

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022439Orig1s000**

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

**CLINICAL PHARMACOLOGY REVIEW  
(RESUBMISSION DATED DECEMBER 8, 2010)**

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NDA: 22-439/SDN 22	Type of Submission: Resubmission
Submission Date(s)	December 8, 2010
Accepted Brand Name	Zutripro™
Generic Name	Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution
Reviewer	Elizabeth Y. Shang, Ph.D., R.Ph
Team Leader (Acting)	Suresh Doddapaneni., Ph.D.
OCP Division	DCPII
OND division	DPARP
Sponsor	Cypress Pharmaceuticals
Relevant IND(s)	102,177
Submission Type	505 (b) (2)
Review Priority	Standard
Formulation; Strength(s)	Solution; Five milliliters (5 mL) of Zutripro Oral Solution contains: hydrocodone bitartrate, USP, 5 mg; chlorpheniramine maleate, USP, 4 mg; and pseudoephedrine hydrochloride, USP, 60 mg.
Proposed Indication	Adults 18 years or older: <ul style="list-style-type: none"><li>• Relief of cough and nasal congestion associated with common cold.</li><li>• Relief of symptoms including nasal congestion associated with upper respiratory allergies.</li></ul>
Proposed Dosing Regimen	Five milliliters (5 mL) orally every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

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## 1 Executive Summary

### 1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, the clinical pharmacology information supporting the approval for NDA 22439 is acceptable. As of May 5, 2011, the clinical Pharmacology related labeling language was agreed upon between the Agency and Cypress and as such there are no outstanding labeling issues.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Clinical Pharmacology Findings

The bioequivalence of hydrocodone, chlorpheniramine, and pseudoephedrine components in Zutipro™ Oral Solution formulation relative to respective reference solutions containing hydrocodone bitartrate (hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co., Inc), single-ingredient chlorpheniramine solution and pseudoephedrine solution was demonstrated in Study 11058503. The 90% confidence intervals (CIs) for the geometric mean ratios of  $C_{max}$  and AUC of hydrocodone, chlorpheniramine, and pseudoephedrine were within the 80-125% limits for bioequivalence. The summary of bioequivalence statistics on pharmacokinetic parameters for hydrocodone, chlorpheniramine, and pseudoephedrine are provided in Table 1, Table 2, and Table 3, respectively.

**Table 1 Summary Statistics on Bioequivalence of Hydrocodone Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Hydrocodone Bitartrate and Homatropine Methylbromide Syrup Manufactured by Hi-Tech Pharmacal Co., Inc (RLD for Hydrocodone)**

**Geometric Means, Ratio of Means, and 90% Confidence Intervals  
Based on ANOVA of Ln-Transformed Data  
Analyte: Hydrocodone (N = 98)**

Parameter	Test A	Reference B	Ratio	CI*	Intra-Subject %CV
AUC0-t (pg·hr/mL)	67540.16	69723.40	0.9687	0.9465 - 0.9914	9.7130
AUC0-inf (pg·hr/mL)	69747.27	72063.25	0.9679	0.9452 - 0.9911	9.9706
Cmax (pg/mL)	10290.79	11364.25	0.9055	0.8795 - 0.9324	12.2931

\* Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

Source: Clinical Study Report, Page 36 of 75

**Table 2 Summary Statistics on Bioequivalence of Chlorpheniramine Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Chlorpheniramine Solution (Reference for Chlorpheniramine)**

**Geometric Means, Ratio of Means, and 90% Confidence Intervals  
Based on ANOVA of Ln-Transformed Data  
Analyte: Chlorpheniramine (N = 97)**

Parameter	Test A	Reference D*	Ratio	CI**	Intra-Subject %CV
AUC0-t (pg·hr/mL)	159719.72	155681.52	1.0259	0.9992 - 1.0534	11.0456
AUC0-inf (pg·hr/mL)	181409.61	174224.49	1.0412	1.0174 - 1.0657	9.6529
Cmax (pg/mL)	6923.48	6789.48	1.0197	0.9946 - 1.0456	10.4537

\*N=96 for AUC0-inf for Reference product D.

\*\*Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

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**Table 3 Summary Statistics on Bioequivalence of Pseudoephedrine Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Pseudoephedrine Solution (Reference for Pseudoephedrine)**

**Geometric Means, Ratio of Means, and 90% Confidence Intervals  
Based on ANOVA of Ln-Transformed Data  
Analyte: Pseudoephedrine (N = 100)**

Parameter	Test A	Reference C	Ratio	CI*	Intra-Subject %CV
AUC0-t (ng·hr/mL)	1824.27	1813.41	1.0060	0.9815 - 1.0311	10.4633
AUC0-inf (ng·hr/mL)	1943.05	1926.70	1.0085	0.9809 - 1.0368	11.7857
Cmax (ng/mL)	207.17	204.90	1.0111	0.9931 - 1.0294	7.6000

\* Bioequivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

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Since this is a pivotal bioequivalence study, Division of Scientific Investigations (DSI) audited the study and concluded that the study data be accepted for review (Memorandum dated April 14, 2011 by Dr. Sripal Mada). As of May 5, 2011, the clinical pharmacology related labeling language was agreed upon between the Agency and Cypress and as such there are no outstanding labeling issues.

## 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?

Cypress Pharmaceuticals submitted NDA 22439 originally on November 6, 2008 (SDN 1) following the NDA 505 (b) (2) pathway. First resubmission (SDN 11) occurred on December 10, 2009 in response to the Complete Response (CR) Letter of September 9, 2009 for the original NDA. Second resubmission (SDN 22) occurred on December 8, 2010 in response to the CR Letter of June 11, 2010 for the first resubmission.

The accepted trade name for this product is Zutripro™. However, the proposed trade name in NDA first resubmission was (b) (4) Oral Solution while (b) (4) Oral Solution was proposed in the original NDA submission. Zutripro™ has been used in this review although previous reviews refer to this product as (b) (4) Oral Solution and (b) (4) Oral Solution .

In the original submission, the Sponsor submitted data from a single dose bioequivalence study (S08-0179) between Zutripro™ and Hycodan®, single-ingredient pseudoephedrine and chlorpheniramine solutions to support NDA submission, and the Agency agreed with the plan. The hydrocodone component of the test product, Zutripro™ Oral Solution, was not bioequivalent to hydrocodone in the reference, Hycodan® syrup, although chlorpheniramine and pseudoephedrine components were bioequivalent to their respective single component solutions. In the CR letter dated September 9, 2009, the Agency provided the Sponsor two options to address the deficiency: a) conduct a single-dose clinical pharmacology study to establish the bioequivalence of Zutripro™ Oral Solution to the reference products; or b) conduct a clinical development program with clinical efficacy and safety studies to support the Sponsor's combination product.

The Sponsor chose Option A and in the resubmission dated December 10, 2009 submitted a new single dose bioequivalence study (SAM-09-1010) to demonstrate that hydrocodone component of Zutripro™ is bioequivalent to the hydrocodone component of the reference hydrocodone bitartrate and homatropine methylbromide syrup manufactured by Hi-Tech Pharmacal Co., Inc. The change of reference in this new bioequivalence study was acceptable due to withdrawal of Hycodan® syrup from the market. However, due to deficiencies both in the conduct of the study and in the methods used at the analytical sites found in the DSI inspection in Study S08-0179 from SDN1 and Study SAM 09-1010 from SND2, a CR Letter was issued on June 11, 2010. In the CR letter, the Agency provided the Sponsor two options to address the deficiency: a) conduct another single-dose clinical pharmacology study to establish the bioequivalence of the proposed hydrocodone 5 mg/chlorpheniramine 4 mg/pseudoephedrine 60 mg/ per 5 ml oral solution to the reference products; or b) conduct a clinical development program with clinical efficacy and safety studies to support Sponsor's combination product.

The Sponsor again chose Option A and in the resubmission dated December 8, 2010, data from a new a single dose bioequivalence study (11058503) was submitted demonstrating that each active ingredient in Zutripro™ is bioequivalent to the corresponding components in the respective reference products.

#### 2.1.2 What is the status of pediatric studies and/or any pediatric plan for study?

In the original NDA submission, the Sponsor proposed usage of Zutripro™ (b) (4)

Waiver for children below 6 years of age is based on the fact that the proposed product contains hydrocodone which is contraindicated for use in children less than 6 years of age (because of the risk of respiratory depression). The need for conducting pediatric safety and pharmacokinetics study in patients 6 to 17 years (inclusive) was verbally communicated to the Sponsor during the review cycle. The Sponsor submitted their revised pediatric plan proposal to the Agency on May 6, 2010. Sponsor's proposed pediatric plan and Division's assessment were presented to Pediatric Review Committee (PeRC) on May 26, 2010. PeRC agreed with the waiver of studies in children less than 6 years of age and a deferral for patients 6 to 17 years of age, with recommendations to incorporate efficacy assessments and population PK in the proposed safety study. The proposed usage of Zutripro™ (b) (4) to be prescribed in adults (age 18 years and over) only in the current draft label.

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

Adults: Five milliliters (5 mL) orally every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

### 2.2 General Clinical Pharmacology

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

The Clinical Pharmacology program consisted of a single-dose bioequivalence study (Study 11058503). This study is an open-label, single-dose, randomized, four-period cross-over study under fasting conditions. The objectives of the study were to determine and compare the rate and extent of absorption of hydrocodone, pseudoephedrine, and chlorpheniramine from Zutripro™ Oral Solution to that from homatropine methylbromide/ hydrocodone bitartrate 1.5 mg/5 mg per 5 mL syrup (manufactured by Hi-Tech Pharmacal Co, Inc.), pseudoephedrine solution, and chlorpheniramine solution. Ninety-eight healthy adult subjects completed the study. The

study results showed bioequivalence for the hydrocodone, pseudoephedrine, and chlorpheniramine components of the Zutripro™.

No clinical studies to determine safety and efficacy of the product were carried out in this NDA. Per agreement reached with the Agency, Cypress is relying on previous findings of safety and efficacy on Agency's DESI review finding for Hycodan syrup, NDA 05213 and OTC Monographs for pseudoephedrine and chlorpheniramine.

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

Hydrocodone, chlorpheniramine, and pseudoephedrine in the plasma samples were measured.

2.2.3 What are the single dose pharmacokinetic parameters?

The arithmetic mean plasma pharmacokinetic parameters for testing product and reference products are summarized in Table 4, Table 5, and Table 6.

