CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-585

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-585
Proprietary Drug Name:	MUCINEX™ D
Generic Name:	Guaifenesin/pseudoepherine
Indication:	Expectorant/Nasal decongestant.
Dosage Form:	Bilayer Tablet: immediate/Extended Release Tablet
Strength:	1200mg/120 mg and 600/60 mg
Route of Administration:	Oral
Dosage and administration:	adults and children 12 years and older: For the 600mg/60mg product, two tablets every 12 hours; not more than 4 tablets in 24 hours For the 1200mg/120mg product: one tablet every 12 hours; not more than 2 tablets in 24 hours. children under 12 years of age: do not use
Applicant:	Adams Laboratories, Inc.
Clinical Division:	DPADP (HFD-570)
Submission Dates:	January 31, 2003
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.

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2. EXECUTIVE SUMMARY

Adams Laboratories, Inc. is seeking approval of Mucinex-D extended release/immediate tablets for the treatment of cough/nasal decongestion. Mucinex-D tablets contain guaifenesin and pseudoephedrine HCl (PSE) at doses currently marketed as OTC products. Mucinex-D tablets are presented in two dosage strengths, 1200mg guaifenesin/ 120 mg PSE (Maximum Strength) and 600 mg guaifenesin/60 mg PSE (Regular Strength) and will be marketed as an OTC product. The proposed dosing regimen is 1200mg/120mg every 12 hours; not more than 2400/240 mg in 24h.

The sponsor assessed the clinical pharmacology of Mucinex in 7 studies, but only 5 were considered to be relevant to the NDA. There are no major clinical pharmacology issues.

2.1 Comments to sponsor

- The following dissolution criterion specifications are recommended for guaifenesin and pseudoephedrine HCl from the Mucinex-D regular and maximum strength:

Maximum Strength

Time	
1 hour	
2 hour	
6 hour	
12 hour	

Regular Strength

Time	
1 hour	
2 hour	
6 hour	
12 hour	

- The interim dissolution specifications will be finalized when you provide in-vitro dissolution data at release and during stability of the batches produced under new manufacturing parameters.
- You are requested to provide the appropriate information (refer to principles of SUPAC-MR guidance for industry) to link the batches of Mucinex-D produced under new manufacturing conditions to the batch of Mucinex-D used in the pivotal BE study.

2.2 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-585 submitted on January 31st, 2003. We found this NDA acceptable from a CPB standpoint provided that the sponsor agrees with the Agency's recommendations for dissolution specifications. The above comments should be conveyed to the sponsor.

Reviewer
Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader

cc: NDA 21-585 : Division File
HFD-870: Malinowski, Hunt

HFD-570: Fadiran, Lee, Chowdhury, Zeccola, Suarez-Sharp

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2.3. Summary of clinical Pharmacology and Biopharmaceutics Findings

The sponsor, Adams Laboratories, Inc., is seeking approval of Mucinex-D an extended release bilayer tablet for the treatment of cough and nasal congestion. This NDA is a 505(b)(2) application for guaifenesin and PSE extended release formulation at the proposed dose regimen of 1200mg/120mg every 12 hours; not more than 2400/240 mg in 24 hours. The sponsor requests approval of two dosage strength tablets: guaifenesin 600 mg/PSE 60 mg tablets, and guaifenesin 1200 mg/PSE 120 mg tablets.

Mucinex™, a single-ingredient, extended release tablet formulation of guaifenesin (NDA 21-282) received FDA's approval for two dosage strengths of product (600- and 1200 mg). Currently, the Mucinex™ product is the only extended release guaifenesin product that is approved in the United States. Pseudoephedrine hydrochloride in oral dosage form has been approved by the agency as an OTC single ingredient extended-release 120 mg and 240 mg tablet dosage strength.

In support of this application the sponsor submitted the results of seven safety and pharmacokinetic studies conducted in healthy male and female volunteers. Two of these studies were not reviewed because they were conducted with experimental formulations of the product. The intention of the PK studies were to determine the in vivo BE of Mucinex-D compared to an already approved reference, to establish dose proportionality of the two strengths of Mucinex proposed for marketing, to assess the effect of food on the BA of guaifenesin and PSE delivered from the Mucinex-D product, to assess a possible drug-drug interaction between guaifenesin and PSE, and to characterize the PK parameters of Mucinex-D at steady state. Dissolution data was also provided to support the dissolution methods and specification proposed for this product.

BE Assessment

In a single dose, three-way crossover study the sponsor showed that Mucinex-D was bioequivalent to the reference products Mucinex extended released tablet and Sudafed 12hrs extended released tablets. The 90% CI for both guaifenesin and PSE were within BE specifications (see Table 1).

Table 1. Point estimates and 90% confidence intervals for the log-transformed Cmax, AUCt, and AUCinf values of guaifenesin and PSE following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer' findings	Sponsor's findings	This reviewer' findings
	Guaifenesin				
TRT B/ TRT A	Cmax	92.3	92.3	83.7-102	83.65-101.99
	AUCt	102	101.8	96-108	96.0-107.84
	AUCinf	99.2	99.16	93.8-105	93.76-104.87
	PSE				
TRT B/ TRT A	Cmax	105	105.06	101-109	100-.93-109.36
	AUCt	104	101.01	99.3-108	96.16-106.10
	AUCinf	101	101.27	96.8-106	96.84-105.9

TRT A: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour with 240 mL of water after an overnight fast.

TRT B: 1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation with 240 mL of water after an overnight fast.

Dose Proportionality

Following single administration (in a cross-over study) the sponsor showed that the maximum strength of Mucinex-D was proportional to the regular strength of Mucinex D in terms of Cmax and AUC. The 90% CI for the log-transformed and dose-normalized PK parameters (Cmax and AUC) meet the goal post for BE requirements for both guaifenesin and PSE. This indicated that the 1200 mg/120mg strength of Mucinex-D was proportional for both guaifenesin and PSE to the 600 mg/ 60mg strength of Mucinex-D.

PK at Steady State

A comparable systemic exposure (in terms of Cmax and AUC) between the extended release formulation and the reference products (Mucinex and Sudafed-12hrs) was demonstrated in a 2-way crossover, multiple dose study (steady state).

Mucinex-D (guaifenesin/PSE/1200mg/120mg) and the reference product (Mucinex + Sudafed) were bioequivalent in terms of PSE and guaifenesin following multiple administration under fasted conditions (see Table 2). Ninety percent CI for the ratio of the log-transformed PK parameters were within goal post for BE (80-125) for Cmax and AUCss. The arithmetic mean for the Cmin of guaifenesin released from the Mucinex-D tablet was 2.25-fold higher compared to that for the reference (Mucinex: guaifenesin 1200 mg) (see Table 2).

This 2.25-fold increased in guaifenesin Cmin from the Mucinex-D formulation may not be clinically relevant: higher Cmin may improve the efficacy of the drug product and since the Cmin is less than 10% of Cmax, safety may not be a concern.

Table 2. Point estimates and 90% confidence intervals for the log-transformed Cmax, Cmin and AUCss values of guaifenesin and PSE following multiple administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
Mucinex-D/ Reference	Cmax	99	90.9-108
	AUCss	111	102-119
	Cmin	244	155-383
	Pseudoephedrine		
Mucinex-D/ Reference	Cmax	101	95.3-107
	AUCss	95.4	86-106
	Cmin	101	95.7-106

Drug-Drug Interaction (DDI)

The possible DDI between guaifenesin and PSE was addressed in a single dose, 3-way crossover study. The pharmacokinetics of guaifenesin were not affected by the presence of PSE and vice-versa. Ninety percent confidence intervals for the log-transformed PK parameters of guaifenesin (Cmax, AUCt, AUCinf) and PSE administered alone (Mucinex or Sudafed) versus the coadministration of the combined products were within goal post for BE.

Effect of Food

The effect of food on the BA of guaifenesin and PSE from the Mucinex-D formulation was assessed in two studies. One of these studies was a single dose, 2-way crossover study comparing the Mucinex-D maximum strength with and without food. This study showed that a high-fat and high-caloric meal had no effect on the bioavailability of PSE from the Mucinex-D tablets. Ninety percent CI were within BE requirements (80-125). However, food (high-fat

breakfast) decreased the Cmax and AUCinf of guaifenesin by 26.5% and 8.5%, respectively. The Tmax was delayed by approximately one hour (see Table 3).

Table 3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
Fed/fasted	Cmax	74	65.9-83.2
	AUCt	90	84.6-95.5
	AUCinf	90.2	84.7-96
	Pseudoephedrine		
Fed/fasted	Cmax	106	101-112
	AUCt	98.5	93.5-104
	AUCinf	98.6	93.6-104

The other study was a single dose, 2-way crossover study conducted to determine the relative bioavailability of an experimental formulation containing 1200 mg guaifenesin and 120 mg PSE compared to reference formulation (Mucinex and Sudafed 12hrs) given both in the presence of food. This study showed that food did not have an effect on the BA (Cmax and AUC) of PSE delivered from Mucinex-D. The 90% CI comparing the test and reference were within BE specifications. However, food decreased the Cmax of guaifenesin from the Mucinex D formulation compared to the reference product. The arithmetic mean for the Cmax of guaifenesin released from the Mucinex-D tablet in the presence of food was 25% lower than that for reference Mucinex (guaifenesin 1200 mg)

This reviewer is of the opinion that the 26.5% decreased in Cmax and delayed on Tmax of guaifenesin may not be clinically relevant and therefore, Mucinex-D can be taken without regards of meals.

Dissolution Information

The dissolution method and specification for Mucinex-D regular and maximum strengths proposed by the sponsor are as follows:

Maximum Strength

Method: USP basket,

Time	
1 hour	
2 hour	
6 hour	
12 hour	

Regular Strength

Method: USP basket,

Time	
1 hour	
2 hour	
6 hour	
12 hour	

These method and specifications were established based on previous recommendations by the FDA for the already approved extended release product Mucinex and also and most importantly, based on dissolution studies using different media and dissolution speeds.

Upon review of the submitted data, this reviewer aggress that the USP Apparatus 1 (basket), a [redacted] is a discriminating dissolution method for the dissolution testing of Mucinex® D, since both active ingredients reach a release plateau at the 12-hour interval and release at least [redacted] of both active ingredients at the 8-hour interval.

However, in terms of specifications, this reviewer proposes a modification (bolded number) to the specifications proposed at the latest time point (12 hour). The suggested specifications for Mucinex-D for both regular and maximum strength are as follows:

Maximum Strength
Method: USP basket

Time	
1 hour	[redacted]
2 hour	
6 hour	
12 hour	

Regular Strength
Method: USP basket

Time	
1 hour	[redacted]
2 hour	
6 hour	
12 hour	

Due to friability and moisture content failures, the sponsor adjusted tableting manufacturing parameters and produced additional pilot scale batches after the primary stability batch manufacture. According to the sponsor, the tablets manufactured under new manufacturing parameters [redacted]) had a tendency to [redacted] after a few days, however, this [redacted] did not affect the friability or dissolution profile of the tablets. In fact, mean dissolution profiles for guaifenesin and PSE from Mucinex-D regular and maximum strength were within dissolution specifications (data not shown here). However, no release or stability data for batches made with the improved parameters have been provided. Therefore, the dissolution specifications proposed are interim until they provide dissolution testing data obtained at release and during stability of the batches produced under new manufacturing parameters.

3. QUESTION BASED REVIEW

3.1 General Attributes

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

Drug Substance

The active ingredients in Mucinex™ D are guaifenesin and pseudoephedrine HCl. Guaifenesin, has been used widely in the United States for over 50 years and is a well known expectorant. The sponsor, has received marketing approval for Mucinex 600 mg and 1200 mg tablets (Guaifenesin ER). Pseudoephedrine HCl, is also a well known active pharmaceutical ingredient used as a decongestant.

Drug Product

Mucinex™ D (guaifenesin/pseudoephedrine HCl) extended release tablets were designed as a line extension to Mucinex 600 mg and 1200 mg tablets approved under NDA 2 1-282. Mucinex D tablets are presented in two dosage strengths, 1200mg guaifenesin/ 120 mg PSE (Maximum Strength) and 600 mg guaifenesin/60 mg PSE (Regular Strength). Mucinex D tablets are manufactured using standard pharmaceutical technology using [redacted]. The Maximum Strength product consists of a white immediate release layer (IR) containing 200 mg of guaifenesin and a pink modified release layer (MR) containing 1000 mg of guaifenesin and 120mg of pseudoephedrine HCl. The Regular Strength product consists of a white immediate release layer (IR) containing 100 mg of guaifenesin and an orange modified release layer (MR) containing 500mg of guaifenesin and 60 mg of pseudoephedrine HCl. The formulation rationale for Mucinex-D was based on Mucinex (600 mg and 1200 mg) tablets (NDA 2 1-282) including PSE as the decongestant in an amount not to exceed the recommended daily dose. The IR layer in Mucinex-D is identical to the IR layer used in the approved Mucinex product (NDA 21-282). The MR layer in Mucinex-D is very similar to the MR layer used in Mucinex tablets with minor adjustments in the polymeric blend to control the release profile of the decongestant and keep the release profile of the expectorant as close to Mucinex as possible. The components and composition on Mucinex-D regular and maximum strength are shown in the Tables below.

Table 3.1.1.1. Mucinex D Maximum Strength Tablet (1200 mg Guaifenesin/120 mg Pseudoephedrine HCl)

Component	Amount (mg/tablet)	Representative batch (kg) IR layer	Representative batch (kg)[1] MR layer
Guaifenesin	[redacted]	[redacted]	[redacted]
Hydroxypropyl methylcellulose	[redacted]	[redacted]	[redacted]
Pseudoephedrine HCl	[redacted]	[redacted]	[redacted]
Microcrystalline cellulose	[redacted]	[redacted]	[redacted]
Sodium starch glycolate	[redacted]	[redacted]	[redacted]
Carbomer 934P	[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]	[redacted]
FD&C Red #40 Aluminun Lake	[redacted]	[redacted]	[redacted]
Water purified[3]	[redacted]	[redacted]	[redacted]
Total weight	1587	[redacted]	[redacted]

[1] Based on batch size o [redacted] tablets

[2] Guaifenesin direct compression used in the manufacturing process consists of [redacted] guaifenesin, USR an[redacted] hydroxypropyl methylcellulose, USP [redacted] l with purified water, USP.

Table 3.1.1.2. Mucinex D Regular Strength Tablet (1200 mg Guaifenesin/120 mg Pseudoephedrine HCl)

Component	Amount (mg/tablet)	Representative batch (kg) IR layer	Representative batch (kg)[1] MR layer
Guaifenesin			
Hydroxypropyl methylcellulose			
Pseudoephedrine HCl			
Microcrystalline cellulose			
Sodium starch glycolate			
Carbomer 934P			
Magnesium stearate			
FD&C Yellow #6 Aluminum Lake			
Water purified[3]			
Total weight	794.1		

[1] Based on batch size of tablets

[2] Guaifenesin direct compression used in the manufacturing process consists of guaifenesin, USR and hydroxypropyl methylcellulose, USP , with purified water, USP.

[3]

The tablet size for all the batches used in the PK studies was tablets for the regular and maximum strengths, respectively which represents more than of the commercial batch size (respectively).

3.1.2 What are the proposed therapeutic indication and dosage recommendations for Mucinex-D tablets?

Mechanism of Action and Proposed Indication:

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

The proposed indications for Mucinex-D tablet are as follows:

- help loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive
- temporarily relieves nasal congestion due to: common cold, hay fever, upper respiratory allergies,
- temporarily restores freer breathing through the nose
- promotes nasal and/or sinus drainage
- temporarily relieves sinus congestion and pressure

DOSAGE AND ADMINISTRATION (as per proposed label)

Adults and children 12 years and older: For the 600mg/60mg product, two tablets every 12 hours; not more than 4 tablets in 24 hours

For the 1200mg/120mg product: one tablet every 12 hours; not more than 2 tablets in 24 hours.

Children under 12 years of age: do not use

3.2 General Clinical Pharmacology

3.2.1 Is the systemic exposure after single administration of the extended release formulation comparable (by bioequivalent standards) to that after the administration of the reference products (Mucinex and Sudafed-12hrs)?

Study 2002-01A was a prospective, open-label, single dose, randomized, 3-way crossover study in 36 healthy male and female volunteers conducted to determine the relative bioavailability of an experimental formulation of Mucinex-D containing 1200 mg guaifenesin and 120 mg PSE compared to that of two reference formulations in normal. The subjects were randomized and placed into one of three treatment groups.

