

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-620

MEDICAL REVIEW

TEAM LEADER MEMORANDUM

Date: April 19, 2004 (PDUFA date 4/30/04)
To: NDA 21-620
From: Peter Starke, MD
Medical Team Leader
Division of Pulmonary and Allergy Drug products, HFD-570
Product: Mucinex[®] DM (extended-release bi-layer tablets)
Applicant: Adams Laboratories, Inc.

Administrative and Introduction

NDA 21-620 for Mucinex[®] DM is an extended-release combination drug product containing guaifenesin and dextromethorphan hydrobromide (HBr). The NDA was submitted by Adams Laboratories, Inc. on June 30, 2003, as a 505(b)(2) application for OTC marketing. The expectorant/cough suppressant combination of guaifenesin and dextromethorphan is permitted in the OTC monograph 21CFR 341.40(h). The proposed monographed indication is to "loosen phlegm (mucus) and thin bronchial secretions" and to "temporarily relieve cough due to minor throat and bronchial irritation as may occur with the common cold or inhalant irritants in adults and children 12 years of age and older." The drug product is a bi-layer combination consisting of both immediate and extended release layers, each of which contains both active ingredients. There are two proposed dosage strengths, (1) guaifenesin 600 mg / dextromethorphan HBr 30 mg, and (2) guaifenesin 1200 mg / dextromethorphan HBr 60 mg, to be administered as 1-2 tablets of the lower strength tablet or 1 tablet of the higher strength tablet twice daily.

Guaifenesin is an expectorant which enhances the flow of respiratory tract secretions. Guaifenesin, when used as an expectorant, is under the regulation of the OTC monograph 21CFR 341.18. It is generally recognized as safe and effective (GRASE) in multiple age groups at various doses, down to 2 years of age [21 CFR 341.78]. In the age/dose group of adults and children 12 years of age and older, the monographed dose is 200 to 400 mg every 4 hours, not to exceed (NTE) 2400 mg in 24 hours. The NDA for Mucinex DM builds upon the recent approval of Mucinex[®] (guaifenesin) 600 mg and 1200 mg extended-release tablets, granted to Adams Laboratories (NDA 21-282, approved July 12, 2002). Mucinex is currently the **only** extended release guaifenesin-containing drug product approved by the Agency; **all** other guaifenesin drug products are immediate release OTC-monographed formulations.

Dextromethorphan HBr is a centrally-acting antitussive agent used in cough and cold medicines. Dextromethorphan HBr, when used as an antitussive, is under the regulation of 21CFR 341.14. It is considered GRASE in multiple age groups at various doses, down to 2 years of age [21 CFR 341.74]. In the age/dose group of adults and children 12 years of age and older, the monographed dose is 10 to 20 mg every 4 hours or 30mg every 6 to 8 hours, NTE 120 mg in 24 hours, or as directed by a doctor. Currently there is only one approved extended-release formulation of dextromethorphan, Delsym[®] (extended-release.

phencyclidine. Massive overdosage with dextromethorphan may result in respiratory depression, excitation, confusion, toxic psychosis, and hallucinations.¹

Clinical Pharmacology and Biopharmaceutics

The applicant conducted six clinical pharmacology studies, of which one was a pilot study and four were definitive studies using the to-be-marketed formulation of the high-strength tablets.

Study 2001-04 was a pilot, single dose study that compared the bioavailability of guaifenesin and dextromethorphan from two experimental prototypes of Mucinex DM extended-release tablets to reference extended-release guaifenesin (Mucinex[®]) and extended-release dextromethorphan polistirex (Delsym[®]). Guaifenesin from the experimental formulations was bioequivalent to reference guaifenesin.

Dextromethorphan bioavailability in both experimental formulations was more bioavailable than reference dextromethorphan. One of the experimental formulations was carried forward into the four definitive studies.

Study 2001-15 was a single dose, drug interaction, bioavailability, and dose proportionality study that demonstrated that the bioavailability of guaifenesin was not affected by co-administration with dextromethorphan. The C_{max} , AUC_{0-t} , AUC_{∞} for guaifenesin were within the 80-125% bioequivalence limits compared to the reference standards. Dextromethorphan in the Mucinex DM was slightly outside the 90% CI with ratios between 66.1-153%. However, the point estimates ranged from 0.78 to 1.30 and were greater than 0.85, indicating that the changes in pharmacokinetics were not likely to be clinically significant. No evidence of drug-drug pharmacokinetic interaction between dextromethorphan and guaifenesin occurred when the various treatments were compared and the pharmacokinetics of dextromethorphan were linear over the range studied.

Study 2002-08 was a single dose, bioavailability study that demonstrated that guaifenesin from the Mucinex DM was bioequivalent to reference guaifenesin (Mucinex[®]) for C_{max} and AUC_{inf} , with ratios of the 90% confidence intervals all contained within 80 to 125%. Dextromethorphan from Mucinex DM was found to be bioequivalent to reference dextromethorphan (Vicks[®] 44[®] Cough Relief) administered 30 mg every 6 hours as well as 20 mg every 4 hours, in terms of C_{max} and AUC_{inf} , with ratios between 70 and 143%. The Applicant proposed equivalence criteria for the 90% confidence intervals to be contained within 70 to 143% for highly variable drugs such as dextromethorphan. The point estimates of the ratios for C_{max} and AUC were greater than 0.85 indicating similar bioavailability between the test and reference products. Subjects that were poor dextromethorphan metabolizers were outliers between treatment groups and had a 6 to 20 fold higher C_{max} compared to the mean and median, respectively. However, these elevated levels did not reflect an increase in adverse events in these poor metabolizers compared to subjects with normal dextromethorphan metabolism.

Study 2002-10 was a multiple dose study that compared the bioavailability of guaifenesin and dextromethorphan from the proposed Mucinex DM to a reference

¹ Ben JL, Peck R. Dextromethorphan. An overview of safety issues. Drug Safety 1992; 7(3):190-199.

treatment consisting of extended-release guaifenesin (Mucinex[®]) and Vicks cough formula at steady state, after eleven 12-hour dosing periods. Mean C_{max} and AUC_{ss} values for guaifenesin for the proposed product were within 80 to 125% bioequivalence limits compared to the reference standards. The C_{min} for guaifenesin in the proposed product was below the C_{min} for reference guaifenesin (Mucinex[®]) at a three to four-fold lower concentration; however, this low C_{min} was within the effective concentration level associated with approved, reference guaifenesin. Mean C_{max} and AUC_{ss} values for dextromethorphan for the proposed product were lower than the 80 to 125% bioequivalence limits compared to the reference standards. Although the C_{min} was outside the 90% CI at values down to 71.8%, the point estimates of the ratios for C_{min} were 0.84 indicating similar bioequivalence between the test and reference products.

Study 2002-12 was a single dose study that compared the bioavailability of guaifenesin and dextromethorphan from Mucinex DM administered under both fasting and fed conditions. The ratios of AUC and C_{max} were within 90% CI for the established bioequivalence criteria between 80-125%. Food caused a delay in T_{max} of guaifenesin by approximately 1.5 hours as well as an increase in C_{max} by 21% and in the rate of absorption of dextromethorphan, but had no effect on AUC for either. Subjects who were poor metabolizers of CYP2D6 had elevated plasma concentrations of guaifenesin and dextromethorphan; however, this did not manifest as a significant difference in AEs in these outliers compared to normals. Subjects who were administered Mucinex DM in the fasted state had a greater number of AEs compared to those in the fed state. The 21% increase in C_{max} of DM and delay of 1.5 hrs in T_{max} of guaifenesin is not clinically significant. Therefore, this was not considered to be a clinically relevant food effect.

Summary of definitive studies

Study #	Study Type	Design/Population	Treatment*	N
2001-15	Drug interaction, bioavailability and dose proportionality	Single-dose, open-label, R, 4-way crossover design with 14 day washout period between treatments Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	G 1200 mg/DM 60 mg	32
			G 1200 mg, (Mucinex), plus	32
			DM 30 mg q6h	16
			DM 20 mg q4h	15
			DM 15 mg q6h	16
DM 10 mg q4h	15			
2002-08	Bioavailability	Single-dose, open-label, R, 3-way crossover design with 14 day washout period between treatments Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	G 1200 mg/DM 60 mg	33
			G 1200 mg (Mucinex), plus DM 30mg q 6h	36
			G 1200 mg (Mucinex), plus DM 20 mg q 4h	34
2002-10	Steady state bioavailability	Multiple dose, open-label, R, 3-way crossover design with 14 day washout period between treatment Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	G 1200 mg/DM 60 mg	35
			G 1200 mg (Mucinex), plus DM 30mg q 6h	35
			G 1200 mg (Mucinex), plus DM 20 mg q 4h	35
2002-12	Food effect	Single-dose, open-label, R, 2-way crossover design with 14 day washout period between treatments	G 1200 mg/DM 60 mg, fasted	35
			G 1200 mg/DM 60 mg, following high-fat	36

Study #	Study Type	Design/Population	Treatment*	N
		Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	breakfast	

*G = Guaifenesin; All guaifenesin reference used Mucinex drug product. DM = Dextromethorphan; All dextromethorphan reference used OTC-monographed immediate-release products. To-be-marketed product is in **bold text**

Clinical and Statistical

The clinical program for Mucinex DM consisted of the four definitive PK studies, as discussed above. There were no efficacy or safety studies in the development program for this drug product. Efficacy is discussed above under **Clinical Pharmacology and Biopharmaceutics**. In summary, the clinical pharmacology studies showed bioequivalence of Mucinex DM to the reference drug products. The drug interaction study indicated that the pharmacokinetics of guaifenesin and dextromethorphan were not affected by the presence of one another. When co-administered with a high fat meal, there was a delay in T_{max} of guaifenesin by approximately 1.5 hours, but no effect on the rate, C_{max} , or AUC. A high-fat meal minimally increased by 21% the C_{max} of dextromethorphan, but there was no effect on the AUC or T_{max} . These differences are not considered clinically relevant.

In support of the safety of Mucinex[®] DM, the Applicant submitted data from six clinical pharmacology studies and an evaluation of safety information from the US AERS database and the clinical literature. Review of the integrated safety data from the Applicant's clinical pharmacology studies revealed no evidence of new safety signal. There were no meaningful differences in adverse events (AEs), withdrawals due to AEs, or serious adverse events (SAEs) between Mucinex DM and reference products. Data from the AERS database support the safety of guaifenesin and dextromethorphan and do not present new safety issues. There were not sufficient numbers of subjects in the subpopulations to stratify safety data in terms of age, gender, race, pregnancy or lactation, or consumers with hepatic or renal disease

In summary, the data submitted by the Applicant provided no evidence of a safety signal that had not been previously identified and the Applicant's integrated review of safety supports the proposed indication of their product.

Abuse Considerations

There are concerns for abuse of dextromethorphan. Since this drug product contains a high dose of dextromethorphan, this concern was raised and discussed during the review cycle, and a consult was requested from the Controlled Substance Staff. (HFD-009) They suggested a post-marketing review of reports of abuse of dextromethorphan.

The Office of Drug Safety, Division of Drug Risk Evaluation (HFA-430) performed a review of the AERS database from November 13, 2000 to October 17, 2003, looking for reports regarding use of dextromethorphan. A total of 1886 adverse events were reported during this time period, with 1621 of these reporting nervous system disorders. There were 71 unduplicated cases of drug abuse, drug overdose, and/or suicides. Of these, 67 were drug overdoses, 18 of which were accidental in children less than 18 years of age. Abuse was specifically mentioned in 42 cases, all of which involved abuse of multiple drugs. There were 33 deaths, of which 2 were not drug-related and the rest were related

to overdose of multiple drugs. The findings of this review were consistent with previous reviews, indicating that dextromethorphan-containing products continue to be used improperly by both children and adults, leading to serious outcomes.

If approved, Mucinex DM will have the highest OTC dose of dextromethorphan available in a single dose tablet. However, the each of the bilayer IR and MR layers each contain both guaifenesin and dextromethorphan, so a potential abuser cannot separate the two drugs (although there is more dextromethorphan in the IR layer). In addition, the extended-release formulation makes it likely that abusers will ingest sufficient guaifenesin to cause stomach irritation prior to ingesting sufficient quantities of dextromethorphan to cause the desired abuse effects. No PK studies were performed to evaluate whether breaking up a tablet would affect absorption of the component drugs.

In response to a query from the Division regarding whether the Applicant had developed a risk management plan for the eventuality that their drug product is abused, the Applicant indicated that they will monitor MedWatch regularly for spontaneous AE reports and if a safety signal is detected, then a risk management plan will be devised and implemented to reduce rates of abuse. In addition, the Office of Drug Safety will be looking at the postmarketing surveillance data and if they suspect a safety signal, the Agency will request the Applicant to submit a risk management plan.

Data Quality, Integrity, and Financial Disclosure

There was one study center and one analytical site for all of the clinical pharmacology studies. DSI audited the study center. **Study 2002-08** (definitive single-dose bioequivalence and dose proportionality study) and **Study 2002-10** (definitive multiple-dose bioequivalence and dose proportionality at steady state) were audited for the quality or integrity of the data submitted in reference to the PK blood samples. No serious deficiencies were noted, and DSI recommended acceptance of these studies. During review of the studies, no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. There were no financial disclosure concerns raised during the review process.

Pediatric Considerations

The applicant is proposing use of Mucinex DM in patients 12 years of age and older. However, because there are two strengths and the lower dose tablet is smaller and easier to swallow, it is conceivable that a younger population could and would use this dose off-label. However, the dose of one lower strength tablet twice daily matches the monographed dose for children ≥ 6 to 12 years of age. Because of the extended-release dosage form, and the fact that immediate release formulations are available for lower age populations down to the lowest recommended age (2 years) for use of both dextromethorphan hydrobromide and guaifenesin, there is no reason to request studies below 12 years of age. Therefore, a waiver of pediatric studies under PREA is appropriate.

Product Name

The trade name of Mucinex[®] is approved and has been used by Adams Laboratories for the extended-release dosage formulations containing single-ingredient guaifenesin. The suffix 'DM' is an acceptable addition to Mucinex[®] distinguish that this drug product contains dextromethorphan HBr. The suffix 'extended-release bi-layer tablets' is appropriate for this dosage form. The Division of Over-the-Counter Drug Products recommends that the product name be: 'Mucinex[®] DM Extended-release Bi-layer Tablets.'

Labeling

This product is intended for OTC use. OTC labeling was submitted, and reviewed by the Division of Over-the-Counter Drug Products (HFD-560). The OTC monograph labeling for guaifenesin requires no special directions or warnings for adults and children 12 years and older, the population for which the sponsor's product is proposed. The OTC labeling for dextromethorphan has specific warnings regarding drug interactions with monoamine oxidase inhibitors (MAOI) in this same population. This warning is present on the proposed Mucinex DM label. Other minor changes to the Applicant's labeling were recommended.

Summary and Action

The clinical pharmacology studies showed bioequivalence of Mucinex DM to reference drug products, with no safety signal identified either in the studies or in the review of MedWatch reports. The product is proposed as an extended-release formulation for use in patients 12 years of age and older as an OTC antitussive/expectorant. Immediate-release formulations are available in lower dosages appropriate for lower age ranges via the OTC-monograph process. Therefore, a waiver of pediatric studies under PREA is appropriate. While there are concerns for abuse of dextromethorphan especially because of the high dose of dextromethorphan in this drug product, the extended-release and combination bilayer formulation makes it likely that abusers will ingest sufficient guaifenesin to cause stomach irritation prior to ingesting sufficient quantities of dextromethorphan to cause the desired abuse effects. However, the Applicant has agreed to monitor MedWatch reports for signs of abuse, and to address potential safety issues with regard to abuse, should the need arise. No Phase 4 studies or post-marketing commitments are needed.

The clinical team recommends that the regulatory action on this application be an APPROVAL.

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/s/

Peter Starke
4/19/04 05:29:29 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

APPLICATION:	NDA 21-620	TRADE NAME:	Mucinex[®] DM (Extended-Release Bi-layer Tablets)
APPLICANT/SPONSOR:	Adams Laboratories, Inc. 14801 Sovereign Road Fort Worth, Texas 76155-2645	ESTABLISHED NAME:	Mucinex[®] DM (guaifenesin and dextromethorphan HBr) Extended-Release Bi-layer Tablets
MEDICAL OFFICER:	Katherine Szema, MD	USAN NAME:	Guaifenesin /Dextromethorphan HBr
TEAM LEADER:	Peter Starke, MD	DRUG CLASS:	Expectorant/antitussive
PDUFA DUE DATE:	April 30, 2004	FORMULATION:	Extended-release tablet
		ROUTE:	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
June 30, 2003	July 2, 2003	NDA 21-620 N000	Original submission, 91 volumes
November 3, 2003	November 4, 2003	NDA 21-620 N000SU	Safety update
November 11, 2003	November 12, 2003	NDA 21-620 N000B2	IR response and safety update
February 27, 2004	March 1, 2004	NDA 21-620 N000BB	Treatment group data
March 3, 2004	March 4, 2004	NDA 21-620 N000C	DM abuse, postmarketing commitment
March 12, 2004	March 12, 2004	NDA 21-620 N000 BL	Labeling modification

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
June 29, 2000	NDA 21-282	NDA submission, Mucinex [®] , guaifenesin extended-release tablets
August 31, 2000	IND 60,922	IND submission, Mucinex [®] DM, guaifenesin/dextromethorphan extended-release tablets

REVIEW SUMMARY

This is the Medical Officer Review of a 505 (b)(2) application for a new, extended-release formulation of guaifenesin and dextromethorphan HBr. The Applicant, Adams Laboratories, Inc., has submitted NDA 21-620 for Mucinex[®] DM (Extended-Release Bi-layer Tablets) and requests the approval of two dosage strengths, (1) guaifenesin 600mg/dextromethorphan HBr 30mg, and (2) guaifenesin 1200mg/dextromethorphan HBr 60mg to be administered twice daily to adults and children 12 years of age and older. It is a bi-layer formulation with immediate-release (IR) and modified (MR) layers containing both guaifenesin and dextromethorphan. This drug product is proposed to be marketed as an over-the-counter (OTC) combination expectorant and antitussive. The proposed indication is "to loosen phlegm (mucus) and thin bronchial secretions and to temporarily relieve cough due to minor throat and bronchial irritation as may occur with the common cold or inhalant irritants." Six clinical pharmacology studies were submitted in support of the application. The application is based on the demonstration of bioequivalence between Mucinex[®] DM and reference guaifenesin and dextromethorphan drug products.

The Applicant has established bioequivalence for Mucinex[®] DM at the high dose guaifenesin 1200mg/dextromethorphan HBr 60mg strength and has demonstrated linearity of dissolution between the low dose formulation containing guaifenesin 600mg/dextromethorphan HBr 30mg and the high dose formulation. Review of safety in the single-dose and multiple dose PK studies shows no unusual safety signals. Adams Laboratories Inc. will monitor Medwatch for any safety signals regarding Mucinex[®] DM and has agreed to devise and implement a risk management plan to reduce the rates of abuse if a safety signal is detected for Mucinex[®] DM. Hence, from a clinical perspective, I recommend a regulatory action of Approval.

OUTSTANDING ISSUES: If a safety signal is noted in postmarketing surveillance, the Applicant will devise and implement a risk management plan to reduce rates of abuse. Adams Laboratories is not seeking an indication for pediatric use in children less than 12 years of age. I recommend granting a pediatric waiver.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	X	APPROVAL	APPROVABLE	NOT APPROVABLE

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EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendation on Approvability

From a clinical perspective, the data submitted in this NDA provide adequate support for approval.

1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps

Mucinex[®] DM, when approved, will have the highest dose of dextromethorphan in an over-the-counter drug. Adams Laboratories Inc. has agreed to monitor Medwatch for any safety signals regarding Mucinex[®] DM and has agreed to devise and implement a risk management plan to reduce the rates of abuse [NDA 21-620, N000 C; 3/3/04] if a safety signal is detected for Mucinex[®] DM. This is acceptable as part of postmarketing surveillance. It is this Medical Officer's opinion that if a safety signal is detected due to dextromethorphan abuse, especially in the adolescent population, consideration should be given as to whether the drug product should be placed behind the pharmacy counter to deter individuals from purchasing large quantities at a single time.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of Clinical Program

This NDA is a 505(b)(2) application for an extended-release formulation of guaifenesin and dextromethorphan. The Applicant requests the approval of two dosage strengths, (1) guaifenesin 600 mg/dextromethorphan 30 mg tablets, and (2) guaifenesin 1200 mg/dextromethorphan 60 mg tablets. The product is an extended-release, bi-layer tablet formulation and is proposed as an over-the-counter (OTC) combination expectorant and antitussive intended for oral use. The proposed labeled indication is "to loosen phlegm (mucus) and thin bronchial secretions, to temporarily relieve cough due to the common cold or inhalant irritants, and to relieve the intensity and impulse to cough". The Applicant's proposed trade name is Mucinex[®] DM and the product name is Mucinex[®] DM Extended-Release Bi-layer Tablets for both dosage strengths of the drug product.

The section of the monograph for Combination Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use that specifies permitted combinations of active ingredients was recently published [Federal Register, December 23, 2002 (67 FR 78168)]. The monograph considers the combination of any single monograph oral antitussive active ingredient (such as DM) with any single expectorant active ingredient (such as guaifenesin) to be a permitted combination [21 CFR § 341.40(h)], when used as shown below.

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Guaifenesin, an expectorant, is known chemically as 3-(2-methoxyphenoxy)-1,2-propanediol and is generally recognized as safe and effective (GRASE) in the following age groups at the indicated oral doses [21 CFR § 341.78]:

- Adults and children 12 years of age and older: 200 to 400mg every 4 hours, not to exceed(NTE) 2400mg in 24 hours
- Children ≥ 6 to 12 years of age: 100 to 200mg every 4 hours, NTE 1200mg in 24 hours
- Children ≥ 2 to ≤ 6 years of age: 50 to 100mg every 4 hours, NTE 600mg in 24 hours
- Children under 2 years of age: consult a doctor

Dextromethorphan, an antitussive, acts centrally to elevate the threshold for coughing and is GRASE in the following age groups at the indicated oral doses [21 CFR § 341.74]:

- Adults and children 12 years of age and older: 10 to 20 mg every 4 hours or 30mg every 6 to 8 hours, NTE 120mg in 24 hours, or as directed by a doctor
- Children ≥ 6 to 12 years of age: 5 to 10mg every 4 hours or 15 mg every 6 to 8 hours, NTE 60mg in 24 hours, or as directed by a doctor
- Children ≥ 2 to ≤ 6 years of age: 2.5 to 5mg every 4 hours or 7.5 mg every 6 to 8 hours, NTE 30mg in 24 hours, or as directed by a doctor
- Children under 2 years of age: Consult a doctor

The Applicant's proposed dose for the 1200 mg guaifenesin/60 mg dextromethorphan HBr dosage strength is one tablet every 12 hours, not more than 2 tablets in 24 hours [Volume 1.1, pages 43-45]. The proposed labeling for the 600 mg guaifenesin/30 mg dextromethorphan HBr dosage strength is 1 to 2 tablets every 12 hours, not more than 4 tablets in 24 hours [Volume 1.1, pages 40-42]. These doses are within the specified OTC monograph doses for guaifenesin and dextromethorphan over this dosing interval. The proposed labeling for both dosage strengths instructs consumers not to use the product in children under 12 years of age.

The Applicant's NDA was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act (FD&C Act), which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved reference product. The applicant's drug development program relied on a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved reference product. The Applicant's drug development program relied on six clinical pharmacology studies of which four were definitive studies. Only the higher strength Mucinex[®] DM containing guaifenesin 1200 mg and dextromethorphan 60 mg was used in the studies. The two strengths of Mucinex[®] DM are compositionally proportional, and based on dissolution studies, the similarity (f₂) factor between Mucinex[®] DM 1200/60 mg and 600/30 mg strengths was within established equivalence criteria. The f₂ factor for guaifenesin between 1200 mg and 600 mg was 63.5 and the f₂ factor for DM between 60 mg and 30 mg was 61.5. The reference products for the clinical pharmacology studies were extended-release guaifenesin product (Mucinex[®], NDA 21-282) and dextromethorphan products Benylin[®] (immediate-release dextromethorphan syrup, 15mg/5cc), Delsym[®] (extended-release suspension of dextromethorphan polistirex, 30mg/5cc, NDA 18-658, approved October 8, 1982) and

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Vick's Formula 44[®] Cough Relief (immediate-release dextromethorphan syrup, 30mg/15cc). Delsym[®] was only used in the two pilot studies.

- Studies 00-02 and 2001-04 were identical open-label, single-dose, randomized, 3-way crossover studies with 7 day washout periods between treatments which examined the relative bioavailability and safety of two different experimental formulations of the proposed product in healthy men and women. Once the proposed to-be-marketed formulation was determined in Study 2001-04, the four subsequent studies used this to-be-marketed formulation.
- Study 2001-15, was a definitive single-dose, open-label, randomized, 4-way crossover study that examined potential drug interactions between individual component drugs.
- Study 2002-08, was a definitive single-dose, open-label, randomized, 3-way crossover study that examined the relative bioavailability of the product.
- Study 2002-10, was a definitive multiple dose study that examined the steady state bioavailability of the product.
- Study 2002-12, was a single dose study that examined the effect of effects of food on the bioavailability of the product in healthy men and women.

A total of 178 healthy, non-smoking males and females between the ages of 18 and 55 years, with a weight within 15% of ideal body weight, participated in the clinical program and were exposed to at least one dose of the proposed high-dose marketed drug containing 1200 mg extended-release guaifenesin plus 60 mg dextromethorphan HBr. There was an equal distribution of male (51%) and female (49%) subjects, and nearly all were Caucasian (95%). A total of 166 subjects received all treatments according to protocol.

The Applicant did not perform any controlled clinical trials to support the safety and efficacy of the new formulation and relied on the OTC monograph for determinations of safety and efficacy. The Applicant supported the safety of Mucinex[®] DM with integrated safety data from the clinical pharmacology studies in their drug development program, spontaneous adverse event reports from the Adverse Event Reporting System (AERS) database, and a review of the literature for safety information relevant to guaifenesin and dextromethorphan.

2.2. Efficacy

As noted above, this application has been submitted under Section 505(b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety to an approved reference product. The applicant's drug development program relied on a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved reference product. Therefore, no clinical studies of the efficacy of the product or integrated summary of efficacy were required for approval. The reference products for the clinical pharmacology studies in this 505(b)(2) application were the Applicant's approved and marketed extended-release single-ingredient guaifenesin product (Mucinex[®], NDA 21-282) and approved and marketed OTC monograph products Benylin[®], Delsym[®] (NDA 18-658, approved October 8, 1982) and Vick's Formula 44[®] Cough Relief.

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The clinical pharmacology studies in this application confirmed the bioequivalence of Mucinex[®] DM to the reference drug products. The drug interaction study indicated that the pharmacokinetics of guaifenesin and dextromethorphan were not affected by the presence of one another. There was no effect on the rate, C_{max} , or extent of systemic exposure (AUC) to guaifenesin when the product was administered after consumption of a high fat meal. Food caused a delay in T_{max} of guaifenesin by approximately 1.5 hours. The C_{max} to dextromethorphan was minimally increased by 21% when the product was administered after consumption of a high-fat meal. There was no effect on the extent of systemic exposure or T_{max} .

The two different proposed dosage strengths of Mucinex[®] DM were dose proportional based on a dissolution study. Studies indicated that the pharmacokinetics of guaifenesin and dextromethorphan HBr were linear over the dose range studied. Based on the 505(b)(2) approach, the data from the Applicant's clinical pharmacology studies was sufficient to support the efficacy of their products.

2.3. Safety

The Applicant provided data from the six submitted clinical pharmacology studies and an evaluation of safety information from the US AERS database and the clinical literature. Integrated safety data from the Applicant's clinical pharmacology studies demonstrated no evidence of new safety signal. There were no meaningful differences in adverse events (AEs), withdrawals due to AEs, or serious adverse events (SAEs) between Mucinex[®] DM and reference products. Data from the AERS database support the safety of guaifenesin and dextromethorphan and do not present new safety issues. There were not sufficient numbers of subjects in the subpopulations to stratify safety data in terms of age, gender, race, pregnancy or lactation, or consumers with hepatic or renal disease

The OTC labeling for dextromethorphan has specific warnings regarding drug interactions with monoamine oxidase inhibitors (MAOI) for adults and children 12 years and older. This warning is present on the proposed Mucinex[®] DM label.

In summary, the data submitted by the Applicant provided no evidence of a safety signal that had not been previously identified and the Applicant's integrated review of safety supports the proposed indication of their product. In response to a query from the Division regarding whether the Applicant had developed a risk management plan for the eventuality that their drug product is abused, the Applicant indicated that they will monitor MedWatch regularly for spontaneous AE reports and if a safety signal is detected, then a risk management plan will be devised and implemented to reduce rates of abuse. Furthermore, the Office of Drug Safety will be looking at the postmarketing surveillance data and if they suspect a safety signal, the Agency will request the Applicant to submit the risk management plan.