**Table 4 Arithmetic Mean (SD) of Plasma Pharmacokinetic Parameters of Hydrocodone Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Hydrocodone Bitartrate and Homatropine Methylbromide Syrup Manufactured by Hi-Tech Pharmacal Co., Inc. (Reference)**

**Summary of Pharmacokinetic Parameters  
Untransformed Data  
Analyte: Hydrocodone (N = 98)**

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)	
	Test A	Reference B
AUC <sub>0-t</sub> (pg·hr/mL)	69401.3314 ± 16433.6643 (23.6792)	71785.3004 ± 18328.4015 (25.5322)
AUC <sub>0-inf</sub> (pg·hr/mL)	71759.8232 ± 17539.3146 (24.4417)	74293.9576 ± 19573.8121 (26.3464)
C <sub>max</sub> (pg/mL)	10616.4388 ± 2634.2446 (24.8129)	11829.5000 ± 3598.8372 (30.4226)
T <sub>max</sub> (hr)	1.3806 ± 0.5513 (39.9328)	1.2248 ± 0.4929 (40.2400)
K <sub>el</sub> (1/hr)	0.1440 ± 0.0229 (15.8926)	0.1414 ± 0.0204 (14.4431)
T <sub>½</sub> (hr)	4.9246 ± 0.7340 (14.9041)	5.0060 ± 0.7424 (14.8294)

Source: Clinical Study Report, Page 36 of 75

**Table 5 Arithmetic Mean (SD) of Plasma Pharmacokinetic Parameters of Chlorpheniramine Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Chlorpheniramine Solution (Reference)**

**Summary of Pharmacokinetic Parameters  
Untransformed Data  
Analyte: Chlorpheniramine (N = 97)**

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)	
	Test A	Reference D*
AUC <sub>0-t</sub> (pg·hr/mL)	170939.1008 ± 60670.6833 (35.4926)	169040.6387 ± 73085.0690 (43.2352)
AUC <sub>0-inf</sub> (pg·hr/mL)	200844.9726 ± 96259.5622 (47.9273)	190371.4343 ± 81311.4355 (42.7120)
C <sub>max</sub> (pg/mL)	7203.6392 ± 1979.3166 (27.4766)	7108.8763 ± 2067.1756 (29.0788)
T <sub>max</sub> (hr)	3.4692 ± 1.5764 (45.4380)	3.8637 ± 3.5482 (91.8341)
K <sub>el</sub> (1/hr)	0.0323 ± 0.0106 (32.7556)	0.0334 ± 0.0100 (30.1088)
T <sub>½</sub> (hr)	24.1356 ± 10.0853 (41.7858)	22.6116 ± 6.6990 (29.6264)

\*N=96 for AUC<sub>0-inf</sub>, K<sub>el</sub>, and T<sub>½</sub> for Reference product D.

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**Table 6 Arithmetic Mean (SD) of Plasma Pharmacokinetic Parameters of Pseudoephedrine Following Single Dose Administration of 5 mL Zutripro™ Oral Solution (Test) and Pseudoephedrine Solution (Reference)**

**Summary of Pharmacokinetic Parameters  
Untransformed Data  
Analyte: Pseudoephedrine (N = 100)**

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)	
	Test A	Reference C
AUC <sub>0-t</sub> (ng·hr/mL)	1876.1802 ± 474.5503 (25.2934)	1867.1775 ± 481.3987 (25.7822)
AUC <sub>0-inf</sub> (ng·hr/mL)	2020.8583 ± 652.4217 (32.2844)	1996.6786 ± 577.1783 (28.9069)
C <sub>max</sub> (ng/mL)	211.8165 ± 46.1536 (21.7894)	209.6139 ± 46.9436 (22.3953)
T <sub>max</sub> (hr)	1.7753 ± 0.5580 (31.4325)	1.6705 ± 0.6321 (37.8374)
K <sub>el</sub> (1/hr)	0.1309 ± 0.0294 (22.4723)	0.1312 ± 0.0270 (20.6002)
T <sub>½</sub> (hr)	5.6139 ± 1.5689 (27.9463)	5.5348 ± 1.3009 (23.5040)

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## 2.3 General Biopharmaceutics

### 2.3.1 What is the relative bioavailability of the formulations (reference and test) based on the pivotal bioequivalence studies? Was the bioequivalence demonstrated between the two formulations?

The bioequivalence of hydrocodone, chlorpheniramine, and pseudoephedrine component of Zutripro™ has been demonstrated under fasting condition as evident by the observation that the 90% CIs ratios of the geometric means for C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-inf</sub> were within the limits for bioequivalence (80-125%) (Table 1, Table 2, and Table 3).

### 2.3.2 What is the effect of food on the bioavailability of the drug from the dosage form?

No specific pharmacokinetic studies to determine the effect of food on the disposition of hydrocodone, chlorpheniramine and pseudoephedrine were submitted in this NDA. As a post meeting comment in the minutes of the January 14, 2008 pre-IND meeting (b) (4) of this product), the Agency has agreed that no food effect study was needed with the proposed oral solution formulation (b) (4).

## 2.4 Analytical Section

### 2.4.1 What bioanalytical methods are used to assess concentrations?

The analytical portion of the Cypress Pharmaceuticals, Inc. Protocol No. 11058503 conducted at (b) (4).

#### 2.4.1.1 Hydrocodone

Total plasma concentrations of hydrocodone were measured by a validated method utilizing high performance liquid chromatography-tandem mass spectrometry. The method for the analysis of hydrocodone in human heparin plasma was validated over the range of 100 – 20,000 pg/mL. Summary of plasma hydrocodone bioanalytical validation methods is listed in Table 7. The results of sample analysis on hydrocodone are provided in Table 8.

The results are acceptable as evidenced by QC sample precision and accuracy within  $\pm 15\%$  excluding the quality control values which did not meet the acceptance criteria.

**Table 7 Analytical Method Validation Summary on Hydrocodone**

	<b>Hydrocodone (pg/mL)</b>
<b>Standard Concentrations</b>	100, 200, 500, 1000, 2000, 5000, 10000, 20000
<b>Linear Range</b>	100 – 20,000
<b>Corelation Coefficient (r)</b>	≥ 0.998
Accuracy Across Standard Curve Concentrations (%)	98.4% - 101.5%
<b>QC Concentrations (pg/mL)</b>	300, 3000, 16000
<b>Intra-Run Precision (%CV) of QC Samples</b>	
300	3.1%
3000	1.8%
16000	1.3%
<b>Intra-Run Accuracy of QC Samples</b>	
300	97.7%
3000	100.6%
16000	98.5%
<b>Inter-Run Precision of QC Samples (%CV)</b>	
300	3.1%
3000	1.9%
16000	2.1%
<b>Inter-Run Accuracy of QC Samples (%CV)</b>	
300	96.7%
3000	98.9%
16000	96.0%
<b>Recovery (%)</b>	
Analyte	
300	97.5%
3000	100.7%
16000	95.1%
Internal standards	100.1
<b>Stabilities in Plasma</b>	
Room Temperature	24 hours; No instability is detected
Refrigerated (4°C)	24 hours; No instability is detected
Frozen (-20°C)	5 days; No instability is detected
Frozen (-80°C)	At least 92 days; No instability is detected
Freeze-Thaw Stability	3 cycles; No instability is detected.
<b>Processed Batch Stability</b>	24 hours; No instability is detected
<b>Processed Sample Stability</b>	25.5 hours; No instability is detected
<b>Dilution Accuracy (4X High QC, i.e. 64,000 pg/mL)</b>	
x5	93.5%
x10	101.2%
Source: LC-MS/MS-Assay Validation Report VAL-RPT-1261 Rev1	

**Table 8 Plasma Assay Parameters for Hydrocodone**

	Hydrocodone
Lower Limit of Quantitation (pg/mL)	100
Assay Range (pg/mL)	100 to 20000 pg/mL
Linearity (correlation coefficient)	> 0.99
Precision (%CV)	8.3% at 300 pg/mL; 6.1% at 3000 pg/mL; 5.0% at 16000 pg/mL
Accuracy (%Theoretical)	101.0% at 300 pg/mL; 99.4 at 3000 pg/mL; 94.7% at 16000 pg/mL

#### 2.4.1.2 Pseudoephedrine

Total plasma concentrations of pseudoephedrine were measured by a validated method utilizing the technique of protein precipitation, followed by high performance liquid chromatography-positive ionization electrospray-tandem mass spectrometry. The method for the analysis of pseudoephedrine in human heparin plasma was validated over the range of 2.00 – 400.00 ng/mL. Summary of plasma hydrocodone bioanalytical validation methods is listed in Table 9. The results of sample analysis on hydrocodone are provided in Table 10.

The results are acceptable as evidenced by QC sample precision and accuracy within  $\pm 15\%$  excluding the quality control values which did not meet the acceptance criteria.

**Table 9 Analytical Method Validation Summary on Pseudoephedrine**

		<b>Pseudoephedrine (ng/mL)</b>	
<b>Standard Concentrations</b>		2.00, 4.00, 10.00, 20.00, 40.00, 100.00, 200.00, 400.00	
<b>Linear Range</b>		100 – 20,000	
<b>Corelation Coefficient (r)</b>		≥ 0.9984	
Accuracy Across Standard Curve Concentrations (%)		97.6% - 104.1%	
<b>QC Concentrations (ng/mL)</b>		6.00, 60.00, and 320.00	
<b>Intra-Run Precision (%CV) of QC Samples</b>		System K	System N
	6.00	3.8%	1.9%
	60.00	1.3%	1.3%
	320.00	1.3%	1.3%
<b>Intra-Run Accuracy of QC Samples</b>		System K	System N
	6.00	99.7%	96.8%
	60.00	96.6%	95.2%
	320.00	91.0%	91.5%
<b>Inter-Run Precision of QC Samples (%CV)</b>			
	6.00	5.7%	
	60.00	2.7%	
	320.00	3.7%	
<b>Inter-Run Accuracy of QC Samples (%CV)</b>			
	6.00	96.7%	
	60.00	98.4%	
	320.00	93.2%	
<b>Recovery (%)</b>			
Analyte			
	6.00	56.7%	
	60.00	55.4%	
	320.00	60.0%	
Internal standards		61.5%	
<b>Stabilities in Plasma</b>			
	Room Temperature	25 hours; No instability is detected	
	Refrigerated (4°C)	24 hours; No instability is detected	
	Frozen (-20°C)	6 and 10 days; No instability is detected	
	Frozen (-80°C)	6 and 35 days; No instability is detected	
	Freeze-Thaw Stability	3 cycles; No instability is detected.	
<b>Processed Batch Stability</b>		68 hours; No instability is detected	
<b>Processed Sample Stability</b>		73 hours; No instability is detected	
<b>Dilution Accuracy (4X High QC, i.e. 64,000 pg/mL)</b>			
	x5	93.7%	
	x10	96.6%	