TRT A: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg PSE as Sudafed 12 Hour after an overnight fast.
TRT B: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation after an overnight fast.
TRT C: 600mg guaifenesin and 60 mg PSE as an experimental formulation after an overnight fast.

The mean PK parameters and a graphical representation of the individual AUC of guaifenesin and PSE are shown in Table 3.2.1.1 and Figures 3.2.1.1 and 3.2.1.2.

From this study the following conclusion was reached:

- The 1200 mg guaifenesin/120mg of pseudoephedrine hydrochloride extended release formulation (Mucinex-D, TRT B) was bioequivalent to the 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour (TRT A). The 90% CI were within the 80-125 goal post for BE for both guaifenesin and PSE (Table 3.2.1.2)

Table 3.2.1.1. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
	Guaifenesin				
TRT A	1940 (889)	0.77 (0.22)	7764 (3329)	8061 (3329)	4.74 (4.13)
TRT B	1813 (900)	1.04 (0.49)	8002 (3677)	8124 (3677)	2.21 (1.19)
TRT C	920 (481)	0.99 (0.46)	3529 (1437)	3565 (1442)	1.76 (0.92)
	Pseudoephedrine				
TRT A	250 (53.4)	6.9 (1.76)	3479 (805)	3847 (910)	5.8 (1.02)
TRT B	263 (58.5)	5.11 (1.78)	3591 (824)	3650	5.2 (0.9)
TRT C	141 (30.3)	4.9 (1.6)	1781 (445)	1968 (477)	5.6 (1.02)

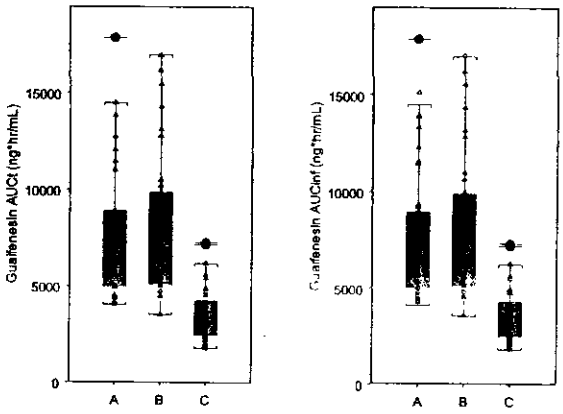


Figure 3.2.1.1. Individual guaifenesin AUCt and AUC inf values following single administration of the treatments: TRT **A:** 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour; TRT **B:** 1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation, and TRT **C:** 600mg guaifenesin and 60 mg pseudoephedrine hydrochloride as an experimental formulation.

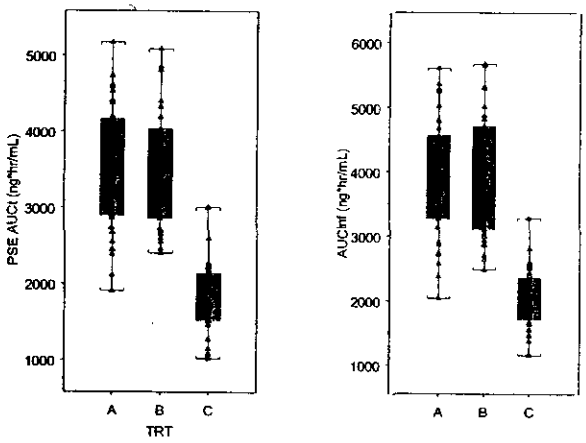


Figure 3.2.1.2. Individual PSE AUCt and AUCinf values following single administration of the treatments.

Table 3.2.1.2. Point estimates and 90% confidence intervals for the log-transformed Cmax, AUCt, and AUCinf values of guaifenesin and PSE following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer's findings	Sponsor's findings	This reviewer's findings
	Guaifenesin				
TRT B/ TRT A	Cmax	92.3	92.3	83.7-102	83.65-101.99
	AUCt	102	101.8	96-108	96.0-107.84
	AUCinf	99.2	99.16	93.8-105	93.76-104.87
	PSE				
TRT B/ TRT A	Cmax	105	105.06	101-109	100-.93-109.36
	AUCt	104	101.01	99.3-108	96.16-106.10
	AUCinf	101	101.27	96.8-106	96.84-105.9

3.2.2 Are the PK parameters of Mucinex-D components linear and dose-proportional?

An additional objective of Study 2002-01 was to assess the dose-proportionality of guaifenesin and PSE between the maximum and the regular strengths of Mucinex-D. The subjects were randomized and placed into one of three treatment groups. In this case, comparison were made between TRT B and TRT C.

TRT B: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation after an overnight fast.

TRT C: 600mg guaifenesin and 60 mg PSE as an experimental formulation after an overnight fast.

The following is a summary of the findings from this analysis:

- 90% CI for the log-transformed and dose-normalized PK parameters showed that the 1200 mg/120mg strength of Mucinex-D is proportional for both guaifenesin and PSE to the 600 mg/ 60mg strength of Mucinex-D (See Table 3.2.2.1). Ninety % CI meet the goal post for BE requirements for both guaifenesin and PSE

Table 3.2.2.1. Point estimates and 90% confidence intervals for the log-transformed and dose-normalized Cmax, AUCt, and AUCinf values of guaifenesin and PSE following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer' findings	Sponsor's findings	This reviewer' findings
	Guaifenesin				
TRT C/ TRT B	Cmax	92.3	98.0	93.7-102	88.6-108.45
	AUCt	102	111.5	96-108	104.9-118.6
	AUCinf	99.2	112.12	93.8-105	105.58-119.06
	PSE				
TRT C/ TRT B	Cmax	105	94.1	101-109	91.2-97.1
	AUCt	104	100.06	99.3-108	94.7-105.7
	AUCinf	98.3	100.3	96.8-106	95.9-104.87

3.2.3 Is the systemic exposure after multiple administration (steady-state) of the extended release formulation comparable to that of the reference products (Mucinex and Sudafed-12hrs)?

Study 2002-03 was an open-label, multiple dose, randomized, 2-way crossover study in 36 healthy male and female volunteers conducted to determine the steady state PK of guaifenesin and PSE from an experimental formulation containing 1200 mg guaifenesin and 120 mg PSE compared to two reference formulations. The subjects into one of two treatment groups administered every 12 hours for 11 doses.

Group A: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg PSE as Sudafed 12 Hour in fasted conditions (reference).

Group B: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation under fasted conditions.

The mean PK parameters and individual Cmin guaifenesin are presented in Table 3.2.3.1 and Figure 3.2.3.1.

Table 3.2.3.1. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following multiple administration of Mucinex-D tablets under fasted conditions (TRT B) and reference product (Mucinex + Sudafed) (TRT A) under fasted conditions..

Treatment	Mean (%CV) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCss (ng*hr/mL)	Cmin (ng/mL)	$C_{Average}$ (ng/mL)
	Guaifenesin				
Reference	1960 (859)	120.81 (0.31)	7209 (3746)	52 (48.1)	604 (311)
Mucinex-D	1983 (1019)	120.96 (0.65)	8183 (5141)	117 (87.2)	686 (431)
	Pseudoephedrine				
Reference	361 (77.7)	124.9 (2.14)	3528 (862)	182 (66.4)	294 (71.9)
Mucinex-D	365 (83.3)	124.1 (1.85)	3550 (898)	173 (55.2)	296 (74.8)

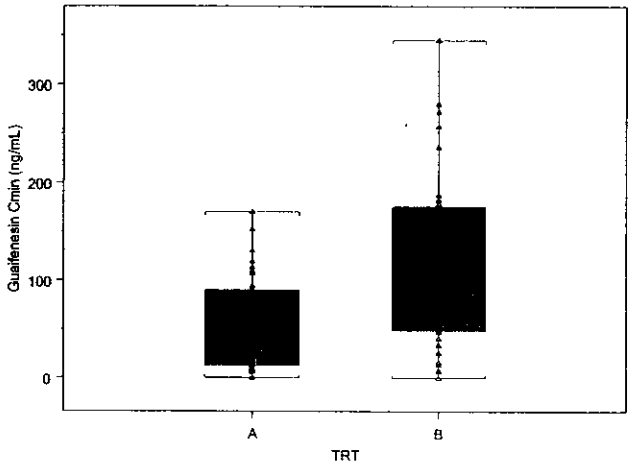


Figure 3.2.3.3. Individual guaifenesin Cmin values following multiple administration of Mucinex-D tablets under fasted conditions (TRT B) and reference product (Mucinex + Sudafed) (TRT A) under fasted conditions.

The following summarizes the findings from this study:

- Mucinex-D (guaifenesin/PSE/1200mg/120mg) and the reference product (Mucinex + Sudafed) were bioequivalent in terms of PSE following multiple administration under fasted conditions. Ninety percent CI for the ratio of the log-transformed PK parameters (Cmax, Cmin and AUCss) were within goal post for BE (80-125) (see Table 3.2.3.2)
- Mucinex-D (guaifenesin/PSE/1200mg/120mg) and the reference product (Mucinex + Sudafed) were bioequivalent in terms of guaifenesin following multiple administration under fasted conditions. Ninety percent CI for the ratio of the log-transformed PK parameters were within goal post for BE (80-125) for Cmax and AUCss. The arithmetic mean for the Cmin of guaifenesin from Mucinex-D product was 2.25-fold higher compared to that for the reference product (Mucinex: guaifenesin 1200 mg). This 2.25-fold increased in guaifenesin Cmin may not be clinically relevant: higher Cmin may improve the efficacy of the drug product and since the Cmin is less than 10% of Cmax, safety may not be a concern.
- Both guaifenesin and PSE reached steady state by the second or third day of administration of the treatments: Mucinex-D and Mucinex and Sudafed 12 hours extended release tablets.

Table 3.2.3.2. Point estimates and 90% confidence intervals for the log-transformed Cmax, Cmin and AUCss values of guaifenesin and PSE following multiple administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
Mucinex-D/ Reference	Cmax	99	90.9-108
	AUCss	111	102-119
	Cmin	244	155-383
	Pseudoephedrine		
Mucinex-D/ Reference	Cmax	101	95.3-107
	AUCss	95.4	86-106
	Cmin	101	95.7-106

3.2.4 What are the basic PK parameters of guaifenesin and PSE?

Guaifenesin is readily absorbed from the intestinal tract and is rapidly metabolized and excreted in the urine. Guaifenesin has a plasma half-life of approximately 1 hour. PSE is not extensively metabolized. It is mainly excreted unchanged in the urine. The mean elimination half-life of PSE is approximately 4-6 hours which is dependent on urine pH. The elimination half-life is decreased at urine pH lower than 6 and may be increased at urine pH higher than 8.

3.3 Extrinsic Factors

3.3.1 Does guaifenesin affect the PK of PSE and viceversa?

Study 2002-04 was an open-label, single dose, randomized, 3-way crossover study in 36 healthy male and female volunteers conducted to determine the pharmacokinetics of guaifenesin and PSE when administered alone compare to when they are co-administered. The subjects were placed into one of three treatment groups.

Group A: 1200 mg controlled release guaifenesin product (Mucinex) after an overnight fast.
Group B: 120mg PSE as Sudafed 12 Hour after an overnight fast.
Group C: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg PSE as Sudafed 12 Hour after an overnight fast.

The mean PK parameters of guaifenesin and PSE following administration of the treatments are summarized in Table 3.3.1.1. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments are presented in Table 3.3.1.2

Table 3.3.1.1. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following single administration of the treatments

	Mean (SD) PK Parameters				
Treatment	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
	Guaifenesin				
TRT A	2009 (819.2)	0.89 (0.42)	7921 (3196.5)	8138 (3253.9)	4 (5.58)
TRT C	1989 (863.4)	0.84 (0.31)	7923 (3337)	8052 (3344)	3.41 (1.7)
	Pseudoephedrine				
TRT B	295.8 (73.3)	6.17 (1.92)	4024 (1047)	4505 (1250)	6.05 (1.4)
TRT C	289.3 (77.6)	5.75 (1.54)	3925 (1089)	4387 (1357)	(6.04 (1.4)

Table 3.3.1.2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
TRT C/ TRT A	Cmax	97.8	90.2-106
	AUCt	100	94.3-104
	AUCinf	98.4	93.6-103
	Pseudoephedrine		
TRT C/ TRT B	Cmax	97.6	94.2-101
	AUCt	97.4	94-101
	AUCinf	97.3	93.5-101

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

The following summarizes the findings from this study:

- The pharmacokinetics of guaifenesin are not affected by co-administration with PSE. Ninety percent confidence intervals for the log-transformed PK parameters of guaifenesin (Cmax, AUCt, AUCinf) administered alone (Mucinex) versus its coadministration with PSE (Sudafed) were within goal post for BE.
- The pharmacokinetics of PSE are not affected by co-administration with guaifenesin. Ninety percent confidence intervals for the log-transformed PK parameters of PSE (Cmax, AUCt, AUCinf) administered alone (Sudafed) versus its coadministration with guaifenesin (Mucinex) were within goal post for BE.

3.4 General Biopharmaceutics

3.4.1 Was the to-be-marketed formulation used in the Pharmacokinetic studies?

NO. Due to friability failures, the sponsor adjusted tableting manufacturing parameters and produced additional pilot scale batches after production of the primary stability batch. Release data were provided for each of the pilot batches referenced above. Further review of the process and materials used for the manufacturing of these three pilot batches revealed that the average level of [redacted] in the guaifenesin intermediate ([redacted] guaifenesin) was higher ([redacted]) than for other pilot lots ([redacted]). In order to further study the correlation between the level of [redacted] in the guaifenesin intermediate and the friability profile of the tablets, several laboratory batches were manufactured with [redacted] guaifenesin containing an average [redacted] level of at least [redacted]. These laboratory batches were manufactured at [redacted] levels between [redacted] SCU. According to the sponsor, the tablets had a tendency to [redacted] after a few days and this [redacted] did not affect the friability or dissolution profile of the tablets.

The sponsor has not provided release or stability data for batches made with the improved parameters. Therefore, the sponsor will be requested to provide the appropriate bridging information between these new batches and the batch used in the BE study.

COMMENT TO SPONSOR

- You are requested to provide the appropriate dissolution data (refer to SUPAC-MR guidance) to link the batches of Mucinex-D produced under new manufacturing conditions to the batch of Mucinex-D used in the pivotal BE study.

3.4.2. What is the effect of food on the BA of guaifenesin and PSE from the Mucinex-D formulation?

Two studies were conducted to assess the effect of food on the PK of guaifenesin and PSE: studies 2002-11 and study 2002-2A.

Study 200211 was an open-label, single dose, randomized, 2-way crossover study in 34 healthy male and female volunteers conducted to determine the effect of a high-fat meal on the relative BA of an experimental formulation containing 1200 mg guaifenesin and 120 mg PSE hydrochloride compared to that in the fasting condition. Subjects were placed into one of two treatment groups described below.

Group A: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation after an overnight fast (reference).
Group B: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation, 30 minutes after the beginning of the consumption of a high-fat breakfast.

The PK parameters for guaifenesin and PSE and individual Cmax of guaifenesin following administration of the treatments are shown in Table 3.4.2.1 and Figure 3.4.2.1. Table 3.4.2.2 shows the point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments.

Table 3.4.2.1. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following single administration of Mucinex-D with and without food

	Mean (%CV) PK Parameters				
Treatment	**Cmax (ng/mL)**	**Tmax (hr)**	**AUCt (ng*hr/mL)**	**AUCinf (ng*hr/mL)**	**T1/2 (hr)**
	Guaifenesin				
Fasted	1857 (838)	1.06 (0.58)	8091 (3501)	8142 (3500)	1.82 (0.7)
Fed	1364 (691)	2.06 (1.16)	7403 (3185)	7469 (3217)	1.39 (0.83)
	Pseudoephedrine				
Fasted	283 (78)	4.6 (1.56)	3477 (152)	3746 (997)	5.01 (1.06)
Fed	301 (80)	5.8 (1.8)	3403 (915)	3660 (963)	4.6 (1.05)

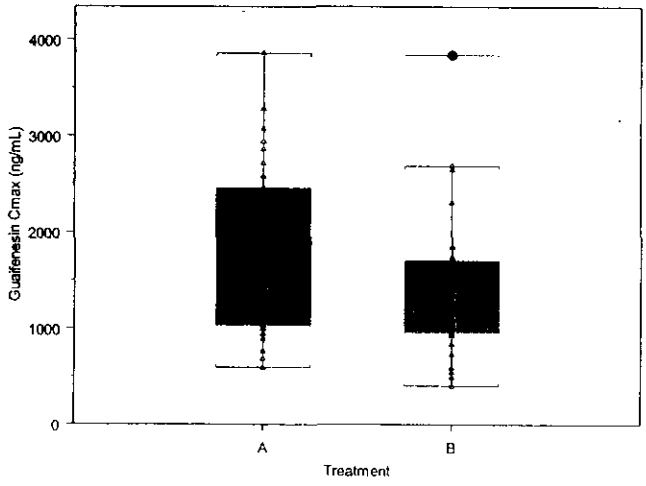


Figure 3.4.2.1. Individual guaifenesin Cmax values following single administration of Mucinex-D tablets under fed (TRT B) and fasted (TRT A) conditions.