2.4. Dosing

The Applicant's product is proposed for use in adults and children 12 years of age and older. The proposed dose for the 1200 mg guaifenesin/60 mg dextromethorphan HBr dosage strength is one tablet every 12 hours, not more than 2 tablets in 24 hours [Volume 1.1, pages

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43-45]. The proposed labeling for the 600 mg guaifenesin/30 mg dextromethorphan HBr dosage strength is one tablet every 12 hours, not more than 2 tablets in 24 hours [Volume 1.1, pages 40-42]. These doses are within the specified OTC monograph doses for guaifenesin and dextromethorphan over this dosing interval. The proposed labeling for both dosage strengths instructs consumers not to use the product in children under 12 years of age.

The proposed labeling includes text that states that the product can be administered without regard to timing of meals. The Applicant's food effect study, Study 2002-12, showed that there was no food effect on the rate of guaifenesin absorption from the proposed product; however, a small increase in the rate of dextromethorphan absorbed occurred with intake of food. Overall, the rate and extent of absorption of the product in the fasted and fed states is similar. The small increase in the rate of dextromethorphan absorption is not likely to be clinically significant, and therefore, the Applicant's claim that the product can be administered without regard to timing of meals is acceptable.

2.5. Special Populations

Both guaifenesin and dextromethorphan are considered safe and effective for their indications at specified OTC monograph doses. The OTC monograph labeling for guaifenesin requires no special directions or warnings for adults and children 12 years and older, the population for which the sponsor's product is proposed. The OTC labeling for dextromethorphan has specific warnings regarding drug interactions with monoamine oxidase inhibitors (MAOI) in this same population. The Applicant's data did not identify any new safety issue for guaifenesin or dextromethorphan in special populations.

The Applicant's review of the literature identified no new safety signal specific to elderly consumers or for the pediatric subpopulation. The dose of active drugs in the product and its formulation are not appropriate for use in children less than 12 years of age. The Applicant's proposed labeling appropriately instructs consumers not to use the product in children under 12 years of age. The Applicant did not apply for a pediatric waiver; however, I recommend that the Agency grant a waiver for this population. The Applicant's review and summary of the literature identified no articles describing safety issues relevant to gender, race, for pregnant or lactating women, or consumers with hepatic or renal disease.

A PUBMED literature review of guaifenesin and dextromethorphan was conducted by myself for this NDA review. My literature review did not yield any new safety signals and was consistent with the findings of the Applicant's literature review.

CLINICAL REVIEW**1. INTRODUCTION AND BACKGROUND****1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups**

This NDA is a 505(b)(2) application for an extended-release formulation of guaifenesin and dextromethorphan HBr. The proposed trade name of the drug product is Mucinex[®] DM (Extended-Release Bi-layer Tablets). For purposes of simplicity, I will use the name Mucinex[®] DM when referring to Mucinex[®] DM extended-release bi-layer tablets in this review. The Applicant requests the approval of two dosage strengths tablets, (1) guaifenesin 600 mg/dextromethorphan HBr 30 mg tablets, and (2) guaifenesin 1200 mg/dextromethorphan HBr 60 mg tablets. The drug product is a bi-layer, immediate and modified-release tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and antitussive. The proposed labeled indication is to "loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive" and to "temporarily relieve(s) cough due to minor throat and bronchial irritation as may occur with the common cold or inhalant irritants." In addition, the label will reflect the product's use in temporarily relieving the intensity of the cough, relieving the impulse to cough to help aid in sleep, and suppressing cough.

The proposed dose for the guaifenesin 1200 mg/dextromethorphan HBr 60 mg tablets is one tablet every 12 hours, not more than 2 tablets in 24 hours [Volume 1.1, pages 40-45]. The proposed dose for the guaifenesin 600 mg/dextromethorphan HBr 30 mg tablets is one or 2 tablets every 12 hours, not more than 4 tablets in 24 hours [Volume 1.1, pages 40-45]. These doses are within the specified OTC monograph doses for guaifenesin and dextromethorphan over this dosing interval. The proposed labeling for both dosage strengths instructs consumers not to use the product in children under 12 years of age.

1.2. State of Armamentarium for Indication(s)

The section of the monograph for Combination Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use that specifies permitted combinations of active ingredients was recently published [Federal Register, December 23, 2002 (67 FR 78168)]. The monograph considers the combination of any single monograph oral antitussive active ingredient (such as DM) with any single expectorant active ingredient (such as guaifenesin) to be a permitted combination [21 CFR § 341.40(h)]; however, the OTC monograph does not include provisions for extended-release formulations. Currently, there are no approved extended-release combination guaifenesin and dextromethorphan drug products; however, there are many unapproved combination products marketed internationally by many manufacturers. On October 11, 2002, the FDA sent warning letters to 81 U.S. pharmaceutical companies who were producing single ingredient extended-release guaifenesin drug products and informed them that as of November 1, 2003, these products

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guaifenesin and dextromethorphan listed in the 2004 PDR are Benylin[®] Cough Suppressant/Expectorant Liquid, Robitussin-DM[®] Infant Drops, Robitussin-DM[®] Liquid, Robitussin[®] Sugar Free Cough Liquid (Wyeth), Vicks[®] 44E[®] Cough and Chest Congestion Relief (Proctor & Gamble), and Pediatric Vicks[®] 44e[®] Cough and Chest Congestion Relief Liquid (Proctor & Gamble).

1.3. Foreign marketing and regulatory history

Many manufacturers market guaifenesin and dextromethorphan hydrobromide internationally. Guaifenesin has been widely used in the U.S. for over 50 years and is a well-known expectorant. According to the Applicant, dextromethorphan HBr is a well-known orally administered antitussive agent with no analgesic and addictive properties. The Applicant stated that they do not make guaifenesin or dextromethorphan hydrobromide or the trade names Mucinex[®] and Mucinex[®] DM available to foreign markets and that to the best of their knowledge, neither active ingredient has been withdrawn from foreign markets for reasons of safety or effectiveness [v 1.1, page 46-47].

The Agency recently approved the Applicant's application for two dosage strengths of Mucinex[®], a single-ingredient, extended-release tablet formulation of guaifenesin (NDA 21-282). The 600 mg dosage strength tablets were approved on July 12, 2002, and the 1200 mg dosage strength tablets were approved on December 18, 2002. The drug development program was based on demonstrating that the exposure of guaifenesin from their product was equivalent to monograph doses of immediate-release guaifenesin. As of November 1, 2003, all previously marketed extended-release guaifenesin products must be approved under an NDA or ANDA as required by the Federal Food, Drug, and Cosmetic Act. Currently, the Applicant's Mucinex[®] product is the only extended-release guaifenesin product approved in the United States.

The proposed Mucinex[®] DM products were designed by Adams Lab. Inc. to be a line extension to the single-ingredient Mucinex[®] 600 mg and 1200 mg products. Currently, there are various combination guaifenesin/dextromethorphan HBr products that are unapproved and illegally marketed in the United States. The Applicant suggests that this NDA "creates an opportunity for the FDA to clean up this unacceptable practice."

1.4. Important Milestones in Product Development (v 1.46, p 15-60)

The drug product was developed under IND 60,922, which was originally submitted to the Agency on August 31, 2000. The FDA had communications to the sponsor dated December 21, 2000, January 24, 2001, October 16, 2001, November 9, 2001, and January 9, 2003. After the IND was reviewed for safety, the Agency made recommendations regarding the drug development plan for Mucinex[®] DM. Communications addressed the design of the pivotal bioequivalence studies, the use of appropriate reference products for comparison, and CMC specifications for dissolution, stability, and impurity of the drug product. The Applicant also submitted summaries of the final protocols for review. There was no End of Phase 2 or Pre-NDA meeting.

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2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

2.1. Chemistry, Manufacturing and Controls

The Applicant's supplier of guaifenesin is [redacted]. The application references the supplier's drug master file, [redacted].

The Applicant's supplier of dextromethorphan is [redacted]. The application references the supplier's drug master files, [redacted].

Both the immediate release (IR) and modified release (MR) layer contain guaifenesin and dextromethorphan HBr [redacted] together with microcrystalline cellulose, sodium starch glycolate, and hypromellose. The components for the IR layer for both strengths of Mucinex[®] DM are identical. The components for the MR layer for both strengths of Mucinex[®] DM are identical, differing only in the color of the layer. The layers are

[redacted] to produce the bi-layer single tablet containing a white immediate release layer and a colored modified release layer. The guaifenesin 1200 mg/dextromethorphan 60 mg dosage strength tablets (Mucinex[®] DM) are light blue and white. The guaifenesin 600 mg/dextromethorphan 30 mg dosage strength tablets (Mucinex[®] DM) are yellow and white [Volume 1.1, page 57].

The composition of both strength tablets is described below in Table 1. Both strengths of Mucinex[®] DM Extended-release Bi-layer Tablets are compositionally proportional.

Table 1 Composition of Mucinex[®] DM (1200 mg/60 mg tablets) and (600 mg/30 mg tablets), [Volume 1.1, page 59].

Component	Mg/tablet(1200 mg/60 mg)	Mg/tablet(600 mg/30 mg)
Guaifenesin	1200.0	600.0
Dextromethorphan HBr	60.0	30.0
Microcrystalline cellulose		
Sodium starch glycolate		
Hypromellose		
Carbomer 934P		
Magnesium stearate		
FD&C Blue #1 Aluminum Lake (11-13%)		
Water, purified		
Total Weight	1530.4	765.2

The to-be-marketed formulation of drug product was used in the four definitive bioequivalence, dose-proportionality, and food effect studies in this application [Volume 1.1, page 76]. Lot numbers of test and reference drug products used in the studies in this application may be found in the individual reviews of the study reports in the Appendix of this review. The manufacturing process will produce [redacted] tablets/batch for the higher dosage strength, and [redacted] tablets/batch for the lower dosage strength. Once manufactured, Mucinex[®] DM Extended-release Bi-layer Tablets will be packaged for commerce in 75 cc (10-count, 20-count, and 40-count) [redacted] bottles. Physician's samples will be packaged in 30 cc (2-count) [redacted] bottles.

Detailed information regarding the drug development program for Mucinex[®] DM Extended-Release Bi-layer Tablets may be found in the Chemistry, Manufacturing, and Controls (CMC) review by chemistry reviewer, David Place, Ph.D.

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2.2. Animal Pharmacology and Toxicology

Guaifenesin is generally recognized as safe and effective (GRASE) as an oral expectorant at the Applicant's proposed doses in adults and children 12 years of age and older.

Dextromethorphan is generally recognized as safe and effective (GRASE) as an oral antitussive at the Applicant's proposed doses in adults and children 12 years of age and older. No animal pharmacology and toxicology data were submitted nor were required since the doses and combination of the two ingredients for the proposed drug product are approved by the OTC monograph. Refer to pharmacology/toxicology review by Gary P. Bond, Ph.D., pharmacology/toxicology reviewer for detailed information.

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3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

This 505(b)(2) NDA application included six clinical pharmacology studies. The design of the studies is described in Section 4 (Description of Clinical Data and Sources) of this review and is reviewed individually in the Appendix under Detailed Study Reviews. Among these six clinical pharmacology studies, there were four definitive studies. A summary of the conclusions from the individual definitive clinical pharmacology studies follows below. More detail on the pharmacokinetics of the product may be found in the Integrated Review of Efficacy under Section 6.3 (Summary of Results by Individual Studies) and in Dr. Kim's review [Shinja Kim, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-620].

Refer to Section 4.2 (Overview of Clinical Trials) for brief review of methodology used for these studies.

Study 2001-04 was a single dose study that compared the bioavailability of guaifenesin and dextromethorphan from two experimental prototypes of Mucinex[®] DM extended-release tablets to reference guaifenesin (Mucinex[®]) and dextromethorphan (Delsym[®]). Guaifenesin from the experimental formulations was bioequivalent to reference guaifenesin. Dextromethorphan bioavailability in both experimental formulations was more bioavailable than reference dextromethorphan (Delsym[®]). Treatment C was carried forward to the four definitive studies, all of which used the to-be-marketed formulation.

Study 2001-15 was a single dose, drug interaction study that demonstrated that the bioavailability of guaifenesin was not affected by co-administration with dextromethorphan. The 90% CI for C_{max} , AUC_{0-t} , AUC_{∞} for guaifenesin in Mucinex[®] DM were within the 80-125% bioequivalence limits compared to the reference standards. Dextromethorphan in the Mucinex[®] DM was slightly outside of bioequivalence range as the 90% CI for the ratios of C_{max} fell between 66.1-153%. However, the point estimates ranged from 0.78 to 1.30, indicating that the changes in pharmacokinetics were not likely to be clinically significant. No evidence of drug-drug pharmacokinetic interaction between dextromethorphan and guaifenesin occurred when the various treatments were compared.

Study 2002-08 was a single dose, bioavailability study that demonstrated that guaifenesin from the Mucinex[®] DM was bioequivalent to reference guaifenesin (Mucinex[®]) for C_{max} and AUC as the ratios of the 90% confidence intervals were all contained within 80 to 125%. Dextromethorphan from Mucinex[®] DM was found to be not bioequivalent to reference dextromethorphan (Vicks[®] 44[®] Cough Relief) administered 30 mg every 6 hours or 20 mg every 4 hours as 90% CI for the ratios of AUC and C_{max} were not within 80 to 125%. However, the point estimates of the ratios for C_{max} and AUC were greater than 0.85 indicating similar bioavailability between the test and reference products. Subjects that were poor dextromethorphan metabolizers were outliers between treatment groups and had a 6- or 20-fold higher C_{max} compared to the mean or median, respectively, and a 10- or 120-fold higher AUC compared to the mean or median, respectively. However, these elevated levels did not reflect an increase in adverse events in these poor metabolizers compared to subjects with normal dextromethorphan metabolism.

Study 2002-10 was a multiple dose study that compared the bioavailability of guaifenesin and dextromethorphan from the proposed Mucinex[®] DM to a reference treatment consisting of

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extended-release guaifenesin (Mucinex[®]) and Vicks cough formula at steady state, after eleven 12-hour dosing periods. Mean C_{max} and AUC_{ss} values for guaifenesin for the proposed product were within 80 to 125% bioequivalence limits compared to the reference standards. The C_{min} for guaifenesin in the proposed product was below the C_{min} for reference guaifenesin (Mucinex[®]) at a three to four-fold lower concentration; however, this low C_{min} was within the effective concentration level associated with approved, reference guaifenesin. Mean $C_{max,ss}$ and AUC_{ss} values for dextromethorphan for the proposed product were within the 80 to 125% bioequivalence limits compared to the reference standards. Although the C_{min} of dextromethorphan was outside the 90% CI at values down to 71.8% (71.8-97.2% range), the point estimates of the ratios for C_{min} were 0.84 indicating similar bioavailability between the test and reference products.

Study 2002-12 was a single dose study that compared the bioavailability of guaifenesin and dextromethorphan from Mucinex[®] DM administered under both fasting and fed conditions. The ratios of AUC and C_{max} were within 90% CI for the established bioequivalence criteria between 80-125%. Food caused a delay in T_{max} of guaifenesin by approximately 1.5 hours. Food caused an increase in C_{max} of dextromethorphan from Mucinex[®] DM by 21% but had no effect on AUC or T_{max} . Subjects who were poor metabolizers of CYP2D6 had elevated plasma concentrations of dextromethorphan; however, this did not manifest as a significant difference in AEs in these outliers compared to normals. Subjects who were administered Mucinex[®] DM in the fasted state had a greater number of AEs compared to those in the fed state. The 21% increase in C_{max} of DM and delay of 1.5 hrs in T_{max} of guaifenesin appear to be clinically insignificant due to the few AEs especially since there were fewer number of AEs under fed conditions. Therefore, Mucinex[®] DM may be taken without regard for timing of meals.

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Table 2. Summary of studies, NDA 21-620 (Volume 1.1, pages 95-101)

Study #	Study Type	Treatment Duration	Design/Population	Treatment*	Batch Number*	N
Pilot studies not using the to-be-marketed product						
00-02	Bioavailability, pilot study	Single dose	Open-label, R, 3-way crossover design with 7 day washout period between treatments Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	G 1200 mg plus DM 60 mg, reference	PB-304A plus 00888	20
				G 1200 mg/DM 60 mg, Treatment B	CB00-04A	21
				G 1200 mg/DM 60 mg, Treatment C	CB00-03A	20
2001-04	Bioavailability, pilot study	Single dose	Open-label, R, 3-way crossover design with 7 day washout period between treatments Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	G 1200 mg plus DM 60 mg, reference	PB-304A plus 00743	15
				G 1200 mg/DM 60 mg, Treatment B	12LB-33A	15
				G 1200 mg/DM 60 mg, Treatment C	PB01-H30A	15
Definitive studies using the to-be-marketed product						
2001-15	Drug interaction, bioavailability and dose proportionality study	Single dose	Open-label, R, 4-way crossover design with 14 day washout period between treatments Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	G 1200 mg/DM 60 mg	PB01-H30A2	32
				G 1200 mg, reference	PB-304A2	32
				DM 30 mg q6h, reference	58315IL	16
				DM 20 mg q4h, reference	58315IL	15
				DM 15 mg q6h, reference	58315IL	16
DM 10 mg q4h, reference	58315IL	15				
2002-08	Bioavailability, definitive study	Single dose	Open-label, R, 3-way crossover design with 14 day washout period between treatments Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	G 1200 mg plus DM 30mg q 6h, reference	PB01-H34A3 plus 1141RX	36
				G 1200 mg plus DM 20 mg q 4h, reference	PB01-H34A3 plus 1141RX	34
				G 1200 mg/DM 60 mg	PB01-H30A3	33
2002-10	Bioavailability and steady state, definitive study	Multiple dose	Open-label, R, 3-way crossover design with 14 day washout period between treatment Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	G 1200 mg plus DM 30mg q 6h, reference	PB01-H34A4 (not PB01-H34R4) 1141RX (not 1129RX)	35
				G 1200 mg plus DM 20 mg q 4h, reference	PB01-H34A4 (not PB01-H34R4) 1141RX (not 1129RX)	35
				G 1200 mg/DM 60 mg	PB01-H30A4	35
2002-12	Food effect	Single dose	Open-label, R, 2-way crossover design with 14 day washout period between treatments Healthy, nonsmokers, 18-55 years Weight within 15% of ideal	G 1200 mg/DM 60 mg, fasted	PB01-H43A2	35
				G 1200 mg/DM 60 mg, following high-fat breakfast	PB01-H43A2	36
*G=Guaifenesin, DM=Dextromethorphan, to-be-marketed product is in bold text *To-be-marketed product is in bold text						

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

This NDA application, containing 91 paper volumes, refers to six clinical pharmacology studies in adults. There were no clinical efficacy or safety studies in this application; however, monitoring for adverse events and laboratory examinations were performed and these results were reviewed.

4.2. Overview of Clinical Trials

This NDA submission consisted of two pilot trials that compared early prototype experimental formulations and four definitive trials that compare the to-be-marketed experimental formulations to reference monograph OTC products. All of the studies were conducted in healthy subjects.

4.2.1. Study 00-02

Study 00-02 was a pilot clinical pharmacology study that evaluated the bioavailability of experimental combination extended-release formulations containing both guaifenesin and dextromethorphan compared to a reference treatment consisting of extended-release guaifenesin (Mucinex[®]) and dextromethorphan HBr (Delsym[®]). Neither combination was the to-be-marketed drug product. The study was performed under fasted conditions. The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study conducted in 21 healthy male and female subjects. Blood samples were obtained as individual venipunctures prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours for plasma guaifenesin and dextromethorphan hydrobromide, and dextrophan content. Hematology, chemistry, 12-lead ECG, viral screen, and urine drug screen were performed at baseline. Urine drug screens were repeated at each visit. Females had urine pregnancy tests at each visit. Subjects were housed at the study site until after their 24-hour sample was drawn. A minimum washout period of seven days separated each treatment period. Safety endpoints reported included adverse events. [Volume 1.1, page 105, Volume 1.47, page 352, 356-357, Vol. 1.88, page 108-113].

4.2.2. Study 2001-04

Study 2001-04 was a pilot clinical pharmacology study that evaluated the bioavailability of two experimental combination extended-release formulations containing both guaifenesin and dextromethorphan compared to a reference treatment consisting of extended-release guaifenesin (Mucinex[®]) and dextromethorphan HBr (Delsym[®]). One of the experimental formulations, Treatment C, was carried forward to three of the four remaining definitive studies, all of which used the to-be-marketed formulation. The study was performed under fasted conditions. The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study conducted in 15 healthy male and female subjects. Blood samples were obtained as individual venipunctures prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 72, and 96 hours for plasma guaifenesin and dextromethorphan hydrobromide, and dextrophan content. Hematology, chemistry, 12-lead ECG, viral screen, and urine drug screen were performed at baseline. Urine drug screens

were repeated at each visit. Females had urine pregnancy tests at each visit. Subjects were housed at the study site until after their 24-hour sample was drawn. A minimum washout period of seven days separated each treatment period. Safety endpoints reported included adverse events. [Volume 1.1, page 105, Volume 1.47, page 352, 356-358, Volume 1.89, page 201-205].

4.2.3. Study 2001-15

Study 2001-15 was a drug interaction study between guaifenesin and dextromethorphan that compared the bioavailability following administration of Mucinex[®] DM to a reference treatment consisting of extended-release guaifenesin (Mucinex[®]) and immediate-release dextromethorphan (Benylin[®]). One group received Mucinex[®] DM containing 1200 mg guaifenesin and 60 mg dextromethorphan, the second group received Mucinex[®] 1200 mg, the third group received the reference treatment containing 60 mg dextromethorphan hydrobromide (Benylin[®]) administered as 30 mg every 6 hours for two doses followed by 60 mg dextromethorphan hydrobromide (Benylin[®]) administered as 20 mg every 4 hours for three doses. The fourth group received 30 mg dextromethorphan hydrobromide (Benylin[®]) administered as 15 mg every 6 hours for two doses followed by 30 mg dextromethorphan hydrobromide (Benylin[®]) administered as 10 mg every 4 hours for three doses. The study was performed under fasted conditions. The study was an open-label, randomized, single dose, four period, four-way crossover study conducted in 33 healthy male and female subjects. Blood samples were taken as individual venipunctures immediately before dosing (0 hours) and at 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 for plasma guaifenesin and dextromethorphan content. Hematology, chemistry, 12-lead ECG, viral screen, and urine drug screen were performed at baseline. Urine drug screens were repeated at each visit. Females had urine pregnancy tests at each visit. Subjects were housed at the study site until after their 24-hour sample was drawn. A minimum washout period of 14 days separated each treatment period except for a washout period of 21 days between Period 3 and Period 4 due to holiday schedules. Safety endpoints reported included adverse events. Three subjects withdrew from the study: two failed to return for the third study period and one withdrew during Period 1 due to difficulty with blood draws. [Volume 1.1, page 106, Volume 1.47, page 353, 356-358, Vol. 1.88, page 435-441].

4.2.4. Study 2002-08

Study 2002-08 was a bioavailability study that compared the bioequivalence of guaifenesin and dextromethorphan from Mucinex[®] DM to a reference treatment consisting of extended-release guaifenesin (Mucinex[®]) and immediate-release dextromethorphan (Vick's Formula 44[®] Cough Medicine). The study was performed under fasted conditions. The study was an open-label, randomized, single dose, three period, three-way crossover study conducted in 37 healthy male and female subjects. Blood samples were taken as individual venipunctures immediately before dosing (0 hours) and at 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, 72, and 96 hours for plasma guaifenesin and dextromethorphan content. Hematology, chemistry, 12-lead ECG, viral screen, and urine drug screen were performed at baseline. Urine drug screens were repeated at each visit. Females had urine pregnancy tests at each visit. Subjects were housed at the study site until after their 24-hour sample was drawn. A minimum washout period of 14 days separated

each treatment period. Safety endpoints reported included adverse events. Five subjects withdrew from the study: Four subjects failed to check in for Period 2 and one subject had a positive pregnancy test and was withdrawn from the study (she later had a spontaneous abortion). [Volume 1.1, page 106, Volume 1.47, page 353, 356-358, Volume 1.89, page 247-254].

4.2.5. Study 2002-10

Study 2002-10 compared the bioavailability of guaifenesin and dextromethorphan from a combination experimental extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex[®]) and immediate-release dextromethorphan (Vick's Formula 44[®] Cough Medicine) at steady state, after eleven 12-hour dosing periods. The study was performed under fasted conditions. The study was an open-label, randomized, multiple dose, randomized, three-way crossover study conducted in 36 healthy male and female subjects. Pharmacokinetic samples (7 mL sodium heparin anticoagulant) were obtained as individual venipunctures at the following times: Day 1 Pre-AM-dose, Day 4 Pre-AM-dose, and Day 5 Pre-AM-dose for all three treatment groups. On Day 6 Treatment A blood samples were taken at 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 blood samples were taken at Pre-Dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.5, 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. On Day 6, Treatment C blood samples were taken at Pre-Dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 36, 48, 72, and 96 hours post dose. Subjects were confined for 1½ days (approximately 36 hours) on Day -1 and returned for subsequent doses on Test Day 1 through 5 and were fasted prior to each dose. During Day 1 through Day 5, each treatment was administered as a single-dose with 240 mL of water while in the fasting state (10 hours pre-dose) with a washout period of 14 days between each leg of the study. Subjects in Treatment groups A and B returned to the clinic every evening to facilitate dosing through the night. On Day 5, subjects were confined until 24 hours after blood sampling on Day 6. Subjects returned to the clinic for subsequent blood sampling (hours 36, 48, 72, and 96). Hematology, chemistry, 12-lead ECG, viral screen, and urine drug screen were performed at baseline. Urine drug screens were repeated at each visit. Females had urine pregnancy tests at each visit. Subjects were housed at the study site from the night before Day 1 until after the blood draw on Day 1 and again from the evening of Day 5 until after the 24-hour sample was drawn on Day 6. A minimum washout period of 14 days separated each treatment period. Safety endpoints reported included adverse events. Two subjects withdrew consent prior to the second and third periods of the study. [Volume 1.1, page 106-107, Volume 1.47, pages 353-354, 356-359, Volume 1.90, page 323-329].

4.2.6. Study 2002-12

Study 2002-12 compared the bioavailability of guaifenesin and dextromethorphan from Mucinex[®] DM administered under both fasting and fed conditions. The study was an open-label, randomized, single dose, two period, two-way crossover, and food effect study conducted in 36 healthy male and female subjects. Blood samples were taken as individual venipunctures before dosing (0 hours) and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72, and 96 hours for plasma guaifenesin and dextromethorphan content. Subjects were housed at the study site until after their 24-hour sample was drawn. A minimum washout period of 14 days separated each treatment period. Safety endpoints reported

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included adverse events. One subject did not check in for Period 2 due to an adverse event (cough and chest tightness). [Volume 1.1, page 107, Vol 1.47, page 354, 356-359, Volume 1.91, page 169-175].

4.3. Postmarketing Experience

Mucinex[®] DM has not been marketed outside the United States of America. A summary of the postmarketing adverse event reports from the AERS database covering the period from November 1, 1997 until November 8, 2002 for guaifenesin, and from November 1, 1997 to March 26, 2003 for dextromethorphan (v 1.47, p 363-381; v 1.48) was submitted by the Applicant. These reports were tabulated and analyzed by the sponsor in later submissions [NDA 21-620, N000 B2, 11/11/03 and NDA 21-620, N000 SU, 11/3/03] which also contained AEs from the updated AERS database up to September 15, 2003 for guaifenesin and up to September 23, 2003 for dextromethorphan. A 120-day safety update was also submitted after the NDA was filed.

4.4. Literature Review

The Applicant conducted a complete scientific/medical literature search for references related to guaifenesin and dextromethorphan. The Applicant employed _____ to perform these searches. Multiple medical and scientific databases were searched. Of the multiple citations retrieved, the sponsor identified 19 articles of interest for guaifenesin and 16 articles for dextromethorphan. In addition, the Applicant submitted a literature review [[NDA 21-620 N000 BZ, 11/11/03, p 4-9] which identified 15 articles regarding the intentional abuse of dextromethorphan.

A PUBMED literature review of guaifenesin and dextromethorphan was conducted by myself for this NDA review. Much of the literature examined the effectiveness of therapies for the treatment of cough and found no significant differences between therapies consisting of guaifenesin, guaifenesin plus dextromethorphan, and guaifenesin plus codeine¹. There were very few articles regarding the abuse of guaifenesin. Some articles yielded information concerning the abuse of dextromethorphan-containing products especially in the adolescent population. My literature review did not yield any new safety signals and was consistent with the findings of the Applicant's literature review.