Source: LC-MS/MS-Assay Validation Report VAL-RPT-1260 Rev 0

**Table 10 Plasma Assay Parameters for Pseudoephedrine**

	Pseudoephedrine
Lower Limit of Quantitation (ng/mL)	2.00
Assay Range (pg/mL)	2.00 to 400.00 ng/mL
Linearity (correlation coefficient)	> 0.99
Precision (%CV)	5.3% at 6.00 ng/mL; 6.9% at 60.00 ng/mL; 5.2% at 320.00 ng/mL
Accuracy (%Theoretical)	94.2% at 6.00 ng/mL; 99.4% at 60.00 ng/mL; 94.9% at 320.00 ng/mL

#### 2.4.1.3 Chlorpheniramine

Total plasma concentrations of chlorpheniramine were measured by a validated method utilizing the technique of protein precipitation, followed by high performance liquid chromatography-positive ionization electrospray-tandem mass spectrometry. The method for the analysis of pseudoephedrine in human heparin plasma was validated over the range of 100 – 20,000 pg/mL. Summary of plasma hydrocodone bioanalytical validation methods is listed in Table 11. The results of sample analysis on hydrocodone are provided in Table 12.

The results are acceptable as evidenced by QC sample precision and accuracy within  $\pm 15\%$  excluding the quality control values which did not meet the acceptance criteria.

**Table 11 Analytical Method Validation Summary on Chlorpheniramine**

		Chlorpheniramine (pg/mL)	
<b>Standard Concentrations</b>		100, 200, 500, 1000, 2000, 5000, 10000, 20000	
<b>Linear Range</b>		100 – 20,000	
<b>Corelation Coefficient (r)</b>		≥ 0.9981	
Accuracy Across Standard Curve Concentrations (%)		96.4% - 101.71%	
<b>QC Concentrations (pg/mL)</b>		300, 3000, and 16000	
<b>Intra-Run Precision (%CV) of QC Samples</b>		System K	System N
	300	5.8%	3.5%
	3000	0.9%	2.6%
	16000	5.8%	3.7%
<b>Intra-Run Accuracy of QC Samples</b>		System K	System N
	300	92.3%	95.0%
	3000	97.5%	94.0%
	16000	97.0%	97.8%
<b>Inter-Run Precision of QC Samples (%CV)</b>			
	300	5.0%	
	3000	2.2%	
	16000	3.8%	
<b>Inter-Run Accuracy of QC Samples (%CV)</b>			
	300	92.7%	
	3000	96.0%	
	16000	97.5%	
<b>Recovery (%)</b>			
Analyte			
	300		94.6%
	3000		87.1%
	16000		84.4%
Internal standards			91.4%
<b>Stabilities in Plasma</b>			
Room Temperature	26 hours;	No instability is detected	
Refrigerated (4°C)	26 hours;	No instability is detected	
Frozen (-20°C)	7 and 16 days;	No instability is detected	
Frozen (-80°C)	7 and 35 days;	No instability is detected	
Freeze-Thaw Stability	3 cycles;	No instability is detected.	
<b>Processed Batch Stability</b>	16 days;	No instability is detected	
<b>Processed Sample Stability</b>	16 days;	No instability is detected	
<b>Dilution Accuracy (4X High QC, i.e. 64,000 pg/mL)</b>			
	x5	100.0%	
	x10	100.6%	

Source: LC-MS/MS-Assay Validation Report VAL-RPT-1266 Rev 0

**Table 12 Plasma Assay Parameters for Chlorpheniramine**

	Chlorpheniramine
Lower Limit of Quantitation (pg/mL)	100
Assay Range (pg/mL)	100 to 20000 pg/mL
Linearity (correlation coefficient)	> 0.99
Precision (%CV)	5.3% at 300 pg/mL; 6.9% at 3000 pg/mL; 5.2% at 16000 pg/mL
Accuracy (%Theoretical)	94.2% at 300 pg/mL; 99.4% at 3000 pg/mL; 94.9% at 16000 pg/mL

### 3 Detailed Labeling Recommendations

Following are the labeling changes proposed by this reviewer in Section 12.3 of the package insert. Strikethrough text was Cypress proposal while underlined text is Agency's proposal. Cypress proposed text gave the impression that the information came from two different studies and Agency's proposed change removes that ambiguity. As of May 5, 2011, the underlined text was agreed upon between the Agency and Cypress and as such there are no outstanding labeling issues.



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ELIZABETH Y SHANG  
05/12/2011

SURESH DODDAPANENI  
05/12/2011

## Addendum to Clinical Pharmacology Review for NDA 22439 on May 3, 2010

Date: May 25, 2010

NDA: 22439

Drug name: (b) (4) Oral Solution

The following information reflects update on the bioequivalence (BE) studies S08-0179 and SAM-09-1010 in the clinical pharmacology review for NDA 22439, which was finalized in DARRTs on May 3, 2010.

On January 26, 2010, the Division of Pulmonary and Allergy Products (DPAP) sent a request to the Division of Scientific Investigations (DSI) to audit both the clinical and analytical portions of the following bioequivalence studies:

1. Study #1: S08-00179 "A Relative Bioavailability and Drug-Drug Interaction Study Of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg Per 5 mL), Chlorpheniramine Oral Solution (4 mg Per 5 mL) and Hycodan<sup>®</sup> Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide Per 5 mL) under Fasted Conditions".
2. Study #2: SAM-09-1010 " A Study to Evaluate the Relative Bioavailability of Hydrocodone Bitartrate in a 5 mg/60 mg/4 mg Hydrocodone Bitartrate/ Pseudoephedrine HCl/ Chlorpheniramine Maleate Oral Solution Compared to Hi-Tech (1.5 mg/5 mg Homatropine Methylbromide/ Hydrocodone Bitartrate) Syrup in Healthy Subjects under Fasted Conditions".

The DSI inspection report was unavailable on May 3, 2010, the primary due date for clinical pharmacology review. Therefore, in the original review, the pharmacokinetic (PK) results of both BE studies were discussed and summarized without DSI inspection results. The PK analyses from Study #1 showed that bioequivalence of chlorpheniramine and pseudoephedrine components in (b) (4) oral solution formulation to respective single-ingredient chlorpheniramine solution and pseudoephedrine solution. The PK analyses from Study #2 showed that bioequivalence has been established for hydrocodone bitartrate component in (b) (4) oral solution compared to that in 1.5 mg/5 mg homatropine methylbromide/ hydrocodone bitartrate syrup manufactured by Hi-Tech Pharmacal Co., Inc.

On May 5, 2010, the DSI inspection memorandum on Study SAM-09-1010 was released in DARRTs. Following the inspection, DSI has found the following issues:

1. Failure to adequately document all aspects of study conduct.
2. Stability samples used for processed sample stability validation were not compared against freshly extracted calibrators.
3. For validation batch HCMI130a, chromatograms with the original integration before the manual change were not maintained, and justification for the manual reintegration was not documented.
4. Failure to establish objective criteria to consistently calculate mean internal standard (IS) response. For example, for analytical batch HydroG66, mean IS

response was calculated based on the IS response of the calibration standards, whereas in batch HydroG85A, mean IS response was calculated from the IS response of the QCs. The justification for how mean IS response was calculated was also not documented.

DSI has made the following conclusions related to the analytical portion of Study SAM-09-1010:

1. The bioequivalence data for Study SAM-09-1010 submitted in the NDA are questionable due to the absence of source documentation at (b) (4), the experiments conducted as part of pre-study method validations cannot be assured.
2. To assure accuracy of bioequivalence data in study SAM-09-1010, the sponsor should provide new stability data (including frozen Long-term, freeze-thaw, refrigerated, room-temperature and processed stability) to support integrity of the BE data generated in the study. The data needs to be generated while maintaining complete source documentation for all the stability experiments.

On May 24, 2010, the DSI inspection memorandum on Study S08-0179 was released in DARRTs. Following the inspection, DSI has found the following issues:

1. Records for the extraction of subject samples in numerous studies were falsified.

The falsification is part of the Agency's 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. The falsification was pervasive for extractions conducted on weekends and holidays over the time period of April 2005 to June 2009 and affected numerous studies for multiple sponsors. Affected data for Study S08-0179 include Runs 11-16 for Hydrocodone/ Chlorpheniramine and Runs 11-18 for Pseudoephedrine.

The complaint also alleged that laboratory staff altered the outcome of analytical runs (i.e., runs were "fixed") through "prep" runs injected prior to the actual subject sample batch. Unexplained discrepancies between the initial system equilibration result ("prep" run) and the actual run result 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. As the (b) (4) investigation to date could not explain this discrepancy.

2. Validation documentation was incomplete in that extraction times for some validation runs were not recorded and the storage location of stability samples to demonstrate freeze/thaw and long term stability was not documented.

Following the above inspection, DSI recommends the followings for Study S08-0179:

1. Study S08-0179 should not be accepted for review at this time due to record falsification and incomplete investigation of complaint allegations by (b) (4).
2. Due to lack of source documentation, free/thaw (F/T) and long term stability (LTS) determinations cannot be assured. Appropriate F/T and LTS data to

demonstrate analyte stability under the same conditions as the subject samples (hydrocodone/ chlorpheniramine/pseudoephedrine in combination) are needed.

Based upon the two DSI inspection results on the two pivotal BE studies in NDA 22439, it is in this reviewer's opinion that unquestionable bioequivalence data is necessary to claim bioequivalence between the (b) (4) oral solution (test product) and respective reference products.

### ***Conclusions***

In conclusion, the results of the bioequivalence studies from S08-0179 and SAM-09-1010 are *not* accepted based on the DSI audit outcome from clinical pharmacology perspective. The Agency will ask the sponsor in the CR letter to address the deficiencies.

