, and 200 mg per 5 mL, respectively. (b) (4) is seeking approval of this cough/cold product for use (b) (4)

The proposed dose in adults (b) (4) is two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)

This NDA is fileable from the clinical pharmacology perspective.

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

This submission is fileable, however, we have identified some potential review issues which should be conveyed to the sponsor. In addition, DSI inspection will be requested and it has been communicated with the project manager.

The following comments should be conveyed to the sponsor:

1. The lower 90% CI for Cmax is not within the acceptance range of 80-125% for guaifenesin of the proposed product when dosed following an overnight fast. In addition, the exposure to guaifenesin of the proposed product does not meet the acceptance criteria (80-125%) under fed versus fasted conditions, indicating a food effect on guaifenesin of the proposed product. Whether these findings are acceptable will be a review issue.
2. In protocol S09-0009 submitted on January 16, 2009, it was mentioned that Hycodan (Endo Pharma) will be used as the reference drug. However, it was not used in this study according to this resubmission. Explain why Hycodan was not used in S09-0009.

<u>Arun Agrawal</u>	Aug 31, 2010
Reviewing Clinical Pharmacologist	Date

<u>Yun Xu</u>	Aug 31, 2010
Team Leader/Supervisor	Date

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

/s/

ARUN K AGRAWAL
12/21/2010

YUN XU
12/28/2010

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-279

Generic Name: Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution

Proprietary Drug Name: Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution

Indication: Cold and Cough medication: antitussive, decongestant, expectorant

Dosage Form: Oral Solution

Strengths: 2.5 mg/30 mg/200 mg per 5 mL

Route of Administration: Oral

Applicant: (b) (4)

OCP Division: Division of Clinical Pharmacology-2

Clinical Division: Division of Pulmonary and Allergy Products (DPAP)

Type of Submission: Original NDA

Submission Date: August 22, 2008

Reviewer: Sandra Suarez Sharp, Ph.D.

Team Leader: Sally Choe, Ph.D.

TABLE OF CONTENTS

ITEM	PAGE NUMBER
1. Executive Summary	2
1.1 Recommendation	2
1.2 Phase IV Commitments	3
1.3 Summary of Clinical Pharmacology Findings	3
2. Question-Based Review	6
2.1 General Attributes	6
2.2 General Biopharmaceutics	13
• BA Study #S070441	13
• Food effect	17
• DDI information	18
3. Labeling Comments	19
4. Appendices	20
Filing Review	20

1. EXECUTIVE SUMMARY

This NDA review is for Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution submitted under 505 (b) (2) of the FDC Act. This triple combination product is an immediate release solution that contains hydrocodone bitartrate (HC) (antitussive), pseudoephedrine hydrochloride (PSE) (nasal decongestant), and guaifenesin (GUA) (expectorant) at the concentration of 2.5 mg, 30 mg, and 200 gm per 5 mL, respectively. (b) (4) is seeking an approval of this cough/cold product for use (b) (4)

(b) (4) he proposed dose in adults and (b) (4) years of age and older is two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)

This submission contains the results of one single dose (10 mL), single arm bioavailability (BA) study (Study #S07-0441) for (b) (4) Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution. It also contains food effect and drug-drug interaction (DDI) information based on journal articles and NDAs for related approved products.

Results of BA Study #S07-0441 showed that the mean systemic exposures (AUC_{inf}) to HC and PSE are higher for the (b) (4) product (92.2 ng*hr/mL and 2636 ng*hr/mL, for HC and PSE, respectively) compared to the data obtained from published literature (77.64 ng*hr/mL and 2109 ng*hr/mL for HC and PSE, respectively). No information was provided on the comparison of GUA AUC since there is no PK data available on the 400 mg dose. The DDI and food effect information included in the present submission based on published information do not support the claim of lack of DDI or food effect of the BA of the proposed product.

On the 74-day letter dated Nov 3, 2008 the sponsor was informed that because the product contains sorbitol, additional clinical pharmacology information (BE study, food effect and DDI information) was needed to support the approval of the proposed product. On January 16, 2009 the sponsor submitted 3 study protocols (a BA/BE study, a DDI study and a Food effect study) to DPAP for comment in response to the 74-day letter. (b) (4) stated, during a telecom with DPAP on February 2009, that it would take about 5 months to complete the studies and submit the reports. The Agency noted that the proposed timeline would extend far beyond the PDUFA date for completion of the review of the application. (b) (4) was reminded that any amendment submitted to the NDA must be received prior to the PDUFA due date, and depending on the time it is submitted, may not be reviewed in this cycle. As of today (April 13, 2009), the results of these studies have not been submitted to the Agency.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 2 (OCP / DCP-2) has reviewed NDA 22-279 submitted on August 22, 2008 and found this NDA NOT acceptable from an OCP standpoint due to lack of key relative bioavailability and/or bioequivalence information as per 505 (b) (2) and CFR 320.25 (g) regulations.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The clinical pharmacology program included in this NDA submission to support the approval of Hydrocodone, Pseudoephedrine, Guaifenesin Oral solution for the relief of symptoms due to the cold and cough consists of the following information:

1. **Study #S07-0441:** “An open-label study to characterize the exposure of hydrocodone, guaifenesin, and pseudoephedrine from a single dose of an oral antitussive, expectorant and decongestant immediate release solution in fasted, healthy, adult subjects”. Subjects received one single dose (10 mL) of the (b) (4) Oral solution equivalent to 5 mg, 60 mg and 400 mg of HC, PSE and GUA, respectively. PK parameters were determined in 18 fasted subjects who received the proposed drug product. Blood samples for PK determination were taken immediately before dosing (0 hours), and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours and analyzed for plasma hydrocodone, pseudoephedrine and guaifenesin (up to 4 hrs only) using a validated LC/MS/MS method. Subjects were confined to the clinic until after the Hour 24 sample was obtained, and returned to the clinic for the hour 36 blood collection. Mean Cmax, Tmax and AUC0-t, AUC0-inf for hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin for the test product were determined using non-compartmental analysis.

This study showed that although the mean HC Cmax value for the (b) (4) Oral Solution was similar to that reported in the literature and related NDAs, the mean systemic exposure (AUCinf) to HC was about (b) (4) than that reported in the literature for similar doses (b) (4) ng*hr/mL vs. 77.64 ng*hr/mL) (Table 1.3.1). In addition, about half of the HC AUCinf individual values were (b) (4) values reported in the literature (range 59.5-93.7 ng*hr/mL). Likewise, the

mean PSE systemic exposure (AUCinf) was about (b) (4) than that reported in the literature (b) (4) ng*hr/mL vs. 2109 ng*hr/mL) for similar PSE doses. In addition, more half of the PSE AUCinf and Cmax individual values were (b) (4) of PSE values reported in the literature (ranges 1800.8-2500 ng*hr/mL for AUCinf and 169.5-236 ng/mL for Cmax) ((Table 1.3.1).

Table 1.3.1: Comparison of PK Parameters (mean, CV) for HC, GUA and PSE from (b) (4) and Published Data

	Hydrocodone			
	Cmax (ng/mL)	AUCinf (ng*hr/mL)	Tmax (hrs)	T1/2 (hrs)
(b) (4)	(b) (4)	(b) (4)	1.67 (0.75-5)	4.39 (19.08)
literature	12.71 (9.1-16.4)	77.64 (59.555-93.7)	1.2 (0.7-1.7)	4.4 (3.5-6.2)
	Pseudoephedrine			
(b) (4)	(b) (4)	(b) (4)	2 (1-8)	5.72 (24.9)
literature	213.2 (169.5-236)	2109 (1800.8-2500)	1.9 (1.5-2.6)	5.4 (4.8-5.9)
	Guaifenesin			
(b) (4)	(b) (4)	(b) (4)	0.5 (0.25-1.67)	0.93 (21.89)
literature	--	--	--	--

No information was provided on the comparison of GUA AUC since there is no PK data available on the 400 mg dose. The sponsor states that the mean GUA Cmax of the test formulation is within the range that would be expected for a 400 mg dose, assuming dose proportionality. The clinical pharmacology review for NDA 21-585¹ showed that the 1200 mg/120 mg strength of Mucinex-D was proportional for both guaifenesin and PSE to the 600 mg/ 60 mg strength of Mucinex-D. Dose normalization of the data provided by (b) (4) shows that the AUCt for their GUA normalized to 1200 mg (7833 ng*hr/mL) is similar to that shown for mucinex 1200 mg (7764 ng*hr/mL).

- Food Effect:** No studies were conducted under this NDA to address the effect of food on the BA of the product. The sponsor claims lack of food effect on the BA of the proposed product based on published information. According to the sponsor, none of these individual drugs (hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin), presently available in liquid dosage forms are documented to have the pharmacokinetic profile affected by food. The sponsor concludes that the immediately available drugs of the oral solution by itself is sufficient to demonstrate that no food effect exists for the proposed drug product.

Although the product is in solution, the product contains sorbitol a substance known to affect the BA of some drugs by changing the gastric emptying time among other effects. This reviewer believes that it may be possible that the presence of sorbitol changes the food-formulation interaction for some formulations resulting in changes in bioavailability, which may be different than that observed for solid dosage forms. For this reason, the sponsor was requested during the 74-day letter of this NDA to address the effect of food on the BA of the proposed product.

¹ Clinical pharmacology review for NDA 21-585 (MucinexD) DFSed by Dr. Sandra Suarez.

3. **DDI Information:** No study was conducted under this NDA to address the potential of DDI between the components of the proposed product. The sponsor believes that the PK results of study S07-044 and its comparability with the published PK on HC, PSE and GUA indicate the absence of DDI. Based on published information, one can conclude that there is no DDI between GUA and PSE as stated under NDA 21-585 (Mucinex-D)¹. The pharmacokinetics of guaifenesin were not affected by the presence of PSE and vice-versa. Ninety percent confidence intervals for the log-transformed PK parameters of guaifenesin (C_{max}, AUC_t, AUC_{inf}) and PSE administered alone (Mucinex or Sudafed) versus the coadministration of the combined products were within goal post for BE. However, there is not data in the public domain that indicate the lack of effect of PSE and GUA on the PK of HC. A cross study comparison of the PK of HC to determine the lack of DDI as proposed by the sponsor is not appropriate due to a confounding potential formulation effect. For this reason, the sponsor was requested to conduct a BE study comparing the proposed product to the monoproducts in a 3 way cross-over study.

Conclusion

The biopharmaceutics information included in the present submission is not sufficient to support the approval of this 505 (b) (2) application which relies exclusively on the active ingredients systemic exposure to bridge the efficacy and safety of previously approved related products for the following reasons:

- The product contains sorbitol (b) (4)% w/v (compared to (b) (4)% for discontinued RLD Hycodan). Sorbitol has been found to affect the BA of several compounds (especially those with low permeability) in a dose-proportional manner². Sorbitol is a polyalcoholic sugar with osmotic cathartic actions poorly absorbed into the systemic circulation. It is used as a hyperosmotic laxative at the doses of 30-150 mL (70% solution) in adults and adolescent 11 year of age and older³. Sorbitol is known to change (decreased) the gastric emptying time^{4,5} and change the critical micellar concentrations of some substances⁶. Because the permeability of HC, PSE, or GUA is not known, the need for BA/BE studies, including food effect studies for solutions containing sorbitol, is warranted.
- This submission is not compliant with the 21 CFR regulation for combinations products (320.25 g) which states the following: “the purpose of an in vivo BA study involving a combination drug product is to determine if the rate and extent of absorption of each active ingredient in the combination product is *equivalent* to the rate and extend of absorption of each active drug ingredient administered concurrently in separate single ingredient preparations”.