Table 3.4.2.2. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
Fed/fasted	Cmax	74	65.9-83.2
	AUCt	90	84.6-95.5
	AUCinf	90.2	84.7-96
	Pseudoephedrine		
Fed/fasted	Cmax	106	101-112
	AUCt	98.5	93.5-104
	AUCinf	98.6	93.6-104

The following summarizes the findings from this study:

- High-fat and high-caloric meal had no effect on the BA of PSE from the Mucinex-D tablets. Ninety percent CI were within BE requirements (80-125).
- Food (high-fat breakfast) decreased the Cmax and AUCinf of guaifenesin by 26.5% and 8.5%, respectively. The Tmax was delayed by approximately one hour.

Study 2002-02A was an open-label, single dose, randomized, 2-way crossover study in 33 healthy male and female volunteers conducted to determine the relative BA of an experimental formulation containing 1200 mg guaifenesin and 120 mg PSE hydrochloride compared to reference formulation. Subjects were randomized and placed into one of two treatment groups as shown below.

Group A: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg PSE as Sudafed 12 Hour with a high-fat breakfast (reference).
Group B: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation with a high-fat breakfast.

Table 3.4.2.3 summarizes the mean PK parameters following administration of the treatments. The point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE are shown in Table 3.4.2.4.

Table 3.4.2.3. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following single administration of Mucinex-D tablets under fed conditions (TRT B) and reference product (Mucinex + Sudafed) (TRT A) under fed conditions..

	Mean (%CV) PK Parameters				
Treatment	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
	Guaifenesin				
Reference	2207 (952)	1.85 (1.06)	8049 (2666)	8067 (2663)	1.22 (0.621)
Mucinex-D	1649 (690)	1.84 (0.82)	7611 (2816)	7663 (2864)	1.4 (0.79)
	Pseudoephedrine				
Reference	268 (69.7)	6.38 (1.26)	3362 (847)	3636 (940)	5.3 (1.08)
Mucinex-D	274 (72)	4.8 (1.3)	3273 (876)	3528 (962)	5.3 (1.02)

Table 3.4.2.4. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
Mucinex-D/ References	Cmax	74.5	97.9-81.8
	AUCt	91.9	87.5-96.5
	AUCinf	92.2	87.8-96.8
	Pseudoephedrine		
Mucinex-D/ References	Cmax	102	99.5-105
	AUCt	96.2	92.9-99.2
	AUCinf	95.8	92.4-99.3

The following summarizes the findings from this study:

- Mucinex-D (guaifenesin/PSE/1200mg/120mg) and the reference product (mucinex + Sudafed) were bioequivalent in terms of PSE when administered under fed conditions. Ninety percent CI for the ratio of the log-transformed PK parameters (Cmax and AUCinf) were within goal post for BE (80-125).
- Mucinex-D (guaifenesin/PSE/1200mg/120mg) and the reference product (mucinex + Sudafed) were NOT bioequivalent in terms of guaifenesin when administered under fed conditions. Ninety percent CI for the ratio of the log-transformed PK parameters (Cmax and AUCinf) were within goal post for BE (80-125) for AUCinf, but not for Cmax. The arithmetic Cmax mean for Mucinex-D in the presence of food was 25% lower compared to that for Mucinex (guaifenesin 1200 mg).

CONCLUSIONS

- High-fat and high-caloric meal had no effect on the BA of PSE from the Mucinex-D tablets. Ninety percent CI were within BE requirements (80-125).
- Food (high-fat breakfast) decreased the Cmax and AUCinf of guaifenesin by about 25% and 8.5%, respectively. The Tmax was delayed by approximately one hour.
- This 26.5% decrease in Cmax and delay on Tmax may not be clinically relevant and therefore, Mucinex-D can be taken without regards of meals.

3.4.3 Are the method and dissolution specifications supported by the data provided by the sponsor?

The dissolution method and specification for Mucinex-D regular and maximum strengths proposed by the sponsor are as follows:

Maximum Strength

Method: USP basket, [redacted]

Time	
1 hour	[redacted]
2 hour	
6 hour	
12 hour	

Regular Strength
Method: USP basket,

Time	
1 hour	
2 hour	
6 hour	
12 hour	

These method and specifications were established based on previous recommendations by the FDA for the already approved extended release product Mucinex and also and most importantly based on dissolution studies using different media and dissolution speeds.

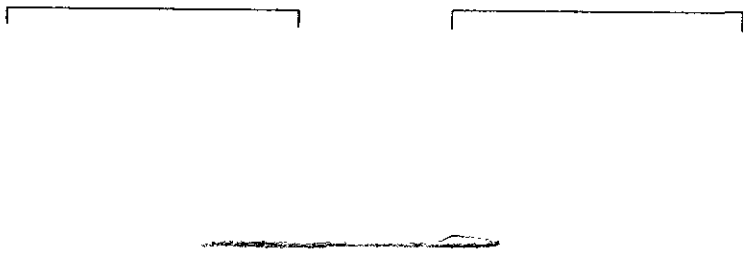
According to the sponsor, during the early phases of development, it was discovered that using USP Dissolution Apparatus to obtain the dissolution profile of bi-layer tablets introduced a high degree of variability in the data. Tablets were observed , sometimes with the immediate release layer sometimes with the modified release layer

Mucinex® D Tablets were then tested using at in three different media: . In order to ensure that provided the most discriminating dissolution profile, additional dissolution experiments were performed at The change in from made a slight difference in dissolution profile (mean data was provided by the sponsor but was not shown in this review).

Figures 3.4.3.1 and 3.4.3.2 show the individual dissolution profiles media for a batch of Mucinex-D maximum and regular strengths, respectively used in the pivotal BE study.

Time (hrs)

Time (hrs)



Upon review of these data, this reviewer aggress that the USP Apparatus 1 (basket), at [redacted] in [redacted] is a discriminating dissolution method for the dissolution testing of Mucinex® D, since both active ingredients reach a release plateau at the 12-hour interval, and release at least [redacted] of both active ingredients at the [redacted] hour interval.

However, in terms of specifications, this reviewer proposes a slight modification to the specifications proposed at the latest time point (12 hour). Ideally, this reviewer is of the opinion that the 2 hour specification may be an extra burden to the sponsor because it does not provide any relevant information in terms of dissolution profile of the components since the one hour point time gives enough information for any dose dumping. However, in order to be consistent with previous specifications proposed and approved for Mucinex extended release tablet, the 2hrs point is acceptable.

The suggested specifications (in bold) for Mucinex-D for both regular and maximum strength are as follows:

Maximum Strength
Method: USP basket, [redacted]

Time	
1 hour	
2 hour	
6 hour	
12 hour	

Regular Strength
Method: USP basket [redacted]

Time	
1 hour	
2 hour	
6 hour	
12 hour	

As mentioned earlier, due to friability failures, the sponsor adjusted tableting manufacturing parameters and produced additional pilot scale batches after production of the primary stability batch. Further review of the process and materials used for the manufacturing of these three pilot batches revealed that the average level of [redacted] in the guaifenesin was higher. Several laboratory batches were manufactured with [redacted] guaifenesin containing an average [redacted] level of at least [redacted] These laboratory batches were manufactured at [redacted] levels between [redacted] SCU. According to the sponsor, the tablets had a tendency to [redacted] after a few days and this [redacted] did not affect the friability or dissolution profile of the tablets. In fact, mean dissolution profiles for guaifenesin and PSE from Mucinex-D regular and maximum strength (maximum strength batches 13LB96A and 13LB96H, regular strength: 13LB97C, 13LB97D) were within dissolution specifications (data not shown here).

However, no release or stability data for batches made with the improved parameters have been provided in the original application or in subsequent amendments. Therefore, the sponsor will be advice that the dissolution specification proposed are interim until they provide dissolution data obtain at release and during stability of the batches produced using the new manufacturing parameters.

Comments to be sent to sponsor:

- You should be aware that the proposed specification for Mucinex-D are interim until you provide dissolution data obtain at release and during stability of the batches produced using the new manufacturing parameters.

3.5 Analytical Methodology

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

Plasma concentrations of guaifenesin and PSE in the pharmacokinetic studies included in this review were determined using a HPLC with a lower limit of quantification (LLQ) of [redacted], respectively. The accuracy and inter-day precision were acceptable for all the studies [redacted] Bias or %CV) for pre-study and in-study validation information. Information regarding stability and % of recovery was also provided. Table below summarizes the findings for the validation method used in the pivotal BE study.

Table 3.5.1.1. Assay performance (in-study validation) for Guaifenesin and PSE

	Guaifenesin	PSE
Linearity	Satisfactory: Standard curve range from [redacted]	Satisfactory: Standard curve range from [redacted]
Accuracy	Satisfactory: % Bias: [redacted]	Satisfactory: % Bias [redacted]
Inter-day Presicion	Satisfactory: %CV: : [redacted]	Satisfactory: %CV: [redacted]
Specificity	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

4. LABELING COMMENTS

There no labeling recommendations at this time.

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

X § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio-_____

FORMULATION

Treatment A: Guaifenesin 1200 mg extended released Tablets and Sudafed® 12 hr 120 mg Tablets

Guaifenesin Lot Number: PBOI-H34A
Guaifenesin Expiration Date: Not Available
Sudafed® Lot Number 12171V
Sudafed® Expiration Date: June. 2003

Treatment B: Guaifenesin and PSE 1200 mg/120 mg Tablets

Lot Number PBOI-M65A2
Expiration Date: Not Available

Treatment C Guaifenesin and PSE 600 mg/60 mg Tablets

Lot Number PB 02-A12A
Expiration Date: Not Available

PHARMACOKINETIC MEASUREMENTS

Blood samples for guaifenesin and PSE determination were collected at predose and at the following times: 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 24 hours post dose.

Analytical Method

Plasma samples were assayed for guaifenesin and PSE using a HPLC (lower limit of quantification, LLQ= [redacted], respectively).

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Pharmacokinetic parameters were determined using the non-compartmental pharmacokinetic analysis program Kinetica 2000 Standard Version 2.1.

Statistical Analysis

Where data were available, bioequivalence was examined between the test (Treatment B - and the reference (Treatment A) groups. The dose proportionality relationship was also examined between the test (Treatment B) and the reference (Treatment C) groups. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of test/reference. Cmax, AUCt, AUC nf, CL, t1/2 were natural log transformed prior to analysis. Cmax, AUCt, AUCnf, were also dose-normalized prior to the ln-transformation.

RESULTS

Analytical Method

Guaifenesin

The limit of quantitation for guaifenesin: [redacted].

Stability and % of Recovery: The recovery of guaifenesin ranged from [redacted]

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was -3.3%. -3.4%, and 0.0% for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: The mean percent differences from theory are -6.4% and -4.3% for the [redacted] bench top concentrations, respectively. Based on these data, extracted samples stored under injection conditions are stable for at least [redacted].

PSE

The limit of quantitation: [redacted]

Stability and % of Recovery: The recovery of guaifenesin ranged from [redacted]

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was 2.4, 5.0 and 5.0 % for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: Samples stored under injection conditions are stable for at least [redacted]

In-Study Validation

Table 1. Assay performance (Pre-study validation) for Guaifenesin and PSE

	Guaifenesin	PSE
Linearity	Satisfactory: Standard curve range from [redacted]	Satisfactory: Standard curve range from [redacted]
Accuracy	Satisfactory: % Bias: [redacted]	Satisfactory: % Bias: [redacted]
Inter-day Presicion	Satisfactory: %CV: [redacted]	Satisfactory: %CV: [redacted]
Specificity	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for guaifenesin and for PSE following administration of the treatments are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for PSE and guaifenesin are summarized in Table 2. Individual guaifenesin Cmax, AUCt and AUC(inf) values following the administration of the treatments are shown in Figures 3 and 4, respectively. Likewise, individual Cmax, AUCt and AUCinf for PSE following administration of the treatments are represented in Figures 5 and 6, respectively.

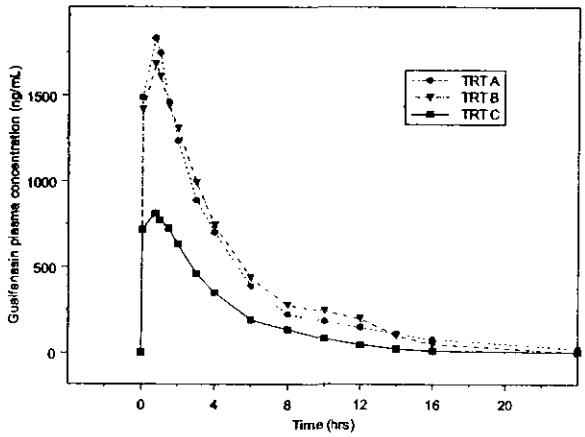


Figure 1. Mean guaifenesin plasma concentration-time profiles following single administration TRT A: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour; TRT **B:** 1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation, and TRT **C:** 600mg guaifenesin and 60 mg pseudoephedrine hydrochloride as an experimental formulation.

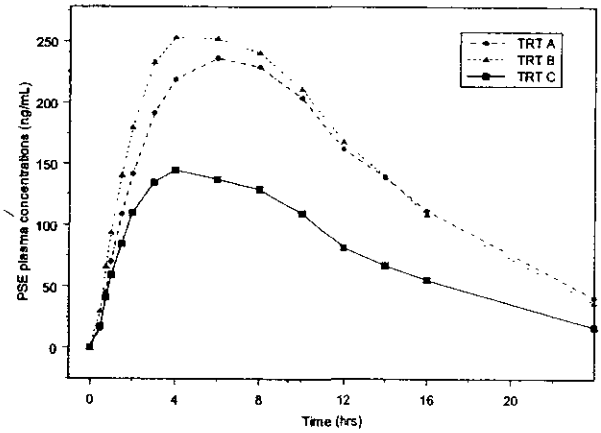


Figure 2. Mean PSE plasma concentration-time profiles following single administration of TRT A: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour; TRT **B:** 1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation, and TRT **C:** 600mg guaifenesin and 60 mg pseudoephedrine hydrochloride as an experimental formulation.

Table 2. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
	Guaifenesin				
TRT A	1940 (889)	0.77 (0.22)	7764 (3329)	8061 (3329)	4.74 (4.13)
TRT B	1813 (900)	1.04 (0.49)	8002 (3677)	8124 (3677)	2.21 (1.19)
TRT C	920 (481)	0.99 (0.46)	3529 (1437)	3565 (1442)	1.76 (0.92)
	Pseudoephedrine				
TRT A	250 (53.4)	6.9 (1.76)	3479 (805)	3847 (910)	5.8 (1.02)
TRT B	263 (58.5)	5.11 (1.78)	3591 (824)	5.22 (0.9)	5.2 (0.9)
TRT C	141 (30.3)	4.9 (1.6)	1781 (445)	1968 (477)	5.6 (1.02)

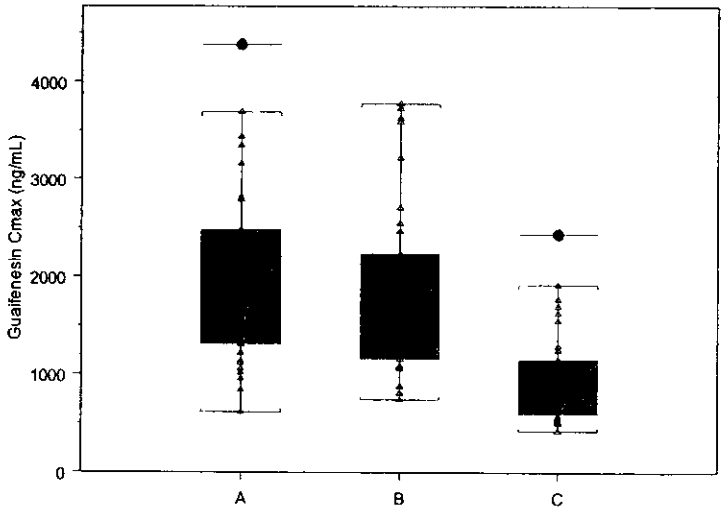


Figure 3. Individual guaifenesin Cmax values following single administration of the treatments: TRT **A:** 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour; TRT **B:** 1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation, and TRT **C:** 600mg guaifenesin and 60 mg pseudoephedrine hydrochloride as an experimental formulation.