The following conclusions from DSI inspection memorandums should be convey to the sponsor:

#### **Study S08-0179**

- a. Study S08-0179 is not accepted for review at this time due to record falsification and incomplete investigation of complaint allegations by (b) (4).
- b. Due to lack of source documentation, free/thaw (F/T) and long term stability (LTS) determinations cannot be assured. Appropriate F/T and LTS data to demonstrate analyte stability under the same conditions as the subject samples (hydrocodone/ chlorpheniramine/pseudoephedrine in combination) are needed.

#### **Study SAM-09-1010**

- a. Due to the absence of source documentation at (b) (4), the experiments conducted as part of pre-study method validations cannot be assured. Hence the bioequivalence data for study SAM-09-1010 submitted in the NDA are questionable.
- b. To assure accuracy of bioequivalence data in study SAM-09-1010, the sponsor should provide new stability data (including frozen Long-term, freeze-thaw, refrigerated, room-temperature and processed stability) to support integrity of the BE data generated in the study. The data needs to be generated while maintaining complete source documentation for all the stability experiments.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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ELIZABETH Y SHANG  
05/25/2010

YUN XU  
05/25/2010

## CLINICAL PHARMACOLOGY REVIEW

<b>NDA:</b>	22-439
<b>Type:</b>	505 (b) (2)
<b>Brand Name:</b>	(b) (4) Oral Solution
<b>Generic Name:</b>	Hydrocodone, Chlorpheniramine and Pseudoephedrine Oral Solution
<b>Indication:</b>	(b) (4)
<b>Dosage Form:</b>	Solution
<b>Route of Administration:</b>	Oral
<b>Strength:</b>	Each (b) (4) (5 mL) of (b) (4) Oral Solution contains: hydrocodone bitartrate, USP, 5 mg; chlorpheniramine maleate, USP, 4 mg; and pseudoephedrine hydrochloride, USP, 60 mg.
<b>Dosing regimen:</b>	Adults (b) (4): <ul style="list-style-type: none"><li>• (b) (4) (5 mL) every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.</li></ul> (b) (4)
<b>Applicant:</b>	Cypress Pharmaceuticals
<b>OCP Division:</b>	Division of Clinical Pharmacology 2
<b>Clinical Division:</b>	Division of Pulmonary and Allergy Products (ONP-570)
<b>Submission Date:</b>	November 17, 2008
<b>Reviewer:</b>	Sheetal Agarwal, Ph.D.
<b>Team Leader:</b>	Sally Choe, Ph. D.

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## 1.0 Executive summary

This is a 505 (b) (2) NDA for an oral solution containing hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride (5 mg, 4 mg, and 60 mg per 5 mL respectively). The proposed proprietary name for this product is [REDACTED] (b) (4) Oral Solution. Hydrocodone bitartrate is approved for the symptomatic relief of cough in HYCODAN (NDA 05-213), chlorpheniramine maleate is an accepted antihistamine in the OTC Monograph (21 CFR §341.12), and pseudoephedrine HCl is an accepted nasal decongestant in the OTC Monograph (21 CFR §341.20).

The proposed indication is for [REDACTED] (b) (4)

## 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the submitted Clinical Pharmacology information for NDA 22-439 for the proposed indication and finds it unacceptable. The hydrocodone component of the test product, [REDACTED] (b) (4) Oral Solution, is not bioequivalent to the reference listed drug (RLD), Hycodan® Syrup in the submitted pivotal relative bioavailability study for this 505 (b) 2 NDA application.

## 1.2 Phase 4 Commitments

Not applicable.

## 1.3 Summary of Important Clinical Pharmacology Findings

The Clinical Pharmacology package submitted for this NDA consisted of a single relative bioavailability and drug-drug interaction study (Study S08-0179) conducted in 25 healthy adult volunteers. The objectives of the clinical study were to determine and compare the rate and extent of absorption of hydrocodone from [REDACTED] (b) (4) Oral Solution to that from Hycodan® Syrup (RLD); and to evaluate the drug-drug interaction impact of pseudoephedrine on hydrocodone and chlorpheniramine in [REDACTED] (b) (4) Oral Solution, and chlorpheniramine on hydrocodone and pseudoephedrine in [REDACTED] (b) (4) Oral Solution. This was an open-label, single-dose, randomized, four period cross-over study under fasted conditions. The dosing regimen and the statistical summary are presented below. This reviewer has reanalyzed the PK information submitted for this pivotal relative BA study by employing WinNonLin version 5.2 to obtain the noncompartmental PK parameters and perform the BE analysis. The results of this reanalysis are in agreement with the results submitted by the sponsor.

### Dosing Regimen

- 5 mL dose of hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg / 60 mg / 4 mg per 5 mL) (**Treatment A**)
- 5 mL dose of pseudoephedrine oral solution (60 mg per 5 mL) (**Treatment B**)
- 5 mL dose of chlorpheniramine oral solution (4 mg per 5 mL) (**Treatment C**)
- 5 mL dose of Hycodan® Syrup (5 mg hydrocodone bitartrate / 1.5 mg homatropine methylbromide per 5 mL) (**Treatment D**)

(b) (4)

Overall, the test product (b) (4) Oral Solution is not bioequivalent to the corresponding reference product for hydrocodone, Hycodan syrup. The lower limit of the 90% CI of the geometric mean of C<sub>max</sub> for hydrocodone was 78.89%, which is outside of the 80% – 125% bioequivalence range. In addition, no information on exposure – response relationship could be found for hydrocodone as evidence to support that a lower C<sub>max</sub> will not affect its efficacy as a cough depressant.

The other two components of the test product (b) (4) Oral Solution, chlorpheniramine and pseudoephedrine are equivalent in terms of both rate and formation to the corresponding test products respectively. The geometric means as well as the 90% CI limits for both chlorpheniramine and pseudoephedrine are well within the 80-125% limits for all the three PK parameters measured, i.e., C<sub>max</sub>, AU<sub>Clast</sub> and AU<sub>Cinf</sub> with respect to those of the reference products.

Since this a simple solution formulation of the three components and does not contain any excipients (b) (4) that can affect the bioavailabilities of the major components, formulation effects on the exposure of the three components is not a major concern. However, the study as designed, in addition to addressing relative BA concerns, also addresses PK drug-drug interaction concerns amongst the three components when administered as a combination. The result from this study indicating that the hydrocodone exposure from the sponsor's product is not equivalent to the reference product could be an indication of a potential PK related drug-drug interaction among the three components such that the hydrocodone exposure is affected by the other two components, chlorpheniramine and pseudoephedrine of the combination product.

Since the other two components of the test product are equivalent in terms of rate and extent of absorption to the reference product, it can be assumed that hydrocodone and chlorpheniramine when administered together, do not alter the PK of pseudoephedrine

and similarly, hydrocodone and pseudoephedrine when administered together do not alter the PK of chlorpheniramine.

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## 2.0 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?*

Hydrocodone, chlorpheniramine, and pseudoephedrine are not currently approved as a combination product in the United States, but each is offered as an approved product or a part of a combination product. Hydrocodone is marketed as Hycodan® syrup, a fixed dose combination oral syrup product containing homatropine methylbromide 1.5 mg/5 ml and hydrocodone bitartrate 5 mg/5 ml under NDA 005213, held by Endo Pharmaceuticals, Inc.) and is a prescription product, chlorpheniramine (chlorpheniramine maleate; 21 CFR 341.12) and pseudoephedrine (pseudoephedrine hydrochloride; 21 CFR 341.20) are marketed as Codeprex®, a fixed dose combination oral syrup product containing chlorpheniramine polistirex equivalent to 4 mg/5 ml of chlorpheniramine maleate and codeine polistirex equivalent to 20 mg/5 ml codeine, and Advil® Allergy Sinus, a fixed dose combination oral suspension product containing 100 mg/ 5 ml ibuprofen, 15 mg/5 ml of pseudoephedrine hydrochloride and 1mg/5 ml chlorpheniramine maleate respectively, and both are over-the-counter (OTC) products.

Hydrocodone bitartrate has been available for over 50 years, demonstrating a long history of use in humans, with an initial approval of Hycodan® Syrup (NDA 005213) in 1943. In 2007, FDA ordered companies making unapproved hydrocodone drug products to cease manufacturing such products on or before December 31, 2007, and for those companies marketing unapproved hydrocodone products labeled for use in children younger than 6 years of age to stop manufacturing and distributing the products by October 31, 2007. The Agency removed these unapproved products from the market, indicating that NDAs should subsequently be submitted. As a result, Cypress submitted a new drug application for (b) (4) Oral Solution (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride).

Cypress submitted IND 102,177 for this and other proposed combination products on April 15, 2008. A type B pre-IND meeting was held on 01/17/2008 to discuss the sponsor's concerns and the meeting minutes for this meeting can be found in DARRTS.

#### 2.1.2 *What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?*

**Hydrocodone Bitartrate** is available as a fine white or slightly yellow-white powder. It is soluble in water (1 g dissolves in 16 g of water), slightly soluble in alcohol (1 g dissolves in 150 g of 95% ethanol), and almost insoluble in ether and chloroform. The pH of a 2% aqueous solution is approximately 3.6.

**Chlorpheniramine Maleate** is a white crystalline powder. It is freely soluble in water (140 mg/mL), soluble in alcohol and chloroform, and it is slightly soluble in ether. The pH of a 1% aqueous solution is between 4.0 and 5.5.

**Pseudoephedrine Hydrochloride** is a white to almost white crystalline powder. It is freely soluble in water. The pH of an aqueous solution is 5.0–6.0 and its pKa is 9.9.

The proposed drug product, (b) (4) Oral Solution (hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride) (b) (4) is a clear, colorless to light-yellow liquid with a grape odor. Each milliliter of the solution contains 1.0 mg of hydrocodone bitartrate, 0.8 mg of chlorpheniramine maleate, and 12 mg of pseudoephedrine hydrochloride as the active ingredients. Based on a discussion in the pre-IND meeting held on 01/14/08, the sponsor has removed (b) (4) (that could have affected the BA of the three components as discussed in the meeting) from the proposed product.

