

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-620**

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

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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<b>NDA:</b>	21-620
<b>Proprietary Drug Name:</b>	MUCINEX™ DM
<b>Generic Name:</b>	Guaifenesin/Dextromethorphan
<b>Indication:</b>	Expectorant/Antitussive
<b>Dosage Form:</b>	Bilayer Tablet.  Extended Release Tablet
<b>Strength:</b>	1200mg/60 mg and 600/30 mg
<b>Route of Administration:</b>	Oral
<b>Dosage and administration:</b>	Adults and children 12 years and older: For the 600mg/30mg product, one or two tablets every 12 hours; not more than 4 tablets in 24 hours. For the 1200mg/60mg product: one tablet every 12 hours; not more than 2 tablets in 24 hours. Children under 12 years of age: do not use
<b>Applicant:</b>	Adams Laboratories, Inc.
<b>Clinical Division:</b>	DPADP (HFD-570)
<b>Submission Date:</b>	June 30, 2003
<b>Reviewer:</b>	Shinja Kim, Ph.D.
<b>Team Leader:</b>	Emmanuel O. Fadiran, Ph. D.

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## 1. EXECUTIVE SUMMARY

The proposed product in this submission is Mucinex<sup>®</sup> DM Extended-release Bi-layer tablet for which the sponsor has requested an OTC approval. Mucinex<sup>®</sup> DM is a combination drug product that contains two active ingredients, guaifenesin and dextromethorphan hydrobromide in two strengths (1200 mg guaifenesin / 60 mg dextromethorphan hydrobromide [HBr] and 600 mg guaifenesin / 30 mg dextromethorphan HBr). Guaifenesin is an expectorant and dextromethorphan HBr (DM) is an antitussive, and this proposed combination product is to be used a twice daily for the temporary relief of cough associated with upper respiratory tract infection and related conditions.

The sponsor conducted six clinical pharmacology studies to assess bioavailability/bioequivalence and food effects of Mucinex DM. Also, a drug-drug interaction study was conducted to ensure the guaifenesin and DM drug components in the proposed Mucinex DM formulation do not interact when administered concurrently. The results from these studies are summarized as follows:

- (1) PK profiles of guaifenesin and DM from Mucinex DM were similar to the reference drugs (e.g., Mucinex<sup>®</sup>, immediate release DM products)
- (2) Food had no effect on bioavailability of guaifenesin and DM
- (3) No drug-drug pharmacokinetic interaction between guaifenesin and DM. There are no major clinical pharmacology issues.

### A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-620. The DSI recommends accepting the data from the pivotal bioequivalence studies except the data from specific samples from one subject in Study 2002-08 and one subject from Study 2002-10 (see DSI report in DFS). The removal of these specific samples will not have any significant impact on the outcome of the studies.

Reviewer

Shinja Kim, 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 21-620 :

Division File

HFD-870:

Malinowski, Hunt

HFD-570:

Fadiran, Szema, Chowdhury, Jackson, Shinja Kim

## B. Summary of clinical Pharmacology and Biopharmaceutics Findings

The sponsor, Adams Laboratories, Inc., is seeking approval of Mucinex DM an extended release bilayer tablet for the treatment of the temporary relief of cough associated with upper respiratory tract infection and related conditions. This NDA is a 505(b)(2) application with an approval for OTC use for guaifenesin and DM at the proposed dose regimen of 1200/60 mg every 12 hours; not more than 2400/120 mg in 24 hours. The sponsor requests approval of two dosage strength tablets: guaifenesin 1200 mg/DM 60 mg tablets, and guaifenesin 600 mg/DM 30 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).

In support of this application the sponsor submitted the results of six 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 DM compared to an already approved reference (or currently on the market) after a single and multiple dose (steady state), to assess the effect of food on the BA of guaifenesin and DM delivered from the Mucinex DM product, to assess a possible drug-drug interaction between guaifenesin and DM. Dissolution data was also provided to support the dissolution methods and specification proposed for this product.

**BE/BA Assessment (Study 2002-08):** In a single dose, three-way crossover study Mucinex® DM was compared to marketed Mucinex® and Vicks® 44® Cough Relief. The study showed that Mucinex DM was bioequivalent to the reference Mucinex® treatment in terms of guaifenesin as the 90% CI for the ratio of  $C_{max}$  and AUC were contained within 80% to 125%. However, the 90% CI for  $C_{max}$  and AUC of DM were out of the 80-125% (Table 1).

**Table 1.** Point estimates and 90% confidence intervals for the log-transformed  $C_{max}$ , AUC<sub>t</sub>, and AUC<sub>inf</sub> values of guaifenesin and DM following single administration of the treatments (Study 2002-08)

Comparison	PK parameter	Point estimates	90% CI	Point estimates	90% CI
		Guaifenesin		Dextromethorphan	
Trt C/Trt A	$C_{max}$	100	91.4-111	95.4	77.4-118
	AUC <sub>t</sub>	93.5	88.8-98.5	86.6	75.0-114
	AUC <sub>inf</sub>	92.5	87.9-97.5	87.8	76.3-101
Trt C/Trt B	$C_{max}$	94.9	86.3-104	93.0	75.1-114
	AUC <sub>t</sub>	96.1	91.2-101	84.8	73.6-98.1
	AUC <sub>inf</sub>	94.3	89.5-99.3	85.8	74.3-98.4

A = Mucinex® plus Vicks® 44® 30 mg q6h for 2 doses - reference

B = Mucinex® plus Vicks® 44® 20 mg q4h for 3 doses - reference

C = Mucinex® DM ;200/60 mg - test

**PK at Steady State (Study 2002-10):** The study was designed same as single dose study (2002-08), except that the dose was administered q12h for 6 days. Guaifenesin and DM from the Mucinex DM tablet were BE at steady-state to the reference formulations in terms of  $C_{max}$  and AUC<sub>SS</sub>, as the 90% CI for treatment comparisons were contained within 80% to 125%. The minimum concentration ( $C_{min}$ ) of guaifenesin from the Mucinex DM tablet was 3- or 4-fold lower compared to that for the reference (Mucinex®: guaifenesin 1200 mg) (Table 2).

The range of effective minimum concentration for guaifenesin is wide for current regimens and they do not have the same total dose per day (e.g., 190 mg IR q8h; 200 or 400 mg q4h).  $C_{min}$  of guaifenesin from the proposed formulation falls within the known effective concentration level associated with guaifenesin (e.g., 190 mg IR formulation q8h; Figure 3 on page 12), thus one could assume that the guaifenesin levels established in the steady-state trial for the proposed Mucinex DM formulation provided clinically effective guaifenesin concentrations.

**Table 2.** Point estimates and 90% confidence intervals for the log-transformed AUC<sub>ss</sub>, C<sub>max</sub> and C<sub>min</sub> of guaifenesin and DM following multiple administration of the treatments

Comparison	PK parameter	Point estimates	90% CI	Point estimates	90% CI
		<i>Guaifenesin</i>		<i>Dextromethorphan</i>	
Trt C/Trt A	AUC <sub>ss</sub>	96	91.1-101	101	87.6-116
	C <sub>max</sub>	93	85.3-100	104	90.2-121
	C <sub>min</sub>	27	18.1-40.5	84	71.8-97.2
Trt C/Trt B	AUC <sub>ss</sub>	97	92.0-102	103	89.8-119
	C <sub>max</sub>	90	83.3-97.8	105	91.2-122
	C <sub>min</sub>	31	20.8-46.5	84	72.1-97.6

A = Mucinex® plus Vicks® 44® 30 mg q6h for 2 doses - reference  
 B = Mucinex® plus Vicks® 44® 20 mg q4h for 3 doses - reference  
 C = Mucinex® DM 1200/60 mg - test

**Effect of Food (Study 2002-12):**

The effect of food on the BA of guaifenesin and DM from the Mucinex DM formulation was assessed in a 2-way crossover design. The study showed that a high-fat and high-caloric meal had no effect on the bioavailability of guaifenesin from the Mucinex DM tablets, however, T<sub>max</sub> of guaifenesin was delayed by approximately 1.5 hours. Food increased the C<sub>max</sub>, but not AUC<sub>inf</sub> of DM by 21% without change in T<sub>max</sub> (Table 3).

**Table 3.** Point estimates and 90% confidence intervals for the log-transformed C<sub>max</sub> and AUCs of guaifenesin and DM following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
<b>Guaifenesin</b>			
TRT B/ TRT A	C <sub>max</sub>	96	82.2-100
	AUC <sub>t</sub>	93	85-94.6
	AUC <sub>inf</sub>	27	85-94.5
<b>Dextromethorphan</b>			
TRT B/ TRT A	C <sub>max</sub>	121	107-136
	AUC <sub>t</sub>	108	96.7-121
	AUC <sub>inf</sub>	107	96.4-120

A = Mucinex® DM 1200/60 mg, under fasted - reference  
 B = Mucinex® DM 1200/60 mg, fed condition- test

This reviewer is of the opinion that the 21% increase in C<sub>max</sub> of DM and delay on T<sub>max</sub> of guaifenesin may not be clinically relevant and therefore, Mucinex DM can be taken without regards to meals.

**Drug-Drug Interaction (DDI):**

Study 2001-15 examined the interaction potential of guaifenesin and DM when administered as Mucinex® DM (1200 mg guaifenesin/ 60 mg DM) and reference products, Mucinex® (1200 mg guaifenesin) and immediate-release DM (Benylin®) liquid (30 and 60 mg administered in divided doses every 4 h or every 6 h over a 12-hour dosing interval). The study concluded that there was no evidence of a drug-drug pharmacokinetic interaction between DM and guaifenesin when the various treatments were compared (Table 4).

**Table 4.** Point estimates and 90% confidence intervals for the log-transformed (dose normalized)  $C_{max}$  and AUCs of guaifenesin and DM following single administration of the treatments

Comparison	PK parameter	Point estimates	90% confidence intervals
<b>Guaifenesin</b>			
TRT A/ TRT B	$C_{max}$	97.3	88.7-107
	$AUC_t$	100	93.8-108
	$AUC_{inf}$	97.0	90.1-104
<b>Dextromethorphan</b>			
TRT A/ TRT C	$C_{max}$	97.6	110-153
	$AUC_t$	101	87.3-118
	$AUC_{inf}$	102	88.2-119
TRT A/ TRT D	$C_{max}$	93.0	77.6-111
	$AUC_t$	77.8	66.0-91.6
	$AUC_{inf}$	77.8	66.1-91.5
TRT E/ TRT C	$C_{max}$	106	89.9-124
	$AUC_t$	101	87.1-117
	$AUC_{inf}$	101	87.7-117
TRT F/ TRT D	$C_{max}$	87.5	73.6-104
	$AUC_t$	88.5	75.7-103
	$AUC_{inf}$	89.9	77.0-105

A = Mucinex<sup>®</sup> DM 1200/60 mg, - test,  
 C = Benlyn<sup>®</sup> 30 mg q6H x 2 doses – reference,  
 E = Benlyn<sup>®</sup> 15 mg q6H x 2 doses – reference,

B = Mucinex<sup>®</sup> - reference  
 D = Benlyn<sup>®</sup> 20 mg q4H x 3 doses – reference  
 F = Benlyn<sup>®</sup> 30 mg q4H x 3 doses – reference

**Dissolution:** The dissolution method and specification for Mucinex DM regular and maximum strengths proposed by the sponsor are as follows:

**Method:** USP basket, \_\_\_\_\_

Specifications				
Time	Maximum Strength (1200/60 mg)		Regular Strength (600/30 mg)	
	Guaifenesin	DM	Guaifenesin	DM
1 hour				
2 hour				
6 hour				
12 hour				

The dissolution method and specifications were established based on previous recommendation by the FDA for the already approved extended release product Mucinex<sup>®</sup> and importantly, based on dissolution studies using different media and dissolution speeds.

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## II. QUESTION BASED REVIEW

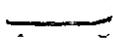
### A General Attributes

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™ DM are guaifenesin and DM hydrobromide. Guaifenesin has been used widely in the United States for over 50 years as an expectorant. The sponsor has received marketing approval for Mucinex 600 mg and 1200 mg tablets (Mucinex™ ER). DM hydrobromide is also a well known active pharmaceutical ingredient used as a cough suppressant.

#### Drug Product

Mucinex™ DM (guaifenesin/Dextromethorphan HBr) extended release tablets were designed as a line extension to Mucinex 600 mg and 1200 mg tablets. Mucinex DM tablets are presented in two dosage strengths, 1200 mg guaifenesin/ 60 mg DM and 600 mg guaifenesin/30 mg DM. Mucinex DM tablets are manufactured as bi-layer formulation by  immediate release layer (IR) and a modified release layer (MR) into a tablet. The components and composition on Mucinex DM for both strengths are shown in the Tables 5 and 6 below.