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5. CLINICAL REVIEW METHODS

5.1. Conduct of the Review

The six clinical pharmacology studies in this application were individually reviewed, with a focus on safety findings. This review includes a brief Integrated Summary of Efficacy since the drug development program was based on clinical pharmacology studies and because there were no clinical studies necessary. Safety data supporting this application were reviewed in depth and integrated safety data from the clinical pharmacology studies, US AERS database, an evaluation of information from the clinical literature, a safety update submitted by the Applicant, and consults performed by the Office of Controlled Substances and the Division of Over-the-counter Drug Products.

5.2. Materials Consulted and Documentation

This is a 91 volume paper submission. The original application arrived on June 30, 2003. A 4-month safety update was submitted on November 3, 2003 (submission NDA 21-620, S000, SU). On November 11, 2003, the Applicant sent a response to the Division's September 4, 2003 filing review letter. This response (submission NDA 21-620, S000, BZ) contained three paper volumes including literature references supporting prescribing precautions for guaifenesin and dextromethorphan and a summary of these articles. Additional safety information and a more detailed literature review regarding the intentional abuse of dextromethorphan, a tabular summary of the AERS database of adverse events for guaifenesin and dextromethorphan, and financial disclosure information from the investigators were also included. Explanations of the friability and stability data and CMC manufacturing process were also included in this filing review response, but these data were not reviewed by this reviewer.

5.3. Data Quality and Integrity

There was one study center and one analytical site for all of the clinical pharmacology studies in this application. DSI audit of the study center was requested. **Study 2002-08** (definitive single-dose bioequivalence and dose proportionality study) and **Study 2002-10** (definitive multiple-dose bioequivalence and dose proportionality at steady state) were audited for the quality or integrity of the data submitted in reference to blood samples analyzed by _____ There were no efficacy or safety studies in the development program for this drug product.

The principal investigator and study center that was audited from December 11, 2003 to January 4, 2004 was:

Dennis N. Morrison, D.O.
Bio-Kinetic Clinical Applications, Inc.
1816 West Mount Vernon
Springfield, MO 65801
Telephone: (417) 831-0456
Fax: (417) 831-0778
[v 1.50, p 47; v 1.73, p 5]

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The Division of Scientific Investigations (DSI) audit concluded that there were errors in accountability records, specifically in the recording of lot numbers for drug, and they were recognized and corrected during the Applicant's monitoring visits. Errors in the report were recognized in part approximately two days before the inspection began, and in part during the inspection. [NDA 21-620, DSI Review submitted by pharmacologist M.F. Skelly, Ph.D. and associate director C.T. Viswanathan, Ph.D.]

The analytical site that was audited from February 23, 2004 to February 27, 2004 was:

The DSI audit concluded that there were errors in concentration data from one sample in each study that were less accurate than validated methods. These samples were:

- Study 2002-08: Dextromethorphan data for Subject 30, Period 3, Treatment A, from 3 hours through 6.75 hours
- Study 2002-10: Guaifenesin data for Subject 32, Period 1, Treatment A, from pre-dose through 125 hours

After both DSI audits, DSI recommended accepting the data from Studies 2002-08 and 2002-10 except for the above noted deficiencies. [NDA 21-620, DSI Review, M.F. Skelly, Ph.D., C.T. Viswanathan, Ph.D.] The Office of Clinical Biopharmaceutics/Division of Pharmaceutical Evaluation – II states that the removal of these specific samples will not have any significant impact on the outcome of the studies.

5.4. Ethical Standards and Financial Disclosure

The following items were included in this submission:

- Form FDA 356h [Volume 1.1, page not numbered]
- Debarment certification [Volume 1.1, page 193]
- Financial disclosure statement [Volume 1.1, pages 198-199]
- Statements of Good Clinical Practice [Vol. 1.50, p.6, Vol.1.55, p.5, Vol. 1.59, p.5, Vol.1.65, p.5, Vol. 1.73, p.5, Vol. 1.82, p.5]

The Applicant stated that all studies were conducted in compliance with 21 CFR § 50 and 56 and all Good Clinical Practices (GCP) regulations. The Applicant certified that they did not use and would not use the services of any person debarred under to Section 306(a) and 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with their application. The Applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The Applicant certified that the clinical investigators did not have a proprietary interest in the proposed product or a significant equity in the Applicant. The Applicant certified that no investigator was the recipient of significant payments.

Clinical Review Methods

6. INTEGRATED REVIEW OF EFFICACY (v 1.47, P 245-347)

6.1. Brief Statement of Conclusions

This NDA was submitted under Section 505 (b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of an approved reference product and a comparison of the bioavailability and the bioequivalence of the proposed new drug to that of the approved reference product. The Applicant primarily relied on the section of the monograph for Combination Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use [Federal Register, December 23, 2002 (67 FR 78168)] to support the safety and efficacy of Mucinex[®] DM at both dosage strengths which contain guaifenesin and dextromethorphan at approved daily dosages. The monograph considers the combination of any single monograph oral antitussive active ingredient (such as DM) with any single expectorant active ingredient (such as guaifenesin) to be a permitted combination [21 CFR § 341.40(h)] which is generally recognized as safe and effective (GRASE). Clinical studies of the efficacy of the product or integrated summary of efficacy were not performed, and none were required to support this application.

Refer to Section 6.4 for detailed conclusions regarding the efficacy of Mucinex[®] DM.

6.2. General Approach to the Efficacy Review

Conclusions regarding Mucinex[®] DM were based on a detailed review of 6 clinical pharmacology studies that are located in the Appendix of this Medical Officer Review.

These six studies (Table 2) exposed 178 subjects to the guaifenesin 1200 mg/ dextromethorphan 60 mg Mucinex[®] DM tablet formulation. The guaifenesin 600 mg/ dextromethorphan 30 mg tablet formulation was not studied in any of the trials. A total of 20 subjects were exposed to a formulation that was not the to-be-marketed product and 158 subjects were exposed to the to-be-marketed product. Five single-dose studies and one multiple-dose study in adults were submitted to support the bioequivalence of guaifenesin and dextromethorphan in an experimental combination (Mucinex[®] DM) to reference guaifenesin and dextromethorphan, to evaluate the effect of food on the pharmacokinetics of the extended-release formulation, and to determine if any drug interactions occur between the guaifenesin and dextromethorphan. The data demonstrated that a meaningful clinical effect was maintained throughout the proposed 12-hour dosing period. The dose proportionality of guaifenesin was established for Mucinex[®] under NDA 21-282.

Study 2001-04 was a pilot clinical pharmacology study that evaluated two experimental combination extended-release formulations of guaifenesin and dextromethorphan compared to a reference treatment consisting of extended-release guaifenesin (Mucinex[®] 1200 mg) plus dextromethorphan HBr (Delsym[®] 60 mg). The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study with a 7-day washout between treatments conducted in 21 healthy male and female subjects [v 1.47, p 254-256].

Study 2001-15 evaluated the drug interaction and bioavailability from Mucinex[®] DM when administered in combination compared to reference guaifenesin (Mucinex[®] 1200 mg) and

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dextromethorphan (Benylin[®] at various regimens to total 60 mg) when administered alone. The study was an open-label, randomized, single dose, four period, four-way crossover bioavailability study with a 14-day washout between treatments conducted in 33 healthy male and female subjects [v 1.47, p 257-265].

Study 2002-08 was a definitive clinical pharmacology study that compared the relative bioequivalence and bioavailability of guaifenesin and dextromethorphan from Mucinex[®] DM compared to a reference treatment consisting of extended-release guaifenesin (Mucinex[®]) plus immediate-release dextromethorphan HBr (Vicks[®] Formula 44[®] Cough Medicine) at various regimens to total 60 mg) at steady state. The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study with a 14-day washout between treatments conducted in 37 healthy male and female subjects [v 1.47, p 266-274].

Study 2002-10 was a definitive clinical pharmacology study that examined the steady-state pharmacokinetics of guaifenesin and dextromethorphan from Mucinex[®] DM compared to reference guaifenesin (Mucinex[®]) and dextromethorphan (Vicks Formula 44[®] Cough Medicine) after 11 doses given every twelve hours. The study was an open-label, randomized, multiple dose, three period, three-way crossover bioavailability study with a 14-day washout between treatments conducted in 36 healthy male and female subjects [v 1.47, p 275-284].

Study 2002-12 was a clinical pharmacology study that compared the bioavailability of guaifenesin and dextromethorphan from an experimental combination extended-release formulation administered under both fasting and fed conditions. The study was an open-label, randomized, single dose, two period, two-way crossover bioavailability and food effect study conducted in 36 healthy male and female subjects [v 1.47, p 285-289].

The criteria for bioequivalence, and thus safety and efficacy, were that guaifenesin and dextromethorphan pharmacokinetic endpoints AUC and C_{max} were bioequivalent (90% confidence interval ratios entirely within the 80 to 125% bioequivalence range). In addition, point estimates of the ratios for C_{max} and AUC provided for approximate estimation of bioavailability for dextromethorphan. Because dextromethorphan is metabolized by cytochrome P450 2D6, it is considered a highly variable drug (CV% values observed in studies for AUC and C_{max} as high as 250%). Due to the highly variable nature of dextromethorphan, the steady-state trial provided the best evidence of bioequivalence according to the Applicant.

6.3. Summary of Results by Individual Studies

Single dose, bioavailability **Study 2001-04** demonstrated favorable in-vivo profiles with guaifenesin from both prototypes of Mucinex[®] DM experimental extended-release tablets showing bioequivalence to reference guaifenesin (Mucinex[®]). Dextromethorphan bioavailability in both experimental formulations was more bioavailable than reference dextromethorphan (Delsym[®]). Treatment C was carried forward to three of the four definitive studies, all of which used the to-be-marketed formulation.

Single dose, drug interaction, bioavailability, and dose proportionality **Study 2001-15** demonstrated that guaifenesin was not affected by co-administration with dextromethorphan and *vice versa*. The 90% CI for C_{max} , AUC_{0-t} , AUC_{∞} for guaifenesin in Mucinex[®] DM were

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within 80-125% bounds compared to reference guaifenesin (Mucinex[®]). Dextromethorphan in Mucinex[®] DM was slightly outside the 90% CI with ratios between 66.1-153%, which is outside the bioequivalence limits of 80-125%. Point estimates ranged from 0.78 to 1.30, indicating that the changes in pharmacokinetics was not likely to be clinically significant in this highly variable drug. No evidence of drug-drug pharmacokinetic interaction between dextromethorphan and guaifenesin occurred when the various treatments were compared. Subjects who were poor metabolizers of dextromethorphan had a 6- or 12-fold higher C_{max} compared to the mean and median, respectively. In addition, the AUC was eight to 20 times greater than the mean and median, respectively. These subjects continued to be outliers after each treatment. Even with these elevated plasma concentrations, they not have a difference in AEs compared to subjects who exhibited normal metabolism of dextromethorphan.

Table 3. 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

Treatment*	PK parameter	Point estimates	90% confidence intervals
Guaifenesin			
TRT A/ TRT B	C _{max}	97.3	88.7-107
	AUC _t	100	93.8-108
	AUC _{inf}	97.0	90.1-104
Dextromethorphan			
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 [®] DM 1200/60 mg, - test, B = Mucinex [®] - reference C = Benylin [®] 30 mg q6H x 2 doses - reference, D = Benylin [®] 20 mg q4H x 3 doses - reference E = Benylin [®] 15 mg q6H x 2 doses - reference, F = Benylin [®] 30 mg q4H x 3 doses - reference			

Single dose, bioavailability, and steady state **Study 2002-08** demonstrated that guaifenesin from Mucinex[®] DM was bioequivalent to reference guaifenesin (Mucinex[®]) for C_{max} and AUC as the ratios of the 90% confidence intervals were all contained within 80 to 125%. Dextromethorphan is a highly variable drug. The point estimates of the ratios for C_{max} and AUC were 0.93-0.94 and were greater than 0.85 indicating similar bioavailability between the test and reference products (Table 4). Because of the high variability, the Applicant proposed equivalence criteria for the 90% confidence intervals to be contained within 70 to 143% for C_{max} and AUC_∞ instead of the normal 80-125% criteria. Using these criteria, the Applicant stated that dextromethorphan from the Mucinex[®] DM was bioequivalent to reference dextromethorphan (Vicks[®] Formula 44[®] Cough Medicine) administered 30 mg every 6 hours as well as 20 mg every 4 hours. Subjects that were poor dextromethorphan metabolizers were outliers between treatment groups and had a 6- or 20 fold higher C_{max} compared to the mean and median, respectively. These elevated plasma concentrations did

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not manifest clinically as increased adverse events in these subjects who were outliers in comparison to subjects with normal dextromethorphan metabolism.

Table 4. Study 2002-08: Point estimates and 90% confidence intervals for the log-transformed C_{max} , AUC_t , and AUC_{inf} values of guaifenesin and DM following single administration of the treatments

Treatment*	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

*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 1200/6C mg - test

Multiple dose, bioavailability at steady state, **Study 2002-10** demonstrated that guaifenesin in Mucinex[®] DM was bioequivalent at steady state to that of the reference guaifenesin (Mucinex[®]) in terms of C_{max} and AUC_{ss} , as the 90% confidence intervals for treatment comparisons were contained entirely within 80 to 125% bioequivalence limits. At the end of the 12-hour proposed dosing interval, the C_{min} for guaifenesin in Mucinex[®] DM was below the C_{min} for reference Mucinex[®] at a three to four-fold lower concentration (Table 5). The range of effective minimum concentrations for guaifenesin is wide for current regimens and at varying total dosages per day (i.e. 190 mg IR q 8hr, 200 or 400 mg q 4hr). Mucinex[®] DM appears acceptable for approval of dosing every 12 hours because the C_{min} for guaifenesin in Mucinex[®] DM was above the lower bound of the effective concentration level associated with guaifenesin (190 mg q 8hr immediate release formulation) which indicates that Mucinex[®] DM provided clinically effective guaifenesin concentrations. Dextromethorphan in Mucinex[®] DM was bioequivalent at steady state to both reference dextromethorphan (Vicks[®] Formula 44[®] Cough Medicine) 30 mg every 6 hours and 20 mg every 4 hours for 11 consecutive 12-hour dosing intervals. The 90% confidence intervals for treatment comparisons were contained entirely within 80 to 125% BE limits in terms of C_{max} and AUC_{ss} . Although the C_{min} was outside the 90% CI at values down to 71.8%, the point estimates of the ratios for C_{min} were 0.84 indicating similar bioequivalence between the test and reference products. Subjects who were poor metabolizers of dextromethorphan had a 11- and 46-fold higher C_{max-ss} compared to the mean and median, respectively, and a 10 to 50-fold higher AUC_{ss} compared to the mean and median. These elevated plasma concentrations, however, did not manifest as a significant difference in AEs in the poor metabolizers compared to normals.

Table 5. Study 2002-10: Point estimates and 90% confidence intervals for the log-transformed AUC_{ss} , C_{max} and C_{min} of guaifenesin and DM following multiple administration of the treatments

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

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Treatment*	PK parameter	Point estimates	90% CI	Point estimates	90% CI
		Guaifenesin		Dextromethorphan	
*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					

Single dose, food effect **Study 2002-12** established that there was no significant food effect on the absorption of guaifenesin or dextromethorphan from Mucinex[®] DM. For guaifenesin, the ratios of AUC and C_{max} were within 90% CI for the established bioequivalence criteria between 80-125%. Food caused a delay in T_{max} of guaifenesin by approximately 1.5 hours. For dextromethorphan, a high fat breakfast caused an increase in C_{max} by 21% in the rate of absorption of dextromethorphan in Mucinex[®] DM but had no effect on AUC or T_{max}. Subjects who were poor metabolizers of CYP2D6 had a 5- and 18-fold higher C_{max} compared to the mean and median, respectively, and a 7- and 80-fold higher AUC compared to the mean and median, respectively. Once again, these elevated plasma concentrations did not manifest as a significant difference in AEs in these outliers compared to normals. Subjects who were administered Mucinex[®] DM in the fasted state had a greater number of AEs for nausea (4/35, 11%), headache (3/35, 8.6%), and vomiting (2/35, 5.7%) compared to those in the fed state with (1/36, 2.8%), (2/36, 5.6%), and (0/36, 0%), respectively. However, these subject numbers were small, and the 21% increase in C_{max} of DM and delay of 1.5 hrs in T_{max} of guaifenesin may not be clinically relevant so Mucinex[®] DM may be taken without regard for timing of meals.

Table 6. Point estimates and 90% confidence intervals for the log-transformed C_{max} and AUCs of guaifenesin and DM following single administration of the treatments

Treatment*	PK parameter	Point estimates	90% confidence intervals
Guaifenesin			
TRT B/ TRT A	C _{max}	96	82.2-100
	AUC _t	93	85-94.6
	AUC _{inf}	27	85-94.5
Dextromethorphan			
TRT B/ TRT A	C _{max}	121	107-136
	AUC _t	108	96.7-121
	AUC _{inf}	107	96.4-120
*A = Mucinex [®] DM 1200/60 mg, under fasted - reference			
B = Mucinex [®] DM 1200/60 mg, fed condition- test			

6.4. Efficacy Conclusions

The clinical development program for this drug included six, PK studies in healthy subjects. Only the guaifenesin 1200 mg/dextromethorphan 60 mg Mucinex[®] DM extended-release tablet formulation and not the guaifenesin 600 mg/dextromethorphan 30 mg tablet formulation was evaluated in these studies. The formulations of both strengths of Mucinex[®] DM tablets are compositionally proportional. Based on dissolution studies, they were shown to have a similarity (f₂) factor, which is within the "sameness" criteria, 63.5 for guaifenesin and 61.5 for dextromethorphan. Thus, linearity was established between the two proposed dosage formulations. The first pilot study did not use the to-be-marketed drug. All studies were PK studies that focused on establishing the bioavailability and bioequivalence of the guaifenesin and dextromethorphan ingredients in an experimental formulation (Mucinex[®] DM) as compared to reference products approved by the

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monograph. The reference products for the four definitive clinical pharmacology studies in this 505(b)(2) application were the Applicant's approved and marketed extended-release single-ingredient guaifenesin product (Mucinex[®], NDA 21-282) and approved and marketed OTC monograph products (Benylin[®] and Vick's Formula 44[®] Cough Relief) both at OTC monograph doses.

Results of the four definitive studies demonstrated that 1200 mg guaifenesin and 60 mg dextromethorphan HBr combined in a bi-layer immediate and modified-release tablet were bioequivalent to a 1200 mg guaifenesin extended-release tablet and 60 mg dextromethorphan HBr liquid co-administered. There was no evidence of drug-drug pharmacokinetic interaction between dextromethorphan and guaifenesin when the various treatments were compared. There was no significant food effect on the bioavailability of guaifenesin and dextromethorphan.

These studies demonstrated that systemic levels of Mucinex[®] DM over a 12 hour period had pharmacokinetic parameters comparable to reference guaifenesin and dextromethorphan and, hence, justify the efficacy of administration of Mucinex[®] DM as a 12-hour expectorant and antitussive.

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7. INTEGRATED REVIEW OF SAFETY (v 1.47, P 348-381, V 1.48)

7.1. Brief Statement of Findings

The Applicant's drug development program for Mucinex[®] DM was based on establishing that their combination product produced equivalent exposures to that of their approved and marketed extended-release single-ingredient guaifenesin product, Mucinex[®], and to an approved and marketed extended-release dextromethorphan product. Both reference products are generally recognized as safe and effective for their respective indications by the OTC monograph (21 CFR § 341.74 and 21 CFR § 341.78). This was a PK development program and included an adequate number of subjects exposed to drug to establish bioequivalence between the experimental formulation and reference. The types of safety assessments utilized in the studies were adequate and consistent with similar drug development programs such as other expectorant and antitussive drug products. The data indicated that headache, followed by nausea and vomiting, were the most frequent adverse events in the treatment group.

7.2. Methods and Content (Materials Utilized in Review)

The following were reviewed in this Integrated Review of Safety:

- Safety data from the submitted studies
- Applicant's evaluation of spontaneous adverse events reports, obtained through the Freedom of Information Act (FOIA), from the AERS database between November 1, 1997 until November 8, 2002 for guaifenesin and between November 1, 1997 and March 26, 2003 for dextromethorphan
- Applicant's review of information related to drug abuse and overdose for guaifenesin and dextromethorphan
- Applicant's review of the literature for safety information relevant to guaifenesin and dextromethorphan
- Applicant's four month safety update for guaifenesin and dextromethorphan
- Review of the AERS database from November 13, 2000 through October 17, 2003 performed by the Division of Over-The-Counter Drug Products
- 2 safety reviews (PID# D00470 and D000694) conducted in 2000 for the Federal Bureau of Investigation encompassing the time period from 1969 through November 13, 2000 that investigated dextromethorphan-containing products and the association with drug abuse, addiction, and overdose
- Consult from the Controlled Substance Staff regarding the abuse potential of the drug product

7.3. Description of Subject Exposure and Disposition (v 1.47, p 350-351)

A total of 178 subjects received at least one dose of study medication and 166 subjects (93%) received all treatments and completed the six studies according to protocol. Five studies (00-02, 200-04, 2001-15, 2002-08, 2002-12) were single-dose pharmacokinetic studies in 142 healthy, adult subjects who were exposed to single doses of 1200 mg guaifenesin and 60 mg dextromethorphan. The sixth study (2002-10) exposed a total of 36 healthy subjects to multiple doses of 1200 mg guaifenesin and 60 mg dextromethorphan

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every 12 hours for a total of 11 twelve-hour periods thus receiving 11 tablets in total of Mucinex[®] DM. A total of 12 subjects were dropped from the six studies for various reasons, with only one subject being replaced.

Table 7. Summary of Study Treatments and Subject Exposure (v 1.47, pages 350)

Study	Treatment	Controlled Release Formulation	Dose of Guaifenesin	Dose of Dextromethorphan HBr	N
Studies NOT using the to-be-marketed product					
00-02	A	Guaifenesin ER + Delsym [®]	1200 mg (single dose)	60 mg (single dose)	20
	B	Experimental	1200 mg (single dose)	60 mg (single dose)	21
	C	Experimental	1200 mg (single dose)	60 mg (single dose)	20
2001-04	A	Guaifenesin ER + Delsym [®]	1200 mg (single dose)	60 mg (single dose)	15
	B	Experimental	1200 mg (single dose)	60 mg (single dose)	15
	C	Mucinex [®] DM	1200 mg (single dose)	60 mg (single dose)	15
Studies using Mucinex[®] DM					
2001-15	A	Mucinex [®] DM	1200 mg (single dose)	60 mg (single dose)	32
	B	Mucinex [®]	1200 mg (single dose)		32
	C	Benylin [®]		30 mg (2 doses)*	16
	D	Benylin [®]		20 mg (3 doses)**	15
	E	Benylin [®]		15 mg (2 doses)*	16
	F	Benylin [®]		10 mg (3 doses)**	15
2002-08	A	Mucinex [®] + Vicks 44 Cough Relief	1200 mg (single dose)	30 mg (2 doses)	36
	B	Mucinex [®] + Vicks 44 Cough Relief	1200 mg (single dose)	20 mg (3 doses)	34
	C	Mucinex [®] DM	1200 mg (single dose)	60mg (single dose)	33
2002-10	A	Mucinex [®] + Vicks 44 Cough Relief	1200 mg (11 doses)***	30 mg (22 doses)*	35
	B	Mucinex [®] + Vicks 44 Cough Relief	1200 mg (11 doses)***	20 mg (33 doses)**	35
	C	Mucinex [®] DM	1200 mg (11 doses)***	60mg (11doses)***	35
2002-12	A	Mucinex [®] DM	1200 mg (single dose)	60 mg (single dose)	35
	B	Mucinex [®] DM	1200 mg (single dose)	60 mg (single dose)	36

*Doses were administered every 6 hours.
 **Doses were administered every 4 hours.
 ***Doses were administered every 12 hours.

Note: The total number of subjects who received at least one dose of study medication were 21 subjects in Study 00-02; 15 subjects in Study 2001-04, 33 subjects in Study 2001-15; 37 subjects in Study 2002-08; 36 subjects in Study 2002-10; and 36 subjects in Study 2002-12.

7.4. Demographics (v 1.47, p 350-351)

The majority of the subjects were Caucasian (169/178, 95%) with males and females evenly represented, with 51% (90/178) female subjects and 49% (88/178) male subjects. Small proportions of the study population were of Black (3/178, 1.7%), Hispanic (1/178, 0.6%), multiracial (3/178, 1.7%), or other (2/178, 1.1%) racial backgrounds. The mean age of the subjects was 28.6 years, ranging from 18 to 55 years.

Reviewer comment:

Non-Caucasian subjects were underrepresented in these studies. Subgroup analysis to assess safety in the subject population in these studies was not performed due to the small numbers of subjects involved. However, both guaifenesin and dextromethorphan are OTC monograph drugs and are GRAS at the doses administered in these studies.

7.5. Safety Findings from Clinical Studies (v 1.47, p 351-381, v 1.48)

7.5.1. AEs, Laboratory AEs, SAEs, Deaths, and Withdrawals

Integrated safety data from the Applicant's studies showed no evidence of a new safety signal. The pharmacokinetics of guaifenesin and dextromethorphan were not affected by the presence of one another. The AE profile of Mucinex[®] DM did not differ from the AE profiles of the marketed reference products. Adverse events (AEs) occurring in the clinical pharmacology studies are integrated and presented in Table 8. All subjects were from 18 to 55 years of age so no subgroup analysis of AEs for pediatric subjects or subjects ≥ 65 years of age was possible. There were too few non-Caucasian subjects to perform a subgroup analysis of AEs by race. According to the Applicant, of the total 178 subjects, 46 subjects (26%) experienced 100 AEs. The majority of events were classified as mild and possibly related to study drug. In reviewing these AEs, two of these AEs occurred in subjects pre-dose. Therefore, headache (11 events), nausea (11), and vomiting (6) were the most common AEs reported during the treatment period and occurred more frequently in those who received single doses of Mucinex[®] DM as compared to those who received multiple doses of Mucinex[®] DM. No subjects experienced dizziness and one subject experienced drowsiness. Subjects who were administered Mucinex[®] DM in the fasted state had a greater number of AEs for nausea (4/35, 11%), headache (3/35, 8.6%), and vomiting (2/35, 5.7%) compared to those in the fed state with (1/36, 2.8%), (2/36, 5.6%), and (0/36, 0%), respectively. However, these numbers were small and may not be clinically relevant. Thus, Mucinex[®] DM may be administered without regard for timing of meals. Subjects who had higher C_{max} and AUC during all the clinical trials were presumed to be poor metabolizers of CYP2D6 and their high values were consistent between treatment groups. However, there was no difference detected in AEs between these subjects and normals.

There were no clinically significant AEs and no meaningful differences between the test and reference products. Vital signs, physical examinations, laboratory studies, and ECGs were not safety endpoints in the Applicant's studies.

There were no serious adverse events or deaths. Two adverse events led to withdrawals of subjects before the end of the study. Subject 21 in Study 2002-08 was dropped from the study due to a positive pregnancy test. Subject 22 in Study 2002-12 experienced chest tightness and cough and discontinued the study. He was treated with Robitussin DM, amantadine, and amoxicillin. Twelve subjects were dropped from the six studies with only one subject being replaced. Nine subjects dropped out of the single dose studies; four withdrew consent, four did not return, one had difficulties with venipuncture procedures, one became pregnant, and one had an adverse event.

Subjects were required to drink a full glass of water with each dose administered and none were observed to have difficulty swallowing study medication.

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literature review [[NDA 21-620 N000 BZ, 11/11/03, p 4-9] which identified 15 articles regarding the intentional abuse of dextromethorphan. The Applicant's review of published literature for guaifenesin- and dextromethorphan- associated adverse events did not provide evidence of new safety concerns and thus support the established prescribing precautions of guaifenesin and dextromethorphan.

A PUBMED literature review was conducted by myself for this NDA review. There were few articles related to the abuse of guaifenesin and most of them duplicate to the Applicant's literature review. Articles concerning dextromethorphan demonstrated the stimulant properties of DM in animal models and suggested that dextrophan, an active metabolite of dextromethorphan, is responsible for the abuse liability of the parent compound when dextromethorphan is taken at high doses. A few articles concerned the abuse of Coricidin HBP Cough and Cold Tablets which contain a combination of dextromethorphan hydrobromide and chlorpheniramine maleate and are abused due to its potent euphoric properties. My literature review did not yield any new safety signals and was consistent with the following findings of the Applicant's literature review.

7.6.1. Guaifenesin

These articles demonstrated that guaifenesin was superior to placebo in the reduction of tenacious sputum. Overdose with guaifenesin was associated with drug-induced kidney stone formation and a report of death in a subject also taking a combination of diphenhydramine and chlorpheniramine. Guaifenesin was not shown to interfere with normal platelet adhesiveness and aggregation but may increase renal clearance for urate and thereby lower serum uric acid levels. A few articles concerned overdose and abuse in guaifenesin-containing products (such as Coricidin HBP Cough and Cold Tablets).