² Chen, ML, et al. A modern view of excipient effects on bioequivalence: case study of sorbitol. Pharm Res. 2007 Jan;24(1):73-80

³ <http://www.umm.edu/altmed/drugs/sorbitol>

⁴ J.H. Reed and D.E. Kidder. The effect of glucose, galactose and sorbitol on gastric emptying in the young pig. Quarterly Journal of Experimental Physiology (1972) 57, 30-36

⁵ B.K. Adams et al. The effects of sorbitol on gastric emptying half-times and small intestinal transit after drug overdose. Am. J. of Emergency Medicine. Vol. 24:1 pages 130-132.

⁶ M. Ueda et. al. Effect of sorbitol and inositol on the critical micelle concentration of nonionic surfactants in water and in aqueous urea. Colloid and polymer Science. (1979) Vol 257:9, pages 973-976.

- This submission is not compliant with 21 CFR Subpart A-General Provisions 330.1 (e) which states that “an over-the-counter (OTC) drug listed in this subchapter is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this part and *each* of the conditions contained in any applicable monograph. Any product which fails to conform to *each* of the conditions contained in this part and in an applicable monograph is liable to regulatory action”.

“e. The product contains *only suitable inactive ingredients* which are safe in the amounts administered and *do not interfere with the effectiveness* of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity”. Because the product contains sorbitol, this reviewer is of the opinion that the relative BA or BE of monograph ingredients in the proposed product should be established.

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Introduction

Hydrocodone is approved in various forms and in combination with other drugs as a narcotic analgesic and as an antitussive. HC was not included in the OTC Monograph process and is available on a prescription only basis (Rx Only). The safety and effectiveness of HC as a prescription drug for the relief of cough are supported by DESI review and by the FDA approval of Hycodan (NDA 5213) (recently discontinued). HC is an opioid, a schedule II controlled substance as a single ingredient (21 CFR 1308.12), a schedule III controlled substance if in combination with active nonnarcotic ingredients and if the product contains not more than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit (21 CFR 1308.13), and a prescription drug product (21 CFR 1306.15). HC, a schedule controlled substance and a prescription drug, is not an OTC monograph antitussive. Therefore, the proposed combinations of HC/PSE/GU is not in compliance with the OTC monograph (21CFR 341.40), and clinical studies would normally be required to provide the evidence of safety and efficacy of the proposed products as the regulation requires (21CFR 300.50). However, there is a regulatory precedent regarding the combination of HC with an OTC monograph product (refer to Medical Officer Review, IND 74,684, Charles E. Lee, M.D., 9/25/2006). Based on Dr. Lee’s review, the FDA has previously determined that clinical studies are not necessary for the combination of HC and a permitted OTC monograph ingredient. Considering this policy, the Division has approved drug development programs for HC and OTC monograph product combinations, concluding that a drug development plan does not need to establish the efficacy, safety, or the contribution of HC or an OTC monograph ingredient to the efficacy and safety of the combination product.

NDA 21-282 for Mucinex® Guaifenesin ER Tablets 600 mg and 1200 mg was approved July 12, 2002. This approval was based on pharmacokinetic studies only; neither preclinical nor toxicological studies were required. 21 CFR§341.78(b) states that the labeling of a product containing Guaifenesin must state, "under the heading "Indications," the following: "Helps loosen phlegm (mucus) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive"). 21CFR§341.40, as per the final rule issued by FDA on December 23,

2004, allows the combination of any single antitussive ingredient and any single expectorant ingredient. The dose of GUA in the proposed product is within OTC monograph specifications.

PSE is generally recognized as safe and effective in over-the counter (OTC) allergy products at doses of: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours for adults and children 12 years of age and over. For children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

Present Submission

The Division agreed during a face-to face meeting held on March 26, 2007 (preIND 76,365 meeting) that the sponsor could perform a small single arm bioavailability study in fasted normal subjects on the test product as the basis of approval along with supporting published information on DDI and food effect to establish a clinical link. The DPAP stated that Tussionex (NDA 19-111, approved 12/31/1987, a polistirex extended release suspension containing 10 mg hydrocodone polistirex per 5 mL) would be the most recently approved NDA, and would contain the most appropriate hydrocodone information to reference in a 505(b)(2) NDA. In addition, the NDA for Hycodan (NDA 05-213, approved 7/26/1988, immediate release tablets and syrup containing hydrocodone bitartrate 5 mg per tablet or 5 mL, homatropine methylbromide 1.5 mg, per tablet or 5 mL) would also be an appropriate reference product.

NDA 22-279 for Hydrocodone, Guaifenesin, and Pseudoephedrine Oral Solution was submitted to the Agency on Aug 22, 2008 through the 505 b (2) route. A preliminary assessment on the pharmacokinetic data included in the NDA resulted on several issues which were conveyed to the sponsor during the 74-day letter (see filing letter dated 11/03/08) issues as follows:

- We have conducted a preliminary assessment on the pharmacokinetic data included in your NDA as supporting information to link the efficacy and safety of your product to related approved products and found the following limitations:
 - We notice that your product contains sorbitol. Sorbitol has been found to affect the bioavailability (BA) of some compounds with low permeability in a dose-proportional manner. Therefore, we recommend that you conduct an in vivo study in which bioequivalence (BE) is established with respect to each active component of your product.
 - We also notice that your program does not address for a potential formulation effect. Section 21 (320.25)(g) of the CFR states that the purpose of an in vivo BA study involving a combination drug product is to determine if the rate and extent of absorption of each active ingredient in the combination product is equivalent to the rate and extent of absorption of each active drug ingredient administered concurrently in separate single ingredient preparations.
 - To address these issues, you may choose to follow the designs proposed in Table 1 or Table 2. The design in Table 1 is recommended assuming that there is a lack of drug-drug interaction (DDI) between the active ingredients. The proposed

design in Table 2 also addresses for potential of DDI and formulation effect in addition to bioequivalence.

Table 1. Proposed PK study design

ARM	BE Study
(b) (4) Oral Solution	√
Hycodan+GUA*+PSE*	√
Number of groups in crossover	2

*OTC products not containing sorbitol .

Table 2. Proposed PK study design

ARM	BE Study
(b) (4) Oral Solution	√
Hycodan	√
Hycodan+GUA*+PSE*	√
PSE*+ GUA*	√
Number of groups in crossover	4

*OTC products not containing sorbitol .

- You need to apply the appropriate statistical analysis to the proposed 4 way-crossover study design.
- In addition, you need to conduct an in vivo study to determine the effect of food on the bioavailability of (b) (4) Oral Solution's active ingredients for the same reason above stated. An equivalence approach is recommended for food-effect BA studies (refer to Guidance for industry: food-effect bioavailability and fed bioequivalence studies). The food effect may be assessed as part of the above mentioned studies.
- The claim of lack of drug-drug interaction effect (DDI) based on the supporting literature information you provided will be a review issue.
- As shown in Tables 1 and 2, the recommended reference products are Hycodan, Guaifenesin and Pseudoephedrine OTC oral solution products not containing sorbitol.

In response to the 74-day letter the sponsor submitted 3 study protocols (a BA/BE study, a DDI study and a Food effect study) to DPAP on January 16, 2009 for comment as follows:

1. **Study Protocol S09-0008:** A relative bioavailability study of Hydrocodone 5 mg/Guaifenesin 400 mg/Pseudoephedrine 60 mg oral solution under fasting conditions.

This study is a randomized, single-dose, two-way open-label crossover study. Subjects (40 healthy volunteers) are to be randomized to the following treatments under fasting (over night) conditions:

A (Test Product): One 10 mL oral solution dose containing HC 2.5 mg / GUA 200 mg / PSE 30 mg per 5 mL ((b) (4))

B (Reference Product): One 5 mL oral solution dose of Hycodan (Endo Pharmaceuticals) containing 5 mg of HC, and one 20 mL oral solution dose of Robitussin Chest Congestion (Wyeth Consumer Health Inc.) containing 100 mg GUA per 5 mL, and one 10 mL oral solution dose of PSE containing 30 mg per 5 mL.

2. **Study Protocol S09-0009:** A Drug-Drug Interaction Study of Hydrocodone 5 mg/Guaifenesin 400 mg/Pseudoephedrine 60 mg oral solution.

This study is a randomized, single-dose, three-way open-label crossover study. Subjects (24 healthy volunteers) are to be randomized to the following treatments under fasting (over night) conditions:

Treatment A: One 5 mL oral solution dose of Hycodan (Endo Pharmaceuticals) containing **5 mg of HC** and one 20 mL oral solution dose of Robitussin Chest Congestion (Wyeth Consumer Health Inc.) containing 100 mg GUA per 5 mL (**GUA 400 mg**) and one 10 mL oral solution dose of PSE containing 30 mg per 5 mL (**PSE 60 mg**) given as a single dose with approximately 240 mL of room temperature water after an overnight fast of at least 10 hours.

Treatment B: One 5 mL oral solution dose of Hycodan (Endo Pharmaceuticals) containing **5 mg of HC** given as a single dose with approximately 240 mL of room temperature water after an overnight fast of at least 10 hours.

Treatment C: one 20 mL oral solution dose of Robitussin Chest Congestion (Wyeth Consumer Health Inc.) containing 100 mg GUA per 5 mL (**GUA 400 mg**) and one 10 mL oral solution dose of PSE containing 30 mg per 5 mL (**PSE 60 mg**) given as a single dose with approximately 240 mL of room temperature water after an overnight fast of at least 10 hours

3. **Study Protocol S09-0010:** A Food Effect Study of Hydrocodone 5 mg/Guaifenesin 400 mg/Pseudoephedrine 60 mg oral solution under fasting conditions.

This study is a randomized, single-dose, two-way open-label crossover study under fed and fasted conditions. Subjects (18 healthy volunteers) are to be randomized to the following:

A (Test Product): One 10 mL oral solution dose containing HC 2.5 mg / GUA 200 mg / PSE 30 mg per 5 mL ((b) (4)) given as a single dose with approximately 240 mL of room temperature water 30 minutes after initiation of a standardized, high-fat and high-calorie meal preceded by an overnight fast of at least 10 hours. (Total Dose = Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg)

B (Reference Product): One 10 mL oral solution dose containing HC 2.5 mg / GUA 200 mg / PSE 30 mg per 5 mL ((b) (4)) given as a single dose with approximately 240 mL of room temperature water after an overnight fast of at least 10 hours. (Total Dose = Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg)

Upon review of these protocols the following comment was conveyed to the sponsor via fax on January 27, 2009: “We recommend that you replace treatment A from study S09-0009 with an arm containing the product under investigation (Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution, (b) (4) Oral Solution). The purpose of this substitution/inclusion is to allow a direct comparison of Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution ((b) (4)) to the approved product containing hydrocodone (Hycodan). Under these conditions, study S09-008 will no longer be necessary”.