**Table 5.** Mucinex DM ER Tablet (1200 mg Guaifenesin/60 mg DM HBr)

Component	Amount (mg/tablet)	Representative batch (kg) <sup>1</sup>	
		IR layer	MR layer
Guaifenesin	1200.0	136.8	606.0
Dextromethorphan HBr	60	10.80	27
Microcrystalline cellulose			
Sodium starch glycolate			
Hypromellose			
Carbomer 934P			
Magnesium stearate			
FD&C Blue #1 Aluminum Lake			
Water purified <sup>2</sup>			
<b>Total weight</b>	<b>1530.4</b>	<b>288.0</b>	<b>678.24</b>

<sup>1</sup> Based on batch size of  tablets

<sup>2</sup>Water is removed during processing

**Table 6.** Mucinex DM ER Regular Strength Tablet (600 mg Guaifenesin/30 mg DM HBr)

Component	Amount (mg/tablet)	Representative batch (kg) <sup>1</sup>	
		IR layer	MR layer
Guaifenesin	600.0	136.8	606.0
Dextromethorphan HBr	30	10.80	27
Microcrystalline cellulose			
Sodium starch glycolate			
Hypromellose			
Carbomer 934P			
Magnesium stearate			
D&C Yellow #10 Aluminum Lake			
Water purified <sup>2</sup>			
<b>Total weight</b>	<b>765.2</b>	<b>288.0</b>	<b>678.24</b>

<sup>1</sup> Based on batch size of  tablets

<sup>2</sup>Water is removed during processing

The batches used in the PK studies, except the food effect study (2002-12;  batch size), were  which represents slightly less than  $\frac{1}{2}$  of the commercial batch size ).

**2. What are the mechanism of action, proposed therapeutic indications and dosage recommendations for Mucinex DM tablets?**

**Mechanism of Action and Proposed Indication:**

Guaifenesin is an expectorant that increases respiratory tract fluid secretions and helps to loosen phlegm and bronchial secretions. By reducing the viscosity of the secretions, guaifenesin increases the efficiency of the cough reflex and of ciliary action in removing accumulated secretions from trachea and bronchi. Guaifenesin is readily absorbed from the intestinal tract and is ~~slowly~~ metabolized and excreted in the urine. Guaifenesin has a plasma half-life of approximately 1 hour.

DM is a well known orally administered antitussive agent which has no analgesic or addictive properties. The drug acts centrally and elevates the threshold of coughing with potency approximately equal to that of codeine in depressing the cough reflex. In therapeutic dosage, DM does not inhibit ciliary activity. DM is  $\longleftrightarrow$  absorbed from the gastrointestinal tract, metabolized by the liver, and excreted primarily in the urine. DM is metabolized by cytochrome P450 2D6 and, thus, undergoes ~~metabolism~~ metabolism. The proposed indications for Mucinex DM tablets are for the temporary relief of cough associated with upper respiratory tract infection and related conditions.

**DOSAGE AND ADMINISTRATION (as per proposed label)**

Adults and children 12 years and older:

- For the 600mg/30mg product, 1 or 2 tablets every 12 hours; not more than 4 tablets in 24 hours.
- For the 1200mg/60mg product: one tablet every 12 hours; not more than 2 tablets in 24 hours.

Children under 12 years of age: do not use

**B. General Clinical Pharmacology**

**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?**

Study 2002-08 was an 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 DM containing 1200 mg guaifenesin and 120 mg DM compared to that of two reference formulations. The subjects were randomized and placed into one of three treatment groups.

- **TRT A:** 1200 mg controlled release guaifenesin product (Mucinex) and DM as an immediate-release liquid formulation (Vicks<sup>®</sup> 44<sup>®</sup>) 30 mg q 6h for 2 doses (reference) after an overnight fast.
- **TRT B:** 1200 mg guaifenesin and Vicks<sup>®</sup> 44<sup>®</sup> 20 mg q 4h for 3 doses (reference) after an overnight fast.
- **TRT C:** 1200 mg controlled release guaifenesin and 60 mg DM formulation (test) after an overnight fast.

Statistical analysis of the PK parameters and a graphical representation of the individual  $C_{max}$  and AUC of guaifenesin and DM are shown in Tables 7-8 and Figures 1-2 below:

**Table 7.** (arithmetic) Mean (%CV) and median PK parameters of guaifenesin and DM following single dose of the treatments

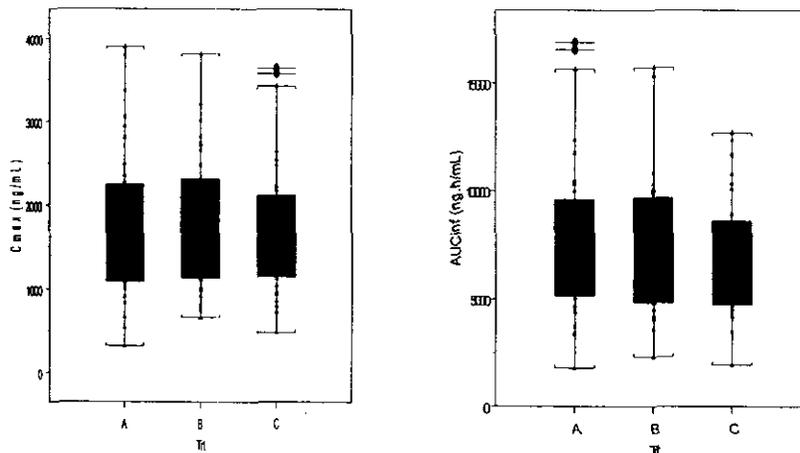
Parameter	Trt	N	Mean (%CV)	Median	Mean (%CV)	Median
			Guaifenesin		DM	
AUC <sub>t</sub> (ng•h/mL)	A	36	7730 (46)	6854	248.1 (232)	31.3
	B	34	7477 (45)	6948	271.1 (237)	31.7
	C	32	7082 (40)	6847	253.2 (239)	24.7
AUC <sub>inf</sub> (ng•h/mL)	A	36	7836 (46)	6956	294.3 (246)	31.5
	B	34	7616 (45)	6948	339.4 (250)	32.0
	C	32	7102 (40)	6899	316.6 (252)	25.0
C <sub>max</sub> (ng/mL)	A	36	1743 (52)	1545	7.95 (156)	2.38
	B	34	1783 (45)	1615	8.60 (158)	2.47
	C	32	1710 (47)	1525	7.48 (165)	2.55
T <sub>max</sub> (hr)*	A	36	1.25 (53)	1.00	8.32 (35)	8.00
	B	34	1.27 (66)	1.00	8.90 (41)	7.75
	C	32	1.55 (51)	1.5	6.30 (42)	1.5
t <sub>1/2</sub> (hr)*	A	36	2.6 (52)	2.27	10.9 (86)	7.57
	B	34	3.19 (57)	2.77	11.3 (101)	7.11
	C	32	1.24 (41)	1.05	12.6 (92)	8.64
CL (L/h)	A	36	192 (57)	173	2044 (105)	1394
	B	34	191 (47)	165	1920 (86)	1374
	C	32	201 (50)	174	2756 (128)	1760

A = Mucinex® plus Vicks® 44® 30 mg q6h for 2 doses – reference

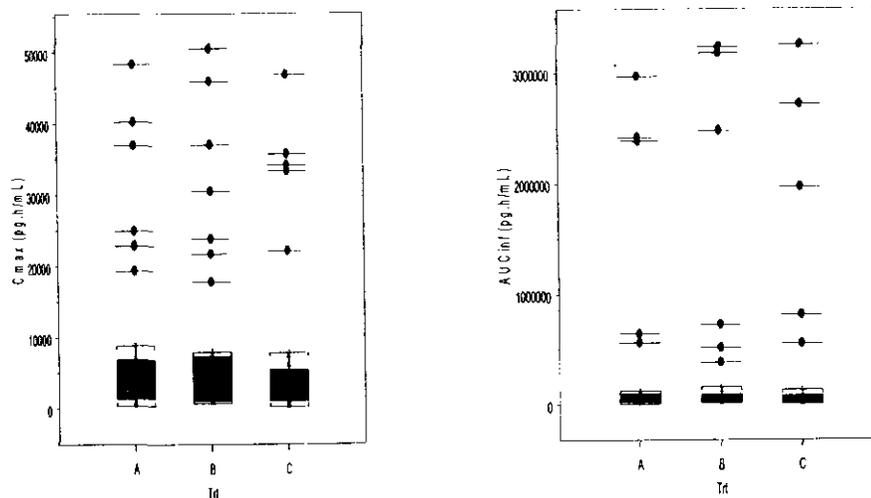
B = Mucinex® plus Vicks® 44® 20 mg q4h for 3 doses – reference

C = Mucinex® DM 1200/60 mg – test

**Figure 1.** Individual guaifenesin C<sub>max</sub> and AUC<sub>inf</sub> values following single administration of the treatments



**Figure 2.** Individual DM  $C_{max}$  and  $AUC_{inf}$  values following single dose of the treatments



**Table 8.** Point estimates and 90% confidence interval ln for the log-transformed  $C_{max}$  and AUCs of guaifenesin and DM following single administration of the treatments

Comparison	PK parameter	Point estimates	90% CI	Point estimates	90% CI
		<i>Guaifenesin</i>		<i>Dextromethorphan</i>	
Trt C/Trt A	$C_{max}$	100	91.4-111	95.4	77.4-118
	$AUC_t$	93.5	88.8-98.5	86.6	75.0-114
	$AUC_{inf}$	92.5	87.9-97.5	87.8	76.3-101
Trt C/Trt B	$C_{max}$	94.9	86.3-104	93.0	75.1-114
	$AUC_t$	96.1	91.2-101	84.8	73.6-98.1
	$AUC_{inf}$	94.3	89.5-99.3	85.8	74.3-98.4

From this study the following conclusions were reached:

- Guaifenesin in the proposed tablet is bioequivalent to that of the reference as 90% CI for the ratio of AUC and  $C_{max}$  are contained within 80-125%.
- DM is widely recognized as a highly variable drug, as shown in this study. This may be explaining the 90% confidence intervals for the ratios of both the  $C_{max}$  and AUC are outside the BE limit of 80-125%. However, the point estimates of the ratios for  $C_{max}$  and AUC are  $\geq 0.85$  this indicating similar BA between the test and reference products.

**2. Is the systemic exposure after multiple administrations (steady-state) of the extended release formulation comparable to that after the administration of the reference products?**

Study 2002-10 was an open-label, multiple dose, randomized, 3-way crossover study in 36 healthy male and female volunteers conducted to determine the steady state PK of guaifenesin and DM from an experimental formulation containing 1200 mg guaifenesin and 60 mg DM compared to two reference formulations. The subjects were randomized and placed into one of three treatment groups administered every 12 hours for 11 doses.

**TRT A:** 1200 mg guaifenesin (Mucinex®) plus 60 mg DM (Vicks® 44® 30 mg q6h x 2 doses) q12h for 11 doses (reference)

**TRT B:** 1200 mg guaifenesin (Mucinex®) plus 60 mg DM (Vicks® 44® 20 mg q 4h x 3 doses) q12h for 11 doses (reference)

**TRT C:** 1200 mg guaifenesin and 60 mg DM (Mucinex DM) q12h for 11 doses (test)

The statistical analysis of PK parameters for guaifenesin and DM are shown in the Tables 9-10. The mean steady-state plasma guaifenesin concentration-time profiles from various dose administrations are shown in Figure 3: these dosing regimens are allowed under the regulation of the OTC monograph for guaifenesin. Distribution of individual PK parameters of guaifenesin and DM is presented in the Figures 4-5 below.

**Table 9.** Mean (%CV) and median PK parameters of guaifenesin and DM following multiple doses of the treatments (Study 2002-10)

Parameter	Trt	N	Mean (%CV)	Median	Mean (%CV)	Median
			Guaifenesin		Dextromethorphan	
AUC <sub>ss</sub> (ng•h/mL)	A	35	7540 (34)	7366	181.9 (220)	39.4
	B	35	7403 (33)	7230	169.2 (238)	36.8
	C	34	7138 (32)	6992	175.3 (211)	37.7
C <sub>max</sub> (ng/mL)	A	35	1935 (39)	1910	17.96 (209)	4.1
	B	35	1938 (33)	1910	17.25 (229)	4.25
	C	34	1780 (36)	1770	17.21 (196)	4.36
C <sub>min</sub> (ng/mL)	A	35	75.5 (98)	59.0	11.95 (235)	2.27
	B	35	59.6 (87)	36.1	11.02 (236)	2.28
	C	34	18.2 (101)	13.7	10.98 (225)	1.86
C <sub>average</sub> (ng/mL)	A	35	631 (34)	614	15.17 (220)	3.31
	B	35	618 (33)	603	14.1 (238)	3.07
	C	34	601 (31)	583	14.61 (211)	3.14
T <sub>max</sub> (hr)	A	35	1.22 (0.7)	121	125 (2.4)	121
	B	35	1.21 (0.4)	121	126 (1.4)	121
	C	34	1.21 (0.7)	121	125 (1.3)	121
t <sub>1/2</sub> (hr)	A	35	3.11 (41)	3.07	3.11 (41)	3.07
	B	35	3.22 (42)	3.05	3.22 (42)	3.05
	C	34	1.91 (44)	1.67	1.91 (44)	1.67

A = Mucinex® plus Vicks® 44® 30 mg q6h for 2 doses - reference

B = Mucinex® plus Vicks® 44® 20 mg q4h for 3 doses - reference

C = Mucinex® DM 1200/60 mg - test

**Table 10.** Point estimates and 90% confidence intervals for the log-transformed AUC<sub>ss</sub>, C<sub>max</sub> and C<sub>min</sub> of guaifenesin and DM following single administration of the treatments

Comparison	PK parameter	Point estimates	90% CI	Point estimates	90% CI
		Guaifenesin		Dextromethorphan	
Trt C/Trt A	AUC <sub>ss</sub>	96	91.1-101	101	87.6-116
	C <sub>max</sub>	93	85.3-100	104	90.2-121
	C <sub>min</sub>	27	18.1-40.5	84	71.8-97.2
Trt C/Trt B	AUC <sub>ss</sub>	97	92.0-102	103	89.8-119
	C <sub>max</sub>	90	83.3-97.8	105	91.2-122
	C <sub>min</sub>	31	20.8-46.5	84	72.1-97.6

Figure 3.