7.6.2. Dextromethorphan

Much of the literature review demonstrated that DM was extensively metabolized in most individuals and approximately 8-14% of the population is a poor metabolizer of dextromethorphan. The articles concerning dextromethorphan emphasized that although it is structurally related to morphine, DM has no analgesic or addictive properties and its potency is similar to that of codeine but with fewer side effects. Adverse drug events were infrequent and DM did not demonstrate properties leading to long-lasting addiction. Most cases of abuse occurred in subjects with known drug dependence who were taking drug products containing short-acting dextromethorphan. Dextromethorphan in combination drug products were used to obtain hallucinogenic effects. Toxic symptoms such as dizziness, diplopia, headache, nausea, and vomiting appeared following doses of 60 mg or more.

7.7. Postmarketing Surveillance (v 1.47, p 363-381; v 1.48)

The Applicant submitted postmarketing adverse event (AE) reports from the AERS database covering the period from November 1, 1997, until November 8, 2002 for guaifenesin and from November 1, 1997 to March 26, 2003 for dextromethorphan (v 1.47, p 363-381; v 1.48). These reports were tabulated and analyzed by the sponsor in later submissions [NDA 21-620, N000 B2, 11/11/03 and NDA 21-620, N000 SU, 11/3/03] which also contained AEs from the updated AERS database up to September 15, 2003 for guaifenesin and up to September 23, 2003 for dextromethorphan.

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Data from the AERS database did not present new safety issues and support the safety of guaifenesin and dextromethorphan. Data for each product are summarized below.

7.7.1. Postmarketing adverse event reports for guaifenesin

The Applicant reported that there were 62 adverse event reports identifying 208 AEs from the AERS database covering the period from November 1, 1997, until November 8, 2002 for guaifenesin-containing products. In the filing review letter response submission (NDA 21-620, N00 BZ, 11/11/03), the Applicant included an updated addendum of AERS database including the time period from November 1, 1997, through September 15, 2003 which detailed 800 AE reports identifying 3,209 AEs for guaifenesin-containing products. A total of 205 of these events were also reported with the same individual safety report (ISR) to dextromethorphan. The discrepancy in the large increase in number of AEs is because several reports may have been submitted to AERS for the same subjects from different companies since the subject data was identical. Of these 800 reports, 54 (6.8%) were associated with guaifenesin as the primary suspect drug. The most common AEs reported for guaifenesin included vomiting (0.4%, 3/800), nausea (0.3%, 2/800), dizziness, headache, and rash (each 0.13%, 1/800). Diarrhea, gastric irritation, and urticaria were not reported. A total of 3,155 adverse reactions were associated with guaifenesin as the secondary suspect drug. Drug reactions commonly accepted as side effects from the use of guaifenesin (as the secondary suspect drug) occurred $\leq 1\%$ as headache (38 events), dizziness (35 events), nausea (13 events), vomiting (12 events), stomach/abdominal irritation (7 events), rash/urticaria (2 events), and diarrhea (1 event).

There were 43 events for cerebrovascular accident listed with the same ISR numbers for both the guaifenesin and dextromethorphan listings. Most of these events were associated with concomitant use of phenylpropanolamine, a drug that has been withdrawn from the market because of an association with stroke.

The Applicant concluded that the postmarketing AE data support the overall safety of guaifenesin as previously concluded by the OTC Monograph Review and do not contain any new information which would change the safety profile of guaifenesin. This reviewer concurs with the Applicant's conclusion since the AEs mimic the most common side effects associated with guaifenesin and dextromethorphan use.

7.7.2. Postmarketing adverse event reports for dextromethorphan

The Applicant reported that there were 689 AE reports for 3,042 AEs for dextromethorphan in the AERS database for the five-year period November 1, 1997, through March 26, 2003. In the filing review letter response submission (NDA 21-620, N00 BZ, 11/11/03), the Applicant included an updated addendum of AERS database including the time period from March 24, 2003 through September 22, 2003. The combined total from these submissions detailed 773 AE reports identifying 3,304 adverse events for dextromethorphan. Of these 773 reports, 101 (13%) were associated with dextromethorphan as the primary suspect drug. Those events that occurred with highest frequency associated with the use of dextromethorphan include confusion (3 events), disorientation (3), vomiting (3), abdominal pain (3), dizziness (2), headache (2), hypersomnia (1 event), and nausea (1 event). Other events reflective of toxicity with overdose were overdose (4 events), coma (3), and loss of

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consciousness (3). A total of 3,203 adverse reactions were associated with dextromethorphan as the secondary suspect drug. Adverse events associated with the use of dextromethorphan that occurred $\leq 1\%$ of the time were headache (28 events), vomiting (22), dizziness (19), nausea (19), drowsiness (11), confusion (10), stomach/abdominal pain (8), and constipation (3).

The Applicant concluded that the postmarketing AE data supported the overall safety of dextromethorphan as previously concluded by the OTC Monograph Review and did not contain any new information which would change the safety profile of guaifenesin or dextromethorphan (NDA 21-620, N000 SU, 11/5/03, Cover Letter). This Medical Officer concurs with the Applicant.

If a safety signal is noted in postmarketing surveillance, the Applicant will devise and implement a risk management plan to reduce rates of abuse. Refer to the discussion below.

7.7.3. Four-Month Safety Update

A two page, four-month safety update on was submitted on November 3, 2003. Study 2004-04 submitted to IND 60,922 was completed on October 29, 2003, and results were not available at the time of submission of the safety update. A summary of findings from the AERS database since the NDA was submitted on June 30, 2003 was included. From November 4, 2002 to September 15, 2003, the AERS line listing provided 738 spontaneous reports for 3,313 adverse events with ingestion of guaifenesin. Of these, 33 were associated with guaifenesin as the primary suspect drug and 2,968 adverse reactions with guaifenesin as the secondary suspect drug. The Applicant reported that no serious adverse events occurred. From March 24, 2003 to September 15, 2003, there were 84 spontaneous adverse reaction reports identifying 262 events. Of these events, there were no reports of dextromethorphan as the primary suspect drug and 262 with dextromethorphan as the secondary suspect drug as part of a multiple-ingredient product.

7.7.4. Consultant Reviews

Previously, two safety reviews (PID# D00470 and D000694) regarding dextromethorphan were conducted in 2000 for the Federal Bureau of Investigation through a consult from the Division of OTC Drug Products. In the time period from 1969 through November 13, 2000, there were 103 unduplicated cases of drug abuse, dependence, addiction, non-accidental overdose, withdrawal syndrome, and tolerance identified.

The Division of Over-The-Counter Drug Products requested a consult from Office of Drug Safety (ODS) to conduct a postmarketing safety review update of dextromethorphan-containing products from November 13, 2000 through October 17, 2003. This consult indicated that dextromethorphan-containing products are used improperly by both children and adults, leading to serious outcomes. Of the 1886 reported cases in the AERS database since November 13, 2000, all were domestic cases of which 1621 were nervous system disorders, 548 were psychiatric disorders, and 71 were unduplicated cases of drug abuse, overdose, and/or suicides. Death was reported in 33 of 71 cases, two of which were not drug related. Coricidin (dextromethorphan/chlorpheniramine) was the most commonly reported product containing dextromethorphan taken alone or in conjunction with other

drug. Coricidin HBP was the subject of a congressional inquiry on June 25, 2000 and the Controlled Substance Staff found evidence that teenagers abused this drug. The conclusions of the ODS consult indicate that although dextromethorphan does not cause physical addiction, strong psychological dependence is reported in the literature and products containing dextromethorphan continue to be used improperly by both children and adults leading to serious outcomes.

A consult was also requested from the Controlled Substance Staff regarding this NDA, the results of which may be found in Section 7.8.

7.8. Drug Withdrawal, Abuse, and Overdose Experience (v 1.49, p 252-292)

The Applicant's literature review identified several cases of abuse related to dextromethorphan. The Applicant stated that dextromethorphan abuse and psychological dependence have occurred specifically for its euphoric effects; however, there is scant evidence of morphine-type dependence associated with dextromethorphan use. Acute overdosage may result in drowsiness, nausea, and dizziness. In addition, excitation and confusion may occur and toxicity can lead to stupor and disturbances in gait. At extremely high doses of dextromethorphan, respiratory depression may occur. Naloxone may be effective in reversing toxicity. Rapid recovery occurs after emesis. Two reported cases in the literature of fatal intoxications from dextromethorphan occurred in an 18-year old female suicide victim and a 27-year old male.² No internal organ damage was noted in the suicide victim although signs of aspiration were found in the second victim. Dextromethorphan levels in these victims were 2-8 times higher than the level of dextrophan, the active metabolite of dextromethorphan, possibly indicating that death occurred soon after intake due to saturation of the enzyme system involved in the degradation of DM, since great individual variations occur in the metabolism of DM. As a result of this report from Sweden, the Swedish National Board of Health and Welfare enforced compulsory prescriptions by a doctor from April 1986 due to increased incidence of DM abuse in teenagers.

Abuse related to guaifenesin was rare. However, a few cases of urinary calculi containing a guaifenesin metabolite occurred in subjects consuming large quantities of OTC preparations containing guaifenesin and ephedrine (v 1.49, p 252, 254-260)³.

Because of the concern for potential abuse, a consult was requested from the Controlled Substance Staff on August 15, 2003 regarding the abuse potential of dextromethorphan in Mucinex[®] DM. Dextromethorphan is excluded from scheduling as a controlled substance under 21 USC 811 (g)(2) of the Controlled Substances Act since it is an OTC product. The CSS consult requested that the Applicant "provide a complete update of the information on abuse of dextromethorphan and describe how the risks of abuse of the product will be managed".

The Applicant submitted a response to a filing review letter on October 11, 2003 that included a more detailed literature review regarding the intentional abuse of dextromethorphan, a tabular summary of the frequencies of adverse events, and their conclusions regarding these events. In addition, on March 2, 2004, the Applicant submitted a response to a February 2, 2004 fax from the Division requesting information regarding our concerns about DM abuse and whether Adams Laboratories Inc. has any concerns about DM

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abuse and if they have developed a risk-management plan in the event that Mucinex[®] DM is abused. They stated that there were no reports of abuse of guaifenesin and limited their discussion to DM abuse. The Applicant referred to the National Ambulatory Medical Care Survey (NAMCS), the Drug Abuse Warning System Emergency Department (DAWN ED), and an internet survey using www.erowid.org to identify cases of DM abuse. There were instances of DM abuse, particularly in adolescents; however, there was no trend towards increasing rates of abuse according to the DAWN ED that cited an incidence of 0.12 per 100,000 population in 2002.

The Applicant states that the extended-release formulation which contains guaifenesin and dextromethorphan in both the IR and MR layers, large size of the tablet, and combination with guaifenesin present a barrier in Mucinex[®] DM being abused as compared to a small tablet with an immediate-release formulation (such as Coricidin[®] HBP Cough and Cold Tablets which contain 30 mg of DM in each tablet). The Applicant stated that they will regularly monitor MedWatch for AEs related to Mucinex[®] DM and if a safety signal is detected, then a risk management plan will be devised and implemented.

The OTC labeling review for this NDA also indicated that an FDA Drug Abuse Advisory Committee held two meetings in 1990 and 1992 to discuss a strategy for assessing the problem of dextromethorphan abuse in teenagers and identify possible solutions. No conclusive decisions were made due to lack of sufficient data in adverse event monitoring systems. The committee recommended that more studies were needed.

Reviewer's comments:

The literature and recent media attention suggests that there is some potential for intentional abuse of DM containing products. If approved, Mucinex[®] DM will have the highest dosage of DM in tablet formulation. During an internal meeting with the Division of Over the Counter Drug Products, consideration of involvement of the Drug Abuse Advisory Committee for recommendations was discussed. The Applicant has agreed to devise and implement a risk management plan to reduce the rates of abuse if a safety signal is detected for Mucinex[®] DM. This is acceptable to the Agency as part of postmarketing surveillance.

It is this Medical Officer's opinion that if a safety signal is detected due to dextromethorphan abuse, especially in the adolescent population, consideration should be given as to whether the drug product should be placed behind the pharmacy counter to deter individuals from purchasing large quantities at a single time.

7.9. Adequacy of Safety Testing

The safety assessments performed in the six clinical pharmacology studies were considered adequate.

7.10. Labeling Safety Issues and Postmarketing Commitments (v 1.1, p 111)

The proposed product conforms to the monograph dosage and labeling for maximum daily dosages of dextromethorphan as specified in Labeling of antitussive drug products [21 CFR § 341.74] and guaifenesin as specified in Labeling of expectorant drug products [21 CFR § 341.78]. Recommended changes included abbreviating the wording under the "USES",

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section of Drug Facts, deleting symptoms such as dizziness and drowsiness suggestive of overdose, and using identical language to the approved Mucinex[®] label regarding stopping use and asking a doctor if certain symptoms occur. Detailed labeling changes are shown in Appendix 2 of this review.

The Applicant did not propose any postmarketing commitments in the NDA application. In response to the Agency's inquiry via fax on February 2, 2004 whether Adams Laboratories Inc. had developed a risk-management plan in the event that Mucinex[®] DM is abused, the Applicant submitted a response [NDA 21-620, N000 C; 3/3/04] which stated that their product did not pose a greater risk of abuse than currently available products. The Applicant indicated that MedWatch will be monitored regularly for spontaneous AE reports and if a safety signal is detected, then a risk management plan will be devised and implemented to reduce rates of abuse. Furthermore, the Office of Drug Safety will be looking at the postmarketing surveillance data and if they suspect a safety signal, the Agency will request the Applicant to submit the risk management plan.

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8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The Applicant's product is proposed for use in adults and children 12 years of age and older. Two dosage forms are proposed. The proposed dose for the 1200 mg guaifenesin/60 mg dextromethorphan HBr dosage strength is one tablet every 12 hours, not more than 2 tablets in 24 hours [v 1.1, p 40-44]. The proposed dose for the 600 mg guaifenesin/30 mg dextromethorphan HBr dosage strength is one or 2 tablets every 12 hours, not more than 4 tablets in 24 hours [v 1.1, p 40-44]. These doses are within the specified OTC monograph doses for total daily doses of guaifenesin and dextromethorphan over this dosing interval. The proposed labeling for both dosage strengths instructs consumers not to use the product in children under 12 years of age. The proposed labeling includes text that states that the product can be administered without regard to timing of meals. The Applicant's food effect study, Study 2002-12, showed that there was no food effect on the rate of guaifenesin absorption from the proposed product; however, a small increase in the rate of dextromethorphan absorption occurred with intake of food. Overall, the rate and extent of absorption of the product in the fasted and fed states is similar. The small increase in the rate of dextromethorphan absorption is not likely to be clinically significant, and therefore, the Applicant's claim that the product can be administered without regard to timing of meals is acceptable.

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9. USE IN SPECIAL POPULATIONS

Both guaifenesin and dextromethorphan are considered to be safe and effective for their indications at specified OTC monograph doses. The OTC monograph labeling for guaifenesin requires no special directions or warnings for adults and children 12 years and older, the population for which the sponsor's product is proposed. The OTC labeling for dextromethorphan has specific warnings regarding drug interactions with monoamine oxidase inhibitors (MAOI) in this same population. Severe and sometimes fatal reactions have been reported following administration of dextromethorphan to subjects receiving MAOIs, and also within 2 to 3 weeks of discontinuing MAOIs. The Applicant's data did not identify any new safety issue for guaifenesin or pseudoephedrine in special populations. Use in individual special populations is discussed below.

9.1. Elderly

OTC monograph labeling for guaifenesin does not require special recommendations or instructions for elderly consumers [21 CFR § 341.78]. All subjects in the Applicant's clinical pharmacology studies were from 18 to 55 years of age, so no subgroup analysis of AEs for subjects ≥ 65 years of age was possible. The Applicant's review of the literature identified no new safety signal specific to elderly consumers [NDA 21-620 N000 BZ, 11/11/03, p 2-11, Exhibit B1, Exhibit B2].

9.2. Pediatric Program

All subjects were from 18 to 55 years of age, so no subgroup analysis of AEs for pediatric subjects was possible. The Applicant's review of the literature identified no new safety signal specific to the pediatric subpopulation. The Applicant's product is proposed for use in adults and children 12 years of age and older. The proposed labeling instructs consumers not to use the product in children under 12 years of age (v 1.1, p 38-45). The dose of active drugs in the product and its formulation are not appropriate for use in children less than 12 years of age. A suitable pediatric dosage form currently exists as per the OTC monograph for guaifenesin

- Children ≥ 6 to 12 years of age: 100 to 200mg every 4 hours, NTE 1200mg in 24 hours
- Children ≥ 2 to ≤ 6 years of age: 50 to 100mg every 4 hours, NTE 600mg in 24 hours
- Children under 2 years of age: consult a doctor

and dextromethorphan

- Children ≥ 6 to 12 years of age: 5 to 10mg every 4 hours or 15 mg every 6 to 8 hours, NTE 60mg in 24 hours, or as directed by a doctor
- Children ≥ 2 to ≤ 6 years of age: 2.5 to 5mg every 4 hours or 7.5 mg every 6 to 8 hours, NTE 30mg in 24 hours, or as directed by a doctor
- Children under 2 years of age: Consult a doctor

According to the 2004 PDR, the only currently available short-acting single ingredient guaifenesin product available for administration to children under 12 years of age is Robitussin[®] Expectorant (Wyeth).

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Currently marketed short acting single-ingredient dextromethorphan products available for administration to children under 12 years of age are Benylin[®] pediatric cough suppressant liquid (Pfizer), Benylin[®] Adult Formula Cough Suppressant (Pfizer), Robitussin[®] Pediatric Cough Suppressant Liquid (Wyeth), Robitussin[®] Honey Cough Liquid (Wyeth), Simply Cough[®] Liquid (McNeil), and Vicks[®] 44[®] Cough Relief (Proctor and Gamble). In this population, the only approved long-acting single ingredient dextromethorphan product is Delsym[®] (NDA 18,658, approved October 8, 1982).

Currently marketed short acting combination drug products containing dextromethorphan and guaifenesin available for administration to children under 12 years of age are Benylin[®] Cough Suppressant/Expectorant Liquid, Robitussin-DM[®] Infant Drops, Robitussin-DM[®] Liquid, Robitussin[®] Sugar Free Cough Liquid (Wyeth), Vicks[®] 44E[®] Cough and Chest Congestion Relief (Proctor & Gamble), and Pediatric Vicks[®] 44e[®] Cough and Chest Congestion Relief Liquid (Proctor & Gamble).

The sponsor did not provide a request for waiver of pediatric studies. The lower strength Mucinex[®] DM containing guaifenesin 600mg and dextromethorphan 30 mg is smaller in size and could potentially be used off label in a younger population. The lower strength Mucinex[®] DM administered as one tablet every 12 hours matches the OTC monographed total daily dose for children ≥ 6 to 12 years of age. I recommend that a full waiver for pediatric studies be granted by the Agency since Mucinex[®] DM is not likely to be used in pediatric patients under 12 years of age since there are immediate-release formulations of dextromethorphan and guaifenesin available for younger populations down to the lowest recommended age (2 years). The higher strength dosage of Mucinex[®] DM has not been found to be safe and efficacious in this age group [Guidance for Industry: Recommendations for Complying with Pediatric Rule (21CFR § 314.55(a) and 601.27(a))].

9.3. Gender

There were too few AEs noted in the Applicant's clinical pharmacology studies to determine if there was an association of AEs with gender for any of the individual formulations studied. The Applicant's review and summary of the literature identified no articles describing safety issues relevant to gender [NDA 21-620 N000 BZ, 11/11/03, p 2-11, Exhibit B1, Exhibit B2]. This review of the literature also did not identify any correlations between dextromethorphan, guaifenesin, and gender. Based on this information, there are no safety concerns regarding the use of Mucinex[®] DM in men versus women.

9.4. Pregnancy and Lactation

The OTC monograph labeling for guaifenesin and dextromethorphan requires no warning for pregnant or lactating women. One article in the Applicant's literature review [NDA 21-620 N000 BZ, 11/11/03, p 6]⁴ refers to a study of 184 women who used DM during their pregnancies and did not have an increased rate of major malformations above the expected baseline rate of 1-3%. These women were matched to a control group according to age, smoking, alcohol use, and upper respiratory tract infections. The Applicant's proposed labeling includes a warning for women who are pregnant or breast-feeding to consult a health professional before use of Mucinex[®] DM (Volume 1.1, pages 38-45).

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9.5. Race

There were too few non-Caucasian subjects in the Applicant's clinical pharmacology studies to perform a subgroup analysis of AEs by race since 95% of the subjects were Caucasian (from data, v 1.46, p 181-182; v 1.47, p 350-351). The Applicant's review and summary of the literature identified no articles describing safety issues relevant to race [NDA 21-620 N000 BZ, 11/11/03, p 2-11, Exhibit B1, Exhibit B2].

9.6. Renal or Hepatic Compromised Subjects

The OTC monograph labeling for guaifenesin and dextromethorphan does not specify special recommendations or precautions for consumers with hepatic or renal disease. The Applicant's review and summary of the literature identified no articles describing safety issues relevant to consumers with hepatic or renal disease [NDA 21-620 N000 BZ, 11/11/03, p 2-11, Exhibit B1, Exhibit B2].

9.7. Poor Metabolizers of Cytochrome P450

The metabolism of dextromethorphan into its active metabolite, dextrophan, is catalyzed by cytochrome P450 2D6. The Sponsor presumes that cytochrome P450 2D6 caused significant interindividual variation in the metabolism of dextromethorphan.⁵ In the six clinical pharmacology trials, subjects who were presumed to be poor metabolizers of cytochrome P450 2D6 demonstrated higher plasma concentration levels of dextromethorphan and guaifenesin in terms of C_{max} and AUC as compared to normals. The majority of these outliers had elevated plasma concentrations between treatment groups throughout the studies. Thus, there was a concern regarding for a higher potential for AEs among the poor metabolizers. However, the data demonstrated there was no difference in AEs between these outliers and those subjects with normal metabolism of cytochrome P450 2D6. Of the 100 AEs that occurred in the trials, the most common AEs were headache (13), nausea (11), and vomiting (6). In multiple-dose Study 2002-10, the most common AEs were flushing, upset stomach, and vomiting/emesis that occurred in 2.9% of subjects, respectively. These AEs, more commonly associated with guaifenesin, may also limit the abuse and overdose potential of Mucinex[®] DM as well as concerns regarding individuals who are slow metabolizers of cytochrome P450 CD6.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions Regarding Safety and Efficacy

In the clinical pharmacology trials submitted with this application, only the high dose extended-release, bi-layer tablet formulation of Mucinex[®] DM (1200 mg guaifenesin/ 60 mg dextromethorphan) was utilized. Mucinex[®] DM high dose was shown to be bioequivalent to approved and over-the-counter (OTC) monograph reference products. The two strengths of Mucinex[®] DM are compositionally proportional and based on dissolution studies, the similarity (f2) factor between Mucinex[®] DM 1200/60 mg and 600/30 mg strengths was within established equivalence criteria. The f2 factor for guaifenesin between 1200 mg and 600 mg was 63.5 and the f2 factor for DM between 60 mg and 30 mg was 61.5. The Applicant demonstrated that the pharmacokinetics of guaifenesin and dextromethorphan were not affected by the presence of one another.

The Applicant's integrated review of safety supports the proposed indications of their product. Safety data was obtained from the clinical pharmacology studies, evaluation of safety information from the US AERS database, and the Applicant's review of published literature and postmarketing adverse events. Integrated safety data from the clinical pharmacology studies showed no evidence of new safety signal and there were no meaningful differences in AEs, withdrawals due to AEs, or SAEs between the test and reference products. Data from the AERS database supported the safety of guaifenesin and dextromethorphan and do not present new safety issues. The adverse events profile of this bi-layer, extended-release tablet was similar to that seen with the reference products. Clinical efficacy studies were not performed and for the purpose of approval, the bioequivalence approach was adequate.

10.2. Recommendations on Approvability

Mucinex[®] DM is recommended for approval based on the establishment of bioequivalence to approved and OTC monograph reference products. The evidence submitted by the Applicant supports the safety of this product and the demonstration of a low incidence of adverse events. If a safety signal is noted in postmarketing surveillance, the Applicant will devise and implement a risk management plan to reduce rates of abuse. It is this Medical Officer's opinion that if a safety signal is detected due to dextromethorphan abuse, especially in the adolescent population, consideration should be given as to whether the drug product should be placed behind the pharmacy counter to deter individuals from purchasing large quantities at a single time.

10.2.1. Pediatric Considerations

The sponsor did not provide a request for waiver of pediatric studies. The lower strength Mucinex[®] DM containing guaifenesin 600mg and dextromethorphan 30 mg is smaller in size and could potentially be used off label in a younger population. The lower strength Mucinex[®] DM administered as one tablet every 12 hours matches the OTC monographed total daily dose for children ≥ 6 to 12 years of age. I recommend that a full waiver for pediatric studies be granted by the Agency to Adams Laboratories, Inc. since Mucinex[®] DM is not likely to be used in pediatric patients under 12 years of age since there are immediate-

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release formulations of dextromethorphan and guaifenesin available for younger populations down to the lowest recommended age (2 years). The higher strength dosage of Mucinex[®] DM has not been found to be safe and efficacious in this age group.

10.3. Labeling

The Applicant submitted a draft label, which was reviewed. Comments were sent to the Applicant ("Labeling Comments to the Applicant") suggesting language that conforms to OTC monograph standards. Recommended changes included the addition of the words *extended-release* to the bi-layer tablet formulation in the DRUG FACTS section as well as listing the ingredients in alphabetical order, abbreviating the wording under USES, deleting symptoms suggestive of overdose, and using identical language to the Mucinex[®] label regarding stopping use and asking a doctor if certain symptoms occur. In addition, lay terminology for cough suppressant is favored over antitussive.

10.4. Comments to the Applicant

The following comments will be addressed in the approval letter.

- A waiver should be granted for pediatric studies under PREA.
- We refer you to your submission dated March 3, 2004 (NDA 21-260 N000C). Adams Laboratories, Inc. has agreed to monitor Medwatch for adverse events related to Mucinex[®] DM. If a safety signal is noted in postmarketing surveillance, you have agreed to devise and implement a risk management plan to reduce rates of abuse of Mucinex[®] DM. If a safety signal is detected, you should consider whether the drug product should be placed behind the pharmacy counter to deter individuals from purchasing large quantities at a single time.

APPENDIX**1. DETAILED STUDY REVIEWS****1.1. Study 00-02: "A Pilot Study Designed to Examine the Bioavailability of Two Different Experimental Controlled Release Formulations of Guaifenesin and Dextromethorphan in Normal Healthy Volunteers Compared to Reference Controlled Release Guaifenesin and Dextromethorphan Products" (v 1.50-1.54)**

Study 00-02 did not utilize the to-be-marketed product.

1.1.1. Protocol 00-02 (Appendix E, v 1.54, p 357-441)**1.1.1.1. Investigators and Centers (Clinical, v 1.50, p 46-47, 66-70, 83-85; Appendix E, v 1.54, p 358-359, 396-417)**

Investigator: Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc.,
1816 West Mount Vernon, Springfield, MO 65802

Study dates: October 18, 2000 to November 13, 2000 (The first study medication was administered on October 29, 2000.)

Study report: January 29, 2003 (There were no protocol amendments.)

Sites: Single-site

IRB: Bio-Kinetic Clinical Applications, Inc. Institutional Review Board (IRB)
Approval date: September 11, 2000

The Applicant states that the study was conducted according to FDA regulations and guidelines and that written informed consent was obtained from each subject prior to participation in the study.

1.1.1.2. Objective/Rationale (Clinical, v 1.50, p 50; Appendix E, v 1.54, p 362)

The objective of this Phase I, pilot study was to examine the relative bioavailability of two experimental sustained release formulations containing 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide compared to that of two reference formulations in 21 normal, healthy male and female subjects ages 18 to 55.

1.1.1.3. Overall Design (Clinical, v 1.50, p 50; Appendix E, v 1.54, p 362)

This was a prospective, open label, single dose, randomized, 3-way crossover pharmacokinetic study.