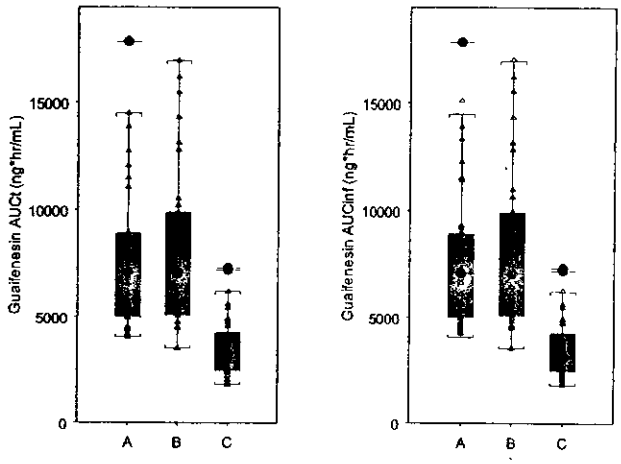


Figure 4. Individual guaifenesin AUCt and AUC inf values following single administration of the treatments: TRT **A:** 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour; TRT **B:** 1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation, and TRT **C:** 600mg guaifenesin and 60 mg pseudoephedrine hydrochloride as an experimental formulation.

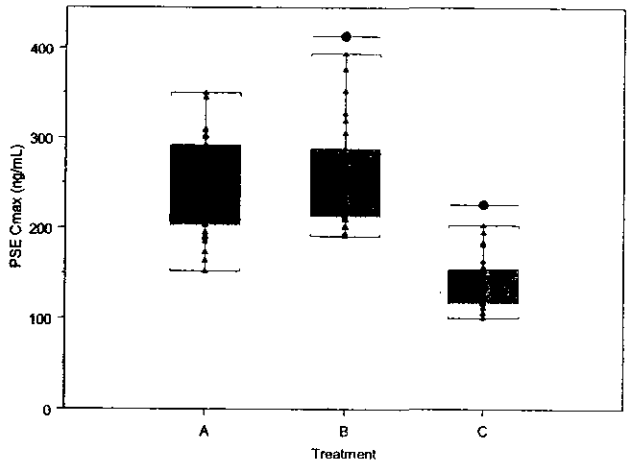


Figure 5. Individual PSE Cmax values following single administration of the treatments: TRT **A:** 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour; TRT **B:** 1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation, and TRT **C:** 600mg guaifenesin and 60 mg pseudoephedrine hydrochloride as an experimental formulation

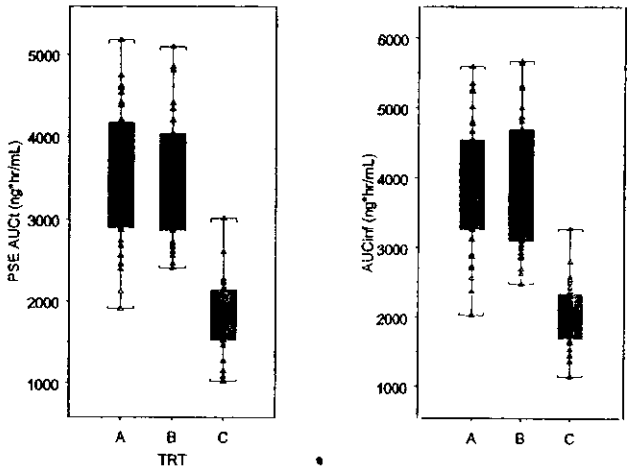


Figure 6. Individual PSE AUCt and AUCinf values following single administration of the treatments.

The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for guaifenesin and PSE are presented in Table 3. The CIs of AUC(t), AUCinf, and Cmax for guaifenesin and PSE after TRTB relative to reference met the 80-125% bioequivalence guideline.

Table 3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer' findings	Sponsor's findings	This reviewer' findings
	Guaifenesin				
TRT B/ TRT A	Cmax	92.3	92.3	83.7-102	83.65-101.99
	AUCt	102	101.8	96-108	96.0-107.84
	AUCinf	99.2	99.16	93.8-105	93.76-104.87
	PSE				
TRT B/ TRT A	Cmax	105	105.06	101-109	100-.93-109.36
	AUCt	104	101.01	99.3-108	96.16-106.10
	AUCinf	101	101.27	96.8-106	96.84-105.9

Dose Proportionality

Table 4 shows the 90% confidence for ratio of the log-transformed and dose-normalized PK parameters. The data suggest the existence of dose-proportionality between doses for both guaifenesin and PSE.

Table 4. Point estimates and 90% confidence intervals for the log-transformed and dose-normalized Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments

Comparison	PK parameter	Point estimates		90% confidence intervals	
		Sponsor's findings	This reviewer' findings	Sponsor's findings	This reviewer' findings
	Guaifenesin				
TRT B/ TRT C	Cmax	92.3	98.0	93.7-102	88.6-108.45
	AUCt	102	111.5	96-108	104.9-118.6
	AUCinf	99.2	112.12	93.8-105	105.58-119.06
	PSE				
TRT B/ TRT C	Cmax	105	94.1	101-109	91.2-97.1
	AUCt	104	100.06	99.3-108	94.7-105.7
	AUCinf	98.3	100.3	96.8-106	95.9-104.87

CONCLUSION

- The 1200 mg guaifenesin/120mg of pseudoephedrine hydrochloride extended release formulation (Mucinex-D, TRT B) was bioequivalent to the 1200 mg controlled release guaifenesin product (Mucinex) and 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour (TRT A). The 90% CI were within the 80-125 goal post for BE for both guaifenesin and PSE.
- The 90% CI for the log-transformed and dose-normalized PK parameters showed that the 1200 mg/120mg strength of Mucinex-D is proportional for both guaifenesin and PSE to the 600 mg/ 60mg strength of Mucinex-D. Ninety % CI meet the goal post for BE requirements for both guaifenesin.

"A Definitive Study Designed to Compared the Steady State Pharmacokinetics of Guaifenesin and Pseudoephedrine from an Experimental Controlled Release Formulations of 1200 mg Guaifenesin and 120 mg Pseudoephedrine Hydrochloride in Normal Healthy Volunteers Compared to Reference Controlled Release Guaifenesin and Pseudoephedrine Hydrochloride Products"

Name of Sponsor:	Adams Laboratories, Inc.
Included Protocols:	2002-03
Development Phase of Study:	I
Study Initiation Date:	February 26, 2002
Study Completion Date:	March 31, 2002
Principal Investigator:	Dennis N. Morrison, D.O.
Date of the Report:	September 30, 2002

OBJECTIVE

- to determine the steady state PK of guaifenesin and PSE from an experimental formulation containing 1200 mg guaifenesin and 120 mg PSE hydrochloride compared to two reference formulations in normal, healthy male and/or female subjects in the fed condition.

Study Population

Thirty-seven normal healthy volunteers entered and thirty-six completed the study according to the protocol. Subject four left the clinic after the first dose of period one due to a conflict. The volunteers averaged 24.2 ± 8.24 years of age (Mean ± SD) with a range of 18 years to 48 years of age. They were 69 ± 3.5 inches tall with a range of 62 to 75 inches. They weighed 169 ± 29.1 pounds with a range of 114-225 pounds. Twenty two were male (62%) and fourteen female (38%). Thirty-three volunteers (89%) were Caucasian, two were Asian (5%), one was multiracial (3%) and one (3%) was Black.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was an, open-label, multiple dose, randomized, 2-way crossover study in healthy male and female volunteers. The subjects were randomized and placed into one of two treatment groups.

Group A: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg PSE as Sudafed 12 Hour with 240 mL of water, in fasted conditions (reference).

Group B: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation with 240 mL of water, in fasted conditions.

Doses were administered every 12 hours for 11 doses. There was at least 7-day washout period between doses.

FORMULATION

1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation with 240 mL of water with food:
Lot number: PB01-M65A3

Sudafed lot number: 12171V
Guaifenesin Lot number: PB01-H34A2

PHARMACOKINETIC MEASUREMENTS

Blood samples for guaifenesin and PSE determination were collected at predose on Days 1, 3, 4, 5 and 6. On Day 6 additional samples were taken the following times: 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 24 hours post dose.

Analytical Method

Plasma samples were assayed for guaifenesin and PSE using a HPLC (lower limit of quantification, LLQ= [redacted] , respectively).

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Pharmacokinetic parameters were determined using the non-compartmental pharmacokinetic analysis program Kinetica 2000 Standard Version 2.1.

Statistical Analysis

Evaluation of Steady State

For each treatment and analyte (Treatment A and Treatment B), steady state was assessed by comparison of Cmin mean values (mean trough concentrations) in natural log (ln) scale using available data from Days 4, 5, and 6. For guaifenesin, prior to ln transformation, Cmin was incremented by 1 since Cmin was zero for some subjects on some days.

Reviewer's comments

The sponsor should not have incremented Cmin by one for those subjects which Cmin was zero. A better approach is to omit this values in the analysis.

Determination of Bioequivalence

Where data were available, bioequivalence was examined between the Test (Treatment B- 1200 mg guaifenesin and 120 mg PSE as an experimental formulation) and the Reference (Treatment A - 1200 mg guaifenesin and 120 mg PSE as two Reference formulations) groups. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of Test/Reference. The steady-state PK, Cmax and AUCss were natural-log (ln) transformed prior to analysis. Cmin was incremented by 1 before natural-log transformation for guaifenesin since the minimum observed Cmin was 0. The corresponding

90% confidence intervals for the geometric mean ratio were obtained by taking the antilog of the 90% confidence intervals for the difference between the means on the log scale.

RESULTS

Analytical Method

Guaifenesin

The limit of quantitation for guaifenesin:

Stability and % of Recovery: The recovery of guaifenesin ranged from

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was -3.3%. -3.4%, and 0.0% for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: The mean percent differences from theory are -6.4% and -4.3% for the bench top concentrations, respectively. Based on these data, extracted samples stored under injection conditions are stable for at least .

PSE

The limit of quantitation:

Stability and % of Recovery: The recovery of guaifenesin ranged from

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was 2.4, 5.0 and 5.0 % for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: Samples stored under injection conditions are stable for at least

In-Study Validation

Table 1. Assay performance (Pre-study validation) for Guaifenesin and PSE

	Guaifenesin	PSE
Linearity	Satisfactory: Standard curve range from	Satisfactory: Standard curve range from
Accuracy	Satisfactory: % Bias:	Satisfactory: % Bias: (
Inter-day Presicion	Satisfactory: %CV: :	Satisfactory: %CV:
Specificity	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for guaifenesin and for PSE following administration of the treatments under fasted conditions are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for PSE and guaifenesin are summarized in

Table 2. Individual guaifenesin Cmax, AUCss and Cmin values following the administration of the treatments under fasted conditions are shown in Figures 3, 4, and 5, respectively. Figure 6 shows the individual PSE Cmin following multiple administration of the treatments. The point estimates and the 90% CIs for the log-transformed Cmax, Cmin and AUCss for guaifenesin and PSE are presented in Table 3. Table 4 shows the statistical analysis results for the determination of Steady State based on Cmin values

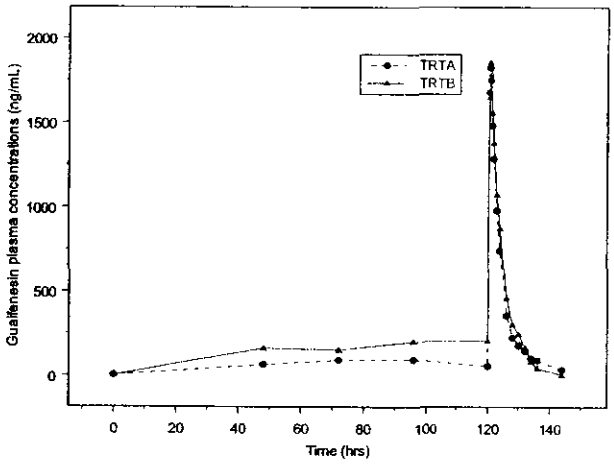


Figure 1. Mean guaifenesin plasma concentration-time profiles following multiple administration of Mucinex-D tablets under fasted conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fasted conditions.

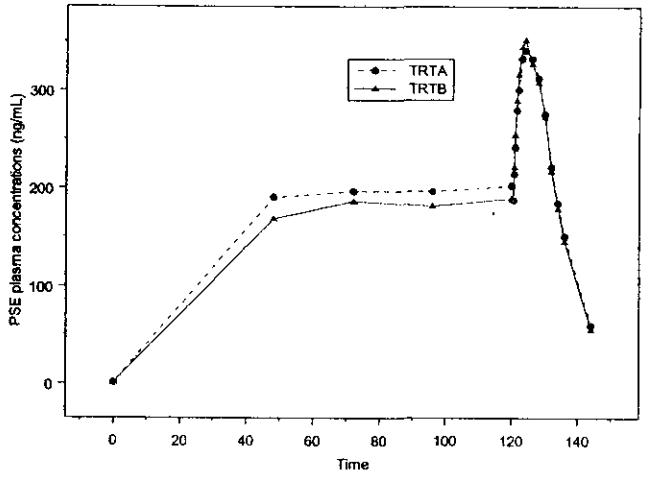


Figure 2. Mean PSE plasma concentration-time profiles following multiple administration of Mucinex-D tablets under fasted conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fasted conditions..

Table 2. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following multiple administration of Mucinex-D tablets under fasted conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fasted conditions..

Treatment	Mean (%CV) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCss (ng*hr/mL)	Cmin (ng/mL)	$C_{Average}$ (ng/mL)
	Guaifenesin				
Reference	1960 (859)	120.81 (0.31)	7209 (3746)	52 (48.1)	604 (311)
Mucinex-D	1983 (1019)	120.96 (0.65)	8183 (5141)	117 (87.2)	686 (431)
	Pseudoephedrine				
Reference	361 (77.7)	124.9 (2.14)	3528 (862)	182 (66.4)	294 (71.9)
Mucinex-D	365 (83.3)	124.1 (1.85)	3550 (898)	173 (55.2)	296 (74.8)

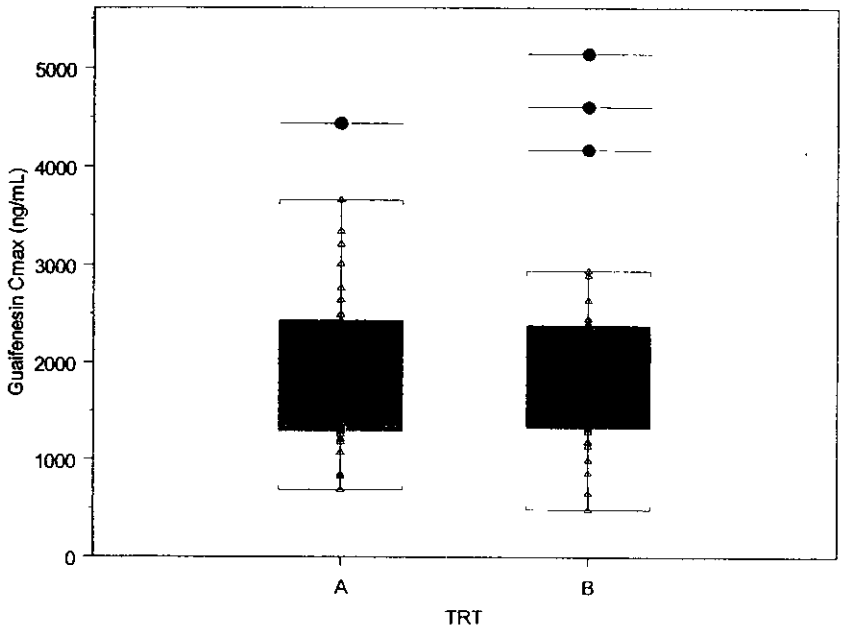


Figure 3. Individual guaifenesin Cmax values following multiple administration of Mucinex-D tablets under fasted conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fasted conditions.