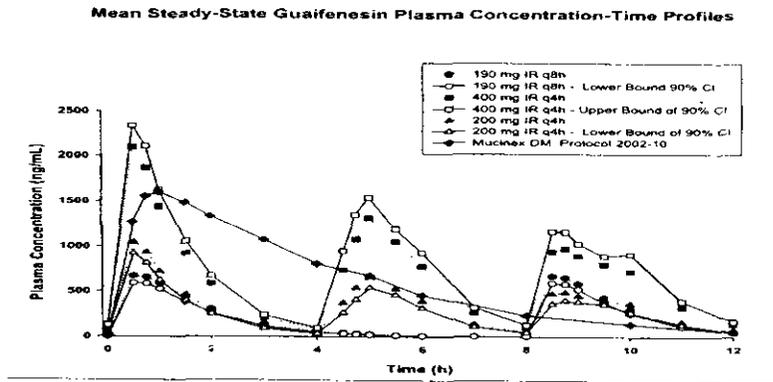


Figure 4. Individual guaifenesin  $C_{min}$  values following multiple administrations of each treatments

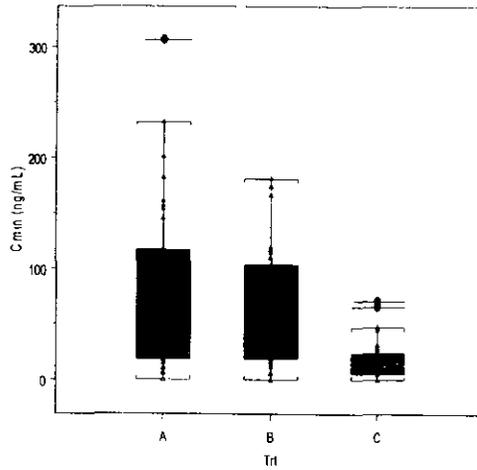
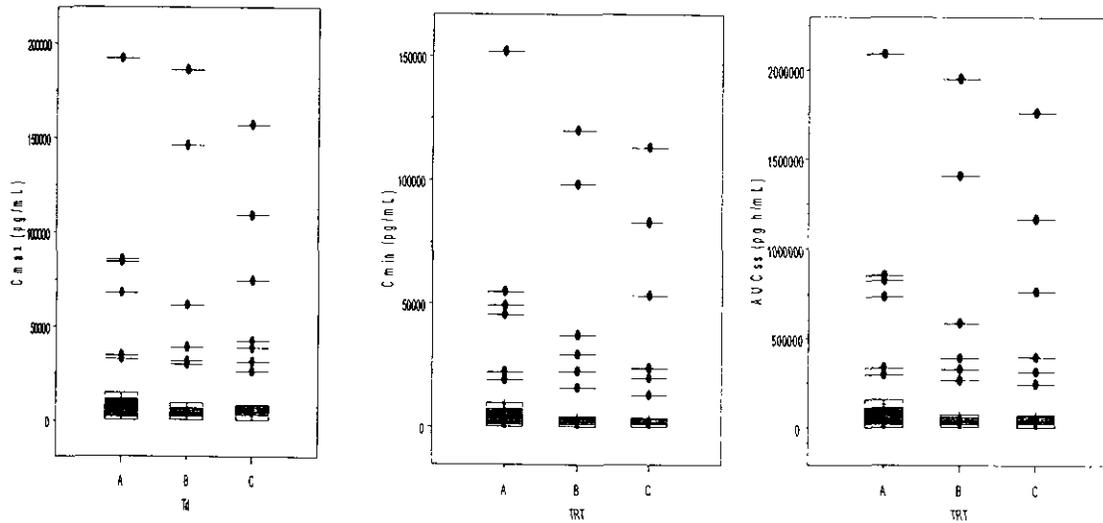


Figure 5. Individual DM  $C_{max}$ ,  $C_{T/in}$  and  $AUC_{ss}$  values following the treatments



The following summarizes the findings from this study:

- Guaifensin in the proposed tablet is bioequivalent to that of the reference as 90% CI for the ratio of  $AUC_{ss}$  and  $C_{max,ss}$  are contained within 80-125%, while  $C_{min}$  was not (3 or 4-fold lower for the test product compared to reference). However, this  $C_{min}$  was within the known effective concentration level associated with guaifensin (e.g., 190 mg IR formulation q8h shown in Figure 3).
- DM in the proposed tablet is bioequivalent to that of the reference as 90% CI for the ratio of  $AUC_{ss}$  and  $C_{max,ss}$  are contained within 80-125%, while  $C_{min}$  was not. However, the point estimates of the ratios for  $C_{min}$  were 0.84, indicating similar BA between the test and reference products.

### C. Extrinsic Factors

#### Does guaifenesin affect the PK of DM and vice versa?

Study 2002-15 was an open-label, single dose, randomized, 4-way crossover study in 36 healthy male and female volunteers conducted to determine the pharmacokinetics of guaifenesin and DM when administered alone compared to when they are co-administered. The subjects were placed into one of 4 treatment groups.

Group 1: Test formulation Mucinex<sup>®</sup> DM 1200/60 mg (Treatment A).

Group 2: Reference Mucinex<sup>®</sup> 1200 mg (Treatment B).

Group 3: 60 mg of DM in a reference IR liquid formulation (Benylin<sup>®</sup>) according to two different dosing regimens (1/2 of the subjects received 30 mg DM q6H x 2 doses [Treatment C], while the other half received 20 mg DM q4H x 3 doses [Treatment D]).

Group 4: 30 mg of DM in a reference IR liquid formulation (Benylin<sup>®</sup>) according to two different dosing regimens (1/2 of the subjects received 15 mg DM q6H x 2 doses [Treatment E], while the other half received 10 mg DM q4H x 3 doses [Treatment F]).

Those subjects that received 30 mg in one treatment period received 15 mg DM in another treatment period; similarly, those that received 20 mg in one treatment period received 10 mg DM in a subsequent treatment period.

Statistical analysis of the PK parameters for guaifenesin and DM following administration of the treatments are summarized in Tables 11-12. Individual DM  $C_{max}$  and AUC following the treatments are shown in Figure 6.

**Table 11.** Mean (%CV) and median PK parameters of guaifenesin and DM from Study 2001-15

Parameter	Trt	N	Mean (%CV)	Median	Trt	N	Mean (%CV)	Median
<b>Guaifenesin</b>					<b>DM</b>			
AUC <sub>t</sub> (ng•h/mL)	A	32	8732 (55)	7579	A	32	68.19 (165)	27.82
	B	32	8657 (49)	8346	C	16	82.28 (150)	23.48
					D	15	44.29 (83)	26.14
					E	16	39.75 (155)	16.06
					F	15	19.83 (81)	12.94
AUC <sub>inf</sub> (ng•h/mL)	A	32	8761 (54)	7734	A	32	68.85 (164)	28.09
	B	32	8953 (48)	8826	C	16	82.67 (149)	23.86
					D	15	44.68 (83)	26.32
					E	16	40.32 (155)	16.23
					F	15	20.11 (80)	13.17
C <sub>max</sub> (ng/mL)	A	32	2176 (61)	1830	A	32	4.83 (128)	2.56
	B	32	2145 (47)	1915	C	16	4.71 (130)	1.67
					D	15	3.13 (75)	2.72
					E	16	2.18 (122)	1.18
					F	15	1.29 (70)	0.8
T <sub>max</sub> (hr)	A	32	1.44 (47)	1.50	A	32	5.06 (18)	5.0
	B	32	0.91 (55)	0.75	C	16	8.31 (19)	8.5
					D	15	7.01 (28)	6.0
					E	16	8.03 (31)	9.0
					F	15	7.73 (31)	6.0
t <sub>1/2</sub> (hr)	A	32	1.31 (86)	1.08	A	32	7.7 (23)	6.9
	B	32	4.79 (101)	3.03	C	16	7.5 (26)	6.8
					D	15	7.0 (22)	6.6
					E	16	7.3 (31)	6.5
					F	15	7.4 (27)	7.0

A = Mucinex<sup>®</sup> DM 1200/60 mg, - test.

C = Benylin<sup>®</sup> 30 mg q6H x 2 doses – reference

D = Benylin<sup>®</sup> 20 mg q4H x 3 doses – reference,

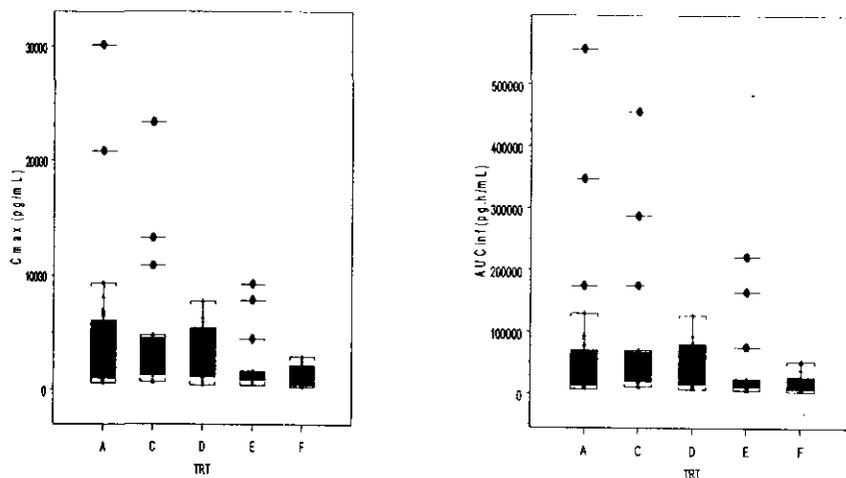
E = Benylin<sup>®</sup> 15 mg q6H x 2 doses – reference

F = Benylin<sup>®</sup> 10 mg q4H x 3 doses – reference

**Table 12.** Point estimates and 90% confidence intervals for the log-transformed (dose normalized) C<sub>max</sub> and AUCs of guaifenesin and DM following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
<b>Guaifenesin</b>			
TRT A/ TRT B	C <sub>max</sub>	97.3	88.7-107
	AUC <sub>t</sub>	100	93.8-108
	AUC <sub>inf</sub>	97.0	90.1-104
<b>DM</b>			
TRT A/ TRT C	C <sub>max</sub>	97.6	110-153
	AUC <sub>t</sub>	101	87.3-118
	AUC <sub>inf</sub>	102	88.2-119
TRT A/ TRT D	C <sub>max</sub>	93.0	77.6-111
	AUC <sub>t</sub>	77.8	66.0-91.6
	AUC <sub>inf</sub>	77.8	66.1-91.5
TRT E/ TRT C	C <sub>max</sub>	106	89.9-124
	AUC <sub>t</sub>	101	87.1-117
	AUC <sub>inf</sub>	101	87.7-117
TRT F/ TRT D	C <sub>max</sub>	87.5	73.6-104
	AUC <sub>t</sub>	88.5	75.7-103
	AUC <sub>inf</sub>	89.9	77.0-105

**Figure 6.** Individual DM  $C_{max}$ , and  $AUC_{inf}$  values following single dose of the treatments



The following summarizes the findings from this study:

- The pharmacokinetics of guaifenesin is not affected by co-administration with DM. Ninety percent confidence intervals for the log-transformed PK parameters of guaifenesin ( $C_{max}$ ,  $AUC_t$ ,  $AUC_{inf}$ ) administered alone (Mucinex) versus its coadministration with DM (Mucinex DM) were within goal post for BE.
- For DM, the  $AUC_{inf}$ ,  $AUC_t$  and  $C_{max}$  ratio comparison of test to reference treatment (comparisons A/C, A/D) showed the confidence interval range from 66.1 - 119%, 66 - 118% and 73.6 - 153%, respectively. While the point estimates ranged from 0.78 to 1.30 indicating that the change in PK is not likely to be clinically significant.