The unit composition, function, and quality of each component in the drug product are presented below in Table 1:

**Table 1: Composition of (b) (4) Oral Solution:**

Component	Reference to Quality Standards	Function	Unit Composition		
			% w/v	mg/mL	mg/480 mL
Hydrocodone Bitartrate	USP	Active ingredient	(b) (4)	1.0	480
Chlorpheniramine Maleate	USP	Active ingredient	(b) (4)	0.8	384
Pseudoephedrine Hydrochloride	USP	Active ingredient	(b) (4)	12.0	5760
Citric Acid, Anhydrous	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Citrate	USP		(b) (4)	(b) (4)	(b) (4)
Sodium Saccharin	USP		(b) (4)	(b) (4)	(b) (4)
Methylparaben	NF		(b) (4)	(b) (4)	(b) (4)
Propylparaben	NF		(b) (4)	(b) (4)	(b) (4)
Sucrose	NF		(b) (4)	(b) (4)	(b) (4)
Glycerin	(b) (4) USP		(b) (4)	(b) (4)	(b) (4)
Propylene Glycol	USP		(b) (4)	(b) (4)	(b) (4)
Grape Flavor	(b) (4) In-house		(b) (4)	(b) (4)	(b) (4)
Water, Purified	USP		(b) (4)	(b) (4)	(b) (4)

NF = National Formulary.

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

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 in therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, and physical and psychological dependence.

Chlorpheniramine is an antihistamine drug (H1 receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

(b) (4) Oral Solution is an antitussive, antihistamine, nasal decongestant potentially indicated for:

(b) (4)

#### **2.1.4 What are the proposed dosage and route of administration?**

Adults (b) (4):

- (b) (4) (5 mL) every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours.

(b) (4)

Each (b) (4) (5 mL) of (b) (4) Oral Solution contains: hydrocodone bitartrate, USP, 5 mg; chlorpheniramine maleate, USP, 4 mg; and pseudoephedrine hydrochloride, USP, 60 mg.

## **2.2 General Clinical Pharmacology**

### **2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

The Clinical Pharmacology package submitted for this NDA consisted of a single relative bioavailability and drug-drug interaction study (Study S08-0179) conducted in 25 healthy

adult volunteers. The objectives of the clinical study were to determine and compare the rate and extent of absorption of hydrocodone from (b) (4) Oral Solution to that from Hycodan Syrup (RLD); and to evaluate the drug-drug interaction impact of pseudoephedrine on hydrocodone and chlorpheniramine in (b) (4) Oral Solution, and chlorpheniramine on pseudoephedrine, and chlorpheniramine in (b) (4) Oral Solution. This was an open-label, single-dose, randomized, four period cross-over study under fasted conditions. The dosing regimen and the statistical summary are presented below.

No clinical study to determine safety and efficacy of the product was carried out in this NDA. The sponsor is relying for safety and efficacy on Agency's DESI review findings for Hycodan syrup, NDA 05-213.

**2.2.2 *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?***

Hydrocodone, chlorpheniramine and pseudoephedrine in the plasma samples were measured.

**2.2.3 *What are the characteristics of the exposure-response relationship (dose response, concentration-response)?***

No exposure-response relationship was characterized in this submission.

**2.2.4 *What are the single dose and multiple dose PK parameters in healthy subjects?***

Single oral doses of hydrocodone, chlorpheniramine and pseudoephedrine were administered in healthy volunteers under fasting conditions. The PK parameters are presented below in Tables 2, 3 and 4. No multiple dose PK studies were conducted.

**Table 2: Pharmacokinetic Parameters for Hydrocodone Bitartrate after Single-dose Administration in Cypress Clinical Study S08-0179:**

(b) (4)

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**Table 3: Pharmacokinetic Parameters for Chlorpheniramine Maleate after Single-dose Administration in Cypress Clinical Study S08-0179:**

(b) (4)

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**Table 4: Pharmacokinetic Parameters for Pseudoephedrine HCl after Single-dose Administration in Cypress Clinical Study S08-0179:**



(b) (4)

**2.2.5 What are the ADME characteristics of the drugs involved?**

No ADME characterization for hydrocodone, chlorpheniramine and pseudoephedrine was carried out in this NDA submission. However, relevant information related to the three drugs from literature review (conducted by the sponsor) is presented below:

Hydrocodone is not extensively protein bound, binding to plasma protein at a range between 19% and 45%. The mean peak serum concentration (C<sub>max</sub>) of hydrocodone is  $23.6 \pm 5.2$  ng/mL when administered as an oral dose of 10 mg. Maximum serum levels are reached in  $1.3 \pm 0.3$  hours and the elimination half-life (t<sub>1/2</sub>) was determined to be  $3.8 \pm 0.3$  hours. Hydrocodone exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6- $\alpha$ - and 6- $\beta$ -hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the O-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone.

Pseudoephedrine is a sympathomimetic amine that acts as an  $\alpha$ -adrenergic agonist. It is indicated for use as a nasal decongestant. Pseudoephedrine does not produce rebound congestion, as a single product or in combination with other ingredients. Frequently, it is used in combination products with analgesics, antihistamines, antitussives and expectorants. The T<sub>max</sub> for pseudoephedrine following 60 mg or 120 mg doses is from 1.4 to 2 hours. Administration of a single large dose of 180 mg pseudoephedrine increases T<sub>max</sub> to 3 hours. The reported t<sub>1/2</sub> is 4-8 hours for pseudoephedrine.

Chlorpheniramine is a propylamine that belongs to the alkylamine class of antihistamines. Chlorpheniramine inhibits histamine action in the gastrointestinal and respiratory tracts by blocking the H1 receptor. Chlorpheniramine is extensively protein bound, binding to plasma protein at a range between (b) (4). It is extensively metabolized in the gastrointestinal mucosa. Following oral administration of immediate-release chlorpheniramine tablets, a C<sub>max</sub> of 16-71 ng/mL is achieved within 2-3 hours for formulation. For extended-release formulations, T<sub>max</sub> is extended to 5.7- 8.1 hours, with C<sub>max</sub> of 17-76 ng/mL.

## 2.3 General Biopharmaceutics

### 2.3.1 *What is the relative bioavailability of the formulations (reference and test) based on the pivotal BE studies?*

**Study S08-0179** was a relative bioavailability study of hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg hydrocodone bitartrate/1.5 mg homatropine methylbromide per 5 mL) under fasted conditions. The dosing regimen and PK summary is presented below.

#### **Dosing Regimen**

- 5 mL dose of hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg / 60 mg / 4 mg per 5 mL) (**Treatment A**)
- 5 mL dose of pseudoephedrine oral solution (60 mg per 5 mL) (**Treatment B**)
- 5 mL dose of chlorpheniramine oral solution (4 mg per 5 mL) (**Treatment C**)
- 5 mL dose of Hycodan® Syrup (5 mg hydrocodone bitartrate / 1.5 mg homatropine methylbromide per 5 mL) (**Treatment D**)

Overall, the test product (b) (4) Oral Solution is not bioequivalent to the corresponding reference product for hydrocodone, i.e., Hycodan syrup since the hydrocodone component from the fixed dose combination oral solution product failed to meet the bioequivalence criterion (Fig.1). The lower limit of the 90% CI of the geometric mean of C<sub>max</sub> for hydrocodone was (b) (4), which is outside of the 80% – 125% bioequivalence range (Table 5). Treatment arm A which tests effect of chlorpheniramine and pseudoephedrine on the pharmacokinetics of hydrocodone, in addition to addressing the the relative BA property of the test product in comparison with the reference product, also addresses an important drug-drug interaction concern. The result from this study indicating that the hydrocodone exposure from the sponsor's product is not equivalent to the reference product could be an indication of a potential drug-drug interaction among the three components such that the hydrocodone exposure is affected by the other two components, chlorpheniramine and pseudoephedrine of the combination product. Essentially it is possible that chlorpheniramine and pseudoephedrine when administered together may alter the pharmacokinetics of hydrocodone.

However, the other two components of the test product (b) (4) Oral Solution. i.e. chlorpheniramine (Fig.2) and pseudoephedrine (Fig.3) are equivalent in terms of both rate and formation to the corresponding test products. The geometric means as well as the

90% CI limits for both chlorpheniramine and pseudoephedrine are well within the 80-125% limits for all the three PK parameters measured, i.e., C<sub>max</sub>, AUC<sub>last</sub> and AUC<sub>inf</sub> with respect to reference (Tables 6 and 7). This result indicates that hydrocodone and chlorpheniramine when administered together do not alter the PK of pseudoephedrine and similarly, hydrocodone and pseudoephedrine when administered together do not alter the PK of chlorpheniramine.

**Fig.1: Linear Plot of Mean Plasma Hydrocodone Concentrations vs. Time after Single-dose Administration in Cypress Clinical Study S08-0179:**



**Table 5: Bioequivalence Comparison Summary Statistics of Pharmacokinetic Parameters for Hydrocodone Bitartrate after Single-dose Administration in Cypress Clinical Study S08-0179:**



**Fig.2: Linear Plot of Mean Plasma Chlorpheniramine Concentrations vs. Time after Single-dose Administration in Cypress Clinical Study S08-0179:**



**Table 6: Bioequivalence Comparison Summary Statistics of Pharmacokinetic Parameters for Chlorpheniramine Maleate after Single-dose Administration in Cypress Clinical Study S08-0179:**



(b) (4)

**Fig.3: Linear Plot of Mean Plasma Pseudoephedrine Concentrations vs. Time after Single-dose Administration in Cypress Clinical Study S08-0179:**



**Table 7: Bioequivalence Comparison Summary Statistics of Pharmacokinetic Parameters for Pseudoephedrine HCl after Single-dose Administration in Cypress Clinical Study S08-0179:**

**2.3.2 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?***

No specific PK studies to determine the effect of food on the disposition of hydrocodone, chlorpheniramine and pseudoephedrine were conducted in this submission. As a post meeting comment to the pre-IND meeting, (can be found in the pre-IND meeting minutes dated 01/14/08 in DARRTS) the Agency had agreed that no food effect study was needed with the proposed oral solution formulation  <sup>(b) (4)</sup>

## 2.4 Analytical Section

### 2.4.1 *What bioanalytical methods are used to assess concentrations?*

The analytical portion of the Cypress Pharmaceuticals, Inc. Protocol No. S08-0179 was conducted at [REDACTED] (b) (4) for hydrocodone and chlorpheniramine and at [REDACTED] (b) (4) for pseudoephedrine.

[REDACTED] (b) (4)

### 2.4.2 *For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total plasma concentrations were measured.

### 2.4.3 *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

[REDACTED] (b) (4)

**2.4.4** *What are the accuracy, precision, and selectivity at these limits?*

(b) (4)

**2.4.5** *What was the QC sample plan?*

(b) (4)

**2.5** **Labeling comments**

Not applicable. The label is not reviewed because of the significant deficiency in this application.