During a teleconference meeting that took place on February 2009, (b) (4) stated that it would take about 5 months to complete the studies and submit the reports. The Agency noted that the proposed timeline would extend far beyond the PDUFA date for completion of the review of the application. (b) (4) was reminded that any amendment submitted to the NDA must be received prior to the PDUFA due date, and depending on the time it is submitted, may not be reviewed in this cycle. As of today (April 13, 2009), the results of these studies have not been submitted to the Agency.

2.1.2 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Guaifenesin is 1,2-Propanediol, 3-(2-methoxyphenoxy)-, (±)-; (b) (4) and has the following chemical structure: C10H14O4 and MW=198.22.

Pseudoephedrine Hydrochloride is Benzenemethanol, a-(1-(methylamino) ethyl)-, (S-(R*,R*))-, hydrochloride and has the following chemical structure: C10H15NO. HCl and MW=201.69.

Hydrocodone Bitartrate is Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (50α)-, (R-(R*,R*)))-2,3-dihydroxybutanedioate (1:1), hydrate (2:5); also known as 4, (b) (4) α-Epoxy-3-methoxy-17-methylmorphinan-6-one tarate (1:1) hydrate (2:5), and has the following MW: 494.490. It is a fine white (b) (4) powder. (b) (4)

(b) (4) Inc. is seeking a market approval for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution indicated (b) (4)

The product will be available in 16 ounce high density polyethylene bottles. The components and composition for Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution is summarized in Table 2.1.2.1.

Table 2.1.2.1: Components and composition for Hydrocodone, Pseudoephedrine, and Guaifenesin Oral Solution

% w/v	mg/5mL	Ingredient	Function	g per Liter
0.050	2.5	Hydrocodone Bitartrate USP	Active Ingredient	0.500
4.000	200.0	Guaifenesin USP	Active Ingredient	40.00
0.600	30.0	Pseudoephedrine Hydrochloride USP	Active Ingredient	6.00
(b) (4)		Sorbitol (b) (4) USP		(b) (4)
		Glycerin USP		
		Polyethylene Glycol (b) (4) NF		
		Methylparaben NF		
		Propylparaben NF		
		Citric Acid (b) (4) USP		
		Sodium Citrate (b) (4) USP		
		Saccharin Sodium		
		D & C Red #33		
		FD & C Blue #1		
		(b) (4) Black Raspberry Flavor (b) (4)		
		Purified Water USP		

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Hydrocodone bitartrate is available on a prescription only basis (Rx Only). It is approved in various forms and in combination with other drugs as a narcotic analgesic and as an antitussive.

Guaifenesin is a monograph. 21 CFR§341.78(b) states that the labeling of a product containing Guaifenesin must state, "under the heading "Indications" the following: "Helps loosen phlegm (mucus) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive")."

Pseudoephedrine is a sympathomimetic amine commonly used as a decongestant. PSE acts directly on alpha-adrenergic receptors and to a lesser extent on beta-adrenergic receptors. Like ephedrine, PSE also has an indirect effect by releasing norepinephrine from its storage sites. PSE acts directly on alpha-adrenergic receptors in the mucosa of the respiratory tract producing vasoconstriction which results in shrinkage of swollen nasal mucous membranes, reduction of tissue hyperemia, edema, and nasal congestion, and an increase in nasal airway patency.

INDICATION, DOSAGE AND ADMINISTRATION (as per proposed labeling for the carton)

The usual antitussive dose of hydrocodone bitartrate is 5 mg every 4 to 6 hours as needed. The approved doses are:

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

Children 6 to 12 years of age: One-half (1/2) tablet or one-half (1/2) teaspoonful of the syrup (2.5 mg HC) every 4 to 6 hours as needed; NTE 3 tablets or 3 teaspoonfuls (15 mg HC) in 24 hours.

Children less than 6 years of age: The administration of hydrocodone in children less than 6 years of age due to the risk of respiratory depression [Reference to NDA 19-111, Tussionex Pennkinetic labeling].

Guaifenesin is a monograph. Directions for products containing guaifenesin identified in 341.18 is as follows: Adults and children 12 years of age and over: oral dosage is 200 to 400 milligrams every 4 hours not to exceed 2,400 milligrams in 24 hours. Children 6 to under 12 years of age: oral dosage is 100 to 200 milligrams every 4 hours not to exceed 1,200 milligrams in 24 hours."

PSE is generally recognized as safe and effective in over-the counter (OTC) allergy products at doses of: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours for Adults and children 12 years of age and over. For Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

The following tables provide a summary of the proposed and maximum doses permitted for HC, GUA and PSE.

Adults (b) (4) :

	Per Dose	Per 24 Hours	Maximum Amount Permitted
Hydrocodone Bitartrate	5 mg	20 mg	20-30 mg
Pseudoephedrine Hydrochloride	60 mg	240 mg	240 mg
Guaifenesin	400 mg	1600 mg	2400 mg



2.2 General Biopharmaceutics

2.2.1 Was Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution bioequivalent to the reference products?

No bioequivalence studies or relative bioavailability studies were conducted to support the approval of this NDA. However, this submission includes the results of one single dose, single arm bioavailability study (Study #S07-0441) for (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution.

Study #S07-0441 was a single-dose bioavailability study conducted in healthy volunteers. PK parameters were determined for 18 fasted subjects who received the proposed drug product. Blood samples for PK determination were taken immediately before dosing (0 hours), and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours and analyzed for plasma hydrocodone, pseudoephedrine and guaifenesin (up to 4 hrs only) using a validated LC/MS/MS method. Subjects were confined to the clinic until after the Hour 24 sample was obtained, and returned to the clinic for the Hour 36 blood collection. Mean C_{max}, T_{max}, AUC_{0-t}, and AUC_{0-inf} for hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin for the test product were determined using non-compartmental analysis. The parameter T_{max} was analyzed using nonparametric methods.

Figures 2.2.1.1 to 2.2.1.3 show box plots for the individual C_{max} and AUC_{inf} for HC, PSE, and GUA, respectively following single dose administration (10 mL) of (b) (4) Oral Solution. Tables 2.2.1.1 to 2.2.1.3 summarize PK parameters for the three active ingredients following administration of (b) (4) Oral Solution. This study showed that although the mean HC C_{max} value was similar to that reported in the literature, the mean systemic exposure (AUC_{inf}) to HC was about (b) (4) than that reported in the literature for similar HC doses (b) (4) ng*hr/mL vs. 77.64 ng*hr/mL). Likewise, the mean PSE systemic exposure (AUC_{inf}) was about (b) (4) than that reported in the literature (b) (4) ng*hr/mL vs. 2109 ng*hr/mL) (Table 2.2.1.2) for similar PSE doses. For guaifenesin, there is no documented pharmacokinetic data for the 400 mg dose (see Comparison of Individual PK Parameter Data to Published Data Section below).

Figure 2.2.1.1 illustrates that half of the HC AUC_{inf} individual values were (b) (4) AUC_{inf} values reported in the literature (range 59.5-93.7 ng*hr/mL). Likewise, Figure 2.2.1.2 shows that that half of the PSE AUC_{inf} and C_{max} individual values (b) (4) PSE values reported in the literature (ranges 1800.8-2500 ng*hr/mL for AUC_{inf} and 169.5-236 ng/mL for C_{max}).

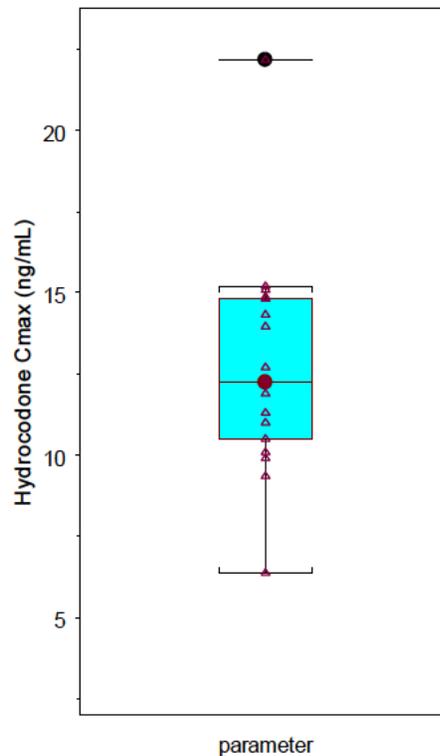


Figure 2.2.1.1. Box plots for the individual Cmax and AUCinf for HC following single dose administration of (b) (4) Oral Solution: Hydrocodone, Guaifenesin, and Pseudoephedrine Oral Solution.

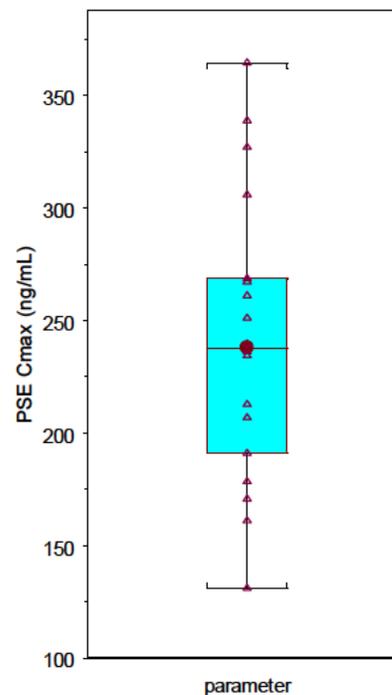
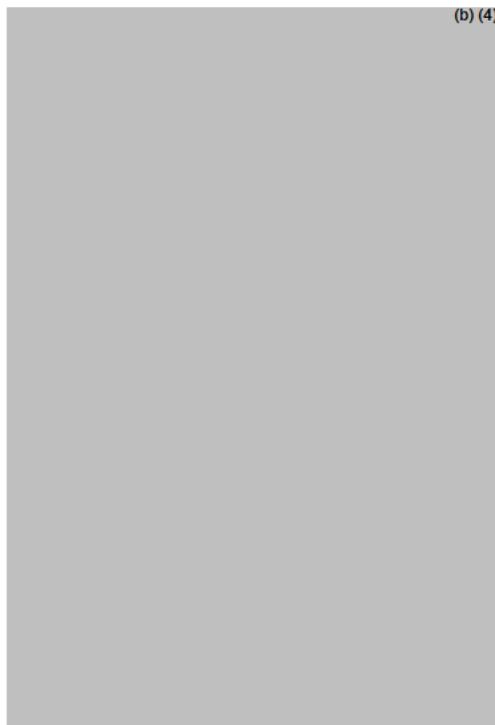


Figure 2.2.1.2. Box plots for the individual Cmax and AUCinf for PSE following single dose administration of (b) (4) Oral Solution: Hydrocodone, Guaifenesin, and Pseudoephedrine Oral Solution.