#### D General Biopharmaceutics

##### 1. Was the to-be-marketed formulation used in the Pharmacokinetic studies?

Yes. The maximum strength batches (lot nos. PB01-H30, PB01-H43 and PB01-H44) and the regular strength batches (lot nos. PB01-H53, PB01-H54 and PB01-H54) were manufactured (between July 31, 2001 and August 13, 2001), and the BE studies were performed using the lot #PB01-H30 (3 studies) and #PB01-H43 (food effect study) only. In addition, batch size for PB01-H30 was \_\_\_\_\_ actual tablets) and \_\_\_\_\_ for PB01-H43 ( \_\_\_\_\_ actual tablets) and PB01-H44. Batch size for regular strength was \_\_\_\_\_ (theoretical) for all \_\_\_\_\_ batches. Biobatch PB01-H30 is considered pilot batch since the size is \_\_\_\_\_ of commercial batch ( \_\_\_\_\_ tablets), while PB01-H43 is not. The similarity ( $f_2$ ) factors for guaifenesin and DM between PB01-H30 and PB01-H43 are \_\_\_\_\_ respectively, therefore, the small batch size of PB01-H30 dose not pose a problem.

##### 2. What is the effect of food on the BA of guaifenesin and DM from the Mucinex DM formulation?

Study 2002-12 was an open-label, single dose, randomized, 2-way crossover study in 36 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 60 mg DM compared to that in the fasting condition. Subjects were placed into one of two treatment groups described below.

TRT A: Mucinex® DM 1200/60 mg, under fasted - reference

TRT B: Mucinex® DM 1200/60 mg, under fed (high-fat breakfast) - test.

Table 13. (Arithmetic) Mean (%CV) and median PK parameters of guaifenesin and DM following single dose of the treatments (Study 2002-12)

Parameter	Trt	N	Mean	Median	Mean	Median
			(%CV)		(%CV)	
			Guaifenesin		Dextromethorphan	
AUCt (ng•h/mL)	A	35	8107 (43)	7777	8107 (43)	7777
	B	36	7077 (39)	6201	7077 (39)	6201
AUCinf (ng•h/mL)	A	35	8128 (43)	7789	466.5 (212)	34.13
	B	36	7093 (39)	6228	472.1 (207)	37.81
C <sub>max</sub> (ng/mL)	A	35	2030 (43)	1760	10.72 (149)	3.02
	B	36	1825 (43)	1520	12.76 (140)	3.47
T <sub>max</sub> (hr)	A	35	1.61 (71)	1.50	6.23 (57)	6.0
	B	36	2.93 (49)	3.00	5.74 (40)	5.0
t <sub>1/2</sub> (hr)	A	35	1.15 (31)	1.04	13.8 (93)	8.52
	B	36	0.85 (14)	0.85	13.5 (99)	8.0
CL (L/h)	A	35	172 (38)	154	2343 (143)	1287
	B	36	190 (32)	193	2246 (129)	1174

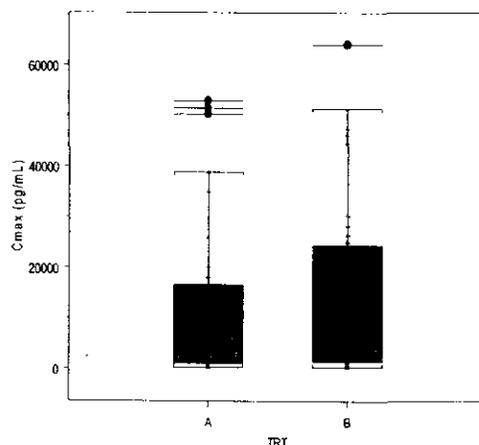
A = Mucinex® DM 1200/60 mg, under fasted - reference

B = Mucinex® DM 1200/60 mg, fed condition- test

Table 14. Point estimates and 90% confidence intervals for the log-transformed C<sub>max</sub> and AUC of guaifenesin and DM following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
<b>Guaifenesin</b>			
TRT B/ TRT A	Cmax	96	82.2-100
	AUCt	93	85-94.6
	AUCinf	27	85-94.5
<b>Dextromethorphan</b>			
TRT B/ TRT A	Cmax	121	107-136
	AUCt	108	96.7-121
	AUCinf	107	96.4-120

Figure 7. Individual DM C<sub>max</sub> values following the treatments



The following summarizes the findings from this study:

- High-fat meal had no effect on the bioavailability of guaifensin from the Mucinex-DM tablets. Ninety percent CI for the ratio of AUC and  $C_{max}$  were within BE requirements (80-125%). Food caused a delay in  $T_{max}$  of guaifensin by approximately 1.5 hours.
- High-fat breakfast increased the  $C_{max}$  of DM by 21%, but had no effect on AUC and  $T_{max}$ .
- 21% increase in  $C_{max}$  of DM and a delay of 1.5 hrs in  $T_{max}$  of guaifensin may not be clinically relevant. Therefore, Mucinex DM can be taken without regards to meals.

3. Can *in vivo* bioavailability/bioequivalence study for lower (Regular) strength be waived?

Yes. *In vivo* BA/BE study for 'Regular' strength can be waived because the formulation of Mucinex DM tablets are compositionally proportional and the similarity ( $f_2$ ) factor between Mucinex DM 1200/60 mg and 600/30 mg strengths are within the 'sameness/equivalent' criteria:  $f_2$  factor for guaifensin between 1200 mg and 600 mg are . Similarly,  $f_2$  factor for DM between 60 mg and 30 mg are .

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

The proposed method is acceptable, however, the modifications are recommended for specifications: The sponsor stated that dissolution method development for Mucinex<sup>®</sup> DM was based on the knowledge gained from dissolution testing of Mucinex<sup>®</sup> tablets.

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**E. Analytical Methodology**

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

Plasma concentrations of guaifenesin and DM in the pharmacokinetic studies included in this review were determined using a HPLC and LC/MS/MS, respectively with a lower limit of quantification (LLQ) of \_\_\_\_\_ respectively. The accuracy and inter-day precision were acceptable for all the studies (\_\_\_\_\_ 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 15. Assay performance (in-study validation) for Guaifenesin and DM**

	<b>Guaifenesin</b>	<b>DM</b>
<b>Linearity</b>	Satisfactory: Standard curve range from [redacted]	Satisfactory: Standard curve range from [redacted]
<b>Accuracy</b>	Satisfactory: % Bias ranged from [redacted] at three QC concentrations	Satisfactory: % Bias ranged from [redacted] at three QC concentrations.
<b>Precision</b>	Satisfactory: %CV from [redacted] at three QC concentrations.	Satisfactory: %CV ranged from [redacted] at three QC concentrations.
<b>Specificity</b>	Satisfactory: sample chromatograms submitted	Satisfactory: sample chromatograms submitted

**F. LABELING COMMENTS**

**There no labeling recommendations at this time.**

2 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(5) Deliberative Process

X § 552(b)(5) Draft Labeling

## B. INDIVIDUAL STUDY REVIEWS

### Protocol #2002-08

**Study Type:** BE/single dose.

**Title:** A definitive bioequivalence study designed to examine the bioavailability of guaifenesin and dextromethorphan from an experimental controlled-release formulation in normal healthy volunteers compared to reference guaifenesin and dextromethorphan products.

**Clinical Investigators:** Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc. Springfield, MO.

**Objectives:** To compare the relative bioavailability of guaifensin and DM from the proposed and refenced product.

**Study Design and Method:** The healthy volunteers were randomized and placed into one of three treatment groups. There was a 14-day washout between doses.

- Treatment A: Mucinex® (lot #PB01-H34A3) plus Vicks® 44® (lot #1141RX) 30 mg q6h for 2 doses (reference)
- Treatment B: Mucinex® (lot #PB01-H34A3) plus Vicks® 44® (lot #1141RX) 20 mg q4h for 3 doses (reference)
- Treatment C: Mucinex® DM (lot #PB01-30A3) (test)

**Criteria for Evaluation:** PK parameters (AUC,  $C_{max}$ ,  $T_{max}$ , CL,  $t_{1/2}$ ) of guaifenesin and DM.

**Blood sampling times:** t = 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.5, 4.75, 5, 5.5, 6, 6.5, 6.75, 7, 7.5, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72 and 96 hours post dose.

#### **Analytical Methodology**

**Assay Method:** HPLC (guaifenesin), LC/MS/MS (DM)

**Assay Sensitivity (standard curves):**

**Accuracy and Precision:** Precision and accuracy for guaifenesin QC ranged \_\_\_\_\_ respectively. Precision and accuracy for DM QC ranged \_\_\_\_\_

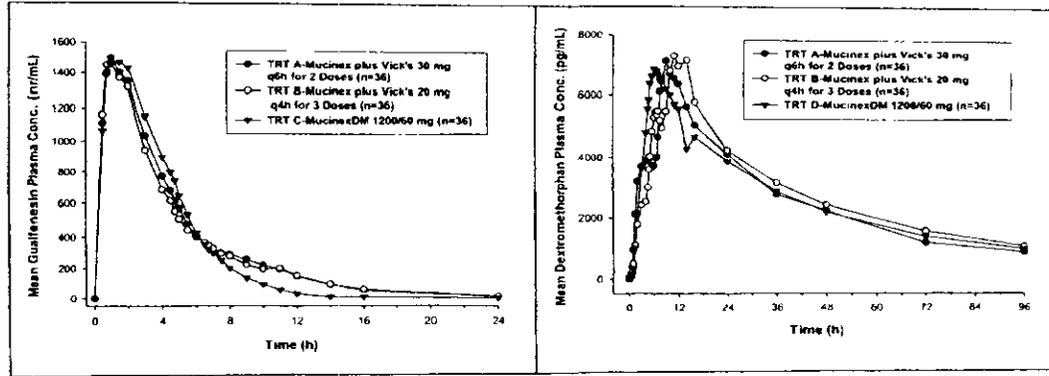
**Data Analysis:** ANOVA was performed on ln-transformed AUCs and  $C_{max}$ , CL and  $t_{1/2}$  were natural-log (ln) transformed prior to analysis. ANOVA was performed and 90% confidence intervals (CI) were generated for the ratio of Test/Reference. 90% CI for the geometric mean ratio were obtained for AUCs and  $C_{max}$  by taking the antilog of the 90% CI for the difference between means on the log scale.

#### **Results:**

**Study Population:** 40 subjects entered, 37 were dosed and 32 completed the study according to the protocol. The subjects averaged  $26.7 \pm 10.6$  years of age with a 18-53 years of age. 27 were male and the remainder was female.

**Pharmacokinetics:** Mean PK profiles of guaifenesin and DM are shown in Figure 1. The PK results are summarized in tables 1-2.

**Figure 1.** Mean plasma concentrations of guaifenesin (ng/mL) and DM (pg/mL)



**Table 1.** Mean (%CV) and median PK parameters and statistics analysis of guaifenesin following Single dose of the treatments

Parameter	Trt	N	Mean (%CV)	Median	Pair	Treatment Comparisons		
						LS Mean <sup>a</sup>	Ratio <sup>b</sup>	90% CI <sup>c</sup>
AUCt (ng•h/mL)	A	36	7730 (46)	6854		6903		
	B	34	7477 (45)	6948	C/B	6720	0.96	91.2-101
	C	32	7082 (40)	6847	C/A	6455	0.94	88.8-98.5
AUCinf (ng•h/mL)	A	36	7836 (46)	6956		6998		
	B	34	7616 (45)	6948	C/B	6871	0.94	89.5-99.3
	C	32	7102 (40)	6899	C/A	6476	0.93	87.9-97.5
C <sub>max</sub> (ng/mL)	A	36	1743 (52)	1545		1505		
	B	34	1783 (45)	1615	C/B	1593	0.95	86.3-104
	C	32	1710 (47)	1525	C/A	1512	1.00	91.4-111
T <sub>max</sub> (hr) <sup>d</sup>	A	36	1.25 (53)	1.00				
	B	34	1.27 (66)	1.00	C/B			p=0.07
	C	32	1.55 (51)	1.5	C/A			p=0.06
t <sub>1/2</sub> (hr)	A	36	2.6 (52)	2.27				
	B	34	3.19 (57)	2.77				
	C	32	1.24 (41)	1.05				

A = Mucinex® 1200 mg plus Vicks® 44® 30 mg q6h for 2 doses – reference

B = Mucinex® 1200 mg plus Vicks® 44® 20 mg q4h for 3 doses – reference

C = Mucinex® DM 1200/60 mg – test

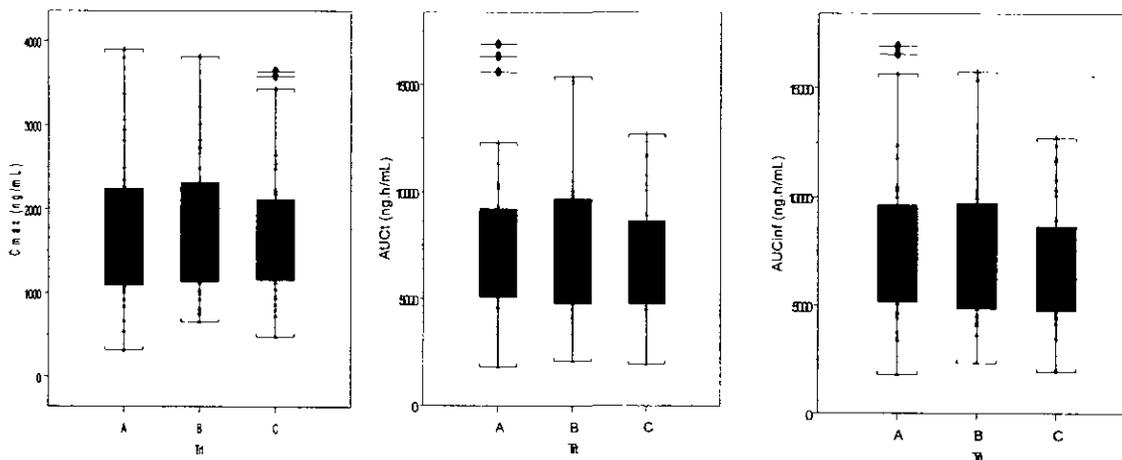
<sup>a</sup> Least-square mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means)