**3.0 Sponsor's proposed labeling**

**FULL PRESCRIBING INFORMATION**

(b) (4)



11 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

#### 4.0 Appendices:

##### 4.1 SYNOPSIS OF STUDY S08-0179

<b>SPONSOR:</b>	Cypress Pharmaceuticals, Inc. 135 Industrial Blvd. Madison, MS 39110, USA
<b>NAME OF TEST PRODUCT:</b>	Hydrocodone bitartrate, psueodephedrine HCl and chlorpheniramine maleate oral solution, 5 mg/60 mg/4 mg
<b>ACTIVE INGREDIENT:</b>	Hydrocodone, pseudoephedrine and chlorpheniramine
<b>STUDY TITLE:</b>	A Relative Bioavailability and Drug-Drug Interaction Study of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan <sup>®</sup> Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide per 5 mL) Under Fasted Conditions
<b>PRINCIPAL INVESTIGATOR AND STUDY SITE:</b>	(b) (4)
<b>STUDY DURATION:</b> 16 May 2008 – 06 July 2008	
<b>STUDY TYPE:</b> Phase 1	
<b>OBJECTIVES:</b> The objectives of this study were: 1) To determine and compare the rate and extent of absorption of hydrocodone from the following products under fasted conditions: a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL) b) Hycodan <sup>®</sup> Syrup (5 mg hydrocodone bitartrate / 1.5 mg homatropine methylbromide per 5 mL) 2) To evaluate the drug-drug interaction of pseudoephedrine with hydrocodone and chlorpheniramine from the following products under fasted conditions: a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL)	

<p>b) Pseudoephedrine Oral Solution (60 mg per 5 mL)</p> <p>3) To evaluate the drug-drug interaction of chlorpheniramine with pseudoephedrine and hydrocodone from the following products under fasted conditions:</p> <p>a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL)</p> <p>b) Chlorpheniramine Oral Solution (4 mg per 5 mL)</p>
<p><b>METHODOLOGY:</b> This was a randomized, four-period crossover, open-label, single dose study conducted under fasting conditions.</p> <p>Subjects were dosed as two groups (Group 1: Subjects 01 – 23 and Group 2: Subjects 24 – 28) and remained housed for 24 hours post-dose. Following an overnight fast of at least 10 hours, subjects received either a single oral dose of 5 mL (5 mg/4 mg/60 mg per 5 mL oral solution) of the test product, hydrocodone bitartrate/chlorpheniramine maleate/pseudoephedrine HCl oral solution or a single oral dose of 5 mL (60 mg per 5 mL oral solution) of the reference product 1, pseudoephedrine HCl oral solution; or a single oral dose of 5 mL (4 mg per 5 mL oral solution) of reference product 2, chlorpheniramine maleate oral solution; or a single oral dose of 5 mL (5 mg/1.5 mg per 5 mL oral solution) of reference product 3, Hycodan® oral solution. Treatments were administered in a randomly assigned sequence. Following a 14-day washout period, subjects returned to the clinical facility to be dosed with the alternative treatments as per the randomization (see <a href="#">Appendix 16.1.7</a>).</p> <p>In each study period, serial pharmacokinetic blood samples to measure the hydrocodone, pseudoephedrine and chlorpheniramine concentrations were to be collected at pre-dose and ending with the 24 hour post-dose sample (for those subjects who had received 5 mL (5 mg/4 mg/60 mg per 5 mL oral solution) of the test product, hydrocodone bitartrate/chlorpheniramine maleate/pseudoephedrine HCl oral solution or 5 mL (4 mg per 5 mL) of reference product 2, chlorpheniramine maleate oral solution. Blood samples were also collected at study hours 36, 48, 72, and 96).</p> <p>Plasma samples were sent to the bioanalytical laboratory at (b)(4) for determination of hydrocodone, pseudoephedrine and chlorpheniramine plasma concentrations.</p>
<p><b>NUMBER OF SUBJECTS:</b> A total of 28 healthy adult subjects participated in this study.</p>
<p><b>MAIN DIAGNOSIS FOR ENTRY:</b> Subjects were asymptomatic, healthy, non-smoking adult subjects between the ages of 18 and 65 years who met the inclusion/exclusion criteria for this study.</p>

<b>TEST PRODUCT: (Treatment A)</b>	Hydrocodone Bitartrate 5 mg per 5 mL / Chlorpheniramine Maleate 4 mg per 5 mL / Pseudoephedrine HCl 60 mg per 5 mL (Cypress Pharmaceuticals, Inc.), Lot No. P08001
<b>REFERENCE PRODUCT 1: (Treatment B)</b>	Pseudoephedrine HCl 60 mg per 5 mL (Cypress Pharmaceuticals, Inc.), Lot No. P08043
<b>REFERENCE PRODUCT 2: (Treatment C)</b>	Chlorpheniramine Maleate 4 mg per 5 mL (Cypress Pharmaceuticals, Inc.), Lot No. P08045
<b>REFERENCE PRODUCT 3: (Treatment D)</b>	HYCODAN®, 5 mg hydrocodone bitartrate/ 1.5 mg homatropine methylbromide per 5 mL, Manufactured for Endo Pharmaceuticals Inc., Manufactured by Novartis, Lot No. 400804NV
<b>ROUTE OF ADMINISTRATION:</b>	Oral
<b>DURATION OF TREATMENT:</b> The subjects received 5 mL of the test product, reference product 1, reference product 2, or reference product 3 in each of the treatment conditions over an 8-week period with a 14 day washout period between dosing time points. Total study participation, exclusive of screening, was 46 days.	
<b>PRIMARY EFFICACY VARIABLE:</b> Not applicable.	
<b>SECONDARY EFFICACY VARIABLE:</b> Not applicable.	
<b>CRITERIA FOR EVALUATION:</b>	
<p><b>Pharmacokinetics:</b> Blood for pharmacokinetic sampling was obtained from all subjects within 90 minutes prior to dosing (0 hour) and after dose administration at study hours 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 for Treatments A and C and for Treatments B and D at post-dose study hours 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24. Analytical data from the blood samples collected during the study conduct were used to calculate values for the following pharmacokinetic parameters: <math>AUC_{0-t}</math>, <math>AUC_{0-inf}</math>, <math>C_{max}</math>, <math>T_{max}</math>, <math>K_{el}</math>, and <math>T_{1/2}</math></p> <p>Analyses of variance (ANOVA) were performed on the ln-transformed pharmacokinetic parameters <math>AUC_{0-t}</math>, <math>AUC_{0-inf}</math> and <math>C_{max}</math> and on the untransformed pharmacokinetic parameters <math>AUC_{0-t}</math>, <math>AUC_{0-inf}</math>, <math>C_{max}</math>, <math>T_{max}</math>, <math>K_{el}</math> and <math>T_{1/2}</math>. The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was</p>	

tested using subject nested within sequence as the error term. A 10% level of significance was used to test the sequence effect. Each analysis of variance included calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with this difference. The above statistical analyses were done using the appropriate SAS<sup>®</sup> procedure. Additional calculations were performed as needed.

In agreement with the two one-sided test for bioequivalence, 90% confidence intervals for the difference between drug formulation least-squares means (LSM) were calculated for the parameters  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  using ln-transformed data. The confidence intervals were expressed as a percentage relative to the LSM of the reference formulation.

Ratios of means were calculated using the LSM for ln-transformed  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$ . The geometric mean values were expressed as a percentage. The comparisons of interest are: D vs. A (hydrocodone); B vs. A (pseudoephedrine); and C vs. A (chlorpheniramine).

**Safety:** All subjects were monitored throughout the confinement portion of the study. Sitting blood pressure, heart rate, temperature, and respirations were measured at each check-in. Blood pressure, heart rate and respirations were measured at 1, 2, 4, and 24 hours after each dose. Subjects were also queried for adverse events at screening, check-in, during the confinement portion of the study, and at study exit (or early termination). All subjects underwent clinical laboratory testing including hematology, biochemistry, urinalysis, and, for women of childbearing potential, pregnancy tests. Clinical laboratory testing (hematology and serum chemistry) was repeated at study exit. Additionally, vital signs were taken and physical examinations were performed at screening and at study exit (or early termination).

**SUMMARY OF RESULTS:**

**Demographic Summary:** The mean age of the subjects was 29 years (Mean = 29.1 yrs ± 10.2 yrs). Ages ranged from 18 to 54 years. Nineteen (19) males and 9 females were enrolled in the study and a majority of the subjects were white (approximately 64.29%).

**Pharmacokinetic Summary:** The bioanalytical laboratory at (b) (4) determined the hydrocodone, pseudoephedrine and chlorpheniramine plasma concentrations and sent the data to the Statistical Division of (b) (4)

Hydrocodone:

(b) (4)



**Safety Summary:** No serious adverse events (SAEs) were reported over the course of this study. No subject was discontinued due to an adverse event (AE). Eight (8) subjects (28.6%) reported 27 adverse events (AEs) during the course of the study. Of the 8 subjects who reported AEs, 1 subject (3.8%) experienced an AE following administration of hydrocodone bitartrate/pseudoephedrine HCl/chlorpheniramine maleate 5 mg/60 mg/4 mg; 2 subjects (7.7%) experienced AEs following administration of pseudoephedrine HCl 60 mg, 3 subjects (11.1%) experienced AEs following administration of chlorpheniramine maleate 4 mg and 5 subjects (18.5%) experienced AEs following administration of Hycodan<sup>®</sup> oral solution. Sixteen (16) of the 27 AEs were reported by 5 subjects after receiving treatment D, Hycodan<sup>®</sup> oral solution.

Overall, the most common AEs were nausea and headache, each reported by 4 subjects (14.3%) Dizziness was reported by 3 subjects (10.8%) and two (2) subjects (7.1%) experienced vessel puncture site pain. All adverse events were mild or moderate in intensity.

There were no clinically significant findings from an assessment of the clinical laboratory test results, vital signs data, or physical examination results.

#### **SUMMARY CONCLUSIONS:**

**Pharmacokinetic:** For the log-transformed hydrocodone data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits (set by FDA, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, Center for Drug Evaluation and Research [CDER], March, 2003) for  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , but not  $C_{max}$ .

For the log-transformed pseudoephedrine and chlorpheniramine data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits (set by FDA, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, Center for Drug Evaluation and Research [CDER], March, 2003) for  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$ .