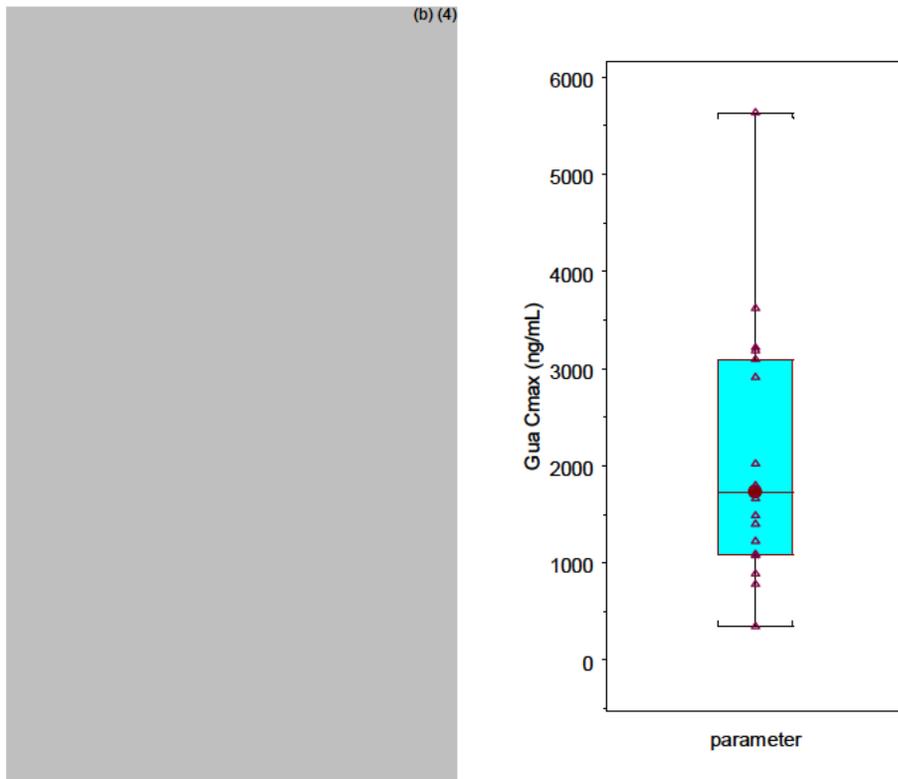


Figure 2.2.1.3. Box plots for the individual Cmax and AUCinf for GUA following single dose administration of (b) (4) Oral Solution: Hydrocodone, Guaifenesin, and Pseudoephedrine Oral Solution.

Table 2.2.1.1. PK parameters for HC following single dose administration of Hydrocodone, Guaifenesin, and Pseudoephedrine Oral Solution.

	AUCt (ngxhr/mL)	AUCinf (ngxhr/mL)	Cmax (ng/mL)	Tmax (hr)	Half-Life (hr)
Mean	(b) (4)			1.7694	4.3903
SD	(b) (4)			0.9854	0.8378
Median	(b) (4)			1.67	4.096
Min	(b) (4)			0.75	3.331
Max	(b) (4)			5	6.318
CV (%)	(b) (4)			55.6916	19.0821

Table 2.2.1.2. PK parameters for PSE following single dose administration of Hydrocodone, Guaifenesin, and Pseudoephedrine Oral Solution.

	AUCt (ngxh/mL)	AUCinf (ngxh/mL)	Cmax (ng/mL)	Tmax (h)	Half-Life (h)
Mean	(b) (4)			2.3344	5.7182
SD	(b) (4)			1.5423	1.3889
Median	(b) (4)			2	5.2325
Min	(b) (4)			1	3.938
Max	(b) (4)			8	9.129
CV (%)	(b) (4)			66.0654	24.2895

Table 2.2.1.3. PK parameters for GUA following single dose administration of Hydrocodone, Guaifenesin, and Pseudoephedrine Oral Solution.

	AUCt (ngxh/mL)	AUCinf (ngxh/mL)	Cmax (ng/mL)	Tmax (h)	Half-Life (h)
Mean	(b) (4)			0.5139	0.9317
SD	(b) (4)			0.3923	0.2039
Median	(b) (4)			0.5	0.9221
Min	(b) (4)			0.25	0.6922
Max	(b) (4)			1.67	1.52
CV (%)	(b) (4)			76.3473	21.8880

Comparison of Individual PK Parameter Data to Published Data

The sponsor conducted a cross-study comparison of the public available (journal articles, Canadian product label, US product label and FOI NDA information) on Hydrocodone 5mg, Pseudoephedrine 60 mg and Guaifenesin 400 mg. The pharmacokinetic parameters (mean (CV%)) obtained for each individual drug from the study along with the mean and range of values (if available) from the literature are shown in Table 2.2.1.4.

Table 2.2.1.4. Comparison of PK Parameters for HC, GUA and PSE from (b) (4) product to Published

	Hydrocodone				
	Cmax (ng/mL)	AUCinf (ng*hr/mL)	Tmax (hrs)	T1/2 (hrs)	
(b) (4)	(b) (4)			1.67 (0.75-5)	4.39 (19.08)
literature	12.71 (9.1-16.4)	77.64 (59.5-93.7)	1.2 (0.7-1.7)	4.4 (3.5-6.2)	
	Pseudoephedrine				
	Cmax (ng/mL)	AUCinf (ng*hr/mL)	Tmax (hrs)	T1/2 (hrs)	
(b) (4)	(b) (4)			2 (1-8)	5.72 (24.9)
literature	213.2 (169.5-236)	2109 (1800.8-2500)	1.9 (1.5-2.6)	5.4 (4.8-5.9)	
	Guaifenesin				
	Cmax (ng/mL)	AUCinf (ng*hr/mL)	Tmax (hrs)	T1/2 (hrs)	
(b) (4)	(b) (4)			0.5 (0.25-1.67)	0.93 (21.89)
literature	--	--	--	--	

This data showed that the mean systemic exposure (AUCinf) to HC and PSE (b) (4) for the (b) (4) product ((b) (4) ng*hr/mL and (b) (4) ng*hr/mL, for HC and PSE, respectively) compared to the data obtained from published literature (77.64 ng*hr/mL and 2109 ng*hr/mL for HC and PSE, respectively).

For guaifenesin, there is no documented pharmacokinetic data for the 400 mg dose. The sponsor states that the mean C_{max} of the test formulation is within the range that would be expected for a 400 mg dose, assuming dose proportionality. The clinical pharmacology review for NDA 21-585 showed that the 1200 mg/120mg strength of Mucinex-D was proportional for both guaifenesin and PSE to the 600 mg/ 60mg strength of Mucinex-D. Dose normalization of the data provided by (b) (4) shows that the AUC_t for their GUA normalized to 1200 mg (7833 ng*hr/mL) is similar to that shown for mucinex 1200 mg (7764 ng*hr/mL) (Table 2.2.1.5).

Table 2.2.1.5. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following single administration of the treatments (data taken from NDA 21-585)

Treatment	Mean (SD) PK Parameters				
	C _{max} (ng/mL)		AUC _t (ng*hr/mL)	AUC _{inf} (ng*hr/mL)	T _{1/2} (hr)
Guaifenesin					
TRT A	1940 (889)	0.77 (0.22)	7764 (3329)	8061 (3329)	4.74 (4.13)
TRT B	1813 (900)	1.04 (0.49)	8002 (3677)	8124 (3677)	2.21 (1.19)
TRT C	920 (481)	0.99 (0.46)	3529 (1437)	3565 (1442)	1.76 (0.92)
Pseudoephedrine					
TRT A	250 (53.4)	6.9 (1.76)	3479 (805)	3847 (910)	5.8 (1.02)
TRT B	263 (58.5)	5.11 (1.78)	3591 (824)	3650	5.2 (0.9)
TRT C	141 (30.3)	4.9 (1.6)	1781 (445)	1968 (477)	5.6 (1.02)

TRT A: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour; TRT B: 1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation, and TRT C: 600mg guaifenesin and 60 mg pseudoephedrine hydrochloride formulation.

2.2.2 What is the effect of food on the BA of HC, GUA and PSE from following administration of the proposed product?

No studies were conducted under this NDA to address the effect of food on the BA of the product. The sponsor claims lack of food effect on the BA of the proposed product based on published information. According to the sponsor, drugs in the proposed Oral Solution are presently commercially available in various dosage forms, i.e., tablets, liquids, liquigels, capsules, caplets, etc. and none of these individual drugs (hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin), presently available in liquid dosage forms, are documented to have the pharmacokinetic profile affected by food. The sponsor concludes that the immediately available drugs of the oral solution by itself is sufficient to demonstrate that no food effect exists for the proposed drug product. Contrary to the sponsor's conclusions on lack of food effect in any of the component of the proposed product, a food effect study for Mucinex-D¹ showed that a high-fat and high-caloric meal decreased the C_{max} and AUC_{inf} of guaifenesin by (b) (4)%, respectively.

Although the product is in solution, the product contains sorbitol, a substance known to affect the BA of some drugs by changing the gastric emptying time among other effects. This reviewer believes that it may be possible that the presence of sorbitol changes the food-formulation interaction for some formulations resulting in changes in bioavailability, which may be different than that observed for solid dosage forms. For this reason, the sponsor was requested during the 74-day letter of this NDA to address the effect of food on the BA of the proposed product.

2.3 Are there any drug-drug interactions between the components of the proposed Hydrocodone, pseudoephedrine, and Guaifenesin Oral Solution?

No study was conducted under this NDA to address the potential of DDI among the components of the proposed product. The sponsor believes that the PK results of study S07-044 and its comparability with the published PK on HC, PSE, and GUA indicate the absence of DDI. Published PK parameters considered for comparison comprised of products containing the drug in combination with other drug entities and the single agent drug product, where applicable.

Based on published information, one can conclude that there is no DDI between GUA and PSE as illustrated in the following example: The possible DDI between guaifenesin and PSE was addressed in a single dose, 3-way crossover study under NDA 21-585 (Mucinex-D)¹. The pharmacokinetics of guaifenesin were not affected by the presence of PSE and vice-versa. Ninety percent confidence intervals for the log-transformed PK parameters of guaifenesin (C_{max}, AUC_t, AUC_{inf}) and PSE administered alone (Mucinex or Sudafed) versus the coadministration of the combined products were within goal post for BE (Table 2.3.1).

Table 2.3.1. Point estimates and 90% confidence intervals for the log-transformed C_{max} and AUC_{inf} values of guaifenesin and PSE following single administration of the treatments (Data taken from reference 1)

Treatment*	PK parameter	Point estimates	90% confidence intervals
Guaifenesin			
TRT C/ TRT A	C _{max}	97.8	90.2-106
	AUC _t	100	94.3-104
	AUC _{inf}	98.4	93.6-103
Pseudoephedrine			
TRT C/ TRT B	C _{max}	97.6	94.2-101
	AUC _t	97.4	94-101
	AUC _{inf}	97.3	93.5-101

TRT A; 1200 mg guaifenesin (Mucinex); TRT B; 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour and TRT C: 1200 mg guaifenesin (Mucinex) and 120mg of pseudoephedrine hydrochloride (Sudafed).

There is no data in the public domain that indicate the lack of effect of PSE and GUA on the PK of HC. A cross study comparison of the PK of HC to determine the lack of DDI as proposed by the sponsor is not appropriate due to a confounding potential formulation effect. For this reason, the sponsor was requested to conduct a BE study comparing the proposed product to the monoproducts in a 3 way cross-over study.

2.4 Analytical Section

2.4.1 Was the suitability of the analytical method supported by the submitted information?

Yes. Plasma calibration curve standards and QC samples data demonstrated acceptable performance of the assay method during the analysis of the study samples. The accuracy and precision for calibration standards and QCs for HC, GUA, and PSE were acceptable for (<10% Diff or %CV) for in-study validation information All the subjects samples showed acceptable chromatograms. The lower limit of quantitation (LLOQ) were 5 ng/mL, 2 ng/mL, and 0.1 ng/mL for guaifenesin, pseudoephedrine, and hydrocodone, respectively.