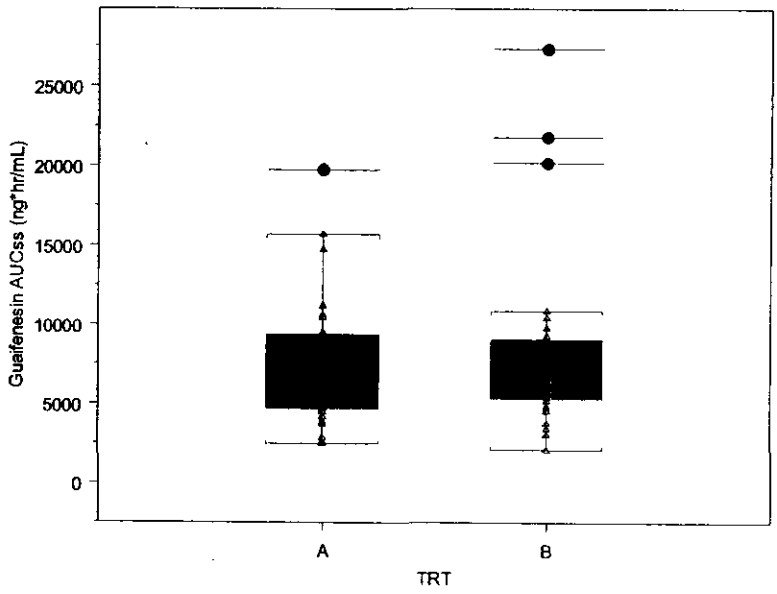


Figure 4. Individual guaifenesin AUCss values following multiple administration of Mucinex-D tablets under fasted conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fasted conditions.

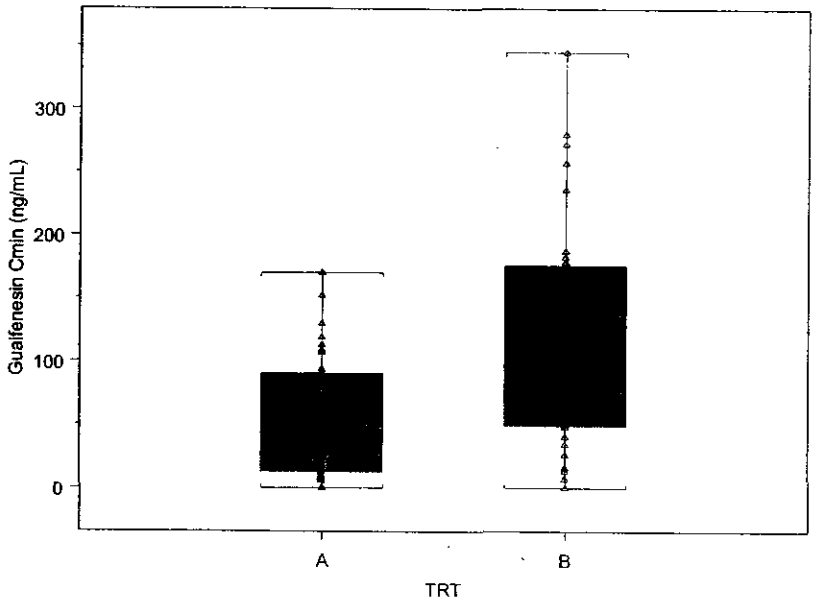


Figure 5. Individual guaifenesin Cmin values following multiple administration of Mucinex-D tablets under fasted conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fasted conditions.

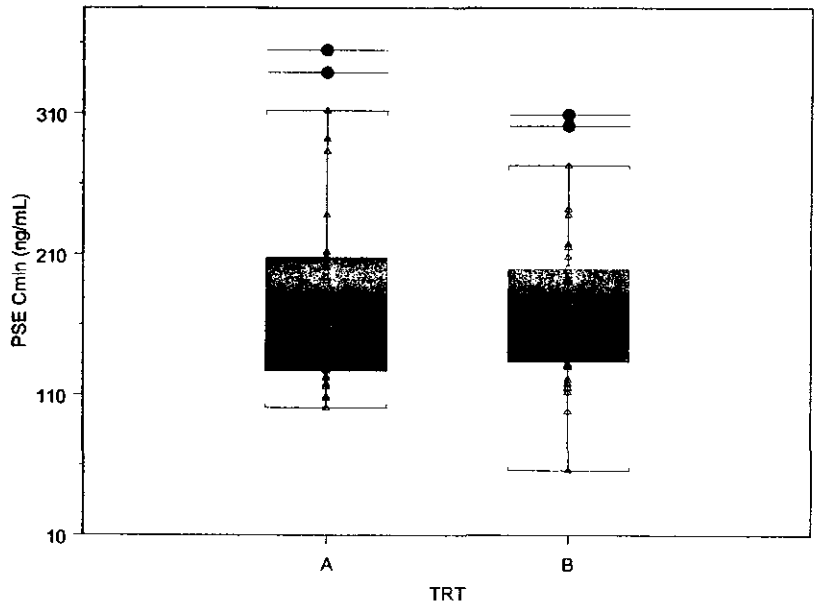


Figure 6. Individual PSE Cmin values following multiple administration of Mucinex-D tablets under fasted conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fasted conditions.

Table 3. Point estimates and 90% confidence intervals for the log-transformed Cmax, Cmin and AUCss values of guaifenesin and PSE following multiple administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
Mucinex-D/ Reference	Cmax	99	90.9-108
	AUCss	111	102-119
	Cmin	244	155-383
	Pseudoephedrine		
Mucinex-D/ Reference	Cmax	101	95.3-107
	AUCss	95.4	86-106
	Cmin	101	95.7-106

Table 4. Statistical analysis results for the determination of Steady State based on Cmin values

TRT	Day 4	Day 5	Day 6	P value
		Guaifenesin		
TRT A	90.8	92.7	54.6	0.0456
TRT B	142	198	208	0.0482
		Pseudoephedrine		
TRT A	191	193	199	0.62
TRT B	181	178	187	0.51

CONCLUSION

- Mucinex-D (guaifenesin/PSE/1200mg/120mg) and the reference product (mucinex + Sudafed) were bioequivalent in terms of PSE following multiple administration under fasted

conditions. Ninety percent CI for the ratio of the log-transformed PK parameters (Cmax, Cmin and AUCss) were within goal post for BE (80-125).

- Mucinex-D (guaifenesin/PSE/1200mg/120mg) and the reference product (mucinex + Sudafed) were bioequivalent in terms of guaifenesin following multiple administration under fasted conditions. Ninety percent CI for the ratio of the log-transformed PK parameters (Cmax, Cmin, and AUCss) were within goal post for BE (80-125) for Cmax and AUCss, but NOT for Cmin. The arithmetic guaifenesin Cmin mean for mucinex-D was 2.25-fold higher compared to that for the reference (mucinex: guaifenesin 1200 mg). This 2.25-fold increased in guaifenesin Cmin may not be clinically relevant: higher Cmin may improve the efficacy of the drug product and since the Cmin is less than 10% of Cmax, safety may not be a concern.
- Both guaifenesin and PSE reached steady state by the second or third day of administration of the treatments: Mucinex-D and Mucinex and Sudafed 12 hours extended release tablets.

"A Definitive Study Designed to Examine the Effect of a High Fat Breakfast on the Bioavailability of an Experimental Controlled Release Formulations Containing 1200 mg Guaifenesin and 120 mg Pseudoephedrine Hydrochloride in Normal Healthy Volunteers"

Name of Sponsor:	Adams Laboratories, Inc.
Included Protocols:	2002-11
Development Phase of Study:	I
Study Initiation Date:	April 22, 2002
Study Completion Date:	May 20, 2002
Principal Investigator:	Dennis N. Morrison, D.O.
Date of the Report:	September 30, 2002

OBJECTIVE

- to determine the effect of a high-fat meal on the relative bioavailability of an experimental formulation containing 1200 mg guaifenesin and 120 mg PSE hydrochloride compared to that in the fasting condition in normal, healthy male and/or female subjects.

Study Population

Thirty-six normal healthy volunteers entered and thirty-four completed the study according to the protocol. Subject 2 was dropped from the study due to a positive drug screen prior to Period 2 and was not replaced. Subject 3 withdrew her consent prior to Period 2 and was not replaced The volunteers averaged 26.2 ± 8.99 years of age (Mean ± SD) with a range of 19 years to 54 years of age. They were 67 ± 4.12 inches tall with a range of 61 to 76 inches. They weighed 156 ± 28.5 pounds with a range of 112 to 210 pounds. Fifteen were male (42%) and twenty-one female (58%). Thirty-four volunteers (94%) were Caucasian, one (3%) was Black.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was an open-label, single dose, randomized, 2-way crossover study in healthy male and female volunteers. The subjects were randomized and placed into one of two treatment groups.

Group A: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation with 240 mL of water after an overnight fast (reference).

Group B: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation with 240 mL of water, 30 minutes after the beginning of the consumption of a high-fat breakfast.

The high fat breakfast was consumed within 30 minutes of dosing. There was at least 7-day washout period between doses. The breakfast consisted of 2 eggs cooked with butter, 2 strips of bacon, 2 pieces of buttered toast, 4 ounces of hash brown potatoes and 8 oz of whole milk.

FORMULATION

1200 mg guaifenesin and 120mg of PSE as an experimental formulation with 240 mL of water with or without food:
Lot number: PB01-M65A4

PHARMACOKINETIC MEASUREMENTS

Blood samples for guaifenesin and PSE determination were collected at predose and at the following times: 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 24 hours post dose.

Analytical Method

Plasma samples were assayed for guaifenesin and PSE using a HPLC (lower limit of quantification, LLQ= respectively).

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Pharmacokinetic parameters were determined using the non-compartmental pharmacokinetic analysis program Kinetica 2000 Standard Version 2.1.

Statistical Analysis

Where data were available, food effect was examined between the test (Treatment B - guaifenesin or pseudoephedrine hydrochloride experimental formulation fed state) and the reference (Treatment A - guaifenesin or PSE experimental formulation fasted state. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of test/reference. Cmax, AUCt, AUCinf, CL, t1/2 were natural log transformed prior to analysis.

RESULTS

Analytical Method

Guaifenesin

The limit of quantitation for guaifenesin:

Stability and % of Recovery: The recovery of guaifenesin ranged from

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was -3.3%. -3.4%, and 0.0% for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: The mean percent differences from theory are -6.4% and -4.3% for the l bench top concentrations, respectively. Based on these data, extracted samples stored under injection conditions are stable for at least .

PSE

The limit of quantitation:

Stability and % of Recovery: The recovery of guaifenesin ranged from

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was 2.4, 5.0 and 5.0 % for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: Samples stored under injection conditions are stable for at least .

In-Study Validation

Table 1. Assay performance (Pre-study validation) for Guaifenesin and PSE

	Guaifenesin	PSE
Linearity	Satisfactory: Standard curve range from	Satisfactory: Standard curve range from
Accuracy	Satisfactory: % Bias	Satisfactory: % Bias
Inter-day Presicion	Satisfactory: %CV:	Satisfactory: %CV:
Specificity	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for guaifenesin and for PSE following administration of Mucinex-D tablets under fed and fasted conditions are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for PSE and guaifenesin are summarized in Table 2. Individual guaifenesin Cmax, AUC(inf) and Tmax values following the administration of the tablet under fed and fasted conditions are shown in Figures 3, 4 and 5, respectively. The point estimates and the 90% CIs for the log-transformed Cmax and AUC(inf) for guaifenesin and PSE are presented in Table 4.

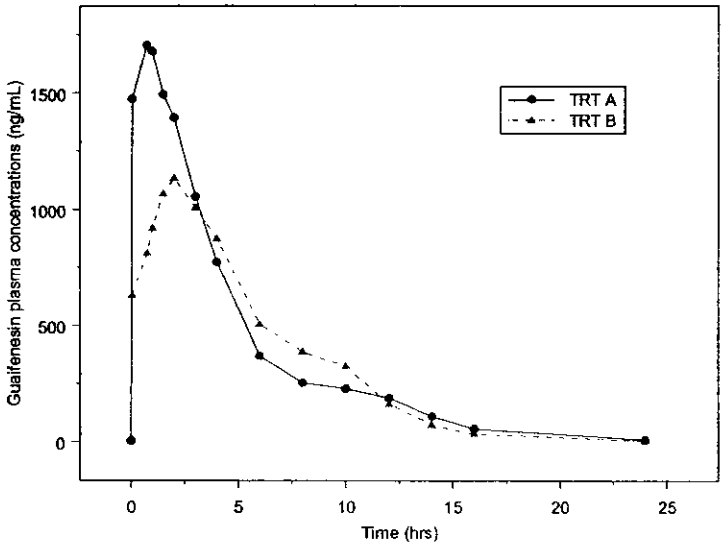


Figure 1. Mean guaifenesin plasma concentration-time profiles following single administration of Mucinex-D tablets under fed (TRT B) and fasted (TRT A) conditions.

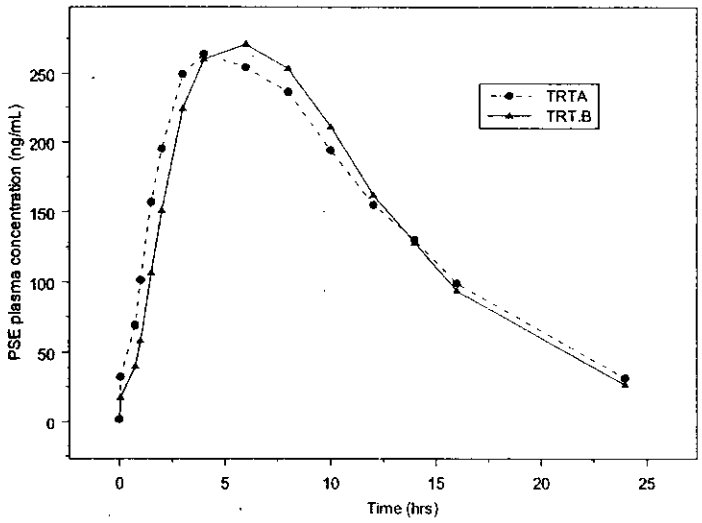


Figure 2. Mean PSE plasma concentration-time profiles following single administration of Mucinex-D tablets fed (TRT B) and fasted (TRT A) conditions.

Table 2. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following single administration of Mucinex-D with and without food

	Mean (%CV) PK Parameters				
Treatment	**Cmax (ng/mL)**	**Tmax (hr)**	**AUCt (ng*hr/mL)**	**AUCinf (ng*hr/mL)**	**T1/2 (hr)**
	Guaifenesin				
Fasted	1857 (838)	1.06 (0.58)	8091 (3501)	8142 (3500)	1.82 (0.7)
Fed	1364 (691)	2.06 (1.16)	7403 (3185)	7469 (3217)	1.39 (0.83)
	Pseudoephedrine				
Fasted	283 (78)	4.6 (1.56)	3477 (152)	3746 (997)	5.01 (1.06)
Fed	301 (80)	5.8 (1.8)	3403 (915)	3660 (963)	4.6 (1.05)

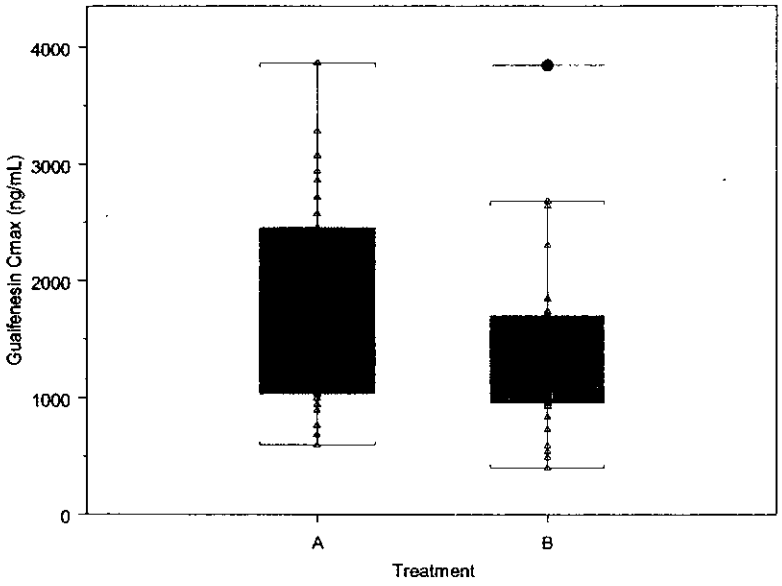


Figure 3. Individual guaifenesin Cmax values following single administration of Mucinex-D tablets under fed (TRT B) and fasted (TRT A) conditions.