<sup>b</sup> LS mean of test/reference

<sup>c</sup> 90% confidence intervals for ratio of parameter geometric means

<sup>d</sup> = p-value from Wilcoxon signed-rank test

**Figure 2.** Individual guaifenesin  $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$  values following single dose of the treatments

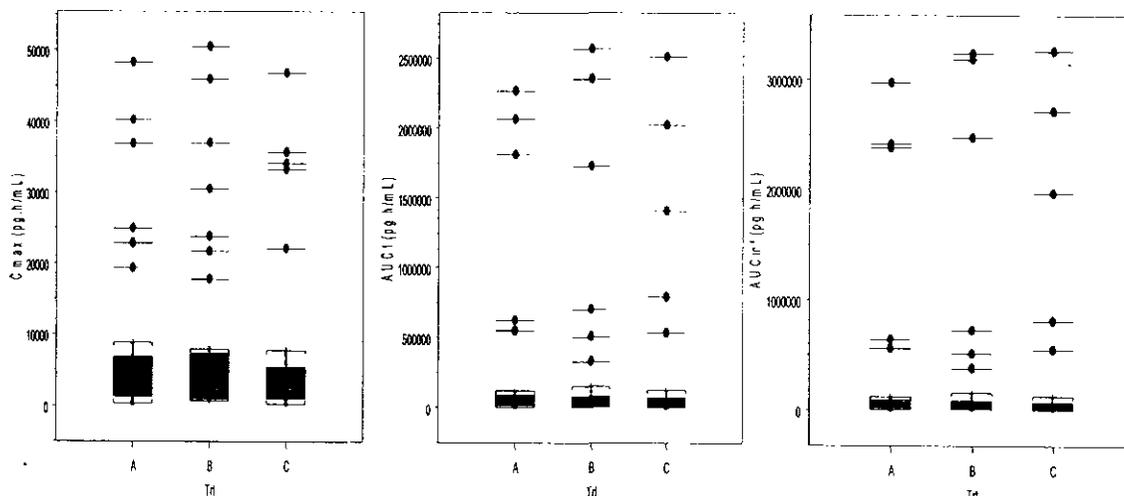


**Table 2.** Mean (%CV) and median PK parameters and statistical analysis of DM following Single dose of the treatments

Parameter	Trt	N	Mean (%CV) <sup>a</sup>	Median <sup>a</sup>	Treatment Comparisons			
					Pair	LS Mean <sup>b</sup>	Ratio <sup>c</sup>	90% CI <sup>d</sup>
$AUC_t$ (ng·h/mL)	A	36	248.1 (232)	31.3		45.0		
	B	34	271.1 (237)	31.7	C/B	45.9	0.85	73.6-98.1
	C	32	253.2 (239)	24.7	C/A	38.9	0.87	75.0-114
$AUC_{inf}$ (ng·h/mL)	A	36	294.3 (246)	31.5		46.6		
	B	34	339.4 (250)	32.0	C/B	47.9	0.86	74.3-98.4
	C	32	316.6 (252)	25.0	C/A	41.0	0.88	76.3-101
$C_{max}$ (ng/mL)	A	36	7.95 (156)	2.38		2.98		
	B	34	8.60 (158)	2.47	C/B	3.07	0.93	75.1-114
	C	32	7.48 (165)	2.55	C/A	2.85	0.95	77.4-118
$T_{max}$ (hr)*	A	36	8.32 (35)	8.00				
	B	34	8.90 (41)	7.75	C/B			$p=0.0001$
	C	32	6.30 (42)	5.5	C/A			$p=0.004$
$t_{1/2}$ (hr)*	A	36	10.9 (86)	7.57				
	B	34	11.3 (101)	7.11				
	C	32	12.6 (92)	8.64				

Notations are the same as in Table 1

**Figure 3.** Individual DM  $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$  values following single dose of Mucinex DM tablets



The 90% CIs, comparing treatment C to A and B, on PK parameters ( $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$ ) for guaifensin were within 80 to 125% of bioequivalence criteria.  $T_{max}$  were not statistically significant at  $\alpha = 0.05$  comparing C versus A or B. As shown in Figure 2, there were a few outliers.

The 90% CIs, comparing treatment C to A and B on PK parameters ( $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$ ) for DM were within 70 to 140% of the sponsor proposed bioequivalence criteria.  $T_{max}$  were statistically significant;  $p = 0.041$  and  $0.001$  for C versus A or B, respectively. As shown in Figure 3, there were outliers.

**Conclusion:**

- Guaifensin in the proposed tablet is bioequivalent to that of the reference as 90% CI for the ratio of AUC and  $C_{max}$  are contained within 80-125%.
- DM is widely recognized as a highly variable drug, as shown in this study. This may be explaining the 90% confidence intervals for the ratios of both the  $C_{max}$  and AUC are outside the BE limit of 80-125%. However, the point estimates of the ratios for  $C_{max}$  and AUC are greater than 0.85 this indicating similar BA between the test and reference products.
- DM outliers (i.e., Poor metabolizers of CYP2D6) had approximately 6- or 20-fold higher  $C_{max}$  compared to the mean and median, respectively, and 10- or 120-fold higher AUC compared to the mean and median, respectively. However, there were no significant differences in AE (adverse events) between subjects in PM and normal (confirmed with the reviewing MD)

## Protocol #2002-10

**Study Type:** BE/multiple dose.

**Title:** A definitive study designed to examine the steady-state pharmacokinetics of guaifenesin and DM from an experimental controlled-release formulation in normal healthy volunteers compared to reference guaifenesin and DM products.

**Clinical Investigators:** Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc. Springfield, MO.

**Objectives:** To compare the relative bioavailability of guaifenesin and DM from the proposed and referenced product at steady state.

**Study Design and Method:** This is an open-label, multiple-dose, randomized, 3-way-crossover study in 36 subjects normal, healthy, male and female volunteers. The subjects were randomized and placed into one of three treatment groups, q12h x 6 days. There was a 14-day washout between doses.

- Treatment A: Mucinex® (lot #PB01-H34A4) plus Vicks® 44® (lot #1141RX) 30 mg q6h for 2 doses (reference)
- Treatment B: Mucinex® (lot #PB01-H34A4) plus Vicks® 44® (lot #1141RX) 20 mg q4h for 3 doses (reference)
- Treatment C: Mucinex® DM (lot #PB01-30A4) (test)

**Criteria for Evaluation:** PK parameters (AUC,  $C_{max}$ ,  $C_{min}$ ,  $T_{max}$ , CL,  $t_{1/2}$ ) of guaifenesin and DM.

**Blood sampling times:** Day 1 pre-AM dose, Day 4 pre-AM dose and Day 5 pre-AM dose for all 3 treatment groups. On Day 6, the samples were taken the following times for each treatment groups:

Treatment A: Pre-dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 6.5, 6.75, 7, 7.5, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, and 96 hours post dose.

Treatment B: Pre-dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.5, 4.75, 5, 5.5, 6, 7, 8, 8.5, 8.75, 9, 9.5, 10, 11, 12, 14, 16, 24, 36, 48, 72 and 96 hours post dose.

Treatment C: Pre-dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72 and 96 hours post dose.

### Analytical Methodology

**Assay Method:** HPLC (guaifenesin), LC/MS/MS (DM)

**Assay Sensitivity (standard curves):** \_\_\_\_\_ (guaifenesin), \_\_\_\_\_ (DM)

**Accuracy and Precision:** Precision and accuracy for guaifenesin QC range \_\_\_\_\_, respectively. Precision and accuracy for DM QC ranged \_\_\_\_\_, respectively.

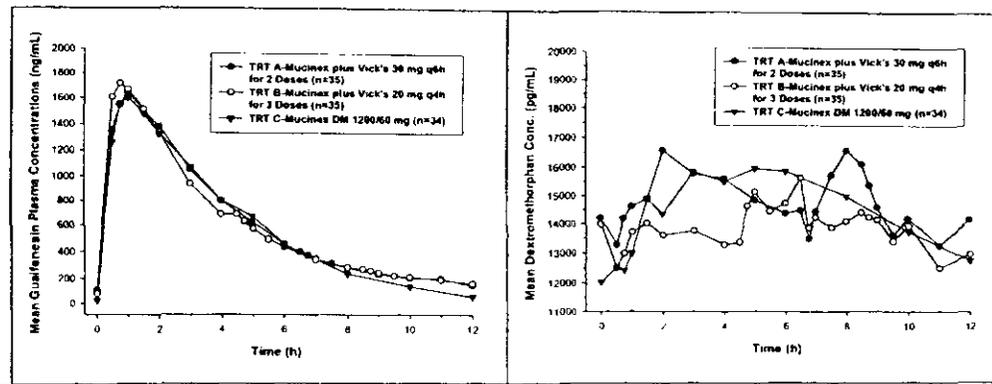
**Data Analysis:** ANOVA was performed on ln-transformed AUCs and  $C_{max}$ , CL and  $t_{1/2}$  were natural-log (ln) transformed prior to analysis. ANOVA was performed and 90% confidence intervals (CI) were generated for the ratio of Test/Reference. 90% CI for the geometric mean ratio were obtained for AUCs and  $C_{max}$  by taking the antilog of the 90% CI for the difference between means on the log scale. Steady state was assessed for each treatment and analyte, by comparison of mean  $C_{min}$  values (mean trough concentrations) in natural log (ln) scale using available data from Days 4, 5, and 6. For guaifenesin, prior to ln transformation,  $C_{min}$  was incremented by 1 since  $C_{min}$  was zero for some subjects on some days (A better approach is to omit this values in the analysis).

**Results:**

**Study Population:** 36 subjects entered and 34 completed the study according to the protocol. The subjects averaged  $34.3 \pm 13.3$  years of age with a range of 19-55 years of age. 21 were male and the remainder was female.

**Pharmacokinetics:** Mean plasma profiles of guaifenesin and DM are shown in Figure 1. The PK results are summarized in tables 1-2. Individual PK parameters of guaifenesin and DM are shown in Figures 2-3.

**Figure 1.** Mean plasma concentrations-time profiles of guaifenesin (ng/mL) and DM (pg/mL)



**Table 1.** Mean (%CV) and median PK parameters and statistical analysis of guaifenesin following multiple doses of the treatments (Study 2002-10)

Parameter	Trt	N	Mean (%CV)	Median	Pair	Treatment Comparisons		
						LS Mean <sup>a</sup>	Ratio <sup>b</sup>	90% CI <sup>c</sup>
AUC <sub>ss</sub> (ng•h/mL)	A	35	7540 (34)	7366		7104		
	B	35	7403 (33)	7230	C/A	7035	0.96	91.1-101
	C	34	7138 (32)	6992	C/B	6828	0.97	92.0-102
C <sub>max,ss</sub> (ng/mL)	A	35	1935 (39)	1910		1787		
	B	35	1938 (33)	1910	C/A	1832	0.93	85.3-100
	C	34	1780 (36)	1770	C/B	1653	0.90	83.3-97.8
C <sub>min</sub> (ng/mL)	A	35	75.5 (98)	59.0		41.2		
	B	35	59.6 (87)	36.1	C/A	35.8	0.27	18.1-40.5
	C	34	18.2 (101)	13.7	C/B	11.1	0.31	20.8-46.5
T <sub>max</sub> (hr) <sup>d</sup>	A	35	1.22 (0.7)	121				
	B	35	1.21 (0.4)	121	C/A			P = 0.533
	C	34	1.21 (0.7)	121	C/B			P = 0.006
t <sub>1/2</sub> (hr)	A	35	3.11 (41)	3.07				
	B	35	3.22 (42)	3.05	C/A			
	C	34	1.91 (44)	1.67	C/B			