3. Labeling Comments

There are no labeling comments to the proposed labeling for this product since it is considered NOT acceptable from a clinical pharmacology standpoint.

4. Appendix: Filing Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology Tracking/Action Sheet for Formal/Informal Consults	
From: Sandra Suarez-Sharp		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission	
DATE OF SUBMISSION: August 22, 2008	NDA No.: 22-279 Serial No.:	BLA No.	DATE OF REVIEW: Sep 29, 2008
NAME OF DRUG: Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution	PRIORITY CONSIDERATION: S or P	Date of informal/Formal Consult: Sep 09, 2008	
NAME OF THE SPONSOR: (b) (4)			
TYPE OF SUBMISSION CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE			
<input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> SAFETY PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN <input type="checkbox"/> CONSULT <input type="checkbox"/> PK/PD- POP PK ISSUES <input type="checkbox"/> PHASE IV RELATED			
<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE			
<input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <i>NDA Filing Review</i>			
REVIEW ACTION			
<input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)			
<input type="checkbox"/> Oral communication with Name: [] <input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: []			
<input checked="" type="checkbox"/> Formal Review/Memo (attached) <input checked="" type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (SPECIFY BELOW): [Please see attached memo]			
REVIEW COMMENT(S)			
<input checked="" type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR			
COMMENTS/SPECIAL INSTRUCTIONS: Executive Summary This NDA filing review is for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution submitted under 505 (b) (2) of the FDC Act. This triple combination product is an immediate release solution that contains hydrocodone bitartrate (antitussive), pseudoephedrine hydrochloride (nasal decongestant) and guaifenesin (expectorant) at the concentration of 2.5 mg, 30 mg, and 200 gm per 5 mL, respectively.			

(b) (4) is seeking approval of this cough/cold product (b) (4)

The proposed dose in adults and (b) (4) years of age and older is two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)

This submission contains the results of one single dose, single arm bioavailability study for (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. It also contains food effect and drug-drug interaction potential information based on journal articles and related approved products.

According to the sponsor, the bioavailability study in this application confirmed the bioavailability of the drug product in comparison to similar approved immediate release drug products containing the active ingredients. In addition, it seems that the PK parameter data demonstrated that the pharmacokinetics were not affected by the presence of one another. The sponsor states that the reference information indicates that the drugs in the proposed oral solution product are not affected by the administration of food.

A preliminary assessment of the data shows that the mean systemic exposure (AUC_{inf}) to HC and PSE (b) (4) (b) (4) for the (b) (4) product (b) (4) ng*hr/mL and (b) (4) ng*hr/mL, for HC and PSE, respectively) compared to the data obtained from published literature (77.64 ng*hr/mL and 2109 ng*hr/mL for HC and PSE, respectively). No information was provided on the AUC of GUA.

The Division agreed during a face-to face meeting held on Mach 26, 2007 that the sponsor could perform a small single arm bioavailability study in fasted normal subjects on the test product as the bases of approval along with supporting published information on DDI and food effect to establish a clinical link. This reviewer believes that because the product contains sorbitol, the regulatory requirements for an immediate release oral solution are more stringent than those for oral solution not containing “problem” inactive ingredients such as sorbitol. In other words, the approval of this drug should rely on demonstration of bioequivalence between the proposed product and the corresponding approved monoproducts as well as on assessment of food effect on the PK of all the active ingredients.

This NDA is fileable from a clinical pharmacology standpoint. The following comments have been conveyed to the sponsor during a telecon that took place on October 27, 2008. These comments should also be conveyed to the sponsor as part of the 74-day letter:

- We have conducted a preliminary assessment on the pharmacokinetic data included in your NDA as supporting information to link the efficacy and safety of your product to related approved products and found the following limitations:
 - We notice that your product contains sorbitol. Sorbitol has been found to affect the bioavailability (BA) of some compounds with low permeability in a dose-proportional manner. Therefore, we recommend that you conduct an in vivo study in which bioequivalence (BE) is established with respect to each active component of your product.
 - We also notice that your program does not address for a potential formulation effect. Section 21 (320.25)(g) of the CFR states that the purpose of an in vivo BA study involving a

combination drug product is to determine if the rate and extent of absorption of each active ingredient in the combination product is equivalent to the rate and extent of absorption of each active drug ingredient administered concurrently in separate single ingredient preparations.

- To address these issues, you may choose to follow the designs proposed in Table 1 or Table 2. The design in Table 1 is recommended assuming that there is a lack of drug-drug interaction (DDI) between the active ingredients. The proposed design in Table 2 also addresses for potential of DDI and formulation effect in addition to bioequivalence.

Table 1. Proposed PK study design

ARM	BE Study
(b) (4) Oral Solution	√
Hycodan+GUA*+PSE*	√
Number of groups in crossover	2

*OTC products not containing sorbitol .

Table 2. Proposed PK study design

ARM	BE Study
(b) (4) Oral Solution	√
Hycodan	√
Hycodan+GUA*+PSE*	√
PSE*+ GUA*	√
Number of groups in crossover	4

*OTC products not containing sorbitol .

- You need to apply the appropriate statistical analysis to the proposed 4 way-crossover study design.
- In addition, you need to conduct an in vivo study to determine the effect of food on the bioavailability of (b) (4) Oral Solution's active ingredients for the same reason above stated. An equivalence approach is recommended for food-effect BA studies (refer to Guidance for industry: food-effect bioavailability and fed bioequivalence studies). The food effect may be assessed as part of the above mentioned studies.
- The claim of lack of drug-drug interaction effect (DDI) based on the supporting literature information you provided will be a review issue.
- As shown in Tables 1 and 2, the recommended reference products are Hycodan, Guaifenesin

21CFR§341.40, as per the final rule issued by FDA on December 23, 2004, allows the combination of any single antitussive ingredient and any single expectorant ingredient. The dose of GUA is within OTC monograph specifications.

PSE is generally recognized as safe and effective in over-the counter (OTC) allergy products (1) at doses of: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours for Adults and children 12 years of age and over. For Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

This submission contains the results of one single dose, single arm bioavailability study for (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. It also contains food effect and drug-drug interaction potential information based on journal articles and related approved products.

Single Dose Bioavailability Study (Study #S07-0441)

This was a single-dose bioavailability study conducted in healthy volunteers. PK parameters were determined for 18 fasted subjects who received the proposed drug product. Blood samples for PK determination were taken immediately before dosing (0 hours), and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours and analyzed for plasma hydrocodone, pseudoephedrine and guaifenesin (up to 4 hrs only). Subjects were confined to the clinic until after the Hour 24 sample was obtained, and returned to the clinic for the hour 36 blood collection. Mean Cmax, Tmax and AUC0-t, AUC0-inf for Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin for the test product were determined using non-compartmental analysis. The parameter Tmax was analyzed using nonparametric methods.

The tables below show the results of the PK parameters for the three active ingredients.

Hydrocodone Bitartrate

	AUCt (ng×hr/mL)	AUCinf (ng×hr/mL)	Cmax (ng/mL)	Tmax (hr)	Half-Life (hr)
Mean	(b) (4)			1.7694	4.3903
SD	(b) (4)			0.9854	0.8378
Median	(b) (4)			1.67	4.096
Min	(b) (4)			0.75	3.331
Max	(b) (4)			5	6.318
CV	(b) (4)			55.6916	19.0821
90% Con	(b) (4)			0.3820	0.3248
Upper	(b) (4)			1.3874	4.0655
Lower	(b) (4)			2.1515	4.7151

Pseudoephedrine Hydrochloride

	AUCt (ng×hr/mL)	AUCinf (ng×hr/mL)	Cmax (ng/mL)	Tmax (hr)	Half-Life (hr)
Mean	(b) (4)			2.3344	5.7182
SD				1.5423	1.3889
Median				2	5.2325
Min				1	3.938
Max				8	9.129
CV				66.0654	24.2895
90% Con				0.5979	0.5385
Upper				1.7365	5.1797
Lower				2.9323	6.2567

Guaifenesin

	AUCt (ng×hr/mL)	AUCinf (ng×hr/mL)	Cmax (ng/mL)	Tmax (hr)	Half-Life (hr)
Mean	(b) (4)			0.5139	0.9317
SD				0.3923	0.2039
Median				0.5	0.9221
Min				0.25	0.6922
Max				1.67	1.52
CV				76.3473	21.8880
90% Con				0.1521	0.0814
Upper				0.3618	0.8504
Lower				0.6660	1.0131

Comparison of Individual PK Parameter Data to Published Data

The PK parameters were then compared to published data (Hydrocodone 5mg, Pseudoephedrine 60 mg and Guaifenesin 400 mg) for the individual drugs in the product to conclude that the bioavailability of each ingredient in the proposed product is the same as the bioavailability of the active ingredients. The comparability of the active ingredients data in the proposed product and in the reference publications was used to verify the lack of a drug-drug interaction. According to the sponsor, the pharmacokinetic data for the 400 mg dose information on Guaifenesin was not documented; therefore it is missing.

The sponsor concludes that the bioavailability of each ingredient in the proposed product is the same as the bioavailability of the ingredient in previously published data.

According to the sponsor, the pharmacokinetic parameters (Mean (CV%)) obtained for each individual drug from the study along with the mean and range of values (if available) from the literature are shown in Table 1.

Table 1. Comparison of PK Parameters for HC, GUA and PSE from (b) (4) product to Published Data

Hydrocodone

	C_{max} (ng/mL)	AUC_{inf} (ng·hr/mL)	T_{max} (h) ^a	$T_{1/2}$ (h)
(b) (4)	(b) (4)	(b) (4)	1.67 (0.75 – 5)	4.39 (19.08)
Literature	12.71 (9.1 – 16.4)	77.64 (59.55 – 93.7)	1.2 (0.7 – 1.7)	4.4 (3.5-6.2)

^a Median (range)

Pseudoephedrine

	C_{max} (ng/mL)	AUC_{inf} (ng·hr/mL)	T_{max} (h) ^a	$T_{1/2}$ (h)
(b) (4)	(b) (4)	(b) (4)	2 (1-8)	5.72 (24.90)
Literature	213.2 (169.5 – 236.0)	2109 (1800.8 - 2500)	1.9 (1.5 – 2.6)	5.4 (4.8 – 5.9)

^a Median (range)

Guaifenesin

	C_{max} (ng/mL)	AUC_{inf} (ng·hr/mL)	T_{max} (h) ^a	$T_{1/2}$ (h)
(b) (4)	(b) (4)	(b) (4)	0.5 (0.25 – 1.67)	0.93 (21.89)
Literature	1600 -2400	--	0.5	1

^a Median (range)

Reviewer’s comments

A preliminary assessment of the data shows that the mean systemic exposure (AUC) to HC and PSE (b) (4) for the (b) (4) product (b) (4) ng*hr/mL and (b) (4) ng*hr/mL, for HC and PSE, respectively) compared to the data obtained from published literature 77.64 ng*hr/mL and 2109 ng*hr/mL for HC and PSE, respectively). No information was provided on the AUC of GUA.