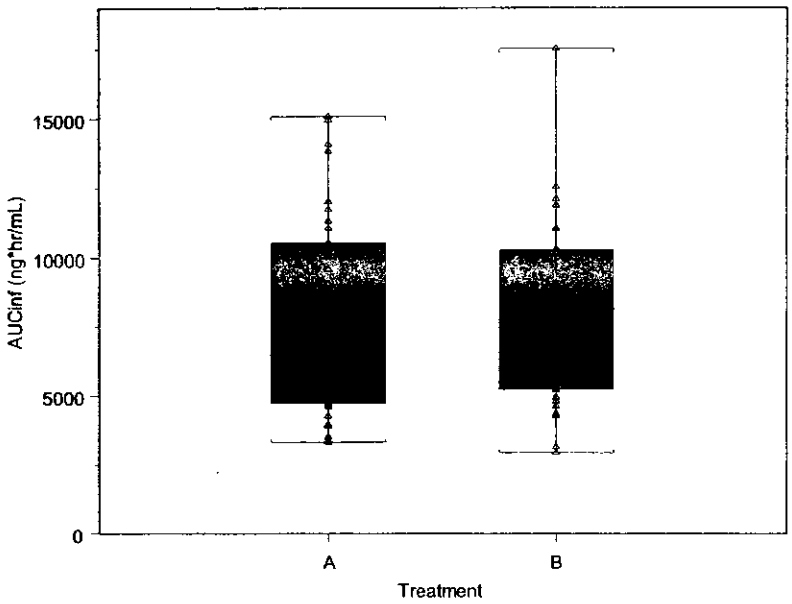


Figure 4. Individual guaifenesin AUCinf values following single administration of Mucinex-D tablets under fed (TRT B) and fasted (TRT A) conditions.

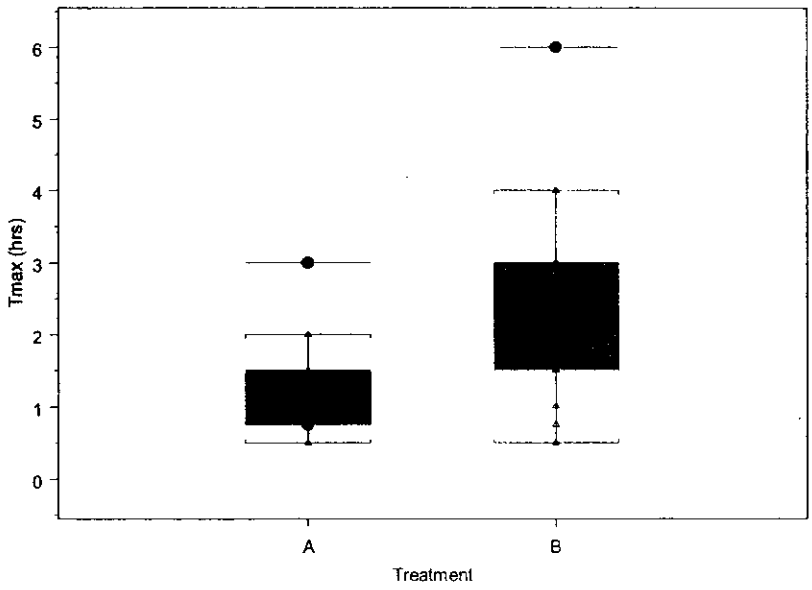


Figure 5. Individual guaifenesin Tmax values following single administration of Mucinex-D tablets under fed (TRT B) and fasted (TRT A) conditions..

Table 3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
Fed/fasted	Cmax	74	65.9-83.2
	AUCt	90	84.6-95.5
	AUCinf	90.2	84.7-96
	Pseudoephedrine		
Fed/fasted	Cmax	106	101-112
	AUCt	98.5	93.5-104
	AUCinf	98.6	93.6-104

CONCLUSION

- High-fat and high-caloric meal had no effect on the bioavailability of PSE from the Mucinex-D tablets. Ninety percent CI were within BE requirements (80-125).
- Food (high-fat breakfast) decreased the Cmax and AUCinf of guaifenesin by 26.5% and 8.5%, respectively. The Tmax was delayed by approximately one hour.

"A Definitive Study Designed to Examine the Effect of a High Fat Breakfast on the Bioavailability of an Experimental Controlled Release Formulations of 1200 mg Guaifenesin and 120 mg Pseudoephedrine Hydrochloride in Normal Healthy Volunteers Compared to Reference Controlled Release Guaifenesin and Pseudoephedrine Hydrochloride Products"

Name of Sponsor:	Adams Laboratories, Inc.
Included Protocols:	2002-02A
Development Phase of Study:	I
Study Initiation Date:	February 05, 2002
Study Completion Date:	February 24, 2002
Principal Investigator:	Dennis N. Morrison, D.O.
Date of the Report:	September 30, 2002

OBJECTIVE

- to determine the relative bioavailability of an experimental formulation containing 1200 mg guaifenesin and 120 mg PSE hydrochloride compared to reference formulation in normal, healthy male and/or female subjects in the fed condition.

Study Population

Thirty-six normal healthy volunteers entered and thirty-three completed the study according to the protocol. Subject one and 27 did not check in for period two and were dropped from the study. Subject 3 did not check in for period two due to an adverse event. The volunteers averaged 24.9 ± 9.6 years of age (Mean ± SD) with a range of 19 years to 54 years of age. They were 69 ± 3.5 inches tall with a range of 62 to 76 inches. They weighed 165 ± 23.8 pounds with a range of 120-225 pounds. Twenty five were male (65%) and eleven female (31%). Thirty-three volunteers (92%) were Caucasian, and three (8%) were Black.

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was a prospective, open-label, single dose, randomized, 2-way crossover study in healthy male and female volunteers. The subjects were randomized and placed into one of two treatment groups.

Group A: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg PSE Sudafed 12 Hour with 240 mL of water, 30 minutes after the beginning of the consumption of a high-fat breakfast (reference).

Group B: 1200 mg guaifenesin and 120mg of PSE as an experimental formulation with 240 mL of water, 30 minutes after the beginning of the consumption of a high-fat breakfast.

There was at least 7-day washout period between doses. The breakfast consisted of 2 eggs cooked with butter, 2 strips of bacon, 2 pieces of buttered toast, 4 ounces of hash brown potatoes and 8 oz of whole milk.

FORMULATION

1200 mg guaifenesin and 120mg of pseudoephedrine hydrochloride as an experimental formulation with 240 mL of water with food:
Lot number: PB 01M65

Sudafed lot number: 12171
Guaifenesin Lot number: PB 314A2

PHARMACOKINETIC MEASUREMENTS

Blood samples for guaifenesin and PSE determination were collected at predose and at the following times: 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 24 hours post dose.

Analytical Method

Plasma samples were assayed for guaifenesin and PSE using a HPLC (lower limit of quantification, LLQ= [redacted] respectively).

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Pharmacokinetic parameters were determined using the non-compartmental pharmacokinetic analysis program Kinetica 2000 Standard Version 2.1.

Statistical Analysis

Where data were available, food effect was examined between the test (Treatment B - guaifenesin or pseudoephedrine hydrochloride experimental formulation fed state) and the reference (Treatment A - mucinex or Sudafed reference products. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of test/reference. Cmax, AUCt, AUCinf, CL, t1/2 were natural log transformed prior to analysis.

RESULTS

Analytical Method

Guaifenesin

The limit of quantitation for guaifenesin: [redacted]

Stability and % of Recovery: The recovery of guaifenesin ranged from [redacted]

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was -3.3%. -3.4%, and 0.0% for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: The mean percent differences from theory are -6.4% and -4.3% for the [redacted] bench top concentrations, respectively. Based on these data, extracted samples stored under injection conditions are stable for at least [redacted] hours.

PSE

The limit of quantitation: [redacted]

Stability and % of Recovery: The recovery of guaifenesin ranged from [redacted]

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was 2.4, 5.0 and 5.0 % for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: Samples stored under injection conditions are stable for at least [redacted]

In-Study Validation

Table 1. Assay performance (Pre-study validation) for Guaifenesin and PSE

	Guaifenesin	PSE
Linearity	Satisfactory: Standard curve range fror [redacted]	Satisfactory: Standard curve range from [redacted]
Accuracy	Satisfactory: % Bias: [redacted]	Satisfactory: % Bias: [redacted]
Inter-day Presicion	Satisfactory: %CV: [redacted]	Satisfactory: %CV [redacted]
Specificity	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for guaifenesin and for PSE following administration of the treatments under fed conditions are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for PSE and guaifenesin are summarized in Table 2. Individual guaifenesin Cmax, and AUC(inf) values following the administration of the treatments under fed conditions are shown in Figures 3 and 4, respectively. The point estimates and the 90% CIs for the log-transformed Cmax and AUC(inf) for guaifenesin and PSE are presented in Table 4.

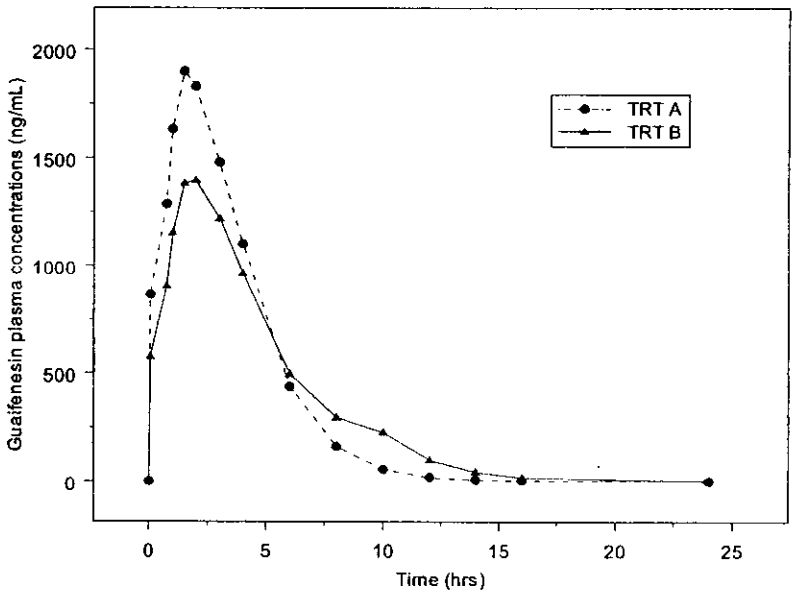


Figure 1. Mean guaifenesin plasma concentration-time profiles following single administration of Mucinex-D tablets under fed conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fed conditions.

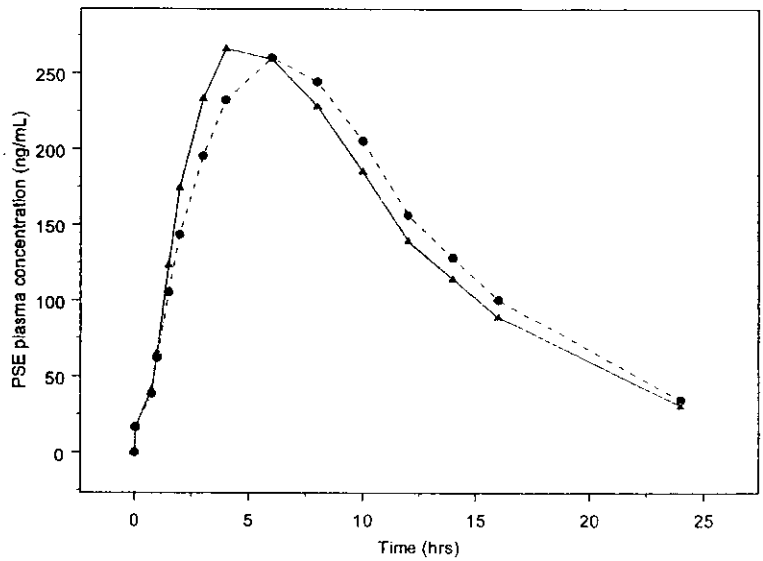


Figure 2. Mean PSE plasma concentration-time profiles following single administration of Mucinex-D tablets under fed conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fed conditions..

Table 2. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following single administration of Mucinex-D tablets under fed conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fed conditions..

	Mean (%CV) PK Parameters				
Treatment	**Cmax (ng/mL)**	**Tmax (hr)**	**AUCt (ng*hr/mL)**	**AUCinf (ng*hr/mL)**	**T1/2 (hr)**
	Guaifenesin				
Reference	2207 (952)	1.85 (1.06)	8049 (2666)	8067 (2663)	1.22 (0.621)
Mucinex-D	1649 (690)	1.84 (0.82)	7611 (2816)	7663 (2864)	1.4 (0.79)
	Pseudoephedrine				
Reference	268 (69.7)	6.38 (1.26)	3362 (847)	3636 (940)	5.3 (1.08)
Mucinex-D	274 (72)	4.8 (1.3)	3273 (876)	3528 (962)	5.3 (1.02)

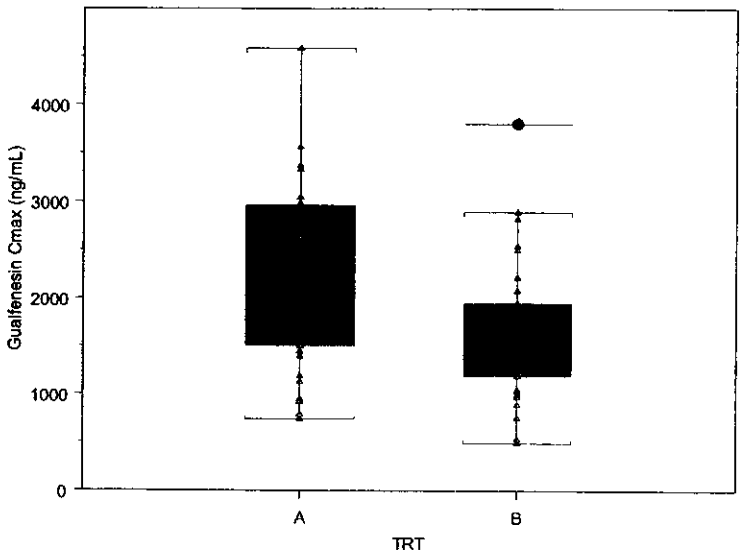


Figure 3. Individual guaifenesin Cmax values following single administration of Mucinex-D tablets under fed conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fed conditions..

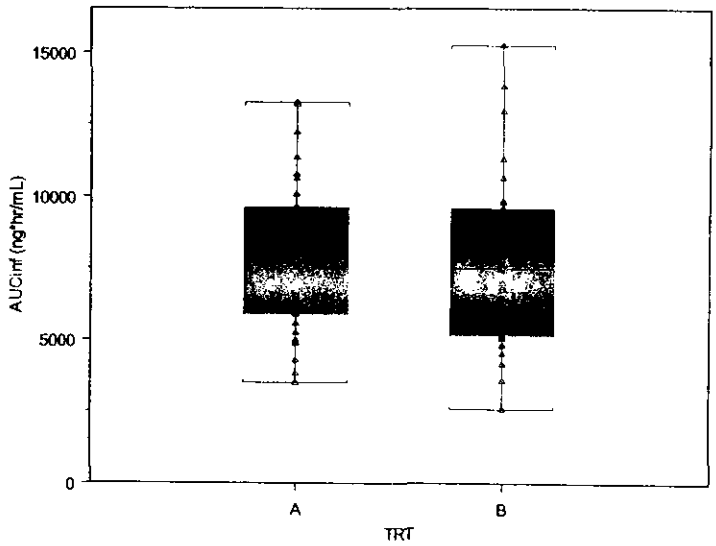


Figure 4. Individual guaifenesin AUCinf values following single administration of Mucinex-D tablets under fed conditions (TRT B) and reference product (mucinex + Sudafed) (TRT A) under fed conditions.

Table 3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
Mucinex-D/ References	Cmax	74.5	97.9-81.8
	AUCt	91.9	87.5-96.5
	AUCinf	92.2	87.8-96.8
	Pseudoephedrine		
Mucinex-D/ References	Cmax	102	99.5-105
	AUCt	96.2	92.9-99.2
	AUCinf	95.8	92.4-99.3

CONCLUSION

- Mucinex-D (guaifenesin/PSE/1200mg/120mg) and the reference product (mucinex + Sudafed) were bioequivalent in terms of PSE when administered under fed conditions. Ninety percent CI for the ratio of the log-transformed PK parameters (Cmax and AUCinf) were within goal post for BE (80-125).
- Mucinex-D (guaifenesin/PSE/1200mg/120mg) and the reference product (mucinex + Sudafed) were NOT bioequivalent in terms of guaifenesin when administered in fed conditions. Ninety percent CI for the ratio of the log-transformed PK parameters (Cmax and AUCinf) were within goal post for BE (80-125) for AUCinf, but not for Cmax. The arithmetic Cmax mean for mucinex-D in the presence of food was 25% lower compared to that for mucinex (guaifenesin 1200 mg).