1.1.1.4. Study Population

Subjects meeting the following criteria were selection for participation:

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Inclusion Criteria (Clinical, v 1.50, p 51; Appendix E, v 1.54, p 363)

1. Males and/or females between the ages of 18 and 55 year, inclusive
2. Good general health as determined by medical history, physical examination, electrocardiogram, and clinical laboratory measures
3. Within 15% of Ideal Body Weight as defined by the 1983 Metropolitan Life chart
4. Non-tobacco users, who have been tobacco free for at least one year
5. Able to read, understand, and sign the informed consent after the nature of the study has been explained
6. Negative finding on tests for Hepatitis B and C antigen as well as HIV

Exclusion Criteria (Clinical, v 1.50, p 51-52; Appendix E, v 1.54, p 363-364)

1. Clinically significant abnormalities detected by medical history, physical, electrocardiographic, or clinical laboratory findings. Any disease or condition which could impart absorption, distribution, metabolism, or elimination of the study drugs
2. History of hypersensitivity reaction to the study drugs or related compounds
3. Receipt of an investigational drug within one month prior to study enrollment
4. Donation of whole blood within 30 days or plasma within 14 days prior to study enrollment
5. Known or suspected use of illicit drugs
6. Receipt of any prescription or over-the-counter medication within 14 days prior to study enrollment, or the use of any medication on a chronic basis (with the exception of oral contraceptives for women of childbearing potential). An appropriate drug free period should be provided to eliminate any special long half-life drugs, e.g. astemizole
7. Use of metabolic enzyme inducer or inhibiting agent within 30 days prior to study enrollment
8. Positive finding on screening for Hepatitis B or C or HIV

1.1.1.5. Study Procedures (Clinical, v 1.50, p 52-65; Appendix E, v 1.54, p 364-394)

The subjects attended a total of four clinic visits that included a screening visit, baseline visit on Day 1 of treatment, and 2 other visits on Day 8 and 15. During the 14-day screening period, subjects had a complete medical history and physical examination, 12 lead ECG, clinical laboratory evaluations (chemistry, hematology, serum pregnancy test, urine drug screen, tests for Hepatitis B and C Antigens and for HIV), and signed written informed consent. Subjects were instructed not to consume any prescription or over the counter medication for 14 days of alcohol for 48 hours before study drug administration or during study participation. Subjects meeting selection criteria were randomized to one of three groups (Groups 1, 2, or 3) on the evening before morning dosing for the total duration of the five-week study and received each treatment (Treatments A, B, and C) during the course of the study.

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- **Treatment A (reference)** - 1200 mg controlled release guaifenesin (Mucinex[®]; Lot No. PB-304A, expiration date NA) and 60 mg controlled release dextromethorphan hydrobromide (Delsym[®]) (Lot No. 00808, expiration date 2/2002)
- **Treatment B (test)** - 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide experimental controlled release tablet (Lot No. CB00-04A, expiration date NA)
- **Treatment C (test)** - 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide experimental controlled release tablet (Lot No. CB00-03A, expiration date NA)

Group	Leg 1	Leg 2	Leg 3
1	Treatment A	Treatment B	Treatment C
2	Treatment B	Treatment C	Treatment A
3	Treatment C	Treatment A	Treatment B

Subjects were confined for 1½ days (approximately 36 hours) on each of three study periods (Days 1, 8, 15) and were fasted prior to each dose. Each treatment was administered during confinement as a one-time single-dose with 240 mL of water while in the fasting state (10 hours pre-dose) with a washout period of seven days between each leg of the study.

Subjects maintained the fast until after collection of the four-hour blood sample. Water was allowed *ad lib* after the two hour-post dose blood sample was obtained. Subjects subsequently received a standardized lunch and dinner following the single dose at 4 and 10 hours after dosing, respectively. A light snack was served at 10:00 PM. No food or drinks containing caffeine or xanthine were permitted during confinement and no concurrent medications were permitted after study enrollment unless authorized by the Investigator.

Adverse events were evaluated by the Investigator and recorded on source documents and case report forms (v 1.88, p 3-113). The AEs were graded in intensity (mild, moderate, severe) using standard criteria, frequency (continuous, intermittent), action taken (relative to study drug), relationship to study medication (probably, possibly, unlikely), and subject outcome (recovery, death) and were followed to resolution.

Each subject had the right to withdraw consent to participate in the study at any time. The investigator had the option to discontinue any subject's participation for any reason. Dropouts exceeding three subjects would be replaced.

Table 9. Study 00-02 Timeline (Clinical, v 1.50, p 75-82)

	Screening	Treatment		
	Visit 1	Visit 2	Visit 3	Visit 4
	Day -2 to -14	Day -1 to 2	Day 8 to 10	Day 15 to 17
General Procedures				
Informed consent	X			
Subject Number Assignment	X			
Medical history	X			
Verification of inclusion/exclusion criteria	X			
Concomitant medication assessment	X	X	X	X
Vital signs	X	X	X	X
Physical examination	X			

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	Screening	Treatment		
	Visit 1	Visit 2	Visit 3	Visit 4
	Day -2 to -14	Day -1 to 2	Day 8 to 10	Day 15 to 17
Clinical laboratory tests	X			
12-Lead electrocardiogram	X			
Urine drug screen	X	X	X	X
Urine pregnancy test (all females)	X	X	X	X
Randomization number assignment		X		
Study medication given		X	X	X
Adverse event assessment		X	X	X
Pharmacokinetic plasma sampling		X	X	X

1.1.1.6. Parameters (Clinical, v 1.50, p 53; Appendix E, v 1.54, p 431)

Blood samples (10 mL sodium heparin anticoagulant) were obtained as individual venipunctures prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours post dose. Plasma was separated and frozen until analyzed for guaifenesin, dextromethorphan hydrobromide, and dextropran content (the active metabolite of dextromethorphan hydrobromide that produces phenylcyclidine-like behavioral effects in animals and exhibits anticonvulsant and neuroprotective properties in a variety of experimental model)⁶. The total blood loss for guaifenesin, dextromethorphan hydrobromide, and dextropran content was 450 mL.

1.1.1.7. Safety Evaluations (Clinical, v 1.50, p 53; Appendix, v 1.54, p 365)

Safety parameters included monitoring for adverse events. Subjects had a complete history and physical examination including vital signs, height, and weight. A 12-lead electrocardiogram, serum chemistry, complete blood count with differential, qualitative urine drug screen, tests for Hepatitis B and C Antigens and for HIV were also performed. Serum pregnancy tests were given for females.

1.1.1.8. Statistical Plan (Clinical, v 1.50, p 57; Appendix E, v 1.54, p 369)

Sample Size:

Calculations regarding sample size for this study were not included in the NDA application.

Statistical analysis:

Pharmacokinetic parameters included the maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), the terminal elimination half-life and area under the plasma concentration-time curve (AUC) for guaifenesin, dextromethorphan hydrobromide, and dextropran. Half-life, the logarithm of C_{max} and the logarithm of AUC were analyzed with an analysis of variance with effects for sequence, subject nested within sequence, period, and formulation.

1.1.2. Results

1.1.2.1. Subject Disposition (Clinical, v 1.50, p 9-10, 17, 60; Appendix E, v 1.54, p 432-433)

A total of 21 healthy male and female subjects were enrolled and randomized to one of three treatment legs. Twenty subjects completed the study. One subject, Subject 19 withdrew from the study after Period 1 due to personal reasons. He was not replaced per protocol. The average age was 21.9 ± 6.6 years (Mean $\pm$ Standard Deviation) with a range of 18 years to 49 years. The average height was 68.2 ± 3.73 inches with a range of 62 to 75 inches. The average weight was 157 ± 27.4 pounds with a range of 118 to 222 pounds. There were eight males (38%) and 13 females (62%) enrolled, of whom 18 (86%) were Caucasian and three (14%) were Multiracial.

1.1.2.2. Protocol Deviations (Clinical, v 1.50, p 56; Appendix E, v 1.54, p 430)

Statistical analysis of the data from this study was not pursued since the data indicated that neither experimental formulation yielded an acceptable bioavailability for both guaifenesin and dextromethorphan hydrobromide.

1.1.2.3. Efficacy Endpoint Outcomes (Appendix E, v 1.54, p 431)

This was a pharmacokinetic study without efficacy evaluations.

1.1.2.4. Safety Outcomes

1.1.2.4.1. Total Drug Exposure (Clinical, v 1.50, p 14; Appendix E, v 1.54, p 434)

Treatment duration was similar among the three groups. Only one subject did not receive all treatments.

1.1.2.4.2. Adverse Events (Clinical, v 1.50, p 55; Appendix E, v 1.54, p 436-437)

According to the Applicant, the experimental guaifenesin and dextromethorphan HBr formulations were well tolerated. Eighteen adverse events listed were from 6 subjects and included 4 cases of nausea, 4 cases of headache, 2 episodes of vomiting, 3 cases of flushing, 3 episodes of lightheadedness, 1 episode of feeling clammy, and 1 episode of diarrhea. All subjects recovered from these adverse events (Table 4) and most cases were judged by the investigator to be unrelated to treatment regimen.

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Table 10. Study 00-02: Common adverse events occurring in more than one subject (Appendix E, v 1.54, p 437)

	Treatment Dose at Onset of Study (N = number of subjects)		
	Reference Treatment A Mucinex [®] + Delysm [®] (N=21)	Experimental Treatment B Guaifenesin 1200 mg + DM* 60 mg (N=21)	Experimental Treatment C Guaifenesin 1200 mg + DM* 60 mg (N=21)
Total subjects with adverse event	2 (10%)	1 (4.8%)	3 (14%)
TOTAL ADVERSE EVENTS	5	2	11
Gastrointestinal system			
Clammy	0 (0%)	0 (0%)	1 (4.8%)
Diarrhea	1 (4.8%)	0 (0%)	0 (0%)
Flushing	1 (4.8%)	1 (4.8%)	1 (4.8%)
Nausea	1 (4.8%)	0 (0%)	3 (14%)
Vomiting	0 (0%)	0 (0%)	2 (10%)
Neurological system			
Headache	1 (4.8%)	0 (0%)	3 (14%)
Lightheaded	1 (4.8%)	1 (4.8%)	1 (4.8%)

*DM = Dextromethorphan

1.1.2.4.3. Discontinuation or treatment interruption due to adverse events (Clinical, v 1.50, p 14; Appendix E, v 1.54, p 428-429)

One subject discontinued study treatment prematurely due to personal reasons and did not return for the second and third periods of the study. He received one tablet of Treatment B (Mucinex[®] DM = 1200 mg guaifenesin + 60 mg dextromethorphan HBr).

1.1.2.4.4. Serious adverse events and death (Clinical, v 1.50, p 15, 56-57, Appendix E, v 1.54, p 439-440)

No subject died or experienced a serious adverse event necessitating withdrawal from the study. Case report forms were not submitted for this study.

1.1.2.4.5. Physical examination, ECG, and laboratory measures (Clinical, v 1.50, p 54; Case Reports, v 1.88, p 4-68)

There were no significant changes in physical examination, vital signs, or laboratory measurements that would indicate an effect of the study drug. There were no significant differences in these parameters between treatment groups. Analyses of these variables by age, gender, and race did not indicate any differential response to treatment.

1.1.2.4.6. Plasma concentrations of guaifenesin and dextromethorphan hydrobromide, and dextrorphan (Clinical, v 1.50, p 18-38)

Table 11. Study 00-02: Mean concentrations following treatment dose (Clinical, v 1.50, p18-38)

Treatment Group	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (hr-ng/mL)	AUC _{0-∞} (hr-ng/mL)	T _{1/2} (hr)
Guaifenesin					
A = Mucinex [®] + Delysm [®]	1953	1.40	8018	8246	3.13
B = Mucinex [®] DM (prototype 1)	1878	1.07	8468	8496	2.13
C = Mucinex [®] DM (prototype 2)	1216	1.76	7620	7730	2.61

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Treatment Group	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (hr-ng/mL)	AUC _{0-∞} (hr-ng/mL)	T _{1/2} (hr)
Dextromethorphan Hydrobromide					
A = Mucinex [®] + Delysm [®]	13.5	6.50	235	1483	48.9
B = Mucinex [®] DM (prototype 1)	13.7	7.57	230	2103	67.3
C = Mucinex [®] DM (prototype 2)	13.3	12.0	231	2816	99.6
Dextroprphan					
A = Mucinex [®] + Delysm [®]	296	4.60	2312	2691	21.7
B = Mucinex [®] DM (prototype 1)	359	3.43	2714	2974	16.8
C = Mucinex [®] DM (prototype 2)	213	6.00	2265	2868	26.6

1.1.3. Discussion and Conclusions (v 1.50, p 14-16)

Study 00-02 was the first of two pilot studies, which compared the relative bioavailability of two experimental sustained release formulations containing 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide with 2 reference formulations in 21 healthy male and female subjects ages 18 to 55. In this study, neither experimental formulation was the to-be-marketed drug product. Subjects were given single doses of medications separated by 7-day washout periods during the course of the five-week study. A total of 21 subjects were included in the intent to treat (ITT) population. Non-Caucasians were underrepresented in this study and thus it was difficult to determine any correlations in terms of racial ethnicity. Subject 19 withdrew prior to the second period of the study. This review did not uncover any outstanding clinical issues or significant safety concerns in this study.

The plasma concentration profiles for C_{max}, t_{max}, AUC_{last}, AUC_∞, and t_{1/2} for the two experimental prototypes of Mucinex[®] DM were not comparable to the reference formulations and did not produce optimal bioavailability for both components. Based on this information, the two experimental formulations were abandoned.

1.2. Study 2001-04: "A Pilot Study Designed to Examine the Bioavailability of Two Different Experimental Controlled Release Formulations of Guaifenesin and Dextromethorphan in Normal Healthy Volunteers Compared to Reference Controlled Release Guaifenesin and Dextromethorphan Products" (v 1.55 – 1.58)

1.2.1. Protocol 00-02 (Appendix F, v 1.58, p 268-352)

1.2.1.1. Investigators and Centers (Clinical, v 1.55, p 41-42, 65-7083-84; Appendix F, v 1.58, p 4269-270, 308-328)

Investigator: Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc.,
1816 West Mount Vernon, Springfield, MO 65802

Study dates: July 31, 2001 to August 29, 2001 (The first study medication was administered on August 11, 2001.)

Study report: January 29, 2003 (There were no protocol amendments.)

Sites: Single-site

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IRB: Bio-Kinetic Clinical Applications, Inc. Institutional Review Board (IRB)
Approval date: August 6, 2001

The Applicant states that the study was conducted according to FDA regulations and guidelines and that written informed consent was obtained from each subject prior to participation in the study.

1.2.1.2. Objective/Rationale (Clinical, v 1.55, p 45; Appendix F, v 1.58, p 273)

The objective of this Phase 1, pilot study was to examine the relative bioavailability of two experimental sustained release formulations containing 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide compared to that of two reference controlled release guaifenesin and dextromethorphan products in 15 normal, healthy male and female subjects.

After the preceding Study 00-02 demonstrated that two experimental formulations of Mucinex[®] DM did not have an acceptable bioavailability to reference guaifenesin and dextromethorphan hydrobromide, Study 2001-04 utilized two new experimental formulations.

1.2.1.3. Overall Design (Clinical, v 1.55, p 45; Appendix F, v 1.58, p 273)

This was a prospective, open label, single dose, randomized, three-way crossover study.

1.2.1.4. Study Population (Clinical, v 1.55, p 46-47)

Inclusion Criteria (Clinical, v 1.55, p 46; Appendix, v 1.58, p 274)

Same inclusion criteria as in Study 00-02

Exclusion Criteria (Clinical, v 1.55, p 46-47; Appendix, v 1.58, p 274-275)

Same exclusion criteria as in Study 00-02

1.2.1.5. Study Procedures (Clinical, v 1.55, p 275-314)

The study methods were identical to Study 00-02. The subjects attended a total of four clinic visits that included a screening visit, baseline visit on Day 1 of treatment, and 2 other visits on Day 8 and 15. During the 14-day screening period, subjects had identical clinical evaluations and study parameters as those subjects in Study 00-02. Subjects meeting selection criteria were randomized to one of three groups (Groups 1, 2, or 3) and received each treatment (Treatments A, B, and C) during the course of the five-week study in the same fashion as subjects involved in Study 00-02.

- **Treatment A** - 1200 mg controlled release guaifenesin (Mucinex[®]; Lot No. PB-304A, expiration date NA) and 60 mg controlled release dextromethorphan hydrobromide (Delsym[®]; Lot No. 00743, expiration date 6/2002)
- **Treatment B** - 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide experimental controlled release tablet (Lot No. 12LB-33A, expiration date NA)
- **Treatment C** - 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide experimental controlled release tablet (Mucinex[®] DM, Lot No. PB01-H30A, expiration date NA)

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Each treatment was administered as a one-time single-dose while in the fasting state with a washout period of 7 days between each leg of the study. Subjects were confined for 1½ days (approximately 36 hours) on each of three study periods (Day 1, Day 8, and Day 15) and were fasted prior to dose. They subsequently received a standardized lunch, dinner, and light snack following the single dose. No food or drinks containing caffeine or xanthine were permitted during confinement. Blood samples (10ml sodium heparin anticoagulant) were obtained as individual venipunctures prior to dosing and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 72, and 96 hours post dose.

Table 12. Study 2001-04 Timeline (Clinical, v 1.55, p 74-82)

	Screening	Treatment		
	Visit 1	Visit 2	Visit 3	Visit 4
	Day -2 to -14	Day -1 to 1	Day 8 to 10	Day 15 to 17
General Procedures				
Informed consent	X	X		
Subject Number Assignment	X			
Medical history	X			
Verification of inclusion/exclusion criteria	X			
Concomitant medication assessment	X	X	X	X
Vital signs	X	X	X	X
Physical examination	X			
Clinical laboratory tests	X			
12-Lead electrocardiogram	X			
Urine drug screen	X	X	X	X
Urine pregnancy test (all females)	X	X	X	X
Randomization number assignment		X		
Study medication given		X	X	X
Adverse event assessment		X	X	X
Pharmacokinetic plasma sampling		X	X	X

1.2.1.6. Parameters (Clinical, a 1.55, p 49; Appendix F, v 1.58, p 57)

Same pharmacokinetic sampling as in Study 00-02.

1.2.1.7. Safety Evaluations (Clinical, a 1.55, p 49; Appendix F, v 1.58, p 57)

Same safety parameters as in Study 00-02.

1.2.1.8. Statistical Plan (Clinical, v 1.55, p 13-16, 54; Appendix F, v 1.58, p 280)

Pharmacokinetic parameters included the maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), the terminal elimination half-life and area under the plasma concentration-time curve (AUC).

Bioavailability between experimental drug product and reference was examined. An analysis of variance (ANOVA) was performed and data for C_{max}, AUC_{0-t}, AUC_{0-inf}, half-life (T_{1/2}) and clearance (CL) were natural log (ln) transformed prior to analysis. The 90% confidence intervals of each test group mean relative to the reference group mean were obtained by taking the antilog of the corresponding 90% confidence intervals for the difference between the means on the log scale. Subject 5 displayed predose levels greater than 5 percent of C_{max} for the third study period. This subject was “dropped from all BE study evaluations” since the predose plasma concentrations did not meet FDA specifications

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according to the Guidance on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, page 24. Subject 2 displayed predose levels less than 5 percent of C_{max}. Data from this subject were included in the dextromethorphan analyses.

1.2.2. Results

1.2.2.1. Subject Disposition (Clinical, v 1.55, p 14; Appendix F, v 1.55, p 59)

A total of 15 healthy male and female subjects were enrolled and randomized to one of three treatment legs. All subjects completed the study. The average age was 37.3 ± 12.2 years (Mean $\pm$ Standard Deviation) with a range of 20 years to 55 years of age. The average height was 65.7 ± 3.2 inches with a range of 61 to 73 inches. The average weight was 156 ± 28.6 pounds with a range of 110 to 208 pounds. There were three males (20%) and 12 females (80%) enrolled of which 14 (93%) were Caucasian and one Black (7%).

1.2.2.2. Protocol Deviations (Clinical, v 1.55, p 14; Appendix F, v 1.58, p 340)

Protocol deviations in the times of blood sampling which were drawn two or more minutes late occurred 8 times in four subjects.

1.2.2.3. Efficacy Endpoint Outcomes (Appendix F, v 1.58, p 341)

This is a pharmacokinetic study without efficacy evaluations.

1.2.2.4. Safety Outcomes

1.2.2.4.1. Total Drug Exposure (Clinical, v 1.55, p 14; Appendix F, v 1.58, p 344)

Treatment duration was the same among the three groups.

1.2.2.4.2. Adverse Events (Clinical, v 1.55, p 52; Appendix F, v 1.58, p 346-348)

According to the Applicant, both guaifenesin and dextromethorphan HBr were well tolerated. Nineteen adverse events listed were from six subjects and included two cases of nausea, six cases of headache, two episodes of vomiting, one upset stomach, two episodes of burning and vibrating (due to musculoskeletal strain), five episodes of diarrhea, and one episode of sleepiness (from sleep deprivation). All subjects recovered from these adverse events (Table 4) and most cases (16) were possibly related to treatment regimen.

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Table 13. Study 2001-04: Common adverse events occurring in more than one subject (Appendix F, v 1.58, p 346-348)

	Treatment Dose at Onset of Study (N = number of subjects)		
	Treatment A Reference Mucinex [®] + Delysm [®] (N=21)	Treatment B Experimental Guaifenesin 1200 mg + DM* 60 mg (N=21)	Treatment C Mucinex [®] DM Guaifenesin 1200 mg + DM* 60 mg (N=21)
Total subjects with adverse event	2 (13%)	4 (27%)	5 (33%)
TOTAL ADVERSE EVENTS	2	8	9
Body as a whole			
Burning and vibrating	0 (0%)	0 (0%)	1 (4.8%)
Gastrointestinal system			
Diarrhea	1 (4.8%)	2 (9.5%)	2 (9.5%)
Nausea	0 (0%)	1 (4.8%)	1 (4.8%)
Upset Stomach	0 (0%)	0 (0%)	1 (4.8%)
Vomiting	0 (0%)	1 (4.8%)	1 (4.8%)
Neurological system			
Headache	1 (4.8%)	3 (14%)	2 (9.5%)
Sleepy	0 (0%)	1 (4.8%)	0 (0%)

*DM = Dextromethorphan

1.2.2.4.3. Discontinuation or treatment interruption due to adverse events (Clinical, v 1.5, p 14; Appendix F, v 1.58, p 339)

There were no discontinued subjects in this study.

1.2.2.4.4. Serious adverse events and death (Clinical, v 1.55, p 10; Appendix F, v 1.58, p 350-351)

No subject died or experienced a serious adverse event necessitating withdrawal from the study. Case report forms were not submitted for this study.

1.2.2.4.5. Physical examination, ECG, and laboratory measures (Case Reports, v 1.88, p 114-205)

There were no significant changes in physical examination, vital signs, or laboratory measurements that would indicate an effect of the study drug. There were no significant differences in these parameters between treatment groups. Analyses of these variables by age, gender, and race did not indicate any differential response to treatment.

1.2.2.4.6. Plasma concentrations of guaifenesin and dextromethorphan hydrobromide (Clinical, v 1.55, p 18-33)

As demonstrated in the table below, the AUC_{0-∞} for guaifenesin in the experimental Treatment B (9366 hr-ng/mL) was 97.6% of the value for the reference product. The AUC_{0-∞} for guaifenesin in the experimental Treatment C (9674 hr-ng/mL) was 100.8% of the value for the reference product. C_{max} for guaifenesin for experimental Treatment B (2038 ng/mL) was 88.6% of the value for the reference product. C_{max} for guaifenesin for experimental Treatment C (2148 ng/mL) was 93.4% of the value for the reference product. T_{1/2} for

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guaifenesin for Treatment B (1.51 hr) and Treatment C (1.69 hr) were less than that for reference (4.35 hr). T_{max} for guaifenesin for Treatment B (1.48 h) and for treatment C (1.63 h) were greater than that of reference (1.03 hr).

The $AUC_{0-\infty}$ for dextromethorphan in the experimental Treatment B (203294 hr-ng/mL) was 111.9% of the value for the reference product. The $AUC_{0-\infty}$ for dextromethorphan in the experimental Treatment C (216393 hr-ng/mL) was 119.1% of the value for the reference product. C_{max} for dextromethorphan for experimental Treatment B (8239 ng/mL) was 132.2% of the value for the reference product. C_{max} for dextromethorphan for experimental Treatment C (8526 ng/mL) was 136.8% of the value for the reference product. $T_{1/2}$ for dextromethorphan for Treatment B (12.5 hr) and Treatment C (12.7 hr) were less than that for reference (15.3 hr). T_{max} for dextromethorphan for Treatment B (5.73 h) and for treatment C (5.87 h) were greater than that of reference (6.33 hr).

Table 14. Study 2001-04: Mean concentrations following Treatment dose (v 1.55, p 18-33)

Treatment Group	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (hr-ng/mL)	$AUC_{0-\infty}$ (hr-ng/mL)	$T_{1/2}$ (hr)
Guaifenesin					
A= Mucinex [®] + Delsym [®]	2300	1.03	9595	9597	4.35
B = Mucinex [®] DM (prototype 1)	2038	1.48	9366	9366	1.51
C= Mucinex [®] DM (prototype 2)	2148	1.63	9674	9674	1.69
Dextromethorphan Hydrobromide					
A= Mucinex [®] + Delsym [®]	6233	6.33	181604	213211	15.3
B = Mucinex [®] DM (prototype 1)	8239	5.73	203294	232467	12.5
C= Mucinex [®] DM (prototype 2)	8526	5.87	216393	216393	12.7

1.2.3. Discussion and Conclusions (v 1.55, p 14-16)

Study 2001-04 compared the relative bioavailability of two experimental sustained release combination formulations containing 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide with two individual reference formulations in 15 healthy male and female subjects ages 18 to 55. Subjects were given single doses of medications separated by seven-day washout periods during the course of the five-week study. A total of 15 subjects were included in the ITT population. Non-Caucasians were underrepresented in this study and thus no conclusions based on racial ethnicity could be made. This review of the plasma concentration profiles for C_{max} , T_{max} , AUC_{last} , AUC_{∞} , and $T_{1/2}$ revealed that the two experimental prototypes of Mucinex[®] DM were bioequivalent to reference guaifenesin (Mucinex[®]) and were more bioavailable than reference dextromethorphan hydrobromide (Delsym[®]). Experimental formulation Treatment C's pharmacokinetic profile was more similar to reference than Treatment B's profile (Table 14). Treatment C was subsequently used in Study 2002-10 and was carried forward as the proposed commercial formulation of Mucinex[®] DM. The AEs in the two test groups were similar in number and distribution and occurred at a slightly higher incidence than the AEs in the reference group. Treatment B was not used in further studies.

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1.3. Study 2001-15: "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" (v 1.59 - 1.64)

Study 2001-15 utilized the to-be-marketed product.

1.3.1. Protocol (Appendix F, v 1.64, p. 407-451)

1.3.1.1. Investigators and Centers (Clinical, v 1.59, p 49-50, 77-82, 99-100; Appendix F, p 408-409, 452-471)

Investigator: Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc.,
1816 West Mount Vernon, Springfield, MO 65802

Study dates: November 6, 2001 to January 10, 2002 (The first study medication was administered on November 18, 2001.)

Study report: January 29, 2003 (There were no protocol amendments.)

Sites: Single-site

IRB: Bio-Kinetic Clinical Applications, Inc. Institutional Review Board (IRB)
Approval date: November 15, 2001

The Applicant states that the study was conducted according to FDA regulations and guidelines and that written informed consent was obtained from each subject prior to participation in the study.

1.3.1.2. Objective/Rationale (Clinical, v 1.59, p 53; Appendix F, v 1.64, p 412)

The objective of this Phase I study was to determine the plasma concentrations of guaifenesin and dextromethorphan when they were co-administered and when they were administered alone. The dose response relationship of dextromethorphan was also studied in healthy male and/or female subjects.

1.3.1.3. Overall Design (Clinical, v 1.59, p 53; Appendix F, v 1.64, p 412)

This was a Phase I, open label, randomized, four-way crossover study in 36 subjects who satisfied the inclusion and exclusion criteria.

1.3.1.4. Study Population (Clinical, v 1.59, p 54-56; Appendix F, v 1.64, p 413-415)

Inclusion Criteria (Clinical, v 1.59, p 54-55; Appendix F, v 1.64, p 413-414)

Same inclusion criteria as in Study 00-02

Exclusion Criteria (Clinical, v 1.59, p 55-56; Appendix F, v 1.64, p 414-415)

Same exclusion criteria as in Study 00-02

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1.3.1.5. Study Procedures (Clinical, v 1.59, p 53-100, 246; Appendix, v 1.64, 451-457)

During the 14-day screening period, subjects had a complete medical history and physical examination, 12-lead EKG, clinical laboratory evaluations (chemistry, hematology, serum pregnancy test, urine drug screen, tests for Hepatitis B and C Antigens and for HIV), and signed written informed consent. Subjects were instructed not to consume any prescription or over the counter medication for 14 days of alcohol for 48 hours before study drug administration or during study participation. Subjects meeting selection criteria were randomized to one of four groups (Groups 1, 2, 3, or 4) on the evening before morning dosing of Visit 2 for the total duration of this 9 week study.