Drug-Drug Interaction Information

According to the sponsor, based on PK data from Study #S07-0441, Tmax, Cmax, and AUC of the individual ingredients (hydrocodone bitartrate, pseudoephedrine hydrochloride, guaifenesin), the comparison to the published data from other studies demonstrated that there was no drug-drug interaction.

Food Effect PK Information

According to the sponsor, based on the PK data from Study #S07 -0441 and published literature, there was no change in PK parameters AUC and Cmax of the individual ingredients of the drug product when compared to data of existing published studies with and without food.

Reviewer’s Remarks

This reviewer believes that because the product contains sorbitol, the regulatory requirements for an immediate release oral solution are more stringent than those for oral solution not containing “problem” inactive ingredients such as sorbitol. In other words, the approval of this drug should rely on demonstration of bioequivalence between the proposed product and the corresponding approved monoproducts and well as on assessment of food effect on the PK of all the active ingredients. This NDA is fileable from a clinical pharmacology standpoint. The comments listed on executive summary section of this review should be conveyed to the sponsor.

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	22-279	Brand Name	Hydrocodone, Guaifenesin, Pseudoephedrine Oral Solution	
OCP Division	II	Generic Name	Hydrocodone, Guaifenesin, Pseudoephedrine Oral Solution	
Medical Division	DPAP	Drug Class	Cough, cold medicine	
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	(b) (4)	
OCPB Team Leader	Wei Qiu	Dosage Form	Oral Solution	
PM Reviewer		Dosing Regimen	Adults and (b) (4) years of age and older: two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> (b) (4)	
Date of Submission	August 22, 2008	Route of Administration	Oral	
Estimated Due Date of OCP Primary Review	February 2009	Sponsor	(b) (4)	
PDUFA Due Date	June 22, 2009	Priority Classification	s	
Division Due Date	April 22, 2009			
3 Clin. Pharm. 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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		Single Dose Bioavailability Study (Study #S07-0441)
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:				
In-vivo effects of primary drug:				
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 -				
Meta analysis:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
QTC STUDIES (PHASE 1)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies			1	

Filability and QBR comments				
	“X” if yes	Comments		
Application filable ?	x	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. Refer to page 1 of this review (comments to sponsor..		
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1. Is the product bioequivalent to the reference products (hydrocodone, guaifenesin and pseudoephedrine)? 2. What is the effect of food on the bioavailability of Hydrocone, Guaifenesin, Pseudoephedrine Oral Solution ((b) (4) Oral Solution)? 3. What is the degree of drug-drug interaction between the active ingredient in the (b) (4) Oral Solution? 4. is there a formulation effect on the bioavailability of (b) (4) Oral Solution? 			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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

/s/

Sandra Suarez
4/23/2009 04:01:10 PM
BIOPHARMACEUTICS

Sally Choe
5/13/2009 02:32:10 PM
BIOPHARMACEUTICS

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	22-279 (resubmission)	Brand Name	Hydrocodone, Pseudoephedrine, Guaifenesin Oral Solution
OCP Division (I, II, III, IV, V)	II	Generic Name	Hydrocodone, Pseudoephedrine, Guaifenesin Oral Solution
Medical Division	DPARP	Drug Class	Cough and cold medicine
OCP Reviewer	Arun Agrawal, Ph.D.	Indication(s)	(b) (4)
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	Oral solution
Pharmacometrics Reviewer		Dosing Regimen	Adults and (b) (4) years of age and older: two (2) teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)
Date of Submission	July 26, 2010	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	(b) (4)
Medical Division Due Date		Priority Classification	S
PDUFA Due Date	January 26, 2011		

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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		Single Dose Bioavailability Study (Study #S09-0009); and Single Dose Relative BA Study Under Fed and Fasted Conditions (Study #S09-0010)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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:				
In-vivo effects of primary drug:				
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:				
replicate design; single / multi dose:				
Food-drug interaction studies				
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	<input checked="" type="checkbox"/>	2		

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	
3	Has the sponsor submitted bioavailability data satisfying the CFR	x			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	requirements?				
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

This NDA resubmission filing review is for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution submitted under 505(b)(2) of the FDC Act. This triple combination product is an immediate release solution that contains hydrocodone bitartrate (antitussive), pseudoephedrine

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

hydrochloride (nasal decongestant) and guaifenesin (expectorant) at the concentration of 2.5 mg, 30 mg, and 200 mg per 5 mL, respectively. (b) (4) is seeking approval of this cough/cold product (b) (4)

The proposed dose in adults and (b) (4) years of age and older is two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)

This NDA is fileable from the clinical pharmacology perspective.

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

This submission is fileable, however, we have identified some potential review issues which should be conveyed to the sponsor. In addition, DSI inspection will be requested and it has been communicated with the project manager.

The following comments should be conveyed to the sponsor:

1. The lower 90% CI for Cmax is not within the acceptance range of 80-125% for guaifenesin of the proposed product when dosed following an overnight fast. In addition, the exposure to guaifenesin of the proposed product does not meet the acceptance criteria (80-125%) under fed versus fasted conditions, indicating a food effect on guaifenesin of the proposed product. Whether these findings are acceptable will be a review issue.
2. In protocol S09-0009 submitted on January 16, 2009, it was mentioned that Hycodan (Endo Pharma) will be used as the reference drug. However, it was not used in this study according to this resubmission. Explain why Hycodan was not used in S09-0009.

Arun Agrawal	Aug 31, 2010
Reviewing Clinical Pharmacologist	Date

Yun Xu	Aug 31, 2010
Team Leader/Supervisor	Date



NDA 22-279

Hydrocodone (HC), Pseudoephedrine (PSE)
and Guaifenesin (GUA) oral solution

Current Sponsor:
(Previous Sponsor:



Arun Agrawal
Clinical Pharmacology
RRP meeting: Aug-31-2010

Proposed Product Overview

Type of submission: 505(b)(2)

Triple combination IR product containing (per 5 mL):

Hydrocodone bitartrate (antitussive) = 2.5 mg

Pseudoephedrine HCl (nasal decongestant) = 30 mg

Guaifenesin (expectorant) = 200 mg

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

Proposed dosage:

(b) (4): 10 mL every 4 hr, not to exceed 4 doses in 24 hr

(b) (4)

History of this NDA

At the PIND (76,365) meeting on March 26, 2007 the Division agreed that the sponsor could perform a small single arm BA study in fasted normal subjects on the test product as the basis for approval along with supporting published information on DDI and food effect to establish a clinical link

Sponsor submitted NDA 22-279 for HC, PSE and GUA oral solution to the Agency on Aug 22, 2008:

- This included data from a single arm BA study (#S07-0441) for proposed product
- Sponsor also provided food effect and DDI information based on literature and NDAs for related approved products
- *However, no study was conducted to address the potential of DDI between the components of the proposed product and the effect of food on the BA of the product components*
 - * AUCs for HC and PSE for the proposed product were found to be higher than the published literature
 - * No information was provided for the AUC of GUA since no published PK data was available for the 400 mg dose
 - * Published DDI and food effect information did not support the claim of lack of DDI or food effect on the BA of the proposed product

History of this NDA (contd.)

On the 74-day letter (Nov 03, 2008) the sponsor was informed that because the product contains sorbitol (b) (4) %, w/v), additional Clin Pharm information (BE study, food effect and DDI information) was needed to support the approval of the proposed product. The sponsor was also given advise on the potential designs for the proposed studies.

In response to the 74-day letter advise, the sponsor submitted following 3 study protocols (a BA/BE study, a DDI study, and a Food effect study) on January 16, 2009

1. Study Protocol S09-0008

A (Test Product): One 10 mL oral solution dose containing HC 2.5 mg/GUA 200 mg/PSE 30 mg per 5 mL (b) (4)

B (Reference Product): One 5 mL oral solution dose of Hycodan (Endo Pharma) containing 5 mg of HC, and one 20 mL oral solution dose of Robitussin Chest Congestion (Wyeth) containing 100 mg GUA per 5 mL, and one 10 mL oral solution dose of PSE containing 30 mg per 5 mL

History of this NDA (contd.)

2. Study Protocol S09-0009

Treatment A: One 5 mL oral solution dose of Hycodan (Endo Pharma) containing 5 mg of HC and one 20 mL oral solution dose of Robitussin Chest Congestion (Wyeth) containing 100 mg GUA per 5 mL (GUA 400 mg) and one 10 mL oral solution dose of PSE containing 30 mg per 5 mL (PSE 60 mg) given as a single dose under fasting conditions

Treatment B: One 5 mL oral solution dose of Hycodan (Endo Pharma) containing 5 mg of HC given as a single dose under fasting conditions

Treatment C: one 20 mL oral solution dose of Robitussin Chest Congestion (Wyeth) containing 100 mg GUA per 5 mL (GUA 400 mg) and one 10 mL oral solution dose of PSE containing 30 mg per 5 mL (PSE 60 mg) given as a single dose under fasting conditions

Sponsor was advised to replace treatment A of this study with an arm containing the proposed product to allow a direct comparison of HC, PSE and GUA oral solution to the approved product containing HC (Hycodan) which will also eliminate the need for study S09-0008 (January 27, 2009).

History of this NDA (contd.)

3. Study Protocol S09-0010

A (Test Product): One 10 mL oral solution dose containing HC 2.5 mg/GUA 200 mg/PSE 30 mg per 5 mL ((b) (4)) given as a single dose after initiation of a standardized, high-fat and high-calorie meal preceded by an overnight fast

B (Reference Product): One 10 mL oral solution dose containing HC 2.5 mg/GUA 200mg/PSE 30 mg per 5 mL ((b) (4)) given as a single dose under fasting conditions

Sponsor was given CR on June 22, 2009 as no new data was provided within the PDUFA timeframe

Resubmission:

Sponsor conducted trials as outlined in Study Protocols S09-0009 (incorporating the Agency's recommendations) and S09-0010, and submitted results on July 26, 2010*

* Hycodan was replaced by Hydrocodone Bitartrate/Homatropine Methylbromide oral solution as Hycodan was not available anymore

Single Dose BE Study (Study #S09-0009)

HC 5 mg/PSE 60 mg/GUA 400 mg oral solution in Healthy Subjects
(n = 18)

Treatment A (Test): Hydrocodone Bitartrate/Pseudoephedrine/Guaifenesin oral solution

Treatment B (Reference 1): Hydrocodone Bitartrate/Homatropine Methylbromide oral solution

Treatment C (Reference 2): Combination of Pseudoephedrine HCl and Robitussin Chest Congestion oral solution

OL, SD, R, three-period, three-treatment XO study under fasting conditions

At least 7-day washout period between doses

Blood samples collected up to 36 hrs for Trt A and C and up to 16 hrs for Trt B

Single Dose BE for Hydrocodone (Fasting)

Ln-Transformed Data - Hydrocodone				
Tiber's combination solution (Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg oral solution) vs. Hydrocodone Bitartrate / Homatropine Methylbromide 5 / 1.5 mg per 5 mL oral solution				
(Treatment A vs. Treatment B)				
N = 39				
Parameter	Treatment A	Treatment B	% Ratio	90% CI
AUC _{0-t} (ng.h/mL)	88.8591	88.0935	100.87	(98.21, 103.60)
AUC _{0-inf} (ng.h/mL)	96.2371	95.1725	101.12	(98.28, 104.04)
C _{max} (ng/mL)	14.3853	16.0187	89.80	(85.81, 93.98)