A = Mucinex® 1200 mg plus Vicks® 44® 30 mg q6h for 2 doses – reference

B = Mucinex® 1200 mg plus Vicks® 44® 20 mg q4h for 3 doses – reference

C = Mucinex® DM 1200/60 mg – test

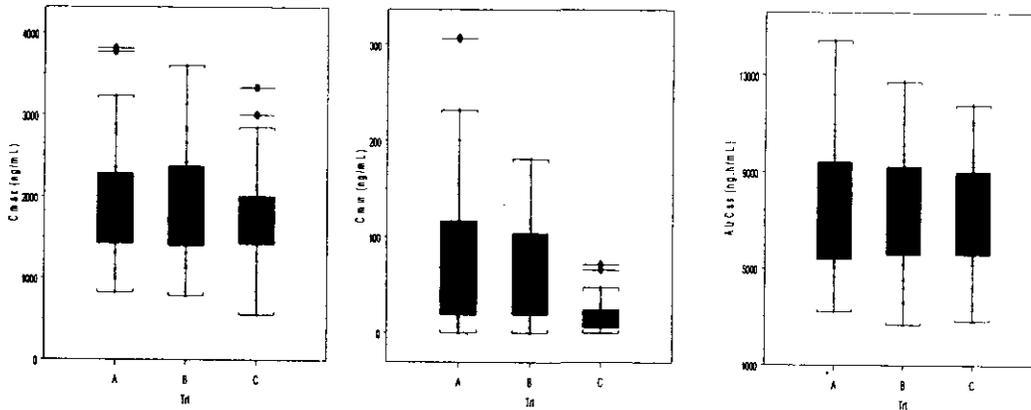
<sup>a</sup> Least-square mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means)

<sup>b</sup> LS mean of test/reference

<sup>c</sup> 90% confidence intervals for ratio of parameter geometric means

<sup>d</sup> = p-value from Wilcoxon signed-rank test

**Figure 2.** Individual guaifenesin  $C_{max,ss}$ ,  $C_{min}$  and  $AUC_{ss}$  values following multiple doses of the treatment



**Table 2.** Mean (%CV) and median PK parameters and statistics analysis of DM following the treatments

Parameter	Trt <sup>a</sup>	N	Mean (%CV) <sup>b</sup>	Median	Treatment Comparisons			
					Pair <sup>c</sup>	LS Mean <sup>d</sup>	Ratio <sup>e</sup>	90% CI <sup>f</sup>
$AUC_{ss}$ (ng·h/mL)	A	35	181.9 (220)	39.4		48.5		
	B	35	169.2 (238)	36.8	C/A	47.3	1.01	87.6-116
	C	34	175.3 (211)	37.7	C/B	48.9	1.03	89.8-119
$C_{max}$ (ng/mL)	A	35	17.96 (209)	4.1		5.24		
	B	35	17.25 (229)	4.25	C/A	5.18	1.04	90.2-121
	C	34	17.21 (196)	4.36	C/B	5.46	1.05	91.2-122
$C_{min}$ (ng/mL)	A	35	11.95 (235)	2.27		2.95		
	B	35	11.02 (236)	2.28	C/A	2.94	0.84	71.8-97.2
	C	34	10.98 (225)	1.86	C/B	2.47	0.84	72.1-97.6
$T_{max}$ (hr)*	A	35	125 (2.4)	121				
	B	35	126 (1.4)	121	C/A			P = 0.92
	C	34	125 (1.3)	121	C/B			P = 0.006
$t_{1/2}$ (hr)*	A	35	3.11 (41)	3.07				
	B	35	3.22 (42)	3.05	C/A			
	C	34	1.91 (44)	1.67	C/B			

Notations are the same as in Table 1

**Figure 3.** Individual DM  $C_{max,ss}$ ,  $C_{min}$  and  $AUC_{ss}$  values following single dose of Mucinex DM tablets

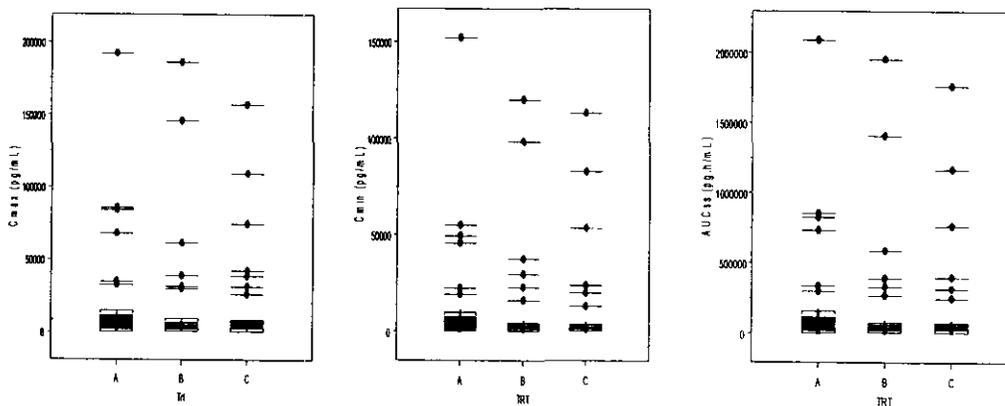
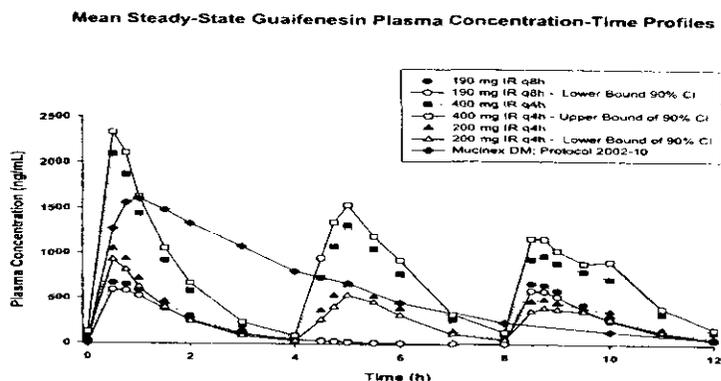


Figure 4.



The 90% CI, comparing treatment C to A or to B for the ratio of  $C_{max}$  and  $AUC_{ss}$  for guaifenesin were within 80 to 125% of bioequivalence criteria, but the  $C_{min}$  was out of the BE range. However, as shown in figure 4, the  $C_{min}$  of guaifenesin from the proposed formulation falls within the known effective concentration level associated with guaifenesin (e.g., 190 mg IR formulation q8h).

The 90% CIs, comparing treatment C to A and B, on PK parameters ( $C_{max}$  and  $AUC_{ss}$ ) for DM were within 80 to 125% of bioequivalence criteria, while  $C_{min}$  was within 70-140%.

**Table 3.** Statistical analysis results for the determination of Steady State based on  $C_{min}$  (ng/mL) values

TRT	Day 4	Day 5	Day 6	P value
<b>Guaifenesin</b>				
TRT A	75.2	94	109	0.255
TRT B	60.4	74.5	76.6	0.599
TRT C	17.5	18.6	24.5	0.497
<b>Dextromethorphan</b>				
TRT A	12.3	13.4	14.4	0.163
TRT B	8.6	12.6	14.2	0.127
TRT C	12.1	12.8	12.3	0.577

**Conclusion:**

- Guaifenesin in the proposed tablet is bioequivalent to that of the reference as 90% CI are contained within 80-125% for  $C_{max}$  and  $AUC_{ss}$ , while  $C_{min}$  was not. However, this  $C_{min}$  was within the known effective concentration level associated with guaifenesin (e.g., 190 mg IR formulation q8h; Figure 4).
- DM is widely recognized as a highly variable drug, as shown in this study. This may be explaining the 90% confidence intervals for the ratios of both the  $C_{max}$  and AUC are outside the BE limit of 80-125%. However, the point estimates of the ratios for  $C_{max}$  and AUC are greater than 0.85 this indicating similar BA between the test and reference products.
- Both guaifenesin and DM appears to be reached steady state by the 2<sup>nd</sup> or 3<sup>rd</sup> day of administration of the treatments.
- DM outliers (i.e., Poor metabolizers of CYP2D6) had approximately 11- or 46-fold higher  $C_{max,ss}$  compared to the mean and median, respectively, and 10- or 50-fold higher  $AUC_{ss}$  compared to the mean and median, respectively. However, there were no significant differences in AE (adverse events) between subjects in PM and normal (confirmed with the reviewing MD).

**Protocol #2002-12**

**Study Type:** Food effect/single dose.

**Title:** A study designed to examine the effect of the consumption of a high fat meal on the bioavailability of guaifenesin and DM from an experimental controlled release formulation.

**Clinical Investigators:** Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc. Springfield, MO.

**Objectives:** To compare the relative bioavailability of guaifenesin and DM from the proposed and referenced product following the consumption of high fat meal.

**Study Design and Method:** This was an open label, single dose, randomized, 2-way crossover study in 36 healthy volunteers. The subjects were randomized and placed into one of two treatment groups. There was a 14-day washout between doses.

- Treatment A: Mucinex® DM (lot #PB01-H43A2) under fasted conditions (reference)
- Treatment B: Mucinex® DM (lot #PB01-H43A2) following a high-fat meal (test)

**Criteria for Evaluation:** PK parameters (AUC,  $C_{max}$ ,  $T_{max}$ , CL,  $t_{1/2}$ ) of guaifenesin and DM.

**Blood sampling times:** t = Pre-dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72 and 96 hours post dose (total 280 mL).

**Analytical Methodology**

**Assay Method:** HPLC (guaifenesin), LC/MS/MS (DM)

**Assay Sensitivity (standard curves):** \_\_\_\_\_ (guaifenesin), \_\_\_\_\_ (DM)

**Accuracy and Precision:** Precision and accuracy for guaifenesin QC ranged \_\_\_\_\_, respectively. Precision and accuracy for DM QC ranged \_\_\_\_\_, respectively.

**Results:**

**Study Population:** 36 subjects entered and 35 completed the study according to the protocol. The subjects averaged  $26.4 \pm 9.45$  years of age with 18-51 years of age. 16 were male and the remainder was female.

**Data Analysis:** ANOVA was performed on ln-transformed AUCs and  $C_{max}$ , CL and  $t_{1/2}$  were natural-log (ln) transformed prior to analysis. ANOVA was performed and 90% confidence intervals (CI) were generated for the ratio of Test/Reference. 90% CI for the geometric mean ratio were obtained for AUCs and  $C_{max}$  by taking the antilog of the 90% CI for the difference between means on the log scale.

**Pharmacokinetics:** Mean plasma profiles of guaifenesin and DM are shown in Figure 1. The PK results are summarized in the tables below.

Figure 1. Mean plasma concentration-time profiles of guaifenesin (ng/mL) and DM (pg/mL)

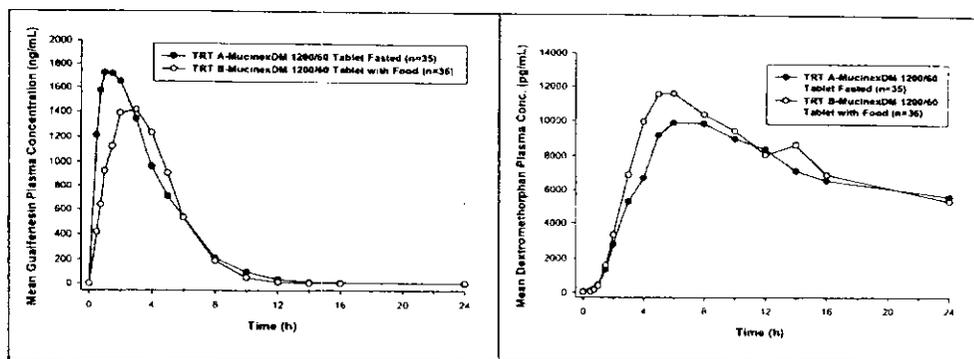


Table 1. Mean (%CV) and median PK parameters and Statistical analysis of guaifenesin following single dose of the treatments (Study 2002-12)

Parameter	Trt	N	Mean (%CV)	Median	Pair	Treatment Comparisons		
						LS Mean <sup>a</sup>	Ratio <sup>b</sup>	90% CI <sup>c</sup>
AUC <sub>t</sub> (ng•h/mL)	A	35	8107 (43)	7777	B/A	7420	0.90	85-94.6
	B	36	7077 (39)	6201		6651		
AUC <sub>inf</sub> (ng•h/mL)	A	35	8128 (43)	7789	B/A	7439	0.90	85-94.5
	B	36	7093 (39)	6228		6668		
C <sub>max</sub> (ng/mL)	A	35	2030 (43)	1760	B/A	1854	0.91	82.2-100
	B	36	1825 (43)	1520		1683		
T <sub>max</sub> (hr) <sup>d</sup>	A	35	1.61 (71)	1.50	B/A			0.0001
	B	36	2.93 (49)	3.00				
t <sub>1/2</sub> (hr)	A	35	1.15 (31)	1.04				
	B	36	0.85 (14)	0.85				