All subjects were randomized to receive both Treatments A and B, with one-half of the subjects randomized to receive Treatments C and E and the remaining subjects randomized to receive Treatments D and F. Each treatment was administered as a one-time single-dose while in the fasting state with a washout period of 14 days between each leg of the study except for a washout period of 21 days between Period 3 and 4 due to holiday schedules.

- **Treatment A** - 1200 mg guaifenesin and 60 mg controlled release dextromethorphan hydrobromide (Mucinex[®] DM; Lot No. PB01-H30A2, expiration date NA) administered as an experimental formulation which was also the to-be-marketed formulation
- **Treatment B** - 1200 mg guaifenesin administered as Mucinex[®] following an overnight fast (Mucinex[®]; Lot No. PB-304A2, expiration date NA)
- **Treatment C (reference)** - 60 mg dextromethorphan hydrobromide administered as 30 mg every 6 hours for two doses (Benylin[®]; Lot No. 58351L, expiration date 4/2003)
- **Treatment D (reference)** - 60 mg dextromethorphan hydrobromide administered as 20 mg every 4 hours for three doses (Benylin[®]; Lot No. 58351L, expiration date 4/2003)
- **Treatment E (test)** - 30 mg dextromethorphan hydrobromide administered as 15 mg every 6 hours for two doses (Benylin[®]; Lot No. 58351L, expiration date 4/2003)
- **Treatment F (test)** - 30 mg dextromethorphan hydrobromide administered as 10 mg every 4 hours for three doses (Benylin[®]; Lot No. 58351L, expiration date 4/2003)

Group	Leg 1	Leg 2	Leg 3	Leg 4
1	Treatment A	Treatment B	Treatment C/D	Treatment E/F
2	Treatment B	Treatment C/D	Treatment E/F	Treatment A
3	Treatment C/D	Treatment E/F	Treatment A	Treatment B
4	Treatment E/F	Treatment A	Treatment B	Treatment C/D

Subjects were confined for 1½ days (approximately 36 hours) on each of four study periods (Day 1, Day 15, Day 29, Day 60) and were fasted prior to dose. They subsequently received a standardized lunch, dinner, and light snack following the single dose. No food or drinks containing caffeine or xanthine were permitted during confinement. Blood samples (10 mL

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sodium heparin anticoagulant) were obtained as individual venipunctures prior to dosing and 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.

Table 15. Study 2001-15 Timeline (Clinical, v 1.59, p 88-98)

	Screening	Treatment				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	
	Day -2 to -14	Day -1 to 2	Day 15 to 17	Day 29 to 31	Day 60 to 62	
General Procedures						
Informed consent	X					
Subject Number Assignment	X					
Medical history	X					
Verification of inclusion/exclusion criteria	X					
Concomitant medication assessment	X	X	X	X	X	
Vital signs	X	X	X	X	X	
Physical examination	X					
Clinical laboratory tests	X					
12-Lead electrocardiogram	X					
Urine drug screen	X	X	X	X	X	
Urine pregnancy test (all females)	X	X	X	X	X	
Randomization number assignment		X				
Study medication given		X	X	X	X	
Adverse event assessment		X	X	X	X	
Pharmacokinetic plasma sampling		X	X	X	X	

1.3.1.6. Parameters (Clinical, v 1.59, p 57; Appendix F, v 1.64, p 416)

Pharmacokinetic sampling (10 mL sodium heparin anticoagulant) was obtained prior to dosing and 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. Plasma was analyzed for guaifenesin and dextromethorphan content after

1.3.1.7. Safety Evaluations (Clinical, v 1.59, p 57-58; Appendix F, v 1.64, p 416-417)

Safety parameters included monitoring for adverse events. Subjects had a complete history and physical examination including vital signs, height, and weight. A 12-lead electrocardiogram, serum chemistry, complete blood count with differential, qualitative urine drug screen, tests for Hepatitis B and C Antigens and for HIV were also performed. Serum pregnancy tests were given for females.

1.3.1.8. Statistical Plan (Clinical, v 1.59, p 18-19, 63-64; Appendix F, v 1.64, p 422-433)

Pharmacokinetic parameters included the maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), the terminal elimination half-life and area under the plasma concentration-time curve (AUC), and apparent oral clearance (CL).

Bioavailability between experimental drug product and reference was examined. An analysis of variance (ANOVA) was performed and data for C_{max}, AUC_{0-t}, AUC_{0-inf},

half-life (T_{1/2}) and clearance (CL) were natural log (ln) transformed prior to analysis. The 90% confidence intervals of each test group mean relative to the reference group mean were obtained by taking the antilog of the corresponding 90% confidence intervals for the difference between the means on the log scale.

1.3.2. Results

1.3.2.1. Subject Disposition (Clinical, v 1.59, p 15, 69-76, p 87: Appendix F, v 1.64, p 487-488)

A total of 33 healthy male and female subjects entered the study. Thirty subjects completed the study. Subjects received medication on November 18, December 2, December 16, 2001 and January 6, 2002. Subject 3 withdrew during Period 2 due to difficulty with blood draws. Subjects 14 and 16 did not return for Period 3 and were dropped from the study. No subjects were replaced. The average age was 24.9 ± 7.68 years (Mean $\pm$ Standard Deviation) with a range of 18 years to 49 years of age. The average height was 67.8 ± 3.16 inches with a range of 61 to 73 inches. The average weight was 160.5 ± 25.6 pounds with a range of 122 to 210 pounds. There were 15 males (45%) and 18 females (55%). The clinical report differed from the demographic charts in that the former stated that all subjects except one (subject 23) were Caucasian and the latter stated that all were Caucasian. A fax was sent to the Applicant on February 20, 2004 requesting the Applicant to clarify the discrepancy. A letter sent on February 27, 2004 by the Applicant included demographic information for Subject 23 classifying her as a Hispanic female or "Other" ethnicity (v. 1.88, p 207) and therefore, 32 (97%) of the subjects in this study were Caucasian.

1.3.2.2. Protocol Deviations (Clinical, v 1.59, p 16; Appendix F, v 1.64, p 484-485)

Protocol deviations in the times of blood samples which were drawn two or more minutes late occurred 54 times due to instances of difficulties with blood draws (27), late returns (22), not returning for blood draws (5).

According to the study report, Subject 17, Period 1, Treatment B had taken medication on the afternoon before dose day that contained dextromethorphan. No case reports were submitted for this study. The Agency sent a fax on February 20, 2004 requesting case reports for Subject 17. The Applicant sent a letter dated February 27, 2004 that included the case reports for this subject. The Applicant stated that at the time of check-in for Period 1, the subject responded that he had not taken any prescription or over-the-counter medications when questioned. Dextromethorphan analysis of samples was completed on some of Treatment B group and Subject 17 was found to have positive values. A follow-up phone call with Subject 17 was done and it was learned that he had taken cough syrup consisting of dextromethorphan on the afternoon before dose day. The case report form was not revised to reflect this information; however, it was documented in the study file and the study report. Treatment B was 1200 mg guaifenesin and there was a 14-day washout period before the next Treatment C/D (1200 mg guaifenesin plus 60 mg dextromethorphan hydrobromide) was given. Due to the short half-life, there was no impact of the cough syrup containing dextromethorphan prior to Treatment B on the plasma levels of dextromethorphan taken

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after Treatment C/D. Additionally, Subject 17 was not an outlier in terms of dextromethorphan plasma levels.

1.3.2.3. Efficacy Endpoint Outcomes (Appendix F, v 1.64, p 486)

This is a pharmacokinetic study without efficacy evaluations.

1.3.2.4. Safety Outcomes

1.3.2.4.1. Total Drug Exposure (Clinical, v 1.59, p 71; Appendix F, v 1.64, p 489)

Treatment duration was similar among the three groups. Three subjects (Subjects 3, 14, 16) who withdrew from the study did not receive all treatments.

1.3.2.4.2. Adverse Events (Clinical, v 1.59, p 62; Appendix F, v 1.64, p 49-492)

According to the Applicant, both guaifenesin and dextromethorphan HBr were well tolerated. A total of 22 adverse events listed were from 13 subjects and included 13 cases of headache, one episode of restlessness, one episode of drowsiness, one incidence of lightheadedness, one episode of irritability, one upset stomach, one episode of vomiting, one episode of dry mouth, one episode of lower back pain, and one toothache. All subjects recovered from these adverse events (Table 10) and most cases (17) were possibly related to treatment regimen.

Table 16. Study 2001-15: Common adverse events reported by subjects (Appendix F, v 1.64, p 491-492)

	Treatment Dose at Onset of Study (N = number of subjects)					
	Treatment A Mucinex [®] DM (N=32)	Treatment B Mucinex [®] (N=32)	Treatment C Benylin [®] 30 mg q 6 hr X 2 doses (N=30)	Treatment D Benylin [®] 20 mg q 4 hr X 3 doses (N=31)	Treatment E Benylin [®] 15 mg q 6 hr X 2 doses (N=30)	Treatment F Benylin [®] 10 mg q 4 hr X 3 doses (N=31)
Total subjects with adverse event	4 (12.5%)	3 (9.4%)	4 (13.3%)	1 (3.2%)	2 (6.7%)	2 (6.5%)
TOTAL ADVERSE EVENTS	4	5	6	1	2	2
Body as a whole						
Back pain	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal system						
Dry mouth	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Upset Stomach	0 (0%)	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	0 (0%)	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)
Neurological system						
Headache	2 (6.3%)	1 (3.1%)	3 (10%)	1 (3.2%)	2 (6.7%)	2 (6.5%)
Lightheaded	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Drowsy	0 (0%)	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)
Irritable	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Toothache	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Restless	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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1.3.2.4.3. Discontinuation or treatment interruption due to adverse events (Clinical, v 1.59, p87; Appendix F, 1.64, p 482-483)

A total of 33 participants started the study due to five people not checking in for Period 1. Subject 3 withdrew consent due to difficulty with blood draws and did not complete Period 2. Subjects 14 and 16 did not check in for Period 3, were dropped from the study, and were not replaced.

Table 17. Study 2001-15: Subjects who discontinued therapy (Appendix F, 1.64, p 482-483)

Subject#	Treatment	Dose	Reason for discontinuation
3	D = Benylin [®]	20 mg q 4 hr.	Difficult blood draws
14	A = Mucinex [®] DM	1 tablet	Did not return
16	B = Mucinex [®]	1 tablet	Did not return

1.3.2.4.4. Serious adverse events and death (Clinical, v 1.59, p 10; Appendix F, v 1.64, p 494-495)

No subject died or experienced a serious adverse event necessitating withdrawal from the study. Case report forms were not submitted for this study.

1.3.2.4.5. Physical examination, ECG, and laboratory measure (Appendix F, v 1.64, p 493; Case reports, v 1.89)

There were no significant changes in physical examination, vital signs, or laboratory measurements that would indicate an effect of the study drug. There were no significant differences in these parameters between treatment groups. Analyses of these variables by age, gender, and race did not indicate any differential response to treatment.

1.3.2.4.6. Plasma concentrations of guaifenesin and dextromethorphan hydrobromide (Clinical, v 1.59, p 21-41)

Some subjects were classified as outliers in terms of guaifenesin plasma concentrations that were two standard deviations above the mean. Intrasubject variability occurred within these outliers according to the Biopharmacology reviewer, Dr. Shinja Kim. There was no evidence of a drug-drug pharmacokinetic interaction between guaifenesin and dextromethorphan. Subjects who were administered 30 mg dextromethorphan hydrobromide as Treatment E (15 mg q 6hr) had a mean dextromethorphan C_{max} of 2180 ± 2650 pg/mL (53.89% $\pm$ 17.62% of that of Treatment C) and an AUC_{inf} of 40324 ± 62644 hr-pg/mL (51.73% $\pm$ 16.77% of that of Treatment C). Subjects who were administered 30 mg dextromethorphan in Treatment F (10 mg q 4 hr) had a mean dextromethorphan C_{max} of 1286 ± 903 pg/mL (53.41% $\pm$ 12.82% of that of Treatment D) and an AUC_{inf} of 20114 ± 16158 hr-pg/mL (54.32% $\pm$ 16.37% of that of Treatment D). These data suggest that the pharmacokinetics of dextromethorphan were linear over the range investigated.

Table 18. Study 2001-15: Mean concentrations following Treatment dose (Clinical, v 1.59, p 21-41)

Treatment Group	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (hr- ng/mL)	$AUC_{0-\infty}$ (hr- ng/mL)	$T_{1/2}$ (hr)	Clearance (L/hr)
Guaifenesin						
A = Mucinex [®] DM	2176	1.44	8732	8761	1.31	179
B = Mucinex [®]	2145	0.91	8657	8953	4.79	171

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Treatment Group	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (hr- ng/mL)	AUC _{0-∞} (hr- ng/mL)	T _{1/2} (hr)	Clearance (L/hr)
Dextromethorphan Hydrobromide						
A = Mucinex [®] DM	4834	5.06	68189	68851	7.73	1697
C = Benylin [®] 30 mg q 6 hr X 2 doses	4711	8.31	82279	82655	7.46	1291
D = Benylin [®] 20 mg q 4 hr X 3 doses	3130	7.01	44287	44683	7.04	1335
E = Benylin [®] 15 mg q 6 hr X 2 doses	2180	8.03	39746	40324	7.32	2940
F = Benylin [®] 10 mg q 4 hr X 3 doses	1286	7.73	19833	20114	7.44	3894

1.3.3. Discussion and Conclusions (Clinical v 1.59, p 15-19)

Study 2001-15 determined the relative bioavailability of an experimental sustained release formulation containing 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide as compared to reference guaifenesin and dextromethorphan products in 33 healthy male and female subjects ages 18 to 49. Subjects were given single doses of medications separated by 14-day washout periods (except for a 21-day washout between Period 3 and Period 4) during the course of the nine-week study. A total of 33 subjects were included in the ITT population. Review of the plasma concentration profiles for C_{max}, t_{max}, AUC_{0-t}, AUC_∞, and t_{1/2} for the experimental formulation of Mucinex[®] DM showed that the experimental formulations were comparable to the reference formulations and the pharmacokinetics of guaifenesin were not affected by the presence of dextromethorphan. In addition, the data comparing the 30 mg and 60 mg doses of dextromethorphan administered as Benylin[®] demonstrated that the pharmacokinetics of immediate-release dextromethorphan were linear over the range studied. The experimental formulation used in this study is the proposed commercial formulation of Mucinex[®] DM.

1.4. Study 2002-08: "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" (v 1.65-1.72)

Study 2002-08 utilized the to-be-marketed product.

1.4.1. Protocol and Investigators

1.4.1.1. Investigators and Centers (Clinical, v 1.65, p 44-45, 69-74 p 102-103; Appendix 1.72, p 363-364, 404-424)

Investigator: Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc.,
1816 West Mount Vernon, Springfield, MO 65802

Study dates: March 4, 2002 to May 1, 2002 (The first study medication was administered on March 15, 2002.)

Study report: February 1, 2003 (There were no protocol amendments.)

Sites: Single-site

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IRB: Bio-Kinetic Clinical Applications, Inc. Institutional Review Board (IRB)
Approval date: March 4, 2002

The Applicant states that the study was conducted according to FDA regulations and guidelines and that written informed consent was obtained from each subject prior to participation in the study.

1.4.1.2. Objective/Rationale (Clinical, v 1.65, p 48; Appendix F, v 1.72, p 367)

The objective of this Phase I study was to determine the relative bioavailability of an experimental to-be-marketed formulation containing 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide compared to that of two reference formulations in normal, healthy male and/or female volunteers.

1.4.1.3. Overall Design (Clinical, v 1.65, p 48; Appendix F, v 1.72, p 367)

This was an open label, single dose, randomized, 3-way crossover study.

1.4.1.4. Study Population (Clinical, v 1.65, p 49-50; Appendix F, v 1.72, p 368-369)

Inclusion Criteria (Clinical, v. 1.65, p 49-50; Appendix F, v 1.72, p 368-369)

Same inclusion criteria as in Study 00-02

Exclusion Criteria (Clinical, v. 1.65, p 49-50; Appendix F, v 1.72, p 368-369)

Same exclusion criteria as in Study 00-02

1.4.1.5. Study Procedures (Clinical, v 1.65, p 50-68, Appendix, v 1.72, p 369-403)

Following an initial 14-day screening period, subjects meeting selection criteria were randomized to one of three treatment groups on the evening before morning dosing for the total duration of the seven-week study. The subjects attended a total of four clinic visits that included a screening visit, baseline visit on Day 1 of treatment, and 2 other visits on Day 15 and 29. During the 14-day screening period, subjects had a complete medical history and physical examination, 12-lead EKG, clinical laboratory evaluations (chemistry, hematology, serum pregnancy test, urine drug screen, tests for Hepatitis B and C Antigens and for HIV), and signed written informed consent. Subjects were instructed not to consume any prescription or over the counter medication for 14 days of alcohol for 48 hours before study drug administration or during study participation. Subjects meeting selection criteria were randomized to one of 3 groups (Groups 1, 2, or 3) on the evening before morning dosing of Visit 2 for the total duration of this 7 week study and received each treatment (Treatments A, B, and C) during the course of the study.

- **Treatment A** - 1200 mg controlled release guaifenesin (Mucinex[®]; Lot No. PB-01H34A3, expiration date NA) and 60 mg dextromethorphan hydrobromide administered as 15 mL of Vick's Formula 44[®] Cough Medicine (30 mg) [Lot No. 1141RX] while in the fasting state and a second 15 mL dose six hours later.
- **Treatment B** - 1200 mg controlled release guaifenesin (Mucinex[®]; Lot No. PB-01H34A3, expiration date NA) and 60 mg dextromethorphan hydrobromide

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administered as 10 mL of Vick's Formula 44[®] Cough Medicine (20 mg) [Lot No. 1141RX] while in the fasting state and a second 10 mL dose four hours later and a third 10 mL dose four hours later.

- **Treatment C** - 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide experimental controlled release tablet (Mucinex[®] DM, Lot No. PB01H30A3, expiration date NA) administered while in the fasting state.

Group	Period 1	Period 2	Period 3
1	Treatment A	Treatment B	Treatment C
2	Treatment B	Treatment C	Treatment A
3	Treatment C	Treatment A	Treatment B

Each treatment was administered as a one-time single-dose while in the fasting state with a washout period of 14 days between each period of the study. Subjects were confined for 1½ days (approximately 36 hours) on each of three study periods (Day 1, Day 15, and Day 29) and were fasted prior to dose. They subsequently received a standardized lunch, dinner, and light snack following the single dose. No food or drinks containing caffeine or xanthine were permitted during confinement. Pharmacokinetic sampling (7ml sodium heparin anticoagulant) was obtained prior to dosing and 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, 72, and 96 hours post dose. The total blood loss per subject for the guaifenesin and dextromethorphan PK analyses was estimated to be 609 mL.

Table 19. Study 2002-08 Timeline (Clinical, v 1.65, p 79-101)

	Screening	Treatment		
	Visit 1	Visit 2	Visit 3	Visit 4
	Day -2 to -14	Day -1 to 2	Day 15 to 17	Day 29 to 31
General Procedures				
Informed consent	X			
Subject Number Assignment	X			
Medical history	X			
Verification of inclusion/exclusion criteria	X			
Concomitant medication assessment	X	X	X	X
Vital signs	X	X	X	X
Physical examination	X			
Clinical laboratory tests	X			
12-Lead electrocardiogram	X			
Urine drug screen	X	X	X	X
Serum pregnancy test (all females)	X	X	X	X
Tests for HBV, HCV, HIV	X			
Randomization number assignment		X		
Study medication given		X	X	X
Adverse event assessment		X	X	X
Pharmacokinetic plasma sampling		X	X	X

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1.4.1.6. Parameters (Clinical, v 1.65, p 51; Appendix F, v 1.72, p 370)

Pharmacokinetic sampling (7 mL sodium heparin anticoagulant) was obtained prior to dosing and 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, 72, and 96 hours post dose. The total blood loss per subject for the guaifenesin and dextromethorphan PK analyses was estimated to be 609 mL.

1.4.1.7. Safety Evaluations (Clinical, v 1.65, p 51; Appendix F, v 1.72, p 370)

Safety parameters included monitoring for adverse events. Subjects had a complete history and physical examination including vital signs, height, and weight. A 12-lead electrocardiogram, serum chemistry, complete blood count with differential, qualitative urine drug screen, tests for Hepatitis B and C Antigens and for HIV were also performed. Serum pregnancy tests were given for females.

1.4.1.8. Statistical Plan (Clinical, v 1.65, p 56-57; Appendix F, v 1.72, p 375-376)

Pharmacokinetic parameters included the maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), the terminal elimination half-life and area under the plasma concentration-time curve (AUC) and apparent oral clearance (CL).

An analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for the ratio of Test/Reference. C_{max}, AUC_{0-t}, AUC_{0-inf}, half-life (T_{1/2}) and clearance (CL) were natural log (ln) transformed prior to analysis. 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.

1.4.2. Results

1.4.2.1. Subject Disposition (Clinical, v 1.65, p 16-18; Appendix F, v 1.72, p 439-440)

A total of 40 healthy male and female subjects were screened for the study. Thirty-seven subjects were randomized to one of three treatment legs. Thirty-two subjects completed the study. The average age was 26.7 ± 10.6 years (Mean $\pm$ Standard Deviation) with a range of 18 to 53 years. The average height was 68.6 ± 3.84 inches with a range of 60 to 78 inches. The average weight was 169 ± 26.6 pounds with a range of 115 to 225 pounds. There were 27 males (69%) and 12 females (31%) enrolled of whom 36 (92%) were Caucasian, two were Black (5%), and one (3%) was Hispanic. Eight subjects were classified as being withdrawn from the study; however, in actuality, only five randomized subjects who had received at least one dose of study medication were dropped from the study. Subjects 28, 29, and 35 were not dosed for Period 1, and did not receive any study medication, and were dropped from the study and replaced by Subjects 128, 129, and 135. Subjects 7, 18, and 36 did not check in for Period 2 and were dropped from the study. Subject 135 did not check in for Period 2 and was dropped from the study. Subject 21 had a positive pregnancy test and was dropped from the study. Disposition of the subjects is shown in Table 2.

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Table 20. Study 2002-08: Subject Disposition and Reasons for Withdrawal (Appendix F, v 1.72, p 425-436)

	Group 1 (A, B, C)*	Group 2 (B, C, A)*	Group 3 (C, A, B)*
Number randomized	13	12	12
Number completed	9	12	11
Reasons for discontinuation:			
Adverse event	1	0	0
Treatment failure	0	0	0
Lost to follow-up	2	0	0
Consent withdrawn	1	0	1
Non-compliance	0	0	0
Did not meet entry criteria	0	0	0
*A = Mucinex [®] + Vicks [®] 30 mg q 6 hr. X 2 doses B = Mucinex [®] + Vicks [®] 20 mg q 4 hr. X 3 doses C = Mucinex [®] DM			

1.4.2.2. Protocol Deviations (Clinical, v 1.65, p 75-76; Appendix F, v 1.72, p 437)

Protocol deviations in the times of blood sampling which were drawn two or more minutes late occurred 28 times due to instances of difficulties with blood draws (6), late returns (15), not returning for blood draws (6), and one adverse event.

1.4.2.3. Efficacy Endpoint Outcomes (Appendix F, v 1.72, p 438)

This is a pharmacokinetic study without efficacy evaluations.

1.4.2.4. Safety Outcomes

1.4.2.4.1. Total Drug Exposure (Clinical, v 1.65, p 16; Appendix F, v 1.72, p 435-436)

Treatment duration varied among the three groups. Five subjects did not receive all treatments. Four subjects were on Treatment Dose A at the onset of the study and did not return for Period 2 or 3 and one was on Treatment Dose C at the onset of the study and did not return for Period 2 and 3.

1.4.2.4.2. Adverse Events (Clinical, v 1.65, p 55; Appendix F, v 1.72, p 443-444)

According to the Applicant, both guaifenesin and dextromethorphan HBr were well tolerated. Eight adverse events listed were from six subjects and included three cases of nausea, two cases of headache, one episode of diarrhea, one episode of lightheadedness, and one incidence of a positive pregnancy test. All subjects recovered from these adverse events (Table 4) and most cases (6) were possibly related to treatment regimen.

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Table 21. Study 2002-08: Common adverse events reported by subjects (Appendix F, v 1.72, p 443-444)

	Treatment Dose at Onset of Study		
	Treatment A Mucinex [®] + Vicks [®] 30 mg q 6hr X 2 doses (N=36)	Treatment B Mucinex [®] + Vicks [®] 20 mg q 4hr X 3 doses (N=34)	Treatment C Mucinex [®] DM (N=33)
Total subjects with adverse event	3 (8.3%)	2 (5.9%)	2 (6.1%)
TOTAL ADVERSE EVENTS	4	2	2
Body as a whole			
Pregnancy	0 (0%)	1 (2.9%)	0 (0%)
Gastrointestinal system			
Diarrhea	0 (0%)	0 (0%)	1 (3.0%)
Nausea	2 (5.6%)	1 (2.9%)	0 (0%)
Neurological system			
Headache	1 (2.8%)	0 (0%)	1 (3.0%)
Lightheaded	1 (2.8%)	0 (0%)	0 (0%)

1.4.2.4.3. Discontinuation or treatment interruption due to adverse events (Clinical, v 1.65, p 78; Appendix F, v 1.72, p 435-436; Case reports, v 1.91, p 193-210)

Five subjects discontinued study treatment prematurely due to personal reasons or adverse events and did not return for treatment Period 2 or 3 of the study. These events are listed in Table 5. Subject 21 had a positive pregnancy test on April 12, 2002 and was withdrawn from the study on April 13, 2002 due to lack of compliance. Her previous pregnancy test was negative on March 29, 2002. Case report forms for Subject 21 indicate a spontaneous abortion without complications on May 15, 2002.

Table 22. Study 2002-08: Subjects who discontinued therapy (Appendix F, v 1.72, p 435-436)

Subject #	Treatment	Duration	Dose	Reason for discontinuation
7	A = Mucinex [®] + Vicks [®] 30 mg q 6hr X 2 doses	13 days	1 tablet, 2 X 15 ml	Did not return
18	B = Mucinex [®] + Vicks [®] 20 mg q 4hr X 3 doses	2 days	1 tablet, 3 X 10 ml	Did not return
21	B = Mucinex [®] + Vicks [®] 20 mg q 4hr X 3 doses	14 days	1 tablet, 3 X 10 ml	Positive pregnancy test
36	C = Mucinex [®] DM	1:30	1 tablet	Withdrew consent
135	A = Mucinex [®] + Vicks [®] 30 mg q 6hr X 2 doses	12 days	1 tablet, 15 ml q 6hr.	Withdrew consent

1.4.2.4.4. Serious adverse events and death (Clinical, v 1.65, p 10; Appendix F, v 1.72, p 446-447, v 1.91, p 193-210)

No subject died or experienced a serious adverse event necessitating withdrawal from the study. Case report forms were submitted for Subject 21 who withdrew from the study due to lack of compliance regarding a positive pregnancy test on [redacted]. The pregnancy ended early due to a spontaneous abortion.

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1.4.2.4.5. Physical examination, ECG, and laboratory measure (Case reports, v 1.89)

There were no significant changes in physical examination, vital signs, or laboratory measurements that would indicate an effect of the study drug. There were no significant differences in these parameters between treatment groups. Analyses of these variables by age, gender, and race did not indicate any differential response to treatment.

1.4.2.4.6. Plasma concentrations of guaifenesin and dextromethorphan (Clinical, v 1.65, p 18, 23-36)

Subject 17, Period 1, Treatment B had taken medication containing dextromethorphan on the afternoon before dose day. This subject's plasma concentrations of guaifenesin and dextromethorphan did not cause him to be an outlier between treatment groups although his C_{max} and AUC_{0-t} were the highest within his treatment group (Group 2).