The point estimates and their 90% CIs are all within the acceptance range of 80-125%

Single Dose BE for Pseudoephedrine (Fasting)

Ln-Transformed Data - Pseudoephedrine				
Tiber's combination solution (Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg oral solution) vs. Robitussin® Chest Congestion oral solution (Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg) (Treatment A vs. Treatment C)				
N = 36				
Parameter	Treatment A	Treatment C	% Ratio	90% CI
AUC _{0-t} (ng.h/mL)	2394.6948	2383.3305	100.48	(96.54, 104.57)
AUC _{0-inf} (ng.h/mL)	2454.5881	2436.3557	100.75	(96.92, 104.73)
C _{max} (ng/mL)	253.6698	296.0544	85.68	(82.08, 89.44)

The point estimates and their 90% CIs are all within the acceptance range of 80-125%

Single Dose BE for Guaifenesin (Fasting)

Ln-Transformed Data - Guaifenesin				
Tiber's combination solution (Hydrocodone Bitartrate 5 mg / Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg oral solution) vs. Robitussin [®] Chest Congestion oral solution (Guaifenesin 400 mg / Pseudoephedrine HCl 60 mg) (Treatment A vs. Treatment C)				
N = 38				
Parameter	Treatment A	Treatment C	% Ratio	90% CI
AUC _{0-t} (ng.h/mL)	(b) (4)			
AUC _{0-inf} (ng.h/mL)				
C _{max} (ng/mL)				

AUC: [Redacted] (b) (4)

Cmax: [Redacted] (b) (4)

Sponsor has not provided any data and/or rationale if slightly [Redacted] (b) (4) will/will not be clinically relevant. This will be a Review issue

Single Dose Relative BA Study Under Fed and Fasted Conditions (Study #S09-0010)

HC 5 mg/PSE 60 mg/GUA 400 mg oral solution under fed and fasted conditions in healthy subjects (n = 18)

- OL, SD, R, two-period, two-treatment XO study under fasting and fed conditions
- At least 7-day washout period between doses
- Blood samples were collected up to 36 hrs

Single Dose Relative BA for Hydrocodone (Fed vs. Fasted)

Hydrocodone bitartrate under fed conditions vs. Hydrocodone bitartrate under fasted conditions Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI) Ln-Transformed data N = 18				
Parameter	Hydrocodone bitartrate (Fed) N = 18	Hydrocodone bitartrate (Fasted) N = 18	% Ratio	90% CI
AUC _{0-t} (ng-hr/mL)	95.0655	82.1693	115.7	111.86 – 119.66
AUC _{0-∞} (ng-hr/mL)	102.6032	87.7356	117.0	112.94 – 121.10
C _{max} (ng/mL)	13.8950	13.5463	102.6	97.17 – 108.28

The point estimates and their 90% CIs are all within the acceptance range of 80-125%

Single Dose Relative BA for Pseudoephedrine (Fed vs. Fasted)

Pseudoephedrine HCl under fed conditions vs. Pseudoephedrine HCl under fasted conditions Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI) Ln-Transformed data N = 18				
Parameter	Pseudoephedrine HCl (Fed) N = 18	Pseudoephedrine HCl (Fasted) N = 18	% Ratio	90% CI
AUC ₀₋₄ (ng-hr/mL)	2169.5639	2286.4121	94.9	87.68 – 102.70
AUC _{0-∞} (ng-hr/mL)	2214.6118	2336.3734	94.8	87.37 – 102.83
C _{max} (ng/mL)	242.8839	249.6607	97.3	92.70 – 102.10

The point estimates and their 90% CIs are all within the acceptance range of 80-125%

Single Dose Relative BA for Guaifenesin (Fed vs. Fasted)

Guaifenesin under fed conditions vs. Guaifenesin under fasted conditions Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI) Ln-Transformed data N = 18				
Parameter	Guaifenesin (Fed) N = 18	Guaifenesin (Fasted) N = 18	% Ratio	90% CI
AUC ₀₋₁ (ng-hr/mL)	(b) (4)			
AUC _{0-∞} (ng-hr/mL)				
C _{max} (ng/mL)				

(b) (4)

-- This will be a Review issue

As per Sponsor: It is difficult to ascertain if [redacted] (b) (4) of GUA is of clinical significance. For conservative purposes, it may be suitable to recommend that this solution be administered on an empty stomach

Summary

AUC (Fasting):

(b) (4)

Cmax (Fasting):

(b) (4)

(b) (4)

AUC and Cmax (Fed): The point estimates and their 90% CIs are all within the acceptance range of 80-125% for HC and PSE, however, (b) (4)

Issues Identified

- An IR was send to the sponsor to clarify under which NDA/ANDA the hydrocodone reference product was approved
- Not BE for the GUA component compared to reference product
- Food effect ((b) (4)) on GUA component.
The spon
effect will not affect the efficacy o prove that the food
- A DSI inspection will be requested

For Internal Discussion

Based on preliminary assessment, this submission **has** ^{(b) (4)}
potential review issue for the reason that

In addition, the sponsor did not provide evidence to prove that the food effect will not affect the efficacy for GUA.

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22279

ORIG-1

(b) (4)


HYDROCODONE
HCL/GUAIFENESIN/PSEUDOEP
HEDR

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

/s/

ARUN K AGRAWAL
09/08/2010

YUN XU
09/09/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology Tracking/Action Sheet for Formal/Informal Consults	
From: Sandra Suarez-Sharp		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission	
DATE OF SUBMISSION: August 22, 2008	NDA No.: 22-279 Serial No.:	BLA No.	DATE OF REVIEW: Sep 29, 2008
NAME OF DRUG: Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution	PRIORITY CONSIDERATION: S or P	Date of informal/Formal Consult: Sep 09, 2008	
NAME OF THE SPONSOR: (b) (4)			
TYPE OF SUBMISSION CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE			
<input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> SAFETY PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POP PK ISSUES <input type="checkbox"/> PHASE IV RELATED			
<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE			
<input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input checked="" type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): <i>NDA Filing Review</i>			
REVIEW ACTION			
<input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)			
<input type="checkbox"/> Oral communication with Name: [] <input type="checkbox"/> Comments communicated in meeting/Telecon. see meeting minutes dated: []			
<input checked="" type="checkbox"/> Formal Review/Memo (attached) <input checked="" type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): [Please see attached memo]			
REVIEW COMMENT(S)			
<input checked="" type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR			
COMMENTS/SPECIAL INSTRUCTIONS: Executive Summary This NDA filing review is for Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution submitted under 505 (b) (2) of the FDC Act. This triple combination product is an immediate release solution that contains hydrocodone bitartrate (antitussive), pseudoephedrine hydrochloride			

(nasal decongestant) and guaifenesin (expectorant) at the concentration of 2.5 mg, 30 mg, and 200 gm per 5 mL, respectively. (b) (4) is seeking approval of this cough/cold product (b) (4)

(b) (4) The proposed dose in adults and (b) (4) years of age and older is two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)

This submission contains the results of one single dose, single arm bioavailability study for (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. It also contains food effect and drug-drug interaction potential information based on journal articles and related approved products.

According to the sponsor, the bioavailability study in this application confirmed the bioavailability of the drug product in comparison to similar approved immediate release drug products containing the active ingredients. In addition, it seems that the PK parameter data demonstrated that the pharmacokinetics were not affected by the presence of one another. The sponsor states that the reference information indicates that the drugs in the proposed oral solution product are not affected by the administration of food.

A preliminary assessment of the data shows that the mean systemic exposure (AUC_{inf}) to HC and PSE (b) (4) for the (b) (4) product ((b) (4) ng*hr/mL and (b) (4) ng*hr/mL, for HC and PSE, respectively) compared to the data obtained from published literature (77.64 ng*hr/mL and 2109 ng*hr/mL for HC and PSE, respectively). No information was provided on the AUC of GUA.

The Division agreed during a face-to face meeting held on Mach 26, 2007 that the sponsor could perform a small single arm bioavailability study in fasted normal subjects on the test product as the bases of approval along with supporting published information on DDI and food effect to establish a clinical link. This reviewer believes that because the product contains sorbitol, the regulatory requirements for an immediate release oral solution are more stringent than those for oral solution not containing “problem” inactive ingredients such as sorbitol. In other words, the approval of this drug should rely on demonstration of bioequivalence between the proposed product and the corresponding approved monoproducts as well as on assessment of food effect on the PK of all the active ingredients.

This NDA is filaeble from a clinical pharmacology standpoint. The following comments have been conveyed to the sponsor during a telecon that took place on October 27, 2008. These comments should also be conveyed to the sponsor as part of the 74-day letter:

- We have conducted a preliminary assessment on the pharmacokinetic data included in your NDA as supporting information to link the efficacy and safety of your product to related approved products and found the following limitations:

- We notice that your product contains sorbitol. Sorbitol has been found to affect the bioavailability (BA) of some compounds with low permeability in a dose-proportional manner. Therefore, we recommend that you conduct an in vivo study in which bioequivalence (BE) is established with respect to each active component of your product.
- We also notice that your program does not address for a potential formulation effect. Section 21 (320.25)(g) of the CFR states that the purpose of an in vivo BA study involving a combination drug product is to determine if the rate and extent of absorption of each active ingredient in the combination product is equivalent to the rate and extend of absorption of each active drug ingredient administered concurrently in separate single ingredient preparations.
- To address these issues, you may choose to follow the designs proposed in Table 1 or Table 2. The design in Table 1 is recommended assuming that there is a lack of drug-drug interaction (DDI) between the active ingredients. The proposed design in Table 2 also addresses for potential of DDI and formulation effect in addition to bioequivalence.

Table 1. Proposed PK study design

ARM	BE Study
(b) (4) Oral Solution	√
Hycodan+GUA*+PSE*	√
Number of groups in crossover	2

*OTC products not containing sorbitol .

Table 2. Proposed PK study design

ARM	BE Study
(b) (4) Oral Solution	√
Hycodan	√
Hycodan+GUA*+PSE*	√
PSE*+ GUA*	√
Number of groups in crossover	4

*OTC products not containing sorbitol .

- You need to apply the appropriate statistical analysis to the proposed 4 way-crossover study design.

- In addition, you need to conduct an in vivo study to determine the effect of food on the bioavailability of (b) (4) Oral Solution's active ingredients for the same reason above stated. An equivalence approach is recommended for food-effect BA studies (refer to Guidance for industry: food-effect bioavailability and fed bioequivalence studies). The food effect may be assessed as part of the above mentioned studies.
- The claim of lack of drug-drug interaction effect (DDI) based on the supporting literature information you provided will be a review issue.
- As shown in Tables 1 and 2, the recommended reference products are Hycodan, Guaifenesin and Pseudoephedrine OTC oral solution products not containing sorbitol.

1.1 Recommendation

The Division of Clinical Pharmacology 2 (DCP2) has reviewed NDA 22-279 for filing purposes submitted on August 22, 2008. The NDA is fileable from a clinical pharmacology perspective. The above comments should be conveyed to the sponsor as part of the 74-day letter.