**Safety:** Eight (8) subjects (28.6%) experienced 27 AEs during the course of the study. No serious adverse events (SAEs) were reported over the course of this study. Sixteen (16) of the 27 AEs were reported by 5 subjects after receiving treatment D, Hycodan<sup>®</sup> oral solution

Overall, hydrocodone bitartrate/pseudoephedrine HCl/chlorpheniramine maleate oral solution,

5 mg/60 mg/4 mg was well tolerated as a single dose of 5 mL (5 mg/60 mg/ 4 mg per 5 mL) administered under fasted conditions. Overall, the most common AEs were nausea and headache, each reported by 4 subjects (14.3%). Dizziness was reported by 3 subjects (10.7%) and two (2) subjects (7.1%) experienced vessel puncture site pain. All adverse events were mild or moderate in intensity.

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this page is the manifestation of the electronic signature.**  
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/s/

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Sheetal Agarwal  
7/20/2009 05:44:09 PM  
BIOPHARMACEUTICS

Sally Choe  
7/20/2009 09:41:02 PM  
BIOPHARMACEUTICS

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</b>		<b>Clinical Pharmacology Tracking/Action Sheet for Formal/Informal Consults</b>	
<b>From: Sandra Suarez-Sharp</b>		<b>To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission</b>	
<b>DATE OF SUBMISSION:</b> November 6, 2008	<b>NDA No.:</b> 22-439 <b>Serial No.:</b>	<b>BLA No.</b>	<b>DATE OF REVIEW:</b> December 4, 2008
<b>NAME OF DRUG:</b> (b) (4)  (Hydrocodone Bitartrate, Chlorpheniramine maleate, and Pseudoephedrine Hydrochloride) Oral Solution	<b>PRIORITY CONSIDERATION:</b> <b>S or P</b>	<b>Date of informal/Formal Consult:</b> November 12, 2008	
<b>NAME OF THE SPONSOR:</b> Cypress Pharmaceutical, Inc.			
<b>TYPE OF SUBMISSION</b>  <b>CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE</b>			
<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>			
<b>REVIEW ACTION</b>			
<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 type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER ( <i>SPECIFY BELOW</i> ): [Please see attached memo]			
<b>REVIEW COMMENT(S)</b>			
<input checked="" type="checkbox"/> NEED TO BE COMMUNICATED TO THE SPONSOR <input type="checkbox"/> HAVE BEEN COMMUNICATED TO THE SPONSOR			
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> <b>1. Summary</b>			

This NDA filing review is for (b) (4) Oral Solution. (b) (4) Oral Solution is a combination product containing Hydrocodone Bitartrate (HC) 5 mg, Chlorpheniramine (CPM) 4 mg, and Pseudoephedrine Hydrochloride (PSE) 60 mg per 5 mL. The sponsor is seeking approval of (b) (4) for (b) (4)

(b) (4). The proposed dosing regimen is 5 mL every 4-6 h, as needed, NTE 4 doses (20 mL) in 24 h in adults (b) (4)

(b) (4) HC is approved for the symptomatic relief of cough in Hycodan (NDA 05-213), CPM is an accepted antihistamine in the OTC Monograph (21 CFR §341.12), and PSE is an accepted nasal decongestant in the OTC Monograph (21 CFR §341.20).

The sponsor is filing the NDA for (b) (4) through 505(b)(2) pathway, relying on the Agency's findings in DESI review for HC and OTC Monograph for PSE and CPM to support the safety and efficacy of their combination drug product. In support of this NDA the sponsor has included the results of one clinical pharmacology study (S08-0179) entitled "A Relative Bioavailability and Drug-Drug Interaction Study of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide per 5 mL) Under Fasted Conditions" This study is a randomized, four-period crossover, open-label, single dose study conducted in 28 healthy adult volunteers. Following an overnight fast of at least 10 hours, subjects received a single oral dose of the following treatments with a washout period of 14 days between treatments:

- A. 5 mL (5 mg/4 mg/60 mg per 5 mL oral solution) of the test product, hydrocodone bitartrate/chlorpheniramine maleate/pseudoephedrine HCl oral solution or
- B. 5 mL (60 mg per 5 mL oral solution) of pseudoephedrine HCl oral solution; or
- C. 5 mL (4 mg per 5 mL oral solution) of chlorpheniramine maleate oral solution; or
- D. 5 mL (5 mg/1.5 mg per 5 mL oral solution) of Hycodan® oral solution.

Serial blood samples for PK determination of HC, PSE and CPM were collected at pre-dose and up to 96 hours. Plasma samples were analyzed using a validated LC/MS/MS method. Analyses of variance (ANOVA) were performed on the relevant pharmacokinetic parameters. The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. 90% confidence intervals for the difference between drug formulation least-squares means (LSM) were calculated for the parameters AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> using ln-transformed data. The comparisons of interest are: D vs. A (hydrocodone); B vs. A (pseudoephedrine); and C vs. A (chlorpheniramine).

The results of the statistical analysis for the comparison of interest are summarized in Table 1 below. A preliminary assessment of the data indicates that (b) (4) is equally bioavailable to Hycodan solution in terms of AUC. However, the 90% CI of the ratio of geometric C<sub>max</sub> means was outside of the goal post for BE (78.9-93.8). (b) (4) was bioequivalent to the reference products CPM solution and PSE solution, indicating that HC and CPM do not affect the systemic

exposure of PSE when the 3 components are coadministered. The data also indicate that HC and PSE do not affect the systemic exposure of CPM when the 3 components are coadministered. The PK study, however, was not designed to determine the effect of PSE and CPM on the systemic exposure of HC. A comparison of the test product vs. Hycodan does not address for the potential effect of CPM or PSE on the PK of HC due to the possibility of a confounded formulation effect.

**Table 1.** Summary of statistical analysis of the log-transformed data (b) (4)



It is noted that information on the potential for food effect on the PK of REZIRA<sup>(b) (4)</sup> was not included in the present submission. Reference is made to the pre-IND meeting with the sponsor where the DPAP recommended the assessment of food effect (b) (4)

It is also noted that no study was conducted to determine if the proposed product is bioequivalent to the monoproducts administered concurrently in separate ingredient preparations (formulation effect). This reviewer is of the opinion that formulation effect can be indirectly determined if the following is demonstrated: 1) the combination product under investigation is bioequivalent to the monoproducts administered in separate arms and 2) there is no drug-drug interaction between the active components in the combination product.

### 1.1 Recommendation

The Division of Clinical Pharmacology 2 (DCP2) has reviewed NDA 22-439 submitted on November 6, 2008 for filing purposes. The NDA is filable from a clinical pharmacology perspective. The following comments should be conveyed to the sponsor as part of the 74-day letter.

#### Comments to Sponsor:

- A preliminary assessment of the data indicates that the Hydrocodone C<sub>max</sub> for your product is out of the 80-125% goal post of BE. The approval of the proposed product will be a review issue.
- Provide the formulation (components and composition) of the reference products

(Chlorpheniramine maleate and Pseudoephedrine HCl) used in Study S08-0179. You should note that a claim in terms of lack of drug-drug interaction between the components of your proposed product may not hold true if the formulation of the references products for pseudoephedrine (PSE) and chlorpheniramine (CPM) are substantially different than that for (b) (4).

- The PK study (S08-0179) as designed would not determine the effect of PSE and CPM on the systemic exposure of Hydrocodone (HC). A comparison of (b) (4) vs. Hycodan (TRT A vs. D) may not address for the potential effect of CPM or PSE on the PK of HC due to the possibility of a confounded formulation effect. This information is required especially because NDA 21-442 (REZIRA (b) (4) : Hydrocodone, Pseudoephedrine Oral Solution) relies on the results of this study. Therefore, you are requested to provide information on the potential effect of PSE and CPM on the PK of hydrocodone. You may rely on published information or conduct an additional PK study.
- It is noted that information on the potential of food effect on the PK of (b) (4) was not included in the present submission. Reference is made to the pre-IND meeting for IND 76402 (01/14/2008) with the sponsor where the DPAP recommended the assessment of food effect (b) (4). Therefore, you are requested to provide information on the effect of food on the BA of HC, PSE and CPM. You may choose to submit food effect information based on published literatur (b) (4) or conduct and additional food effect study.

General Comment (not to be submitted to sponsor):

- It was discussed during the filing meeting that DSI inspection is not needed for this product because it failed bioequivalence.

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

**Background**

The sponsor is filing the NDAs for their combination drug product through 505(b)(2) pathway, relying on the Agency’s findings in DESI review for hydrocodone and OTC Monograph for PSE and CPM to support the safety and efficacy of their combination

drug product. HC is approved for the symptomatic relief of cough in Hycodan (NDA 05-213), CPM is an accepted antihistamine in the OTC Monograph (21 CFR §341.12), and PSE is an accepted nasal decongestant in the OTC Monograph (21 CFR §341.20).

HC is an analgesic opioid and antitussive. The precise mechanism of action of HC and other opioids is not known. It is believed to relate to the existence of opioid receptors in the central nervous system. HC and related compounds are used for the symptomatic relief of non-productive cough associated with upper and lower respiratory tract congestion. HC's binding to plasma protein ranges between 19% and 45%. The mean peak serum concentration (C<sub>max</sub>) of HC is 23.6 ± 5.2 ng/mL when administered as an oral dose of 10 mg. Maximum serum levels are reached in 1.3 ± 0.3 hours and the elimination half-life (t<sub>1/2</sub>) was determined to be 3.8 ± 0.3 hours. HC exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6- $\alpha$ - and 6- $\beta$ -hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the O-demethylation of HC and contributes to the total analgesic effect of HC.

PSE is a sympathomimetic amine that acts as an  $\alpha$ -adrenergic agonist. It is indicated for use as a nasal decongestant. The T<sub>max</sub> for PSE following 60 mg or 120 mg doses is from 1.4 to 2 hours. Administration of a single large dose of 180 mg PSE increases T<sub>max</sub> to 3 hours. The reported t<sub>1/2</sub> is 4-8 hours for pseudoephedrine.

CPM is a propylamine that belongs to the alkylamine class of antihistamines. CPM inhibits histamine action in the gastrointestinal and respiratory tracts by blocking the H<sub>1</sub> receptor. CPM binding to plasma protein ranges between 69% and 72%. It is extensively metabolized in the gastrointestinal mucosa. Following oral administration of immediate-release CPM tablets, a C<sub>max</sub> of 16-71 ng/mL is achieved within 2-3 hours.