"A Study Designed to Test the Interaction Potential of 1200 mg Guaifenesin and 120 mg Pseudoephedrine Hydrochloride (PSE) in Normal Healthy Volunteers"

Study no.:	2002-04
Development Phase of Study:	Phase I
Principal investigator:	Dennis N. Morrison, D.Q. BIO-KINETIC Clinical Applications, Inc. 1816 West Mount Vernon Springfield, MO 65802
Study Dates:	January 8th, 2002 to February 10th, 2002

Objectives

- to determine the pharmacokinetics of guaifenesin and pseudoephedrine when administered alone compare to when they are co-administered to normal, healthy male and/or female subjects.

Study Population

Thirty-six normal healthy volunteers entered and thirty-six completed the study according to the protocol. The volunteers averaged 31.06 ± 11.5 years of age (Mean ± SD) with a range of 18 years to 53 years of age. They were 68.3 inches tall with a range of 118 to 75 inches. They weighed 163.56 ± 34.9 pounds with a range of 118 to 242 pounds. Twenty-one were male (58%) and fifteen female (42%). Thirty-two volunteers (89%) were Caucasian, two were Hispanic, (3%), one was Asian (3%) and one was multiracial (3%).

STUDY DESIGN, TREATMENT AND ADMINISTRATION

This was a prospective, open-label, single dose, randomized, 3-way crossover study in healthy male and female volunteers. The subjects were randomized and placed into one of three treatment groups.

Group A: 1200 mg controlled release guaifenesin product (Mucinex) with 240 mL of water after an overnight fast.

Group B: 120mg PSE as Sudafed 12 Hour with 240 mL of water after an overnight fast.

Group C: 1200 mg controlled release guaifenesin product (Mucinex) and 120mg PSE as Sudafed 12 Hour with 240 mL of water after an overnight fast.

There was at least a 7-day washout between treatments.

FORMULATION

Treatment A: Guaifenesin 1200 mg Tablets and Sudafed® 12 hr 120 mg Tablets

Guaifenesin Lot Number: PB315A2

Treatment B: Sudafed® 12 hr 120 mg Tablets

Lot Number: 1271V

Treatment C: Guaifenesin 1200 mg Tablets and Sudafed® 12 hr 120 mg Tablets
Lot Number: PB315A2 and 1271V, respectively.

PHARMACOKINETIC MEASUREMENTS

Blood samples for guaifenesin and PSE determination were collected at predose and at the following times: 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 24 hours post dose.

Analytical Method

Plasma samples were assayed for guaifenesin and PSE using a HPLC (lower limit of quantification, LLQ= respectively).

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, and vital sign evaluations.

DATA ANALYSIS

Pharmacokinetic Data Analysis

Pharmacokinetic parameters were determined using the non-compartmental pharmacokinetic analysis program Kinetica 2000 Standard Version 2.1.

Statistical Analysis

Where data were available, drug-drug interaction was examined between the test (Treatment C- guaifenesin or pseudoephedrine hydrochloride) and the reference (Treatments A - guaifenesin and B pseudoephedrine hydrochloride) groups. An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of test/reference. Cmax, AUCt, AUC nf, CL, t1/2 were natural log transformed prior to analysis. Cmax, AUCt, AUCnf, were also dose-normalized prior to the ln-transformation.

RESULTS

Analytical Method

Guaifenesin

The limit of quantitation for guaifenesin:

Stability and % of Recovery: The recovery of guaifenesin ranged from

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was -3.3%. -3.4%, and 0.0% for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: The mean percent differences from theory are -6.4% and -4.3% for the bench top concentrations, respectively. Based on these data, extracted samples stored under injection conditions are stable for at least .

PSE

The limit of quantitation:

Stability and % of Recovery: The recovery of guaifenesin ranged from [redacted]

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations of guaifenesin in human plasma, the low, medium and high controls were designated as freeze/thaw controls and stored with the other controls made for this validation. The percent difference from theory was 2.4, 5.0 and 5.0 % for the low, medium and high freeze/thaw concentrations, respectively.

Bench Top Stability: Samples stored under injection conditions are stable for at least [redacted]

In-Study Validation

Table 1. Assay performance (Pre-study validation) for Guaifenesin and PSE

	Guaifenesin	PSE
Linearity	Satisfactory: Standard curve range from [redacted]	Satisfactory: Standard curve range from [redacted]
Accuracy	Satisfactory: % Bias: [redacted]	Satisfactory: % Bias: [redacted]
Inter-day Presicion	Satisfactory: %CV: : [redacted]	Satisfactory: %CV [redacted]
Specificity	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

Pharmacokinetic Results

The mean plasma concentration-time profiles for guaifenesin and for PSE following administration of the treatments are shown in Figures 1 and 2, respectively. The mean pharmacokinetic parameters for PSE and guaifenesin are summarized in Table 2. The point estimates and the 90% CIs for the log-transformed Cmax and AUC(I) for guaifenesin and PSE are presented in Table 3. The CIs of AUC(t), AUCinf, and Cmax for guaifenesin and PSE after test relative to reference met the 80-125% bioequivalence guideline.

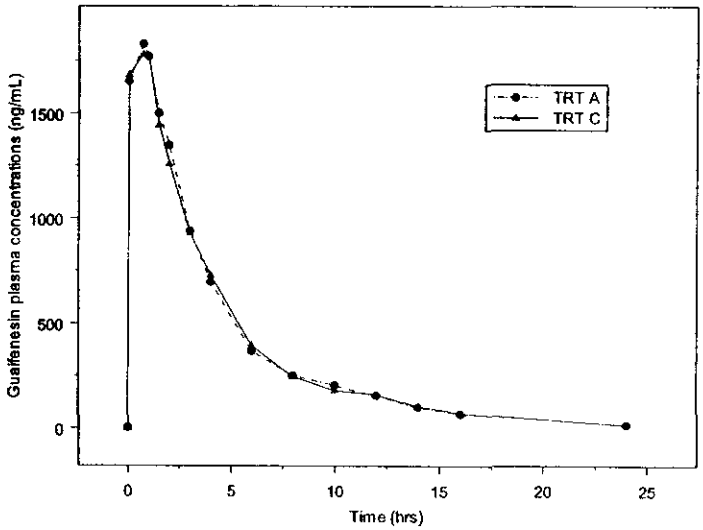


Figure 1. Mean guaifenesin plasma concentration-time profiles following single administration TRT A: 1200 mg controlled release guaifenesin product (Mucinex) and TRT C: 1200 mg guaifenesin (mucinex) and 120mg of pseudoephedrine hydrochloride (Sudafed).

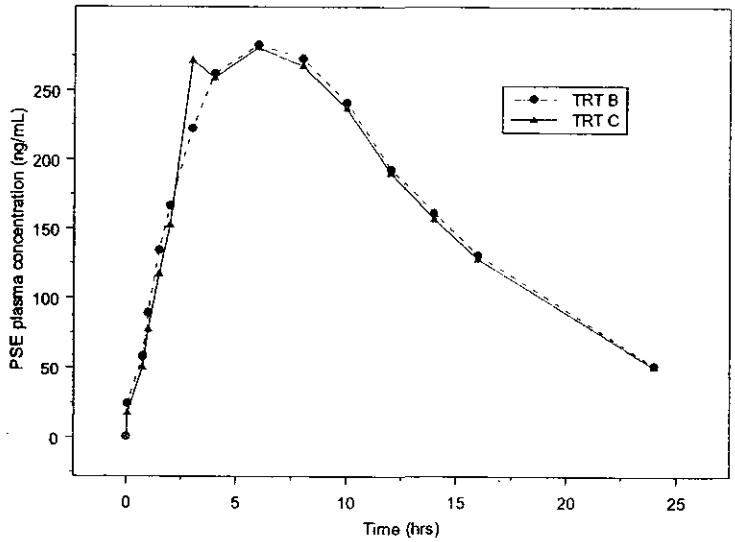


Figure 2. Mean PSE plasma concentration-time profiles following single administration of TRT B: 120mg pseudoephedrine hydrochloride as Sudafed 12 Hour and TRT C: 1200 mg guaifenesin (mucinex) and 120mg of pseudoephedrine hydrochloride (Sudafed).

Table 2. Mean (%CV) pharmacokinetic parameters of guaifenesin and PSE following single administration of the treatments

Treatment	Mean (SD) PK Parameters				
	Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCinf (ng*hr/mL)	T1/2 (hr)
	Guaifenesin				
TRT A	2009 (819.2)	0.89 (0.42)	7921 (3196.5)	8138 (3253.9)	4 (5.58)
TRT C	1989 (863.4)	0.84 (0.31)	7923 (3337)	8052 (3344)	3.41 (1.7)
	Pseudoephedrine				
TRT B	295.8 (73.3)	6.17 (1.92)	4024 (1047)	4505 (1250)	6.05 (1.4)
TRT C	289.3 (77.6)	5.75 (1.54)	3925 (1089)	4387 (1357)	(6.04 (1.4)

Table 3. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf values of guaifenesin and PSE following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
	Guaifenesin		
TRT C/ TRT A	Cmax	97.8	90.2-106
	AUCt	100	94.3-104
	AUCinf	98.4	93.6-103
	Pseudoephedrine		
TRT C/ TRT B	Cmax	97.6	94.2-101
	AUCt	97.4	94-101
	AUCinf	97.3	93.5-101

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

CONCLUSION

- The pharmacokinetics of guaifenesin is not affected by the presence of PSE. Ninety percent confidence intervals for the log-transformed PK parameters of guaifenesin (Cmax, AUCt, AUCinf) administered alone (mucinex) versus its coadministration with PSE (Sudafed) were within goal post for BE.
- The pharmacokinetics of PSE is not affected by the presence of guaifenesin. Ninety percent confidence intervals for the log-transformed PK parameters of PSE (Cmax, AUCt, AUCinf) administered alone (Sudafed) versus its coadministration with guaifenesin (mucinex) were within goal post for BE.

5.3 Filing/review form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-585	**Brand Name**	Mucinex-D
OCPB Division (I, II, III)	II	**Generic Name**	Guaifenesin/pseudoephedrine
Medical Division	DPADP	**Drug Class**	Expectorant/decongestant
OCPB Reviewer	Sandra Suarez-Sharp	**Indication(s)**	Treatment of COPD
OCPB Team Leader	Emmanuel Fadiran	**Dosage Form**	Extended-released tablets
PM Reviewer		**Dosing Regimen**	Adult and children 12 years and older: Guafenasin 600mg/PSE60mg tablet: two tablets BID. No more than 4 tablets per day. Guafenasin 1200mg/PSE120mg tablet: one tablets BID. No more than 2 tablets per day.
Date of Submission	January 31, 2003	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	October, 2002	**Sponsor**	Adams Laboratories, Inc.
PDUFA Due Date	November 30, 2003	**Priority Classification**	Standard
Division Due Date	November 9, 2003		

3 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:		1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1	1	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		1	1	
Bioequivalence studies -				
traditional design; single / multi dose:	x	4	1	
replicate design; single / multi dose:				
Food-drug interaction studies:	x	4	2	
Dissolution:	x	x		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		7	5	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. • The proposed regimen of [redacted], for PSE is not supported by the data submitted in the NDA. Additional efficacy data may be required if the sponsor chooses to request for approval of this dose regimen in the label • Submit individual dissolution-time profiles data in a tabulated form for all the batches of mucinex-D extended release tablets used in the definitive pharmacokinetic studies
QBR questions (key issues to be considered)	1. Is mucinex-D bioequivalenct to the reference products following single and multiple administration? 2. Does food affect the BA of guaifenesin/PSE from the mucinex-D extended release tablet? 3. Is there any drug-drug interaction between guaifenesin and PSE delivered from the mucinex-D product?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-585, HFD-870 (Electronic Entry or Lee), HFD-570 (Jackson), HFD-870 (Fadiran, ,Hunt, Malinowski)), CDR (B. Murphy)

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

/s/

Sandra Suarez
10/24/03 11:02:17 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
10/24/03 01:52:35 PM
BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

TYPE:	**Response to questions in Approvable Letter**
NDA:	21-585
Proprietary Drug Name:	MUCINEX™ D
Generic Name:	Guaifenesin/pseudoepherine
Indication:	Expectorant/Nasal decongestant.
Dosage Form:	Bilayer Tablet: immediate/Extended Release Tablet
Strength:	1200mg/120 mg and 600/60 mg
Route of Administration:	Oral
Dosage and administration:	adults and children 12 years and older: For the 600mg/60mg product, two tablets every 12 hours; not more than 4 tablets in 24 hours For the 1200mg/120mg product: one tablet every 12 hours; not more than 2 tablets in 24 hours. children under 12 years of age: do not use
Applicant:	Adams Laboratories, Inc.
Clinical Division:	DPADP (HFD-570)
Submission Dates:	January 31, 2003, December 22, 2003
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel O. Fadiran, Ph. D.

1. EXECUTIVE SUMMARY

Adams Laboratories, Inc. is seeking approval of Mucinex-D extended release/immediate tablets (NDA 21-585) for the treatment of cough/nasal decongestion. Mucinex-D tablets contain guaifenesin and pseudoephedrine HCl (PSE) at doses currently marketed as OTC products. Mucinex-D tablets are presented in two dosage strengths, 1200mg guaifenesin/ 120 mg PSE (Maximum Strength) and 600 mg guaifenesin/60 mg PSE (Regular Strength) and will be marketed as an OTC product. The proposed dosing regimen is 1200mg/120mg every 12 hours; not more than 2400/240 mg in 24h.

The sponsor received an approvable letter on November 24, 2003 for this NDA. The letter contained chemistry related comments and 2 biopharmaceutics related comments. In the present submission (dated December 22, 2003), the sponsor provided responses related to these comments. The sponsor provided supporting evidence that the changes made to produce the batches using new manufacturing parameters correspond to as defined by guidance for industry and therefore, no in vivo BE study is required. In addition, a comparison of the dissolution profiles stability between the batches used in the bioequivalence studies and those produced under new manufacturing conditions showed similar dissolution profiles. Therefore, the Agency considers that the dissolution specifications for mucinex-D maximum and regular strengths can be finalized as follows:

Maximum Strength

Time	Specification	
	Guaifenesin	PSE
1 hour		
2 hour		
6 hour		
12 hour		

Regular Strength

Time	Specification	
	Guaifenesin	PSE
1 hour		
2 hour		
6 hour		
12 hour		

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed the response to comments in the approvable letter for NDA 21-585 and found them satisfactory. The dissolution specifications for mucinex –D maximum and regular strengths can be finalized as described above.

Reviewer
Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader

cc: NDA 21-585 : Division File
HFD-870: Malinowski, Hunt
HFD-570: Fadiran, Lee, Chowdhury, Jackson, Suarez-Sharp

2. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Adams Laboratories, Inc. is seeking approval of Mucinex-D extended release/immediate tablets (NDA 21-585) for the treatment of cough/nasal decongestion. Mucinex-D tablets contain guaifenesin and pseudoephedrine HCl (PSE) at doses currently marketed as OTC products. Mucinex-D tablets are presented in two dosage strengths, 1200mg guaifenesin/120 mg PSE (Maximum Strength) and 600 mg guaifenesin/60 mg PSE (Regular Strength) and will be marketed as an OTC product. The proposed dosing regimen is 1200mg/120mg every 12 hours; not more than 2400 mg/240 mg in 24h.

The sponsor received an approvable letter on of November 24, 2003 for this NDA. The letter contained chemistry related comments and 2 biopharmaceutics related comments. On December 22, 2003, the Agency received a response related to these comments as follows:

Agency's comment # 1:
The following interim dissolution specifications are recommended for guaifenesin and pseudoephedrine HCl from the Mucinex-D regular and maximum strengths:

Maximum Strength

Time	Specification	
	Guaifenesin	PSE
1 hour		
2 hour		
6 hour		
12 hour		

Regular Strength

Time	Specification	
	Guaifenesin	PSE
1 hour		
2 hour		
6 hour		
12 hour		

Sponsor's Response:
"The recommended interim dissolution specifications for guaifenesin and pseudoephedrine HC1 for Mucinex® D regular and maximum strength tablets have been incorporated into a new revision (09) of Drug Product Acceptance Specifications DPS-1201 (Maximum Strength) and DPS-1202 (Regular Strength), respectively. These same dissolution specifications have also been added to the Stability Protocol."

Agency's comment # 2:
The interim dissolution specifications will be finalized when you provide in-vitro dissolution data at release and during stability of the batches produced under new manufacturing parameters.

Sponsor's Response:
"We acknowledge that the interim dissolution specifications will be finalized when in-vitro dissolution data at release and during stability of the batches produced under the new manufacturing parameters are provided."