SIGNATURE OF REVIEWER: Sandra Suarez-Sharp, Ph.D. _____	Date _____
SIGNATURE OF TEAM LEADER (acting): Wei Qiu, Ph.D. _____	Date _____
CC.: HFD # []; TL: []; DD: []	Project Manager: _____ Date _____

Background

(b) (4) has developed a triple combination product which contains an antitussive (hydrocodone bitartrate 2.5 mg per 5 mL), a nasal decongestant (pseudoephedrine hydrochloride 30 mg per 5 mL) and an expectorant (guaifenesin 200 gm per 5 mL).

(b) (4) is seeking approval of this cough/cold product (b) (4)

The proposed dose in adults and (b) (4) years of age and older is two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)

Hydrocodone bitartrate is available on a prescription only basis (Rx Only). It is approved in various forms and in combination with other drugs as a narcotic analgesic and as an antitussive. The usual antitussive dose of hydrocodone bitartrate is 5 mg every 4 to 6 hours as needed [Hycodan Tablets and Syrup, NDA 5-213, Tussionex Suspension, NDA 19- 111). HC was not included in the OTC Monograph process and is available on a prescription only basis (Rx Only). It is approved in various forms and in combination with other drugs as a narcotic analgesic and as an antitussive. The usual antitussive dose of hydrocodone bitartrate is 5 mg every 4 to 6 hours as needed [Hycodan Tablets and Syrup, NDA 5-213, Tussionex Suspension, NDA 19- 111). The dose of HC to be used in the sponsor's proposed combination product is similar to doses for HC products approved for the relief of cough.

NDA 21-282 for Mucinex® Guaifenesin ER Tablets 600 mg and 1200 mg was approved July 12, 2002. This approval was based on pharmacokinetic studies only; neither preclinical nor toxicological studies were required. 21 CFR§341.78(b) states that the labeling of a product containing Guaifenesin must state, "under the heading "Indications," the following: "Helps loosen phlegm (mucus) and thin bronchial secretions to" (select one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive")." 341.78(d) states "The labeling of the product contains the following information under the heading "Directions" for products containing guaifenesin identified in 341.18: Adults and children 12 years of age and over: oral dosage is 200 to 400 milligrams every 4 hours not to exceed 2,400 milligrams in 24 hours. Children 6 to under 12 years of age: oral dosage is 100 to 200 milligrams every 4 hours not to exceed 1,200 milligrams in 24 hours." 21CFR§341.40, as per the final rule issued by FDA on December 23, 2004, allows the combination of any single antitussive ingredient and any single expectorant ingredient. The dose of GUA is within OTC monograph specifications.

PSE is generally recognized as safe and effective in over-the counter (OTC) allergy products (1) at doses of: 60 milligrams every 4 to 6 hours not to exceed 240 milligrams in 24 hours for Adults and children 12 years of age and over. For Children 6 to under 12 years of age: 30 milligrams every 4 to 6 hours not to exceed 120 milligrams in 24 hours. Children 2 to under 6 years of age: 15 milligrams every 4 to 6 hours not to exceed 60 milligrams in 24 hours. Children under 2 years of age: consult a doctor.

This submission contains the results of one single dose, single arm bioavailability study for (b) (4) Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution. It also contains food effect and drug-drug interaction potential information based on journal articles and related approved products.

Single Dose Bioavailability Study (Study #S07-0441)

This was a single-dose bioavailability study conducted in healthy volunteers. PK parameters were determined for 18 fasted subjects who received the proposed drug product. Blood samples for PK determination were taken immediately before dosing (0

hours), and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, and 36 hours and analyzed for plasma hydrocodone, pseudoephedrine and guaifenesin (up to 4 hrs only). Subjects were confined to the clinic until after the Hour 24 sample was obtained, and returned to the clinic for the hour 36 blood collection. Mean Cmax, Tmax and AUC0-t, AUC0-inf for Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin for the test product were determined using non-compartmental analysis. The parameter Tmax was analyzed using nonparametric methods.

The tables below show the results of the PK parameters for the three active ingredients.

Hydrocodone Bitartrate

	AUCt (ng×hr/mL)	AUCinf (ng×hr/mL)	Cmax (ng/mL)	Tmax (hr)	Half-Life (hr)
Mean	(b) (4)			1.7694	4.3903
SD				0.9854	0.8378
Median				1.67	4.096
Min				0.75	3.331
Max				5	6.318
CV				55.6916	19.0821
90% Con				0.3820	0.3248
Upper				1.3874	4.0655
Lower				2.1515	4.7151

Pseudoephedrine Hydrochloride

	AUCt (ng×hr/mL)	AUCinf (ng×hr/mL)	Cmax (ng/mL)	Tmax (hr)	Half-Life (hr)
Mean	(b) (4)			2.3344	5.7182
SD				1.5423	1.3889
Median				2	5.2325
Min				1	3.938
Max				8	9.129
CV				66.0654	24.2895
90% Con				0.5979	0.5385
Upper				1.7365	5.1797
Lower				2.9323	6.2567

Guaifenesin

	AUCt (ng×hr/mL)	AUCinf (ng×hr/mL)	Cmax (ng/mL)	Tmax (hr)	Half-Life (hr)
Mean	(b) (4)			0.5139	0.9317
SD	(b) (4)			0.3923	0.2039
Median	(b) (4)			0.5	0.9221
Min	(b) (4)			0.25	0.6922
Max	(b) (4)			1.67	1.52
CV	(b) (4)			76.3473	21.8880
90% Con	(b) (4)			0.1521	0.0814
Upper	(b) (4)			0.3618	0.8504
Lower	(b) (4)			0.6660	1.0131

Comparison of Individual PK Parameter Data to Published Data

The PK parameters were then compared to published data (Hydrocodone 5mg, Pseudoephedrine 60 mg and Guaifenesin 400 mg) for the individual drugs in the product to conclude that the bioavailability of each ingredient in the proposed product is the same as the bioavailability of the active ingredients. The comparability of the active ingredients data in the proposed product and in the reference publications was used to verify the lack of a drug-drug interaction. According to the sponsor, the pharmacokinetic data for the 400 mg dose information on Guaifenesin was not documented; therefore it is missing.

The sponsor concludes that the bioavailability of each ingredient in the proposed product is the same as the bioavailability of the ingredient in previously published data.

According to the sponsor, the pharmacokinetic parameters (Mean (CV%)) obtained for each individual drug from the study along with the mean and range of values (if available) from the literature are shown in Table 1.

Table 1. Comparison of PK Parameters for HC, GUA and PSE from (b) (4) product to Published Data

Hydrocodone

	C_{max} (ng/mL)	AUC_{inf} (ng·hr/mL)	T_{max} (h) ^a	$T_{1/2}$ (h)
(b) (4)			1.67 (0.75 – 5)	4.39 (19.08)
Literature	12.71 (9.1 – 16.4)	77.64 (59.55 – 93.7)	1.2 (0.7 – 1.7)	4.4 (3.5-6.2)

^a Median (range)

Pseudoephedrine

	C_{max} (ng/mL)	AUC_{inf} (ng·hr/mL)	T_{max} (h) ^a	$T_{1/2}$ (h)
(b) (4)			2 (1-8)	5.72 (24.90)
Literature	213.2 (169.5 – 236.0)	2109 (1800.8 - 2500)	1.9 (1.5 – 2.6)	5.4 (4.8 – 5.9)

^a Median (range)

Guaifenesin

	C_{max} (ng/mL)	AUC_{inf} (ng·hr/mL)	T_{max} (h) ^a	$T_{1/2}$ (h)
(b) (4)			0.5 (0.25 – 1.67)	0.93 (21.89)
Literature	1600 -2400	--	0.5	1

^a Median (range)

Reviewer’s comments

A preliminary assessment of the data shows that the mean systemic exposure (AUC) to HC and PSE (b) (4) for the (b) (4) product ((b) (4) ng*hr/mL and (b) (4) ng*hr/mL, for HC and PSE, respectively) compared to the data obtained from published literature 77.64 ng*hr/mL and 2109 ng*hr/mL for HC and PSE, respectively). No information was provided on the AUC of GUA.

Drug-Drug Interaction Information

According to the sponsor, based on PK data from Study #S07-0441, Tmax, Cmax, and AUC of the individual ingredients (hydrocodone bitartrate, pseudoephedrine hydrochloride, guaifenesin), the comparison to the published data from other studies demonstrated that there was no drug-drug interaction.

Food Effect PK Information

According to the sponsor, based on the PK data from Study #S07 -0441 and published literature, there was no change in PK parameters AUC and Cmax of the individual

ingredients of the drug product when compared to data of existing published studies with and without food.

Reviewer's Remarks

This reviewer believes that because the product contains sorbitol, the regulatory requirements for an immediate release oral solution are more stringent than those for oral solution not containing “problem” inactive ingredients such as sorbitol. In other words, the approval of this drug should rely on demonstration of bioequivalence between the proposed product and the corresponding approved monoproducts and well as on assessment of food effect on the PK of all the active ingredients. This NDA is fileable from a clinical pharmacology standpoint. The comments listed on executive summary section of this review should be conveyed to the sponsor.

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission			
	Information		Information
NDA Number	22-279	Brand Name	Hydrocodone, Guaifenesin, Pseudoephedrine Oral Solution
OCP Division	II	Generic Name	Hydrocodone, Guaifenesin, Pseudoephedrine Oral Solution
Medical Division	DPAP	Drug Class	Cough, cold medicine
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	(b) (4)
OCPB Team Leader	Wei Qiu	Dosage Form	Oral Solution
PM Reviewer		Dosing Regimen	Adults (b) (4): two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)
Date of Submission	August 22, 2008	Route of Administration	Oral
Estimated Due Date of OCP Primary Review	February 2009	Sponsor	(b) (4)
PDUFA Due Date	June 22, 2009	Priority Classification	s
Division Due Date	April 22, 2009		

Clin. Pharm. 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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	x	1		Single Dose Bioavailability Study (Study #S07-0441)
multiple dose:				
<i>Patients-</i>				
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:				
In-vivo effects of primary drug:				
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 -			
Meta analysis:			
Data sparse:			
II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference:			
Bioequivalence studies -			
traditional design; single / multi dose:			
replicate design; single / multi dose:			
Food-drug interaction studies:			
Dissolution:			
(IVIVC):			
Bio-wavier request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
QTC STUDIES (PHASE 1)			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies	x	1	
Filability and QBR comments			
	“X” if yes	Comments	
<u>Application filable ?</u>	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
<u>Comments sent to firm ?</u>		Comments have been sent to firm (or attachment included). FDA letter date if applicable. Refer to page 1 of this review (comments to sponsor..)	
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1. Is the product bioequivalent to the reference products (hydrocodone, guaifenesin and pseudoephedrine)? 2. What is the effect of food on the bioavailability of Hydrocone, Guaifenesin, Pseudoephedrine Oral Solution ((b) (4) Oral Solution)? 3. What is the degree of drug-drug interaction between the active ingredient in the (b) (4) Oral Solution? 4. is there a formulation effect on the bioavailability of (b) (4) Oral Solution? 		
Other comments or information not included above			
Primary reviewer Signature and Date			

Secondary reviewer Signature and Date	
--	--

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

/s/

Sandra Suarez
10/30/2008 12:39:51 PM
BIOPHARMACEUTICS

Wei Qiu
10/30/2008 12:50:05 PM
BIOPHARMACEUTICS