HC, CPM and PSE are not currently approved in combination in the USA as a new drug, but each is offered in approved products separately. In the USA, HC is marketed as Hycodan® syrup and is a prescription product, CPM and PSE are marketed as Codeprex® and Advil Allergy Sinus, respectively, and both are over-the-counter (OTC) products.

### Drug Product

(b) (4) Oral Solution is a clear, colorless to light yellow liquid with a grape odor for oral administration only. Each milliliter of the solution contains 1.0 mg of HC, 0.8 mg of CPM, and 12 mg of PSE as the active ingredients. The components and composition for (b) (4) are shown in Table 1.

Table 1. Unit Composition of (b) (4) Oral Solution						
Component	Reference to Quality Standards	Function	Unit Composition			
			% w/v (b) (4)	mg/mL	(b) (4)	mg/480 mL
Hydrocodone Bitartrate	USP	Active ingredient	(b) (4)	1.0	(b) (4)	480

Chlorpheniramine Maleate	USP	Active ingredient	(b) (4)	0.8	(b) (4)	384					
Pseudoephedrine Hydrochloride	USP	Active ingredient	(b) (4)	12.0	(b) (4)	5760					
Citric Acid, Anhydrous	USP	(b) (4)									
Sodium Citrate	USP										
Sodium Saccharin	USP										
Methylparaben	NF										
Propylparaben	NF										
Sucrose	NF										
Glycerin, (b) (4)	USP										
Propylene Glycol	USP										
Grape Flavor (b) (4)	In-house										
Water, Purified	USP										
NF = National Formulary.											

### Clinical Pharmacology Studies Included in the Present Submission

**Study (S08-0179):** “A Relative Bioavailability and Drug-Drug Interaction Study of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide per 5 mL) Under Fasted Conditions”

### STUDY OBJECTIVES

The objectives of this study were:

- 1) To determine and compare the rate and extent of absorption of hydrocodone from the following products under fasted conditions:
  - a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL)
  - b) Hycodan® Syrup (5 mg hydrocodone bitartrate / 1.5 mg homatropine methylbromide per 5 mL)
- 2) To evaluate the drug-drug interaction of pseudoephedrine with hydrocodone and clorpheniramine from the following products under fasted conditions:
  - a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL)
  - b) Pseudoephedrine Oral Solution (60 mg per 5 mL)
- 3) To evaluate the drug-drug interaction of chlorpheniramine with pseudoephedrine and hydrocodone from the following products under fasted conditions:
  - a) Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg / 60 mg / 4 mg per 5 mL)

b) Chlorpheniramine Oral Solution (4 mg per 5 mL)

**Overall Study Design and Plan**

This study is a randomized, four-period crossover, open-label, single dose study conducted in 28 healthy adult volunteers (male and female). Following an overnight fast of at least 10 hours, subjects received a single oral dose of the following treatments with a washout period of 14 days between treatments:

- A. 5 mL (5 mg/4 mg/60 mg per 5 mL oral solution) of the test product, hydrocodone bitartrate/chlorpheniramine maleate/pseudoephedrine HCl oral solution; or
- B. 5 mL (60 mg per 5 mL oral solution) of pseudoephedrine HCl oral solution; or
- C. 5 mL (4 mg per 5 mL oral solution) of chlorpheniramine maleate oral solution; or
- D. 5 mL (5 mg/1.5 mg per 5 mL oral solution) of Hycodan® oral solution.

**Blood Sampling**

Serial blood samples for PK determination of HC, PSE and CPM were collected at pre-dose and up to 96 hours. For treatments A and C blood samples were to be collected within 90 minutes prior to dosing (0 hour) and after dose administration at study hours 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96. For treatments B and D blood samples were to be collected within 90 minutes prior to dosing (0 hour) and after dose administration at study hours 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24.

**Analytical Methodology**



### Data Analysis

(b) (4)

### Prior and Concomitant Medication

Subjects were not to be allowed to use prescription medications during the 14 days preceding the study and throughout the study with the exception of contraceptive medication . Subjects were not to be allowed to use non-prescription medications during the 7 days preceding the study and throughout the study.

### Results

Figure 1-3 show the concentration-time profile following administration of the treatments. A summary of the mean PK parameters for HC, PSE and CPM following administration of the treatments is shown in Table 1. The results of the statistical analysis for the comparison of interest are summarized in Table 2. A preliminary assessment of the data indicates that REZIRA<sup>(b) (4)</sup> is equally bioavailable to Hycodan solution in terms of AUC. However, the 90% CI of the ratio of geometric Cmax means was outside of the goal post for BE (78.9-93.8). REZIRA<sup>(b) (4)</sup> was bioequivalent to the reference products CPM solution and PSE solution, indicating that HC and CPM do not affect the systemic exposure of PSE when the 3 components are coadministered. The data also indicate that HC and PSE do not affect the systemic exposure of CPM when the 3 components are coadministered. The PK study, however, was not designed to determine the effect of PSE and CPM on the systemic exposure of HC. A comparison of the test product vs. Hycodan does not address for the potential effect of CPM or PSE on the PK of HC due to the possibility of a confounded formulation effect.

It is noted that information on the potential of food effect on the PK of REZIRA<sup>(b) (4)</sup> was not included in the present submission. Reference is made to the pre-IND meeting with the sponsor where the DPAP recommended the assessment of food effect <sup>(b) (4)</sup>



**Figure 1.** Mean plasma concentration-time profile for HC following single dose administration 5 mL (5 mg/4 mg/60 mg per 5 mL oral solution) of HC /CPM/PSE oral solution (Test) and 5 mL (5 mg/1.5 mg per 5 mL oral solution) of Hycodan® oral solution (Reference).



**Figure 2.** Mean plasma concentration-time profile for PSE following single dose administration of 5 mL of Test and 5 mL (60 mg per 5 mL oral solution) of PSE HCl oral solution (Reference).



**Figure 3.** Mean plasma concentration-time profile for CPM following single dose administration of 5 mL of Test and 5 mL (4 mg per 5 mL oral solution) of CPM oral solution (Reference).

**Table 1.** Summary of mean PK parameters following single dose administration of the treatments

Treatments (Dose, Dosage Form, Route) [Product ID]	Drug	Mean Parameters ( $\pm$ SD)				
		AUC (ng·h/mL)	AUC (ng·h/ mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)
5 mg HCB 60 mg PSE Trt A: (1 dose, 5 mL oral solution) [P08001] 4 mg CHL	HC	(b) (4)				
	PSE					
	CPM					
Trt B: (1 dose, 5 mL oral solution) [P08043] 60 mg PSE	PSE					
Trt C: (1 dose, 5 mL oral solution) [P08045] 4 mg CPM	CPM					
Trt D: (1 dose, 5 mL oral solution) [400804NV] 5 mg HYC	HYC					

**Table 2.** Summary of statistical analysis of the log-transformed data

Comparison	PK parameter	Point estimates (ratio of geometric means)	90% CI
Test product/Hycodan TRT A/D	AUC t AUCinf Cmax		(b) (4)
Test product/PSE (TRT A/B)	AUC t AUCinf Cmax		
Test product/CPM (TRT A/C)	AUC t AUCinf Cmax		

### Conclusion

The table below summarizes the overall content of the clinical pharmacology information provided by the sponsor to support the request for the approval of this NDA. The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues.

Study Title/Description	Tabular listing/ PK summary	Analytical method	PK parameters	Statistical analysis
Study (S08-0179):“A Relative Bioavailability and Drug-Drug Interaction Study of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide per 5 mL) Under Fasted Conditions”	√	√	√	√

**Office of Clinical Pharmacology**  
*New Drug Application Filing and Review Form*

<b>General Information About the Submission</b>			
	Information		Information
NDA Number	22-439	Brand Name	(b) (4) Oral Solution
OCP Division	II	Generic Name	(Hydrocodone Bitartrate, Chlorpheniramine maleate, and Pseudoephedrine Hydrochloride) Oral Solution
Medical Division	DPAP	Drug Class	Cough suppressant/antihistamine/nasal decongestant
OCPB Reviewer	Sandra Suarez-Sharp	Indication(s)	(b) (4)
OCP Team Leader (Acting)	Wei Qiu	Dosage Form	Oral Solution
PM Reviewer		Dosing Regimen	The proposed dosing regimen is 5 mL every 4-6 h, as needed, NTE 4 doses (20 mL) in 24 h in adults (b) (4)
Date of Submission	November 6, 2008	Route of Administration	Oral
Estimated Due Date of OCP Primary Review	April 2009	Sponsor	Cyrpass
PDUFA Due Date	Sep 6, 2009	Priority Classification	s
Division Due Date	July 7, 2009		

**Clin. Pharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Meta analysis:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	<b>1</b>	<b>x</b>		Study (S08-0179):“A Relative Bioavailability and Drug-Drug Interaction Study of Hydrocodone, Pseudoephedrine, and Chlorpheniramine Oral Solution (5 mg/60 mg/4 mg per 5 mL), Pseudoephedrine Oral Solution (60 mg per 5 mL), Chlorpheniramine Oral Solution (4 mg per 5 mL) and Hycodan® Syrup (5 mg Hydrocodone Bitartrate/1.5 mg Homatropine Methylbromide per 5 mL) Under Fasted Conditions”
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>QTC STUDIES (PHASE 1)</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>	<b>1</b>	<b>1</b>		

<b>Filability and QBR comments</b>				
	<b>“X” if yes</b>	<b>Comments</b>		
<b><u>Application filable ?</u></b>	<b>X</b>	Reasons if the application is <b>not</b> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
<b><u>Comments sent to firm ?</u></b>		Comments have been sent to firm (or attachment included). FDA letter date if applicable. Please see Clinical Pharmacology filing review for comments/deficiencies.		
<b>QBR questions (key issues to be considered)</b>		<ol style="list-style-type: none"> <li>1. Is (b) (4) (Hydrocodone Bitartrate, Chlorpheniramine maleate, and Pseudoephedrine Hydrochloride) Oral Solution equivalent to the reference products (Hycodan, CPM and PSE oral solutions)?</li> <li>2. What is the degree of drug-drug interaction between HC, PSE and CPM in the combination product (b) (4) ?</li> <li>3. What is the effect of food on the bioavailability of (b) (4) ?</li> </ol>		
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>				
<b>Secondary reviewer Signature and Date</b>				

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/s/

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Sandra Suarez  
1/9/2009 11:34:45 AM  
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Wei Qiu  
1/9/2009 11:48:09 AM  
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