For clarification purposes, certain terminology will be employed to define the various stages of Mucinex® D process refinement and the corresponding Mucinex® D Pilot Batches produced using these enhanced process controls. The terminology to be used is described below:

Set 1: This term will be used to describe the first round of Pilot Batches, including the bioequivalence Pilot Batches PB01-M65 (maximum strength) and PB02-A12 (regular strength). These Pilot Batches were the original ones produced and were produced without screening the Guaifenesin in the modified release (MR) blend and without complete optimization of compression parameters

Set 2: This term will be used to describe the second round of Pilot Batches produced. These Pilot Batches were produced after development studies had identified process controls that reduced the friability of the tablets. These batches were produced by screening the Guaifenesin before weighing and used in the MR blend and by utilizing more stringent [redacted] parameters (i.e.,

Set 3: This term will be used to describe the third round of Pilot Batches produced. These Pilot Batches were produced to assess the impact of [redacted] values and slight increases (from normal process variations) in Guaifenesin [redacted] content on the tablets, specifically the friability and dissolution. These Pilot Batches were manufactured using the same process as the Set 2 Pilot Batches in all other respects.

This reviewer's comments:

According to the sponsor, due to the similarity of the Pilot Batches in Set 2 and Set 3, any requests for results from batches made with the "new manufacturing parameters" or made "under new manufacturing conditions" or "manufactured with the proposed manufacturing changes" will result in data being presented from all Pilot Batches in Set 2 and Set 3. The sponsor stated that batches produced in Sets 1, 2, and 3 use the same manufacturing process. Tighter controls were simply employed with batches produced in Sets 2 and 3.

Figures 1 and 2 showed the mean dissolution profiles at time zero, 2 months, and 3 months stability for guaifenesin for batches used in BE studies and for those produced under new manufacturing conditions for the maximum and regular strengths, respectively. Likewise, Figure 3 and 4 showed the mean dissolution profiles for PSE.

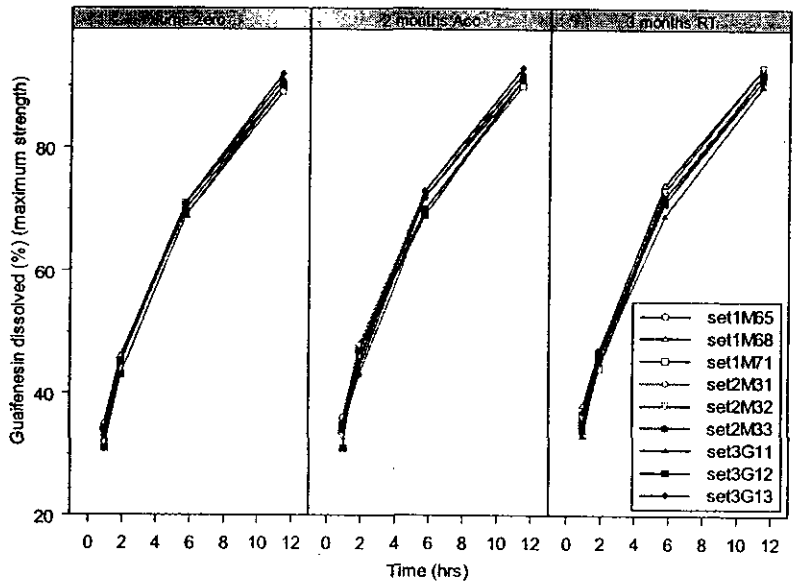


Figure 1. Mean guafenesin dissolved (%) (MAXIMUM strength/20 count bottles) for batches used in pivotal BE studies (set 1) and those produced under new manufacturing conditions (sets 2 and 3) at time zero and under 2 and 3 months stability (n=6 to 12).

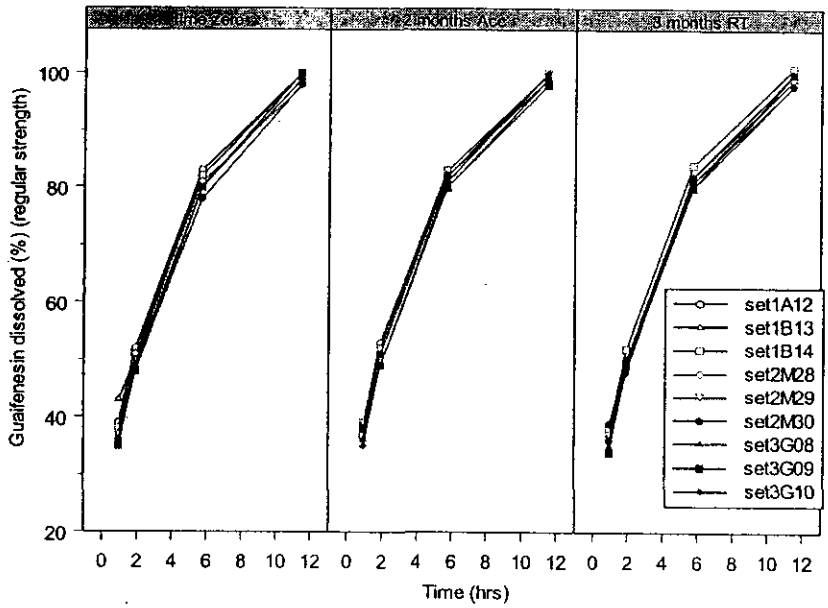


Figure 2. Mean guafenesin dissolved (%) (REGULAR strength/40 count bottles) for batches used in pivotal BE studies (set 1) and those produced under new manufacturing conditions (sets 2 and 3) at time zero and under 2 and 3 months stability (n=6 to 12).

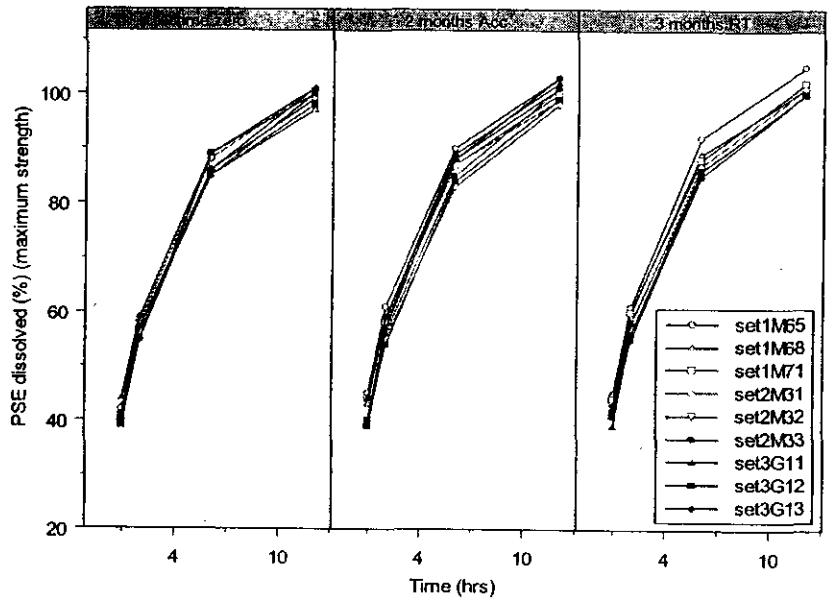


Figure 3. Mean PSE dissolved (%) (MAXIMUM strength/20 count bottles) for batches used in pivotal BE studies (set 1) and those produced under new manufacturing conditions (sets 2 and 3) at time zero and under 2 and 3 months stability (n=6 to 12).

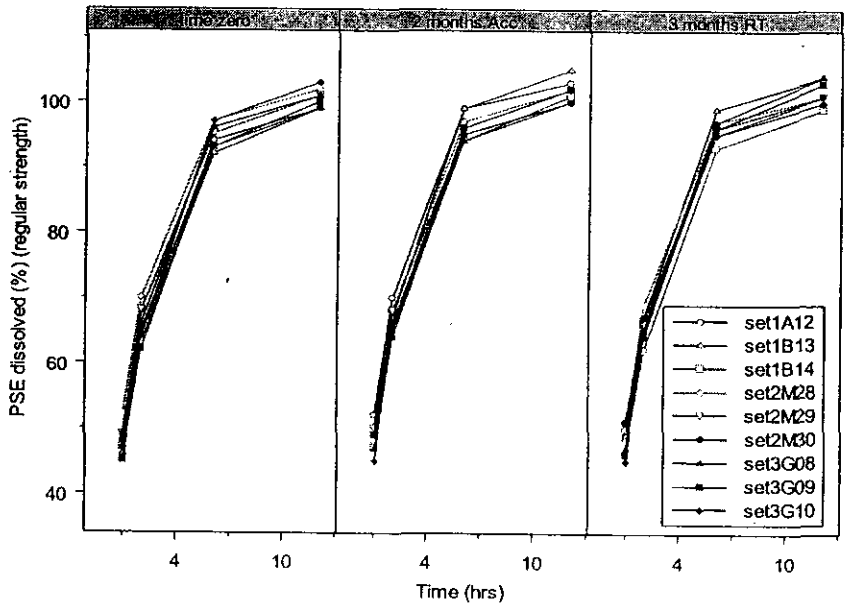


Figure 4. Mean PSE dissolved (%) (REGULAR strength/40 count bottles) for batches used in pivotal BE studies (set 1) and those produced under new manufacturing conditions (sets 2 and 3) at time zero and under 2 and 3 months stability (n=6 to 12.

bioequivalence batches versus the Set 2 and Set 3 Pilot Batches made with the "new manufacturing conditions") is the addition of the Guaifenesin screening step, before weighing the material for the [redacted] step reduced [redacted] within the Guaifenesin and allowed more consistent homogeneity, particle [redacted]

While all [redacted] processes were identical between the Set 2 and Set 3 Pilot Batches, it was desired to study the impact of the Guaifenesin [redacted] content on tablet [redacted] For this reason, Guaifenesin batches with [redacted] contents (yet remaining comfortably within specifications and a result of normal manufacturing cycle fluctuations) were selected for the Set 3 Pilot Batches. These Pilot Batches also exhibited the friability improvement first noted in the Set 2 Pilot Batches.

In reference to the principles of the SUPAC-MR guidance for industry, there have been no component of composition changes for release-controlling excipients or non-release controlling excipients. In addition, no manufacturing site changes, no changes in the batch size, no manufacturing equipment changes, and no manufacturing process changes have occurred".

This reviewer's comments:

According to the sponsor, the minor improvements to the Mucinex® D manufacturing process have no impact on the quality attributes of the drug product (except the desired, favorable impact on tablet friability). This reviewer together with the chemistry reviewer (personal communication) agree with this statement.

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

/s/

Sandra Suarez
5/13/04 12:28:41 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
5/13/04 03:54:55 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-585**	**Brand Name**	**Mucinex-D**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Guaifenesin/pseudoephedrine**
Medical Division	**DPADP**	**Drug Class**	**Expectorant/decongestant**
OCPB Reviewer	**Sandra Suarez-Sharp**	**Indication(s)**	**Treatment of COPD**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**Extended-released tablets**
PM Reviewer		**Dosing Regimen**	**Adult and children 12 years and older: Guafenasin 600mg/PSE60mg tablet — two tablets BID. No more than 4 tablets per day. Guafenasin 1200mg/PSE120mg tablet: one tablets BID. No more than 2 tablets per day.**
Date of Submission	**January 31, 2003**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**October, 2002**	**Sponsor**	**Adams Laboratories, Inc.**
PDUFA Due Date	**November 30, 2003**	**Priority Classification**	**Standard**
Division Due Date	**November 9, 2003**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1		
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	4		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	4		
Dissolution:	x	x		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		7		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. • The proposed regimen of [redacted] for PSE is not supported by the data submitted in the NDA. Additional efficacy data may be required if the sponsor chooses to request for approval of this dose regimen in the label • Submit individual dissolution-time profiles data in a tabulated form for all the batches of mucinex-D extended release tablets used in the definitive pharmacokinetic studies
QBR questions (key issues to be considered)		1. Is mucinex-D bioequivalenct to the reference products following single and multiple administration? 2. Does food affect the BA of guaifenesin/PSE from the mucinex-D extended release tablet? 3. Is there any drug-drug interaction between guaifenesin and PSE delivered from the mucinex-D product?
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-585, HFD-870 (Electronic Entry or Lee), HFD-570 (Jackson), HFD-870 (Fadiran, ,Hunt, Malinowski)), CDR (B. Murphy)

BACKGROUND

This NDA is a 505(b)(2) application for an extended release formulation of guaifenesin and pseudoephedrine HCl (PSE). The sponsor is requesting approval of two dosage strengths, guaifenesin 600 mg/PSE 60 mg tablets, and guaifenesin 1200 mg/PSE 120 mg tablets. The product is a bilayer tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and nasal decongestant. The proposed indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies,

The sponsor's drug development program for Mucinex™ D is based on establishing that their combination guaifenesin/PSE product produces equivalent exposures to that of their approved and marketed extended release single ingredient guaifenesin product and to an approved and marketed extended release PSE product. The sponsor's drug development program also evaluated the effect of food on bioavailability of the proposed product and assessed the potential for interaction between guaifenesin and PSE in the combination product (see Table below).

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects
00-01	Bioavailability, pilot study	G 1200 mg plus fexofenadine 60 mg/120 mg PSE* G 1200 mg/PSE 120 mg, prototype 1 G 1200 mg/PSE 120 mg, prototype 2	Single dose	Single center, randomized, open label, three period, three-way crossover	21	Healthy men and women, 19-49 years
01-01A	Bioavailability, pilot study	G 1200 mg plus 120 mg PSE G 1200 mg/PSE 120 mg, prototype 1 G 1200 mg/PSE 120 mg, prototype 3	Single dose	Single center, randomized, open label, three period, three-way crossover	15	Healthy men and women, 18-50 years
2002-01A	Bioavailability and dose proportionality, definitive study	G 1200 mg plus 120 mg PSE G 1200 mg/PSE 120 mg G 600 mg/PSE 60 mg	Single dose	Single center, randomized, open label, three period, three-way crossover	36	Healthy men and women, 18-48 years
2002-02A	Food effect	G 1200 mg plus 120 mg PSE, fed G 1200 mg/PSE 120 mg, fed	Single dose	Single center, randomized, open label, two period, two-way crossover	36	Healthy men and women, 19-54 years
2002-03	Bioavailability, steady state, definitive study	G 1200 mg plus 120 mg PSE, BID G 1200 mg/120 mg PSE, BID	Multiple dose	Single center, randomized, open label, two period, two-way crossover, 11 doses	37	Healthy men and women, 18-48 years
2002-04	Drug interaction study	G 1200 mg PSE 120 mg G 1200 mg/PSE 120 mg	Single dose	Single center, randomized, open label, three period, three-way crossover	36	Healthy men and women, 18-53 years
2002-11	Food effect	G 1200 mg/PSE 120 mg, fasted G 1200 mg/PSE 120 mg, fed	Single dose	Single center, randomized, open label, two period, two-way crossover	38	Healthy men and women, 189-54 years

G = guaifenesin, PSE = pseudoephedrine
*fexofenadine 60 mg/120 mg PSE = Allegra® D

CPB INFORMATION CONTENT IN SUBMITTED NDA

Study Title/Description	Tabular listing/PK summary	Analytical method	PK parameters (means and individual values)	Statistical analysis
Study 00- 01: Bioavailability, pilot study	√	√	√	√
Study 01- 01A: Bioavailability, pilot study	√	√	√	√
Study 2002- 01A: Bioavailability and dose proportionality, definitive study	√	√	√	√
Study 2002- 02A: Food effect	√	√	√	√
Study 2002- 03: Bioavailability, steady state, definitive study	√	√	√	√
Study 2002- 04: Drug interaction study	√	√	√	√
Study 2002- 11: Food effect	√	√	√	√

CONCLUSION: Submission is filable.

COMMENTS TO SPONSOR:

- The proposed regimen of [redacted] for PSE is not supported by the data submitted in the NDA. Additional efficacy data may be required if the sponsor chooses to request for approval of this dose regimen in the label
- Submit individual dissolution-time profiles data in a tabulated form for all the batches of mucinex-D extended release tablets used in the definitive pharmacokinetic studies

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceuticals / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has conducted a preliminary reviewed of NDA 21-585 submitted on January 31, 2002. The NDA's Human Pharmacokinetics and Bioavailability Section is filable to OCPB. Please conveyed the comments above to the sponsor.

Reviewer

Sandra Suarez-Sharp, Ph.D. _____

Office of Clinical Pharmacology and Biopharmaceuticals

Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader _____

cc

NDA 21-585 :	Division File
HFD-870:	Malinowski, Hunt
HFD-570:	Fadiran, Lee, Chowdhury, Jackson, Suarez-Sharp

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

/s/

Sandra Suarez
3/27/03 12:50:26 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
3/27/03 03:21:16 PM
BIOPHARMACEUTICS
I concur