Table 23. Study 2002-08: Mean concentrations following Treatment dose (Clinical, v 1.65, p 23-36)

Treatment Group	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (hr-ng/mL)	AUC _{0-∞} (hr-ng/mL)	T _{1/2} (hr)	Clearance (L/hr)
Guaifenesin						
A = Mucinex [®] + Vicks [®] 30 mg q 6hr X 2 doses	1743 ± 903	1.25 ± 0.660	7730 ± 3578	7836 ± 3616	2.60	192
B = Mucinex [®] + Vicks [®] 20 mg q 4hr X 3 doses	1783 ± 808	1.27 ± 0.833	7477 ± 3369	7616 ± 3398	3.19	191
C = Mucinex [®] DM	1710 ± 807	1.55 ± 0.789	7082 ± 2805	7102 ± 2807	1.24	201
Dextromethorphan						
A = Mucinex [®] + Vicks [®] 30 mg q 6hr X 2 doses	7,946 ± 12,386	8.32 ± 2.88	248,123 ± 575,122	294,267 ± 724,235	10.9	2044
B = Mucinex [®] + Vicks [®] 20 mg q 4hr X 3 doses	8,598 ± 13,559	8.90 ± 3.62	271,074 ± 641,451	339,447 ± 850,232	11.3	1920
C = Mucinex [®] DM	7,483 ± 12,332	6.30 ± 2.64	253,196 ± 604,557	316,592 ± 796,975	12.6	2756

1.4.3. Discussion and Conclusions (Clinical, v 1.65, p 16-21)

Study 2002-08 determined the relative bioavailability of a the to-be-marketed sustained release formulation containing 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide as compared to reference guaifenesin and dextromethorphan products in 33 normal, healthy male and female subjects ages 18 to 49. Subjects were given single doses of medications separated by 14-day washout periods during the course of the nine-week study. A total of 33 subjects were included in the ITT population. Based on the study data, the Applicant stated that both guaifenesin and dextromethorphan hydrobromide in the experimental tablet were bioequivalent to the reference products. The 90% confidence intervals were all contained within 80% to 125% for guaifenesin in terms of C_{max}, AUC_{0-t}, and AUC_∞. The 90% confidence intervals were all contained within 70% to 143% for dextromethorphan hydrobromide in terms of C_{max}, AUC_{0-t}, and AUC_∞ in the experimental tablet and was considered to be bioequivalent to both 30 mg dextromethorphan hydrobromide every 6 hours and 20 mg every 4 hours. This review did not uncover any outstanding clinical issues or significant safety concerns in this study.

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1.5. Study 2002-10. A Definitive Study Designed to Examine the Steady-State Pharmacokinetics of Guaifenesin and Dextromethorphan from an Experimental Controlled-Release Formulation in Normal Healthy Volunteers Compared to Reference Guaifenesin and Dextromethorphan Products (v 1.73-1.81)

Study 2002-10 utilized the to-be-marketed product. Treatment C formulation was previously evaluated in Study 2001-04.

1.5.1. Protocol (Appendix F, p 293-339)

1.5.1.1. Investigators and Centers (Clinical, v 1.73, p 5, 52-53, 77-83; Appendix F, p 294-298, 341-361)

Investigator: Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc.,
1816 West Mount Vernon, Springfield, MO 65802

Study dates: April 30, 2002 to July 3, 2002 (The first study medication was administered on May 13, 2002.)

Study report: February 5, 2003 (The original protocol dated March 21, 2002 had one protocol amendment dated May 1, 2002 with a revised randomization schedule)

Sites: Single-site

IRB: Bio-Kinetic Clinical Applications, Inc. Institutional Review Board (IRB)
Approval date: April 26, 2002

The Applicant states that the study was conducted according to FDA regulations and guidelines and that written informed consent was obtained from each subject prior to participation in the study.

1.5.1.2. Objective/Rationale (Clinical, v 1.73, p 56; Appendix F, v 1.81, p 301)

The objective of this Phase 1 study was to determine the steady state of an experimental to-be-marketed formulation containing 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide compared to that of two reference formulations in healthy male and female subjects ages 18 to 55.

1.5.1.3. Overall Design (Clinical, v 1.73, p 56; Appendix F, v 1.81, p 301)

This was a prospective, open label, multiple-dose, randomized, three-way crossover pharmacokinetic study.

1.5.1.4. Study Population (Clinical, v 1.73, p 57-58; Appendix F, v 1.81, p 302-303)

Inclusion Criteria (v 1.73, p 57-58; Appendix F, v 1.81, p. 302-303)

Same inclusion criteria as in Study 00-02

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Exclusion Criteria (v 1.73, p 58; Appendix F, v 1.81, p 303)

Same exclusion criteria as in Study 00-02

1.5.1.5. Study Procedures (Clinical, v 1.73, p 58-111; Appendix F, v 1.81, p 303-339)

The subjects attended a total of three clinic visits that included a screening visit, baseline visit on Day 1 of treatment, and 2 other visits on Day 15 and 29. During the 14-day screening period, subjects had a complete medical history and physical examination, 12-lead EKG, clinical laboratory evaluations (chemistry, hematology, serum pregnancy test, urine drug screen, tests for Hepatitis B and C Antigens and for HIV), and signed written informed consent. Subjects were instructed not to consume any prescription of over the counter medication for 14 days of alcohol for 48 hours before study drug administration or during study participation. Subjects meeting selection criteria were randomized to one of three groups (Groups 1, 2, or 3) on the evening before morning dosing for the total duration of the 9 week study and received each treatment (Treatments A, B, and C) during the course of the study. All treatments were administered every 12 hours for a total of 11 dosing periods with morning doses following an overnight fast. There was a 14-day washout between treatments.

- **Treatment A (reference)** - 1200 mg controlled release guaifenesin (Mucinex[®]; Lot No. PB01-H34R4, expiration date NA) and 60 mg controlled release dextromethorphan hydrobromide administered as 30 mg/15 mL of (Vick's Formula 44[®] Cough Relief; Lot No. 1129RX, expiration date April 2003) while in the fasting state and a second 15 mL dose six hours later.
- **Treatment B (test)** - 1200 mg guaifenesin controlled release tablet (Mucinex[®]; Lot No. PB01-H34R4, expiration date NA) and 60 mg controlled release dextromethorphan hydrobromide administered as 20 mg/10 mL of (Vick's Formula 44[®] Cough Relief; Lot No. 1129RX, expiration date April, 2003) while in the fasting state and a second 10 mL dose 4 hours later.
- **Treatment C (test)** - 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide experimental controlled release tablet (Mucinex[®] DM; Lot No. PB01-H30A, expiration date NA) while in the fasting state.

The following lots of drug products were actually used to dose subjects:

- *Guaifenesin Extended-Release Tablets, 1200 mg, Lot PB01-H34A4 (not PB01-H34R4)*
- *Guaifenesin 1200 mg/Dextromethorphan HBr 60 mg Extended-Release Tablets, Lot PB01-H30A4*
- *Vicks 44 Cough Relief Dextromethorphan HBr, Lot 1141RX (not 1129RX)*

The Division of Scientific Investigations (DSI) audit concluded that there were errors in accountability records, specifically in the recording of lot numbers for drug, and they were recognized and corrected during the Applicant's monitoring visits. Errors in the report were recognized in part approximately two days before the inspection began, and in part during the inspection. [NDA 21-620, DSI Review submitted by pharmacologist M.F. Skelly, Ph.D. and associate director C.T. Viswanathan, Ph.D.]

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Group	Period 1	Period 2	Period 3
1	Treatment A	Treatment B	Treatment C
2	Treatment B	Treatment C	Treatment A
3	Treatment C	Treatment A	Treatment B

Subjects were confined for 1½ days (approximately 36 hours) on Day -1 and returned for subsequent doses on Test Day 1 through 5 and were fasted prior to each dose. During Day 1 through Day 5, each treatment was administered as a single-dose with 240 mL of water while in the fasting state (10 hours pre-dose) with a washout period of 14 days between each leg of the study. Subjects in Treatment groups A and B returned to the clinic every evening to facilitate dosing through the night. On Day 5, subjects were confined until 24 hours after blood sampling on Day 6. Subjects returned to the clinic for subsequent blood sampling (hours 36, 48, 72, and 96). Subjects maintained the fast until after collection of the four hour blood sample. Water was allowed *ad lib* after the two hour-post dose blood sample was obtained. Subjects subsequently received a standardized lunch and dinner following the single dose at 4 and 10 hours after dosing, respectively. A light snack was served at 8:00 PM. No food or drinks containing caffeine or xanthine were permitted during confinement and no concurrent medications were permitted after study enrollment unless authorized by the Investigator.

Adverse events were evaluated by the Investigator and recorded on source documents and case report forms (v 1.88, p 3-113). The following parameters including date of onset, duration, intensity, frequency, action taken, relationship to study medication, and subject outcome were reported and followed to resolution.

Each subject had the right to withdraw consent to participate in the study at any time. The investigator had the option to discontinue any subject's participation for any reason.

Table 24. Study 2002-10 Timeline (Clinical, v 1.73, p 88-110)

	Screening	Treatment			
	Visit 1	Visit 2	Visit 3	Visit 4	
	Day -2 to -14	Day -1 to 10	Day 15 to 25	Day 29 to 39	
General Procedures					
Informed consent	X				
Subject Number Assignment	X				
Medical history	X				
Verification of inclusion/exclusion criteria	X				
Concomitant medication assessment	X	X	X	X	
Vital signs	X	X	X	X	
Physical examination	X				
Clinical laboratory tests	X				
12-Lead electrocardiogram	X				
Urine drug screen	X	X	X	X	
Serum pregnancy test (all females)	X	X	X	X	
Tests for HBV, HCV, and HIV	X				
Randomization number assignment		X			
Study medication given		X	X	X	
Adverse event assessment		X	X	X	
Pharmacokinetic plasma sampling		X	X	X	

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1.5.1.6. Parameters (Clinical, v 1.73, p 59; Appendix F, v 1.81, p 304-305)

Pharmacokinetic samples (7 mL sodium heparin anticoagulant) were obtained as individual venipunctures at the following times: Day 1 Pre-AM-dose, Day 4 Pre-AM-dose, and Day 5 Pre-AM-dose for all three treatment groups. On Day 6 Treatment A subjects had blood samples taken at 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 subjects had blood samples taken at Pre-Dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 4.5, 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. On Day 6, Treatment C subjects had blood samples taken at Pre-Dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 24, 36, 48, 72, and 96 hours post dose. The total blood loss per subject for guaifenesin and dextromethorphan PK analyses was estimated to be 588 mL.

1.5.1.7. Safety Evaluations (Clinical, v 1.73, p 60; Appendix F, v 1.81, p 307-309)

Adverse events were recorded for any clinically significant changes in physical examination or vital signs, or upon subject report of any complaint relative to well being. Subjects had a complete history and physical examination including vital signs, height, and weight. A 12-lead electrocardiogram, serum chemistry, complete blood count with differential, qualitative urine drug screen, tests for Hepatitis B and C Antigens and for HIV were also performed. Serum pregnancy test was performed for females.

1.5.1.8. Statistical Plan (Clinical, v 1.73, p 63-64; Appendix F, v 1.81, p 308-309)

Sample Size:

Calculations regarding sample size for this study were not included in the NDA application.

Statistical analysis:

Pharmacokinetic parameters included the maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), the terminal elimination half-life and area under the plasma concentration-time curve (AUC) for guaifenesin and dextromethorphan. Half-life, the logarithm of C_{max} , and the logarithm of AUC were analyzed with an analysis of variance with effects for sequence, subject nested within sequence, period, and formulation. Analysis was based on the ITT population.

1.5.2. Results

1.5.2.1. Subject Disposition (Clinical, v 1.73, p 19-20, 26; Appendix F, v 1.81, p 371-382)

A total of 36 healthy male and female subjects entered the study and were enrolled and randomized to one of three treatment legs. Thirty-four subjects completed the study. Two subjects, subject 19 and subject 10 withdrew consent from the study following the first dose of Period 1 and prior to the start of Period 3 respectively. Neither was replaced. The average age was 34.3 ± 13.3 years (Mean $\pm$ Standard Deviation) with a range of 19 years to 55 years. The average height was 68.6 ± 3.92 inches with a range of 60 to 77 inches. The average weight was 176 ± 26.6 pounds with a range of 132 to 240 pounds. There were 21 males (58%) and 15 females (42%) enrolled, of whom 35 (97%) were Caucasian and one (3%) was Black.

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1.5.2.2. Protocol Deviations (Clinical, v 1.73, p 84; Appendix F, v 1.81, p 296, 374)

Protocol deviations in the times of blood sampling which were drawn two or more minutes late occurred 28 times due to instances of difficulties with blood draws (6), late returns (15), not returning for blood draws (6), and adverse events (1).

Subject 16 was not able to return for Period 3, 36-hour medication administration due to an automobile accident. The sponsor approved her continued enrollment.

1.5.2.3. Efficacy Endpoint Outcomes (Appendix F, v 1.81, p 375)

This was a pharmacokinetic study without efficacy evaluations.

1.5.2.4. Safety Outcomes

1.5.2.4.1. Total Drug Exposure (Clinical, v 1.73, p 19; Appendix F, v 1.81, p 373)

Treatment duration was similar among the three groups. Only two subjects did not receive all treatments.

1.5.2.4.2. Adverse Events (Clinical, v 1.73, p 20; Appendix F, v 1.81, p 380-381)

According to the Applicant, both guaifenesin and dextromethorphan HBr were well tolerated. Sixteen adverse events listed were from five subjects and included two cases of nausea, three episodes of vomiting, one case of flushing, one episode of cough, one case of sinus pressure, one aphthous ulcers in throat, two cases of upset stomach, two cases of heartburn, one episode of back pain, one case of itchy eye, one case of chest congestion. All subjects recovered from these adverse events (Table 4) and most cases (12) were judged by the investigator to be unrelated to treatment regimen.

Table 25. Study 2002-10: Common adverse events reported by subjects (v 1.81, p 380-381)

	Treatment Dose (N = number of subjects)		
	Treatment A Mucinex [®] + Vicks [®] 30 mg q 6hr (N=35)	Treatment B Mucinex [®] + Vicks [®] 20 mg q 4hr (N=35)	Treatment C Mucinex [®] DM q 12hr (N=35)
Total subjects with adverse event	1 (2.9%)	1 (2.9%)	4 (1.1%)
TOTAL ADVERSE EVENTS	1	6	9
Body as a whole			
Back pain	0 (0%)	0 (0%)	1 (2.9%)
Gastrointestinal system			
Flushing	0 (0%)	0 (0%)	1 (2.9%)
Heartburn	0 (0%)	2 (5.7%)	0 (0%)
Nausea	1 (2.9%)	1 (2.9%)	0 (0%)
Upset Stomach	0 (0%)	1 (2.9%)	1 (2.9%)
Vomiting	0 (0%)	2 (5.7%)	1 (2.9%)
ENT/Respiratory			
Sinus pressure	0 (0%)	0 (0%)	1 (2.9%)
Aphthous ulcers in throat	0 (0%)	0 (0%)	1 (2.9%)
Chest congestion	0 (0%)	0 (0%)	1 (2.9%)
Cough	0 (0%)	0 (0%)	1 (2.9%)
Itchy eyes	0 (0%)	0 (0%)	1 (2.9%)

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1.5.2.4.3. Discontinuation or treatment interruption due to adverse events (Clinical, v 1.73, p 84; Appendix F, v 1.81, p 372-373)

Two subjects discontinued study treatment prematurely due to personal reasons and did not return for treatment Period 2 or 3 of the study. Subject 10 received Treatment B (Mucinex[®] and Vicks 44[®] 20mg q4hr) for a total of 13 days. Subject 19 received Treatment C for a duration of 12 hours, which was equivalent to one tablet of Mucinex[®] DM. Subject 16 was not able to return for Period 3 due to an automobile accident; however, the Applicant approved her continued enrollment.

Table 26. Study 2002-10: Subjects who discontinued therapy (Appendix F, v 1.82, p 372-373)

Subject#	Treatment	Duration	Dose	Reason for discontinuation
10	B = Mucinex [®] + Vicks [®] 20 mg q 4hr	13 days	1 tablet of 12, 20 mg q 4 hr.	Withdrew consent
19	C = Mucinex [®] DM	12 hours	1 tablet	Withdrew consent

1.5.2.4.4. Serious adverse events and death (Clinical, v 1.73, p 20; Appendix F, v 1.81, p383)

No subject died or experienced a serious adverse event necessitating withdrawal from the study. Case report forms were not submitted for this study.

1.5.2.4.5. Physical examination, ECG, and laboratory measure (Case reports, v 1.81, p 382)

There were no significant changes in physical examination, vital signs, or laboratory measurements that would indicate an effect of the study drug. There were no significant differences in these parameters between treatment groups. Analyses of these variables by age, gender, and race did not indicate any differential response to treatment.

1.5.2.4.6. Plasma concentrations of guaifenesin, dextromethorphan hydrobromide (Clinical, v 1.73, p 22, 27-41)

Subject 23 had very high levels of dextromethorphan and the dilution QC came out 15.6% off, while the FDA accepts up to 15%. The statistical analyses, therefore, were conducted with and without including Subject 23 and the results including Subject 23 were submitted by the Applicant since the data did not differ from those excluding the data. The C_{min} for guaifenesin was below the C_{min} value for Mucinex[®], however, the C_{min} for the new proposed formulation was within the known effective concentration level associated with guaifenesin.

Table 27. Study 2002-10: Steady-state mean concentrations (Clinical, v 1.73, p 22, 27-41)

Treatment Group	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₄ (hr-ng/mL)	AUC _{0-∞} (hr-ng/mL)
Guaifenesin				
A = Mucinex [®] + Vicks [®] 30 mg q 6hr	1935 + 746	122 + 0.854	7540	3.11
B = Mucinex [®] + Vicks [®] 20 mg q 4hr	1938 + 637	121 + 0.463	7403	3.22
C = Mucinex [®] DM	1780 + 633	121 + 0.864	7138	1.91
Dextromethorphan Hydrobromide				
A = Mucinex [®] + Vicks [®] 30 mg q 6hr	17960 + 37537	125 + 2.94	181904	8.67
B = Mucinex [®] + Vicks [®] 20 mg q 4hr	17251 + 39562	126 + 1.73	169160	11.8
C = Mucinex [®] DM	17213 + 33703	125 + 1.62	175309	7.84

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1.5.3. Discussion and Conclusions (Clinical, v 1.73, p 19-24)

Study 2002-10 determined the steady state of an experimental sustained release formulation containing 1200 mg guaifenesin and 60 mg dextromethorphan hydrobromide compared to two reference formulations in 36 healthy male and female subjects ages 18 to 55. Subjects were given multiple doses of medications for 5 days separated by 14-day washout. A total of 34 subjects were included in the ITT population.

Based on the study data, the Applicant stated that both guaifenesin and dextromethorphan hydrobromide in the experimental tablet were bioequivalent to the reference products. Review of the plasma steady-state concentrations showed that the 90% confidence intervals were all contained within 80% to 125% for guaifenesin in terms of C_{max} and AUC_{SS}. The 90% confidence intervals were all contained within 80% to 125% for dextromethorphan hydrobromide in terms of C_{max} and AUC_{SS} in the experimental tablet and was considered to be bioequivalent to both 30 mg dextromethorphan hydrobromide every 6 hours and 20 mg every 4 hours. Thus, the review of the data demonstrated that guaifenesin and dextromethorphan in Mucinex[®] DM was bioequivalent at steady-state to that of reference products Mucinex[®] and Vicks[®] Formula 44[®] cough medicine. This Medical Officer review did not uncover any outstanding clinical issues or significant safety concerns in this study.

1.6. Study 2002-12. A Study Designed to Examine the Effect of the Consumption of a High Fat meal on the Bioavailability of Guaifenesin and Dextromethorphan from an Experimental Controlled Release Formulation (v 1.82-1.87)

Study 2002-12 utilized the to-be-marketed product.

1.6.1. Protocol (Appendix F, v 1.87, p 318-357)

1.6.1.1. Investigators and Centers (Clinical, v 1.82, p 5, 38-39, 60-65, 76-77; Appendix F, v 1.87, p 319-320, 359-378)

Investigator: Dennis N. Morrison, D.O., Bio-Kinetic Clinical Applications, Inc.,
1816 West Mount Vernon, Springfield, MO 65802

Study dates: April 15, 2002 to May 15, 2002 (The first study medication was administered on April 27, 2002.)

Study report: February 12, 2003 (There were no protocol amendments.)

Sites: Single-site

IRB: Bio-Kinetic Clinical Applications, Inc. Institutional Review Board (IRB)
Approval date: April 15, 2002

The Applicant states that the study was conducted according to FDA regulations and guidelines and that written informed consent was obtained from each subject prior to participation in the study.

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1.6.1.2. Objective/Rationale (Clinical, v 1.82, p 42; Appendix F, v 1.87, p 323)

The objective of this Phase I study was to determine the effect of the consumption of a high fat breakfast on the relative bioavailability of a to-be-marketed formulation containing 1200 mg guaifenesin and 60 mg dextromethorphan in normal, healthy male and female subjects ages 18 to 55.

1.6.1.3. Overall Design (Clinical, v 1.82, p 42; Appendix F, v 1.87, p 323)

This was a prospective, open label, single-dose, randomized, two-way crossover pharmacokinetic study.

1.6.1.4. Study Population (Clinical, v 1.82, p 43-44; Appendix F, v 1.87, p324-325)

Inclusion Criteria (Clinical, v 1.82, p 43; Appendix F, v 1.87, p 324)

Same inclusion criteria as in Study 00-02

Exclusion Criteria (Clinical, v 1.82, p 43-44; Appendix F, v 1.87, p 324-325)

Same exclusion criteria as in Study 00-02

1.6.1.5. Study Procedures (Clinical, v 1.82, p 44-77; Appendix F, v 1.87, p 325-357)

The subjects attended a total of three clinic visits that included a screening visit, baseline visit on Day 1 of treatment, and another visit on Day 15. During the 14-day screening period, subjects had a complete medical history and physical examination, 12 lead EKG, clinical laboratory evaluations (chemistry, hematology, serum pregnancy test, urine drug screen, tests for Hepatitis B and C Antigens and for HIV), and signed written informed consent. Subjects were instructed not to consume any prescription or over the counter medication for 14 days of alcohol for 48 hours before study drug administration or during study participation. Subjects meeting selection criteria were randomized to one of two treatment groups (Groups 1 or 2) on the evening before morning dosing for the total duration of the 5 week study and received each treatment (Treatments A and B) during the course of the study. There will be 14 days between the start of each leg of the study.

- **Treatment A (fasted)** - 1200 mg controlled release guaifenesin and 60 mg controlled release dextromethorphan hydrobromide (Mucinex[®] DM; Lot No. PB01-H43A2, expiration date NA) administered after an overnight fast.
- **Treatment B (fed)** - 1200 mg controlled release guaifenesin and 60 mg controlled release dextromethorphan hydrobromide (Mucinex[®] DM; Lot No. PB01-H43A2, expiration date NA) administered 30 minutes after the beginning of the consumption of a high fat breakfast.

Group	Period 1	Period 2
1	Treatment A	Treatment B
2	Treatment B	Treatment A

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Subjects were confined for 1½ days (approximately 36 hours) on each of two study periods (Day -1 and Day 15) and returned for subsequent blood sampling at 36, 48, 72, and 96 hours following dosing. Subjects were fasted overnight and the fast maintained until after collection of the four hour blood sample, except for the high fat breakfast described below. Each treatment was administered as a single-dose with 240 mL of room temperature water. Half of the subjects were fasted and half fed during each period. Breakfast consisted of two eggs cooked in butter, 2 slices of bacon, four oz. of hash browns, two pieces of buttered toasted white bread and eight oz. whole milk. This meal was consumed in its entirety within 30 minutes of dosing.

Water was allowed *ad lib* after the two hour-post dose blood sample was obtained. Subjects subsequently received a standardized lunch and dinner following the single dose at 4 and 10 hours after dosing, respectively. A light snack was served at 8:00 PM. No food or drinks containing caffeine or xanthine were permitted during confinement and no concurrent medications were permitted after study enrollment unless authorized by the Investigator.

Adverse events were evaluated by the Investigator and recorded on source documents and case report forms (v 1.88, p 3-113). The following parameters including date of onset, duration, intensity, frequency, action taken, relationship to study medication, and subject outcome were reported and followed to resolution.

Each subject had the right to withdraw consent to participate in the study at any time. The investigator had the option to discontinue any subject's participation for any reason. According to the protocol, dropouts were not to be replaced.

Table 28. Study 2002-12 Timeline (Clinical, v 1.82, p 70-75)

	Screening	Treatment	
	Visit 1	Visit 2	Visit 3
	Day -5 to -14	Day -1 to 5	Day 14-19
General Procedures			
Informed consent	X	X	
Subject Number Assignment	X		
Medical history	X		
Verification of inclusion/exclusion criteria	X		
Concomitant medication assessment	X		
Vital signs	X	X	X
Physical examination	X		
Clinical laboratory tests	X		
12-Lead electrocardiogram	X		
Urine drug screen	X	X	X
Serum pregnancy test (all females)	X	X	X
Tests for HBV, HCV, and HIV	X		
Randomization number assignment		X	
Study medication given		X	X
Adverse event assessment		X	X
Pharmacokinetic plasma sampling		X	X

1.6.1.6. Parameters (Clinical, v 1.82, p 45; Appendix F, v 1.87, p 326)

Pharmacokinetic samples (7 mL sodium heparin anticoagulant) were obtained as individual venipunctures prior to dosing and 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. The total blood loss per subject for guaifenesin and dextromethorphan PK analyses was estimated to be 280 mL.

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1.6.1.7. Safety Evaluations (Clinical, v 1.82, p 45; Appendix F, v 1.87, p 326)

Adverse events were recorded for any clinically significant changes in physical examination or vital signs, or upon subject report of any complaint relative to well being. Subjects had a complete history and physical examination including vital signs, height, and weight. A 12-lead electrocardiogram, serum chemistry, complete blood count with differential, qualitative urine drug screen, tests for Hepatitis B and C Antigens and for HIV were also performed. Serum pregnancy test was performed for females.

1.6.1.8. Statistical Plan (Clinical, v 1.82, p 49-50; Appendix F, v 1.87, 330-331)

Sample Size:

Calculations regarding sample size for this study were not included in the NDA application.

Statistical analysis:

Pharmacokinetic parameters included the maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), the terminal elimination half-life and area under the plasma concentration-time curve (AUC) for guaifenesin and dextromethorphan, and apparent oral clearance (CL). Half-life, the logarithm of C_{max} , and the logarithm of AUC were analyzed with an analysis of variance with effects for sequence, subject nested within sequence, period, and formulation.

1.6.2. Results

1.6.2.1. Subject Disposition (Clinical, v 1.82 p 14-15, 18, 55, 57; Appendix F, v 1.87, p 384-385)

A total of 36 healthy male and female subjects entered the study and were enrolled and randomized to one of two treatment legs. Thirty-five subjects completed the study. Subject 22 did not check in for Period 2 due to an adverse event and was not replaced. The average age was 26.4 ± 9.45 years (Mean $\pm$ Standard Deviation) with a range of 18 years to 51 years. The average height was 67.8 ± 4.02 inches with a range of 60 to 76.5 inches. The average weight was 165 ± 31.9 pounds with a range of 113 to 240 pounds. There were 16 males (44%) and 20 females (56%) enrolled, of whom 34 (94%) were Caucasian, one (3%) was black, and one (3%) was multiracial.

1.6.2.2. Protocol Deviations (Clinical, v 1.82, p 15; Appendix F, v 1.87, p 391)

Protocol deviations in the times of blood sampling which were drawn two or more minutes late occurred 24 times due to instances of difficulties with blood draws (10), late returns (12), and adverse events (2).

1.6.2.3. Efficacy Endpoint Outcomes (Appendix F, v 1.87, p 392)

This was a pharmacokinetic study without efficacy evaluations.

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1.6.2.4. Safety Outcomes

1.6.2.4.1. Total Drug Exposure (Clinical, v 1.82, p 13 ; Appendix F, v 1.87, p 395)

Treatment duration was similar between the two groups.

1.6.2.4.2. Adverse Events (Clinical, v 1.82, p 15; Appendix F, v 1.87, p 397-399)

According to the Applicant, both guaifenesin and dextromethorphan HBr were well tolerated. Seventeen adverse events listed were from 10 subjects and included five cases of nausea, two episodes of vomiting, one episode of cough, five episodes of headache, one case of lightheadedness, one case of fever/aches, one case of "tightness and pain in the chest," one episode of feeling shaky. All subjects recovered from these adverse events (Table 4) and most cases (14) were judged by the investigator to be possibly related to treatment regimen.

Table 29. Study 2002-12: Common adverse events reported by subjects (Appendix E, v 1.87, p 397-399)

	Treatment Dose at Onset of Study (N = number of subjects)	
	Treatment A Mucinex [®] DM after an overnight fast (N=35)	Treatment B Mucinex [®] DM after a high fat meal (N=36)
Total subjects with adverse event	6 (17%)	4 (11%)
TOTAL ADVERSE EVENTS	12	5
Body as a whole		
Cough and chest tightness	0 (0%)	1 (2.8%)
Tightness and pain in chest	0 (0%)	1 (2.8%)
Fever/aches	1 (2.9%)	0 (0%)
Shaky	1 (2.9%)	0 (0%)
Gastrointestinal system		
Nausea	4 (11%)	1 (2.8%)
Vomiting	2 (5.7%)	0 (0%)
Neurological system		
Headache	3 (8.6%)	2 (5.6%)
Lightheaded	1 (2.9%)	0 (0%)

1.6.2.4.3. Discontinuation or treatment interruption due to adverse events (Clinical, v 1.82, p 15; Appendix F, v 1.87, p 389-390)

Subject 22 did not check in for Period 2 due to an adverse event (cough and chest tightness). During his involvement in the study, he received one Mucinex[®] DM tablet. He was treated with Robitussin DM, amantadine, and amoxicillin and recovered; he was not replaced per protocol.