A = Mucinex® DM 1200/60 mg, under fasted - reference

B = Mucinex® DM 1200/60 mg, fed condition- test

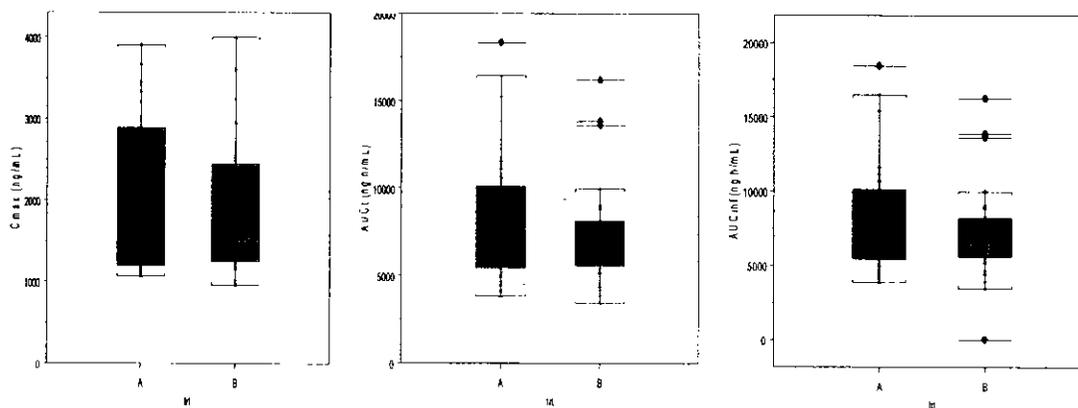
<sup>a</sup> Least-square mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means)

<sup>b</sup> LS mean of test/reference

<sup>c</sup> 90% confidence intervals for ratio of parameter geometric means

<sup>d</sup> = p-value from Wilcoxon signed-rank test

Figure 2. Individual guaifenesin C<sub>max</sub>, AUC<sub>t</sub>, and AUC<sub>inf</sub> values following single dose of the treatments

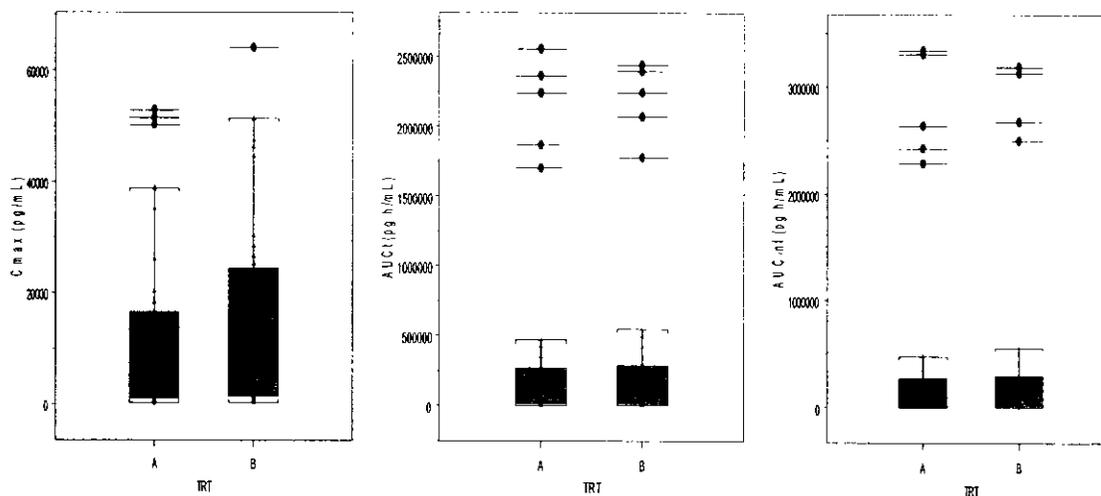


**Table 2.** Mean (%CV) and median PK parameters and statistics analysis of DM following Single dose of the treatments

Parameter	Trt <sup>a</sup>	N	Mean (%CV) <sup>b</sup>	Median	Pair <sup>c</sup>	Treatment Comparisons		
						LS Mean <sup>d</sup>	Ratio <sup>e</sup>	90% CI <sup>f</sup>
AUC <sub>t</sub> (ng•h/mL)	A	35	372.9 (202)	33.8	B/A	55.3	1.08	96.7-121
	B	36	381.4 (198)	37.5		59.8		
AUC <sub>inf</sub> (ng•h/mL)	A	35	466.5 (212)	34.13	B/A	58.3	1.07	96.4-120
	B	36	472.1 (207)	37.81		62.7		
C <sub>max</sub> (ng/mL)	A	35	10.72 (149)	3.02	B/A	3.72	1.21	107-136
	B	36	12.76 (140)	3.47		4.49		
T <sub>max</sub> (hr)*	A	35	6.23 (57)	6.0	B/A		NA	0.8027
	B	36	5.74 (40)	5.0				
t <sub>1/2</sub> (hr)*	A	35	1.15 (31)	1.04				
	B	36	0.85 (14)	0.85				

Notations are the same as in Table 1

**Figure 3.** Individual DM C<sub>max</sub>, AUC<sub>t</sub> and AUC<sub>inf</sub> values following single dose of the treatments



**Conclusion:**

- High-fat meal had no effect on the bioavailability of guaifenesin from the Mucinex-DM tablets. Ninety percent CI for the ratio of AUC and C<sub>max</sub> were within BE requirements (80-125%). Food caused a delay in T<sub>max</sub> of guaifenesin by approximately 1.5 hours.
- High-fat breakfast increased the C<sub>max</sub> of DM by 21%, but had no effect on AUC and T<sub>max</sub>.
- 21% increase in C<sub>max</sub> of DM and a delay of 1.5 hrs in T<sub>max</sub> of guaifenesin may not be clinically relevant. Therefore, Mucinex DM can be taken without regards to meals.
- DM outliers (i.e., Poor metabolizers of CYP2D6) had approximately 5- or 18-fold higher C<sub>max</sub> compared to the mean and median, respectively, and 7- or 80-fold higher AUC compared to the mean and median, respectively. However, there were no significant differences in AE (adverse events) between subjects in PM and normal (confirmed with the reviewing MD)

**Protocol #2002-15**

**Study Type:** BA/single dose/DDI.

**Title:** An interaction and dose-response study designed to examine the bioavailability of guaifenesin and dextromethorphan from an experimental controlled-release formulation in normal healthy volunteers compared to reference guaifenesin and dextromethorphan products.

**Clinical Investigators:** Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc. Springfield, MO.

**Objectives:** To determine the bioavailability of guaifensin and DM when they are co-administered and when they are administered alone. In addition, dose-response relationship of DM is assessed.

**Study Design and Method:** This was an open-label, randomized, 4-way crossover study in 36 healthy male and female volunteers. The subjects were randomized and placed into one of four treatment groups. Group 1 received a test formulation Mucinex<sup>®</sup> DM 1200/60 mg, (Treatment A). Group 2 received a reference Mucinex<sup>®</sup> 1200 mg (Treatment B). Group 3 received 60 mg of DM in a reference IR liquid formulation according to two different dosing regimens (1/2 of the subjects received 30 mg DM q6H x 2 doses [Treatment C], while the other half received 20 mg DM q4H x 3 doses [Treatment D]). Group 4 received 30 mg of DM in a reference IR liquid formulation according to two different dosing regimens (1/2 of the subjects received 15 mg DM q6H x 2 doses [Treatment E], while the other half received 10 mg DM q4H x 3 doses [Treatment F]). Those subjects that received 30 mg in one treatment period received 15 mg DM in another treatment period; similarly, those that received 20 mg in one treatment period received 10 mg DM in a subsequent treatment period.

There was a 14-day washout between doses.

- Treatment A: Mucinex<sup>®</sup> DM (lot #PB01-H30A2) 1200/60 mg - test
- Treatment B: Mucinex<sup>®</sup> 1200 mg (lot #PB-304A2) – reference
- Treatment C: Benylin<sup>®</sup> (lot #58351L) 30 mg q6H x 2 doses – reference
- Treatment D: Benylin<sup>®</sup> (lot #58351L) 20 mg q4H x 3 doses – reference
- Treatment E: Benylin<sup>®</sup> (lot #58351L) 15 mg q6H x 2 doses – reference
- Treatment F: Benylin<sup>®</sup> (lot #58351L) 10 mg q4H x 3 doses – reference

**Criteria for Evaluation:** PK parameters (AUC, C<sub>max</sub>, T<sub>max</sub>, CL, t<sub>1/2</sub>) of guaifenesin and DM.

**Blood sampling times:** t = 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72 and 96 hours post dose.

**Analytical Methodology**

**Assay Method:** HPLC (guaifenesin), LC/MS/MS (DM)

**Assay Sensitivity (standard curves):** \_\_\_\_\_ (guaifenesin), \_\_\_\_\_ (DM)

**Accuracy and Precision:** ?Precision and accuracy for guaifenesin QC ranged \_\_\_\_\_ respectively. Precision and accuracy for DM QC ranged \_\_\_\_\_

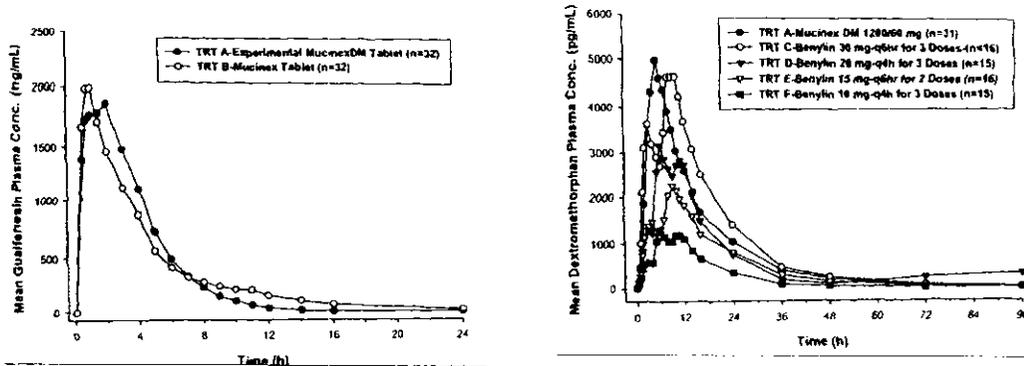
**Data Analysis:** ANOVA was performed on ln-transformed AUCs and C<sub>max</sub>, CL and t<sub>1/2</sub> were natural-log (ln) transformed prior to analysis. ANOVA was performed and 90% confidence intervals (CI) were generated for the ratio of Test/Reference. 90% CI for the geometric mean ratio were obtained for AUCs and C<sub>max</sub> by taking the antilog of the 90% CI for the difference between means on the log scale.

**Results:**

**Study Population:** 33 subjects entered and 30 completed the study according to the protocol. The subjects averaged  $24.9 \pm 7.68$  years of age with a 18-49 years of age. 15 were male and the remainder was female.

**Pharmacokinetics:** Results are summarized in the tables and figures.

**Figure 1.** Mean plasma concentration-time profiles of guaifenesin (ng/mL) and DM (pg/mL)



**Table 1.** Mean (%CV) and median PK parameters and statistics analysis of guaifenesin following Single dose of the treatments

Parameter	Trt	N	Mean (%CV)	Median	Pair	Treatment Comparisons		
						LS Mean <sup>a</sup>	Ratio <sup>b</sup>	90% CI <sup>c</sup>
AUC <sub>t</sub> (ng•h/mL)	A	32	8732 (55)	7579	A/B	6960	0.96	93.8-108
	B	32	8657 (49)	8346		6991		
AUC <sub>inf</sub> (ng•h/mL)	A	32	8761 (54)	7734	A/B	7014	0.97	90.1-104
	B	32	8953 (48)	8826		7231		
C <sub>max</sub> (ng/mL)	A	32	2176 (61)	1830	A/B	1775	0.97	88.7-107
	B	32	2145 (47)	1915		1825		
T <sub>max</sub> (hr) <sup>d</sup>	A	32	1.44 (47)	1.50	A/B			<i>p</i> =0.000
	B	32	0.91 (55)	0.75				
t <sub>1/2</sub> (hr)	A	32	1.31 (86)	1.08				
	B	32	4.79 (101)	3.03				

A = Mucinex<sup>®</sup> DM 1200/60 mg, - test,

B = Mucinex<sup>®</sup> 1200 mg – reference

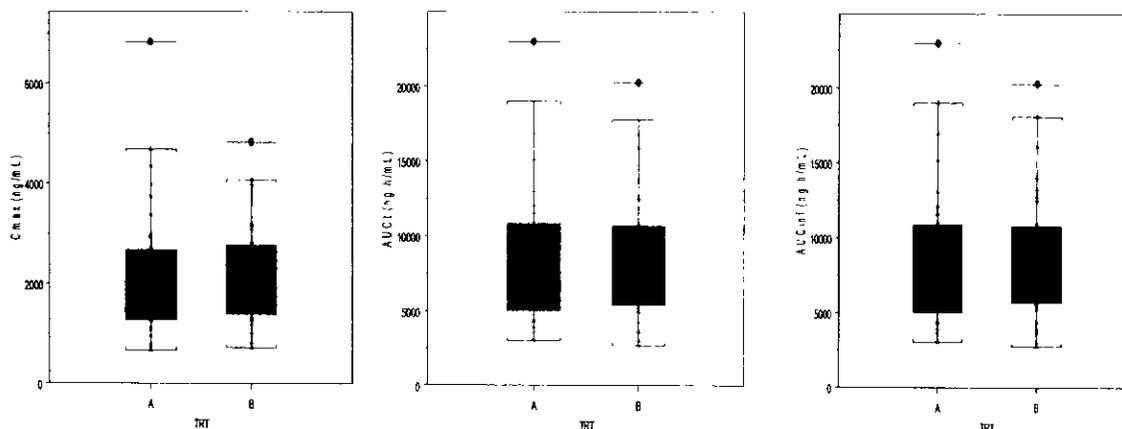
<sup>a</sup> Least-square mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means)

<sup>b</sup> LS mean of test/reference

<sup>c</sup> 90% confidence intervals for ratio of parameter geometric means

<sup>d</sup> = p-value from Wilcoxon signed-rank test

**Figure 2.** Individual guaifenesin  $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$  values following single dose in each treatments

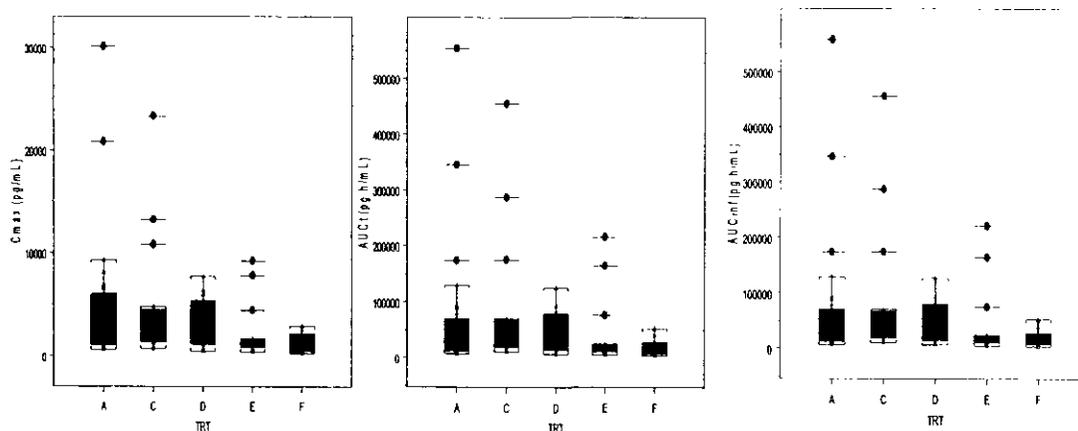


**Table 2.** Mean (%CV) and median PK parameters and statistics analysis of DM following Single dose of the treatments

Parameter	Trt	N	Mean (%CV)	Median	Pair	Treatment Comparisons		
						LS Mean <sup>b,1</sup>	Ratio <sup>b</sup>	90% CI <sup>c</sup>
$AUC_t$ (ng·h/mL)	A	32	68.19 (165)	27.82		466		
	C	16	82.28 (150)	23.48	A/C	459	1.01	87.3-118
	D	15	44.29 (83)	26.14	A/D	599	0.78	66-91.6
	E	16	39.75 (155)	16.06	E/C	463	1.01	87.1-117
	F	15	19.83 (81)	12.94	F/D	530	0.89	75.7-103
$AUC_{inf}$ (ng·h/mL)	A	32	68.85 (164)	28.09		473		
	C	16	82.67 (149)	23.86	A/C	462	1.02	88.2-119
	D	15	44.68 (83)	26.32	A/D	608	0.78	66.1-91.5
	E	16	40.32 (155)	16.23	E/C	469	1.01	67.7-117
	F	15	20.11 (80)	13.17	F/D	547	0.90	77.0-105
$C_{max}$ (ng/mL)	A	32	4.83 (128)	2.56		39.8		
	C	16	4.71 (130)	1.67	A/C	30.7	1.30	110-153
	D	15	3.13 (75)	2.72	A/D	42.8	0.93	77.6-111
	E	16	2.18 (122)	1.18	E/C	32.4	1.06	89.9-124
	F	15	1.29 (70)	0.8	F/D	37.4	0.88	73.6-104
$T_{max}$ (hr) <sup>d</sup>	A	32	5.06 (18)	5.0				
	C	16	8.31 (19)	8.5	A/C			$P=0.0001$
	D	15	7.01 (28)	6.0	A/D			$P=0.0137$
	E	16	8.03 (31)	9.0	E/C			$P=1.0000$
	F	15	7.73 (31)	6.0	F/D			$P=0.4063$
$t_{1/2}$ (hr)	A	32	7.7 (23)	6.9				
	C	16	7.5 (26)	6.8				
	D	15	7.0 (22)	6.6				
	E	16	7.3 (31)	6.5				
	F	15	7.4 (27)	7.0				

A = Mucinex<sup>®</sup> DM 1200/60 mg, - test,  
 C = Benylin<sup>®</sup> 30 mg q6H x 2 doses – reference  
 D = Benylin<sup>®</sup> 20 mg q4H x 3 doses – reference,  
 E = Benylin<sup>®</sup> 15 mg q6H x 2 doses – reference  
 F = Benylin<sup>®</sup> 10 mg q4H x 3 doses – reference  
 Other notations are the same as in Table 1

**Figure 3.** Individual DM  $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$  values following single dose of Mucinex DM tablets



The pharmacokinetics of guaifenesin is not affected by the presence of DM. Ninety percent confidence intervals for the log-transformed PK parameters of guaifenesin ( $C_{max}$ ,  $AUC_t$ ,  $AUC_{inf}$ ) administered alone (mucinex) versus its co-administration with DM (Mucinex-DM) were within goal post for BE (Table 1).

For DM, the  $AUC_{inf}$ ,  $AUC_t$  and  $C_{max}$  ratio comparison of test to reference treatment (comparisons A/C, A/D) showed the confidence interval range from 66.1 - 119%, 66 - 118% and 73.6 - 153%, respectively (Table 2).

**Conclusion:**

- The pharmacokinetics of guaifenesin is not affected by co-administration with DM. Ninety percent confidence intervals for the log-transformed PK parameters of guaifenesin ( $C_{max}$ ,  $AUC_t$ ,  $AUC_{inf}$ ) administered alone (Mucinex) versus its coadministration with DM (Mucinex DM) were within goal post for BE.
- For DM, the  $AUC_{inf}$ ,  $AUC_t$  and  $C_{max}$  ratio comparison of test to reference treatment (comparisons A/C, A/D, E/C and F/D) showed the confidence interval range from 66.1 - 119%, 66 - 118% and 73.6 - 153%, respectively. While the point estimates ranged from — indicating that the change in PK is not likely to be clinically significant.
- DM outliers (i.e., Poor metabolizers of CYP2D6) had approximately 6- or 12-fold higher  $C_{max}$  compared to the mean and median, respectively, and 8- or 20-fold higher AUC compared to the mean and median, respectively. However, there were no significant differences in AE (adverse events) between subjects in PM and normal (confirmed with the reviewing MD)

3 Page(s) Withheld

0 § 552(b)(4) Trade Secret / Confidential

     § 552(b)(5) Deliberative Process

     § 552(b)(5) Draft Labeling

C. OCPB 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	21-620	Brand Name	Mucinex <sup>®</sup> DM
OCPB Division (I, II, III)	DPE-II	Generic Name	Guaifensin (G)/ Dextromethorphan (DM) HBr
Medical Division	HFD-570	Drug Class	G = expectorant DM = antitussive
OCPB Reviewer	Shinja Kim	Indication(s)	Temporary relief of cough
OCPB Team Leader	Emmanuel Fadiran	Dosage Form	Extended-Release Tablets
		Dosing Regimen	B.I.D.
Date of Submission	6/30/03	Route of Administration	Oral
Estimated Due Date of OCPB Review	2/30/04	Sponsor	Adams Laboratories, Inc.
PDUFA Due Date	4/30/04	Priority Classification	S
Division Due Date	3/30/04		

**3 Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	5	5	
multiple dose:	x	1	1	
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	x	G vs. DM
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:				

<b>Population Analyses -</b>				
	Data rich:			
	Data sparse:			
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
	solution as reference:			
	alternate formulation as reference:	x		4 single and 1 multiple dose studies
<b>Bioequivalence studies -</b>				
	traditional design; single / multi dose:	x	4	4
	replicate design; single / multi dose:			
<b>Food-drug interaction studies:</b>				
		x	1	1
<b>Dissolution:</b>				
		x		
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>			6	6
4 studies are pivotal				
<b>Filability and QBR comments</b>				
		<b>"X" if yes</b>	<b>Comments</b>	
Application filable?		x	<ul style="list-style-type: none"> <li>Pivotal single dose study (2002-08): 90% CI for DM <math>C_{max}</math> and <math>AUC_{inf}</math> were not within 80-125% (Table 2)</li> <li>Pivotal multiple dose study (2002-10): 90 CI for <math>C_{max}</math> and <math>AUC_{ssf}</math> for G and DM were within 80-125%. However <math>C_{min}</math> were low, especially for G (Table 1)</li> </ul>	
Comments sent to firm?				
<b>QBR questions (key issues to be considered)</b>			<ul style="list-style-type: none"> <li>Is formulation used in the bio-studies identical to the to-be-marketed formulation?</li> <li>Is the tested formulation bioequivalent to the reference products following single and multiple administration?</li> <li>Does food affect the BA of guaifensin/DM from the mucinex DM extended release tablet?</li> <li>Has the applicant developed adequate dissolution method and specification to assure in vivo performance and quality of the product?</li> </ul>	

**Background:**

This NDA is a 505(b)(2) application for an extended release formulation of guaifenesin and dextromethorphone (DM). It is proposed as an over-the-counter (OTC) combination expectorant and antitussive agent. The proposed indication is loosening of phlegm and bronchial secretions and temporary relief of coughs associated with upper respiratory tract infections and related conditions such as sinusitis, pharyngitis, and bronchitis.

The sponsor is requesting approval of two dosage strengths, guaifenesin 1200 mg/DM 60 mg tablets, and guaifenesin 600 mg/DM 30 mg tablets. Mucinex™ DM tablets are manufactured as bi-layer tablets by compressing an immediate release layer and modified layer into a tablet.

The sponsor conducted 4 pivotal and 2 pilot Clinical Pharmacology and Biopharmaceutics studies to satisfy BA/BE requirements (i.e., BE after single and multiple doses; the effect of food on bioavailability; assessment of the potential for interaction between guaifenesin and DM in the combination product). These studies were conducted with the to-be-marketed formulation with different batches (i.e., PB01-H30A2, PB01-H30A3, PB01-H30A4 and PB01-H43A2).

A cursory review of the study results showed that 90% CI for AUC and  $C_{max}$  comparison for guaifenesin are within 80 to 125%, but between 70 to 143% range for DM. In addition,  $C_{min}$  for guaifenesin at steady state is quite low (see Tables 1-2).

**Table 1**  
**Guaifenesin Between Treatment Comparisons for Study 2002-10**

Parameter (units)	Trt [a]	N	Mean (CV%)	Median	Treatment Comparisons				
					Pair	LS mean [b]	Ratio [c]	90% CI on ratio [d]	p-value
AUC <sub>ss</sub> (ng·h/mL)	A	35	7540 (34%)	7366		7104			
	B	35	7403 (33%)	7230	C/A	7035	0.96	91.1-101	0.4414
	C	34	7138 (32%)	6992	C/B	6828	0.97	92.0-102	0.4414
$C_{max}$ (ng/mL)	A	35	1935 (39%)	1910		1787			
	B	35	1938 (33%)	1910	C/A	1832	0.93	85.3-100	0.0956
	C	34	1780 (36%)	1770	C/B	1653	0.90	83.3-97.8	0.0956
$C_{min}$ (ng/mL)	A	35	75.5 (98%)	59.0		41.2			
	B	35	59.6 (87%)	36.1	C/A	35.8	0.27	18.1-40.5	0.0000
	C	34	18.2 (101%)	13.7	C/B	11.1	0.31	20.8-46.5	0.0000
$t_{max}$ [e] (h)	A	35	122 (0.70%)	121		NA			
	B	35	121 (0.38%)	121	C/A	NA	NA	NA	0.5333
	C	34	121 (0.71%)	121	C/B	NA	NA	NA	0.0060

[a] A = Mucinex® (lot number PBC1-H34A4) plus Vicks® 44® (lot number 1141RX) 30 mg every 6 h for 2 doses - reference

B = Mucinex® (lot number PB01-H34A4) plus Vicks® 44® (lot number 1141RX) 20 mg every 4 h for 3 doses - reference

C = Mucinex® DM 1200/60 mg (lot number BP01-H30A4) - test

[b] Least-squares mean from ANOVA non-weighted analysis. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e., geometric means).

[c] Ratio = LS mean of test / reference

[d] 90% confidence interval for ratio of parameter means of natural log transformed parameters (expressed as percent) transformed back to linear scale

[e] For  $t_{max}$  these are the median values. P-value from Wilcoxon signed-rank test. Time reported as time from first dose of study on Day 1.



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/s/

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Shinja Kim  
3/9/04 12:00:31 PM  
BIOPHARMACEUTICS

Emmanuel Fadiran  
3/10/04 11:27:45 AM  
BIOPHARMACEUTICS  
I concur