Table 30. Study 2002-12: Subjects who discontinued therapy (Appendix F, v 1.87, p 389-390)

Subject#	Treatment	Duration	Dose	Reason for discontinuation
22	Mucinex [®] DM	10 days	1 tablet	Adverse event (cough and chest tightness)

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1.6.2.4.4. Serious adverse events and death (Clinical, v 1.82, p 15; Appendix F, v 1.87, p 401; v 1.91, p 176-192)

Subject 22 experienced cough and chest tightness and received medication and discontinued participation in the study. Case report forms were submitted for Subject 22. No subjects died during the study.

1.6.2.4.5. Physical examination, ECG, and laboratory measure (Case reports, v 1.91, p 3-175)

There were no significant changes in physical examination, vital signs, or laboratory measurements that would indicate an effect of the study drug. There were no significant differences in these parameters between treatment groups. Analyses of these variables by age, gender, and race did not indicate any differential response to treatment.

1.6.2.4.6. Plasma concentrations of guaifenesin, dextromethorphan hydrobromide (Clinical, v 1.73, p 21-30)

No significant effect on the absorption of guaifenesin was observed from the Mucinex[®] DM tablet. There was an effect of food on the rate of absorption of dextromethorphan from the tablet formulation (a minimal increase in C_{max}) but not on the extent (AUC_{inf}) of absorption.

Table 31. Study 2001-12: Mean concentrations (Clinical, v 1.82, p 20-30)

Treatment Group	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-1} (hr-ng/mL)	$AUC_{0-∞}$ (hr-ng/mL)	$T_{1/2}$ (hr)	Clearance (L/hr)
Guaifenesin						
A = Mucinex [®] DM (fed)	2030 + 882	1.61	8107	8128	1.15	172
B = Mucinex [®] DM (fasted)	1825 + 789	2.93	7077	7093	0.849	190
Dextromethorphan Hydrobromide						
A = Mucinex [®] DM (fed)	10722 + 15966	6.23	372897	466518	13.8	2343
B = Mucinex [®] DM (fasted)	12757 + 17914	5.74	381391	472064	13.5	2246

1.6.3. Discussion and Conclusions (Clinical, v 1.82, p 14-16)

Study 2002-12 determined the effect of the consumption of a high fat breakfast on the relative bioavailability of an experimental formulation containing 1200 mg guaifenesin and 60 mg dextromethorphan in 36 healthy male and female subjects ages 18 to 55. Subjects were given single doses of medications separated by 14-day washout periods. A total of 35 subjects were included in the ITT population. The Applicant states that no food effect was found for the absorption of guaifenesin from the experimental tablet. There is an effect of food on the rate of absorption of dextromethorphan from the experimental tablet formulation (a small increase in the rate of absorption) but not on the extent of absorption. This review did not uncover any outstanding clinical issues or significant safety concerns in this study.

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NDA 21-620, Mucinex[®] DM

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2. DETAILED LABELING CHANGES OR REVISED DRUG LABEL

Proposed package labeling (bottle labels, carton labels) was included in the submission [Volume 1.1, pages 8-30]. The Division of Over-the-Counter Drug Products (DOTDP) completed and filed their labeling review on January 12, 2004 [NDA 21-620, OTC Drug Labeling Review, Jianming Li, PhD, MBA, Regulatory Review Scientist].

Clinical comments on labeling are noted below and apply to both strengths of Mucinex[®] DM.

1. Regarding the principal display panel and other side panels:
 - Add "Extended-release bi-layer tablets" as part of the established name and delete
 - Use "EXTENDED-RELEASE BI-LAYER TABLETS" to the declaration of net quantity of contents statement.
 - The "New" flag on the principal display panel on all carton and container labels must be deleted six months after introduction into market place.

2. In the ACTIVE INGREDIENTS section:
 - List active ingredients in alphabetical order.
 - Change the wording) to Active ingredients (in each *extended-release* bi-layer tablet).

3. In the PURPOSE section pertaining to the Active Ingredient, Dextromethorphan:
 - Change the wording to Cough suppressant

4. In the USES section in the draft carton label:
 -
 -

- TO:
 - temporarily relieves:
 - cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants
 - the intensity of coughing
 - the impulse to cough to help you get to sleep

5. In the WARNINGS section, When Using This Product subsection:

6. In the WARNINGS section, Stop Use and Ask a Doctor If subsection:
Change the wording from:

Labeling Changes

CLINICAL REVIEW

NDA 21-620, Mucinex[®] DM

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TO:

- cough lasts more than 7 days, comes back or occurs with fever, rash, or persistent headache

Final comments on proposed labeling will be incorporated in the labeling negotiated with the Applicant.

Labeling Changes

CITATIONS

¹ Croughan-Minihane, et al. "Clinical Trial Examining Effectiveness of Three Cough Syrups" J Am Board Fam Pract 1993 Mar-Apr; 6(2):109-15.

² Rammer L, et al. (1988). "Fatal Intoxication by Dextromethorphan: A Report on Two Cases" Forensic Science International 37: 233-286

³ Pickens CL, et al. (1999). "Abuse of guaifenesin-containing medications generates an excess of a carboxylate salt of beta-(2-methoxyphenoxy)-lactic acid, a guaifenesin metabolite, and results in urolithiasis." Urology 54: 23-7

⁴ Einarson, et al. (2001). "The Safety of Dextromethorphan in Pregnancy. Results of a Controlled Study." Chest 119(2): 466-9.

⁵ Schadel, et al. (1995). "Pharmacokinetics of Dextromethorphan and Metabolites in Humans: Influence of the CYP2D6 Phenotype and Quinidine Inhibition." J Clin Psychopharm 10(6):263-269.

⁶ Wu, et al. (1995). "Effects of route of administration on dextromethorphan pharmacokinetics and behavioral response in the rat." Clinical Research and Treatment Institute of the Addiction Research Foundation, Toronto, Ontario, Canada Sep; 274(3): 1431-7.

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

/s/

Katherine Szema
4/19/04 04:26:35 PM
MEDICAL OFFICER

Peter Starke
4/19/04 05:13:59 PM
MEDICAL OFFICER
I concur with the clinical recommendation for an Approval
action.

8/29/03 =

MEDICAL OFFICER REVIEW			
Division Of Pulmonary and Allergy Drug Products (HFD-570)			
APPLICATION:	NDA 21-620	TRADE NAME:	Mucinex™ DM
APPLICANT/SPONSOR:	Adams Laboratories, Inc.	USAN NAME:	Guaifenesin/Dextromethorphan HBr
MEDICAL OFFICER:	Katherine Szema, MD	ROUTE:	Oral
TEAM LEADER:	Eugene Sullivan, MD, FCCP	CATEGORY:	Expectorant/antitussive
DUE DATE:	August 29, 2003		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
June 30, 2003	July 2, 2003	NDA 21-620	Original NDA with 91 volumes
RELATED APPLICATIONS			
<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>	
June 29, 2000	NDA 21-282	NDA for Mucinex™, guaifenesin extended release tablets	
August 31, 2000	IND 60,922	IND for Mucinex™ DM, guaifenesin/dextromethorphan extended release tablets	
REVIEW SUMMARY:			
This is the Medical Officer Filing and Planning Review of NDA 21-620, a 505(b)(2) application for an extended release formulation of guaifenesin and dextromethorphan HBr. The sponsor, Adams Laboratories, Inc., requests the approval of two dosage strengths, (1) guaifenesin 600mg/detromethorphan HBr 30mg, and (2) guaifenesin 1200mg/detromethorphan HBr 60mg to be given twice daily in adults and children 12 years of age and older. The product is an extended release, bilayer tablet formulation. This NDA is proposed as an over-the-counter (OTC) combination expectorant and antitussive. The proposed indication is to loosen phlegm (mucus) and thin bronchial secretions and to temporarily relieve cough due to minor throat and bronchial irritation as may occur with the common cold or inhalant irritants. This 91 volume paper submission contains six clinical pharmacology studies in support of the application. Adams Laboratories is not seeking an indication for pediatric use in children under 12 years. All pages of this NDA must be numbered and the necessary documents attached. Appropriate disclosure forms from the investigators should be provided. Adams Laboratories, Inc. should submit copies of the articles regarding guaifenesin and dextromethorphan prescribing precautions identified in their review of the literature. In addition, a summary of information gleaned from these articles should be provided. Safety data regarding gender, race, and the pediatric and elderly populations should be provided. Safety information and a more detailed literature review regarding the intentional abuse of dextromethorphan should also be included. Lastly, a summary of the Adverse Events from AERS should be provided. This submission is adequate for in-depth review and is fileable.			
OUTSTANDING ISSUES:			
The project manager, Colette Jackson, will request Adams Laboratories, Inc. to submit the above noted information.			
RECOMMENDED REGULATORY ACTION			
IND/NEW STUDIES:	☐ SAFE TO PROCEED	☐ CLINICAL HOLD	
NDA/SUPPLEMENTS:	☒ FILEABLE	☐ NOT FILEABLE	
	☐ APPROVAL	☐ APPROVABLE	☐ NOT APPROVABLE
OTHER ACTION:			

I. General Information

This NDA is a 505(b)(2) application for an extended release formulation of guaifenesin and dextromethorphan. The sponsor, Adams Laboratories, Inc., (14801 Sovereign Road, Fort Worth, TX 76155-2645) requests the approval of two dosage strength tablets, (1) guaifenesin 600mg/dextromethorphan HBr 30mg, and (2) guaifenesin 1200mg/dextromethorphan HBr 60mg to be given to adults and children 12 years of age and older. The product is an extended release, bilayer tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and antitussive. The proposed indication is to loosen phlegm (mucus) and thin bronchial secretions and to temporarily relieve cough due to minor throat and bronchial irritation as may occur with the common cold or inhalant irritants. Adams Laboratories, Inc. has a proposed trade name of Mucinex™ DM for both strengths of the drug product. The sponsor has provided a paper submission.

Guaifenesin, an expectorant, is generally recognized as safe and effective (GRASE) in the following age groups at the indicated oral doses {21 CFR 341.78}:

- Adults and children 12 years of age and older: 200 to 400mg every 4 hours, not to exceed(NTE) 2400mg in 24 hours
- Children ≥ 6 to 12 years of age: 100 to 200mg every 4 hours, NTE 1200mg in 24 hours
- Children ≥ 2 to ≤ 6 years of age: 50 to 100mg every 4 hours, NTE 600mg in 24 hours
- Children under 2 years of age: consult a doctor

Dextromethorphan is an antitussive GRASE in the following age groups at the indicated oral doses {21 CFR 341.74}:

- Adults and children 12 years of age and older: 10 to 20 mg every 4 hours or 30mg every 6 to 8 hours, NTE 120mg in 24 hours, or as directed by a doctor
- Children ≥ 6 to 12 years of age: 5 to 10mg every 4 hours or 15 mg every 6 to 8 hours, NTE 60mg in 24 hours, or as directed by a doctor
- Children ≥ 2 to ≤ 6 years of age: 2.5 to 5mg every 4 hours or 7.5 mg every 6 to 8 hours, NTE 30mg in 24 hours, or as directed by a doctor
- Children under 2 years of age: Consult a doctor

The section of the monograph for Combination Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use that specifies permitted combinations of active ingredients was recently published [Federal Register, December 23, 2002 (67 FR 78168)]. The monograph considers the combination of any single monograph oral antitussive active ingredient (such as DM) with any single expectorant active ingredient (such as guaifenesin) to be a permitted combination [21 CFR 341.40(h)].

The Agency recently approved the sponsor's application for two dosage strengths of Mucinex™, a single-ingredient, extended release tablet formulation of guaifenesin (NDA 21-282). The 600-mg tablets were approved on July 12, 2002 and the 1200-mg tablets were approved on December 18, 2002. The sponsor's program was based on demonstrating that exposures of guaifenesin were achieved from their product that was equivalent to monograph doses of immediate release guaifenesin. Although there are many unapproved extended

release guaifenesin products marketed in the US, the sponsor's Mucinex™ product is the only extended release tablet guaifenesin product that is FDA approved in the US.

Adams Laboratories, Inc. submitted this NDA under Section 505(b)(2) of the FD&C Act, which permits approvals to be based on the Agency's previous findings of efficacy and safety of the approved reference products and a comparison of the bioavailability and bioequivalence of the proposed new drug to those reference products. The sponsor's drug development program for Mucinex™ DM is based on establishing that their combination guaifenesin/DM 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 DM 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 DM in the combination product.

The sponsor's application includes reports of six PK and bioavailability studies [Volume 1.1, page 95-110] which are described in greater detail in Section IV of this filing and planning review.

1. Protocol 00-02, a pilot open-label, single-dose, randomized, 3-way crossover study with 7 day washout period between treatments to examine the relative bioavailability and safety of two different experimental formulations of the proposed product in healthy men and women.
2. Protocol 2001-04, a second pilot open-label, single-dose, randomized, 3-way crossover study with 7 day washout period between treatments to examine the relative bioavailability and safety of two different experimental formulations of the proposed product in healthy men and women.
3. Protocol 2001-15, a definitive single-dose, open-label, randomized, 4-way crossover design with 14 day washout period between treatments to examine potential drug interactions between individual component drugs.
4. Protocol 2002-08, a definitive single-dose, open-label, randomized, 3-way crossover design with 14 day washout period between treatments to examine the relative bioavailability of the product and dose proportionality of the individual component drugs.
5. Protocol 2002-10, a definitive multiple dose study designed to examine the steady state bioavailability of the product and dose proportionality of the individual component drugs in healthy men and women.
6. Protocol 2002-12, a single dose study designed to examine the effect of fasting versus a high-fat breakfast on the bioavailability of the product in healthy men and women.

II. Regulatory and Foreign Marketing History

A. Regulatory History

Guaifenesin is an approved drug substance under the following NDA held by Adams Laboratories Inc.:

- NDA 21-282 Mucinex™ (guaifenesin) 600mg and 1200mg extended release tablets

Dextromethorphan is a single ingredient approved drug substance under the following NDA held by Celltech Pharmaceuticals Inc.: (approved Oct. 8, 1982)

- NDA 18-658 Delsym™ (dextromethorphan polistirex) 5ml

The initial IND for Mucinex™ DM was opened in August 31, 2000 under IND 60,922. The development plan for Phase II/III protocols was discussed with the FDA in a teleconference on November 9, 2001. The steady state study and the differences in requirements for an ANDA versus a 505(b)(2) application were reviewed during this teleconference. In addition, recommendations were given concerning the use of Mucinex™ as a comparator which at the time of the teleconference was not an approved drug product.

B. Foreign Marketing History

Guaifenesin and dextromethorphan hydrobromide single ingredient products and guaifenesin/dextromethorphan combination products are marketed internationally by other manufacturers. Adams Laboratories, Inc. does not make guaifenesin, dextromethorphan bromide, or Mucinex™, Mucinex™ D, and Mucinex™ DM available to foreign markets. The sponsor states that neither active ingredient has been withdrawn from foreign markets for reasons of safety or effectiveness.

III. Items Required for Filing NDA

C. Necessary Elements (21 CFR 314.50)

The sponsor has provided all of the necessary requirements for filing as outlined in the table below.

Table 1. Necessary Elements for NDA

Item	Type	Status	Location (paper)
1	Application Form (FDA 356h)	Present	Volume 1.1, No page number
2	Index / Table of Contents	Present	Vol. 1.1, p 1-7
	Samples(if applicable) and Labeling	N/A	
	Proposed Labeling	Present	Vol. 1.1, p.39-45
	Proposed Medication Guide (if applicable)	N/A	
3	Summary	Present	Vol. 1.1, p.38-112
	Labeling	Present	Vol. 1.1, p.39-45
	Statement of Pharmacologic Class, Scientific Rationale, Intended Use, and Potential Clinical Benefits	Present	Vol. 1.1, p.46
	Marketing History	Present	Vol. 1.1, p. 47
	Chemistry, Manufacturing, & Controls (CMC)	Present	Vol. 1.1, p. 48-77
	Human Pharmacokinetics and Bioavailability	Present	Vol. 1.1, p.78-94
	Clinical	Present	Vol. 1.1, p.95-110
	Benefits vs. Risks	Present	Vol. 1.1, p.111
4	CMC	Present	Vol. 1.2-1.6
	Environmental Impact statement	Categorical Exclusion under 21 CFR 25.31 (b)	Vol. 1.5, p. 505
5	Nonclinical Pharmacology and Toxicology	N/A	
6	Human Pharmacokinetics and Bioavailability	Present	Vol. 1.7-1.45

Item	Type	Status	Location (paper)
7	Clinical	Present	Vol. 1.46-1.87
	Clinical Report for PK Studies	Present	Vol. 1.50-87
7	Integrated Summary of Effectiveness (subsets for age, gender, and race)	Present	Vol. 1.47, p.245-347
	Integrated Summary of Safety	Present	Vol. 1.47, p.348 - Vol. 1.48
	Drug Abuse and overdose information	Present	Vol. 1.49, p.252-292
	Benefits vs. Risks	Present	Vol. 1.49, p.293-318
	Statements of Good Clinical Practice:	Present	Vol. 1.50, p.6, Vol.1.55, p.5, Vol. 1.59, p.5, Vol.1.65, p.5, Vol. 1.73, p.5, Vol. 1.82, p.5
	Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures	Present	Vol. 1.54, p. 395-400
8	Statistics	Present	Vol. 1.46-1.87
9	Case Report Tabulations	Present	Vol. 1.88, Vol. 1.89, Vo. 1.90 Vol. 1.91, p. 4-175
10	Case Report Forms (for patients with SAEs or discontinuing studies)	Present	Vol. 1.91, p.177-210
11	Patent Information	Present	Vol. 1.1, p. 189-190
12	Patent Certification	Present	Vol. 1.1, p.191
13	Investigator Debarment Certification	Present	Vol. 1.1, p.193
14	Field copy certification (if applicable)	Present	Vol. 1.1, p.194-195
15	User Fee Cover Sheet	Present	Vol. 1.1, p.196-197
16	Financial Disclosure	Present	Vol. 1.1, p.198-199
17	Claimed Marketing Exclusivity	N/A	
18	Pediatric Use	N/A	

IV. Clinical Pharmacology Studies

This submission contains six clinical pharmacology studies. The studies are appropriately indexed to allow review and are summarized in Table 2. More detailed descriptions of these studies follow below.

A. Study 00-02

Study 00-02 was a pilot clinical pharmacology study that compared the bioavailability of guaifenesin and dextromethorphan from two experimental extended release formulations containing both guaifenesin and DM as compared to a reference consisting of extended-release guaifenesin (Mucinex™) and controlled-release dextromethorphan HBR (Delsym™). The study was performed under fasted conditions. The study was an open-label, randomized, single dose, three-way crossover bioavailability study conducted in 21 healthy male and female subjects. Samples were taken immediately before dosing (0 hours) and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours post dose for plasma guaifenesin, dextromethorphan, and dextrophan (an active metabolite of dextromethorphan) levels. A minimum washout period of seven days separated each treatment period. Patients were housed at the study site until after their 24-hour sample was drawn. One patient did not complete study protocol due to personal reasons. Safety endpoints reported included adverse events. There were no SAEs. [Volume 1.1, page 105, Volume 1.47, page 352, 356-357, Vol. 1.88, page 108-113].

B. Study 2001-04

Study 00-01A was a second pilot clinical pharmacology study that compared the bioavailability of guaifenesin and DM from two experimental extended release formulations containing both guaifenesin and DM as compared to a reference consisting of extended-release guaifenesin (Mucinex™) and controlled-release dextromethorphan HBR (Delsym™). The study was performed under fasted conditions. The study was an open-label, randomized, single dose, three-way crossover bioavailability study conducted in 15 healthy male and female subjects. Samples were taken immediately before dosing (0 hours) and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 72, and 96 hours post dose for plasma guaifenesin and DM levels. Patients were housed at the study site until after their 24-hour sample was drawn. A minimum washout period of seven days separated each treatment period. There were no withdrawals from the study. Safety endpoints reported included adverse events. There were no SAEs [Volume 1.1, page 105, Volume 1.47, page 352, 356-358, Volume 1.89, page 201-205].

C. Study 2001-15

Study 2001-15 was a definitive clinical pharmacology study that compared the bioavailability and dose proportionality of guaifenesin and DM from an experimental controlled-release formulation to a reference consisting of guaifenesin (Mucinex™) and DM. All subjects received the sponsor's proposed product containing 1200-mg guaifenesin and 60 mg DM HBr and a reference controlled release tablet containing 1200mg guaifenesin (Mucinex™). Half of the subjects received reference DM HBr (Benylin™) immediate-release liquid formulation at 30mg every 6 hours for a total of 60mg and Benylin™ at 15mg every 6 hours for a total of 30mg. The remaining subjects received Benylin™ at 20mg every 4 hours for a total of 60mg and Benylin™ 10mg every 4 hours for 30mg total. The study was performed under fasted conditions. The study was an open-label, randomized, single dose, four-way crossover bioavailability study conducted in 33 healthy male and female subjects. Samples were taken immediately before dosing (0 hours) and at 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 for plasma guaifenesin and DM levels. Patients were housed at the study site until after their 24-hour sample was drawn. A washout period of 14 days separated each treatment period. There was one patient who withdrew from the study and did not return for the second study period. There were three withdrawals from the study; one due to difficulty with blood draws and two due to noncompliance with visits and. Safety endpoints reported included adverse events. There were no SAEs. [Volume 1.1, page 106, Volume 1.47, page 353, 356-358, Vol. 1.88, page 435-441].

D. Study 2002-08

Study 2003-08 was a definitive bioequivalence study that compared the bioavailability of guaifenesin and DM from an experimental sustained-release formulation to a reference consisting of guaifenesin (Mucinex™) and DM. One group received the sponsor's proposed product containing 1200-mg guaifenesin and 60 mg DM HBr (Mucinex™ DM). A second group received a reference controlled release tablet containing 1200mg guaifenesin (Mucinex™) and 60mg DM HBr (30mg Vicks™ 44™ Cough Relief every 6 hours for 2 doses). A third group received a reference controlled release tablet containing 1200mg guaifenesin (Mucinex™) and 60mg DM HBr (20mg Vicks™ 44™ Cough Relief

every 4 hours for 3 doses). The study was performed under fasted conditions. The study was an open-label, randomized, single dose, three-way crossover bioavailability study conducted in 36 healthy male and female subjects. Samples were taken immediately before dosing (0 hours) and at 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 for plasma guaifenesin and DM levels. Patients were housed at the study site until after their 24-hour sample was drawn. A washout period of 14 days separated each treatment period. There were 8 withdrawals from the study with 4 replacements added. 4 subjects missed visits: one subject had a positive pregnancy test, and 3 subjects missed doses (one due to difficulty with blood draws and two due to noncompliance with visits). Safety endpoints reported included adverse events. There were no SAEs. [Volume 1.1, page 106, Volume 1.47, page 353, 356-358, Volume 1.89, page 247-254].

E. Study 2002-10

Study 2002-10 was a definitive clinical pharmacology study that compared the steady-state bioavailability of guaifenesin and DM from an experimental sustained-release formulation to a reference consisting of extended release guaifenesin (Mucinex™) and DM, after 11 doses given every twelve hours. One group received the sponsor's proposed product containing 1200-mg guaifenesin and 60 mg DM HBr (Mucinex™ DM). A second group received a reference controlled release tablet containing 1200mg guaifenesin (Mucinex™) and 60mg DM HBr (30mg Vicks™ 44™ Cough Relief every 6 hours for 2 doses). A third group received a reference controlled release tablet containing 1200mg guaifenesin (Mucinex™) and 60mg DM HBr (20mg Vicks™ 44™ Cough Relief every 4 hours for 3 doses). The study was performed under fasted conditions. The study was an open-label, randomized, multiple dose, three-way crossover bioavailability study conducted in 36 healthy male and female subjects. Samples were taken immediately before dosing (0 hours) on Days 1, 4, and 5. On day 6, Treatment A patients also had blood samples drawn immediately before dosing (0 hours) and at 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. On day 6, Treatment B patients also had blood samples drawn immediately before dosing (0 hours) and at 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. On day 6, Treatment C patients also had blood samples drawn immediately before dosing (0 hours) and at 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. Plasma guaifenesin and DM levels were performed on these samples. Patients were housed at the study site from the night before Day 1 until after the blood draw on Day 1 and again from the evening of Day 5 until after the 24-hour sample was drawn on Day 6. There was a 14 day washout period between treatments. Two patients withdrew from the study after withdrawing consent. No subjects were replaced. Safety endpoints reported included adverse events. There were no SAEs. [Volume 1.1, page 106-107, Volume 1.47, pages 353-354, 356-359, Volume 1.90, page 323-329].

F. Study 2002-12

Study 2002-12 was a definitive clinical pharmacology study that compared the bioavailability of guaifenesin and DM from an experimental sustained-release formulation administered under both fasting and fed conditions. The study was an open-label,

randomized, single dose, two-way crossover bioavailability and food effect study conducted in 36 healthy male and female subjects. Samples were taken immediately before dosing (0 hours) and at 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 for plasma guaifenesin and DM levels. Patients were housed at the study site until after their 24-hour sample was drawn. A minimum washout period of fourteen days separated each treatment period. One patient withdrew from the study due to missing a visit as a result of an adverse event (cough and chest tightness, the subject was given Robitussin DM, Amantadine, and Amoxicillin). Safety endpoints reported included adverse events. There were no SAEs. [Volume 1.1, page 107, Vol 1.47, page 354, 356-359, Volume 1.91, page 169-175].

V. Brief Review of Proposed Labeling

Proposed package labeling has been included in this submission [Volume 1.1, pages 8-45]. A brief review of proposed labeling was performed. Labeling concerns are noted below.

Pages are not numbered from Vol. 1.1, p. 10-15, 17-22, 24, 26-29, 31, 33-36.

- The labeling states that the product may be administered without regard for timing of meals. This statement will need to be supported by the results of the sponsor's studies.
- The "Ask a doctor before use" section of "Drug Facts" is divided into two columns and it is not clear that the second column is a continuation of the "Ask a doctor before use" section of the label.

Detailed label review will be performed later in the course of review of this NDA.

VI. DSI Review / Audit

DSI clinical audit will not be requested. However, if any irregularity is suspected during the review of this NDA, a DSI clinical audit may be requested.

VII. Summary, Comments, and Decision for Filing

A. Summary

This NDA is a 505(b)(2) application for an extended release formulation of guaifenesin and dextromethorphan. The sponsor, Adams Laboratories, Inc. requests approval of two dosage strengths, (1) guaifenesin 600 mg/DM 30 mg tablets, and (2) guaifenesin 1200 mg/DM 60 mg tablets. It is an extended release 12-hour bilayer tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and cough suppressant drug product. The proposed indication is to loosen phlegm (mucus) and thin bronchial secretions and to temporarily relieve cough due to minor throat and bronchial irritation as may occur with the common cold or inhalant irritants. The sponsor's proposed trade name is Mucinex™ DM for both the strengths of the drug product. The sponsor has provided a paper submission of 91 volumes including six clinical pharmacology studies in support of this NDA application. These studies are appropriately indexed and organized to allow review.

Table 2. Summary of studies, NDA 21-620 (Volume 1.1, pages 95-101)

Study	Design	Treatment	Duration of Treatment	N	Diagnosis, Age of patients
00-02	Phase II open-label, single-dose, randomized, 3-way crossover design with 7 day washout period between treatments	Guaifenesin ER tablets 1200mg and DM 60mg liquid G/DM tablets 1200mg/60mg CB00-04A, 10 Oct 2000 G/DM tablets 1200mg/60mg CB00-03A, 9 Oct 2000	4 weeks; single-dose, 3 treatment, 3 period, randomized, crossover design	20 21 20	Healthy, nonsmokers, 18-55 years Weight within 15% of ideal
2001-04	Phase II open-label, single-dose, randomized, 3-way crossover design with 7 day washout period between treatments	Guaifenesin ER tablets 1200mg and DM 60mg liquid G/DM tablets 1200mg/60mg, prototype 1 G/DM tablets 1200mg/60mg, prototype 2	4 weeks; single-dose, 3 treatment, 3 period, randomized, crossover design	15 15 15	Healthy, nonsmokers, 18-55 years Weight within 15% of ideal
2001-15	Phase II open-label, randomized, 4-way crossover design with 14 day washout period between treatments	Mucinex TM DM tablets 1200mg/60mg Mucinex TM tablets 1200mg Berylin TM liquid 30mg q6hour Benylin TM liquid 20mg q4hour Benylin TM liquid 15mg q6hour Benylin TM liquid 10mg q4hour	9 weeks; 4 treatment, 4 period, randomized, crossover design	32 32 16 15 16 15	Healthy, nonsmokers, 18-55 years Weight within 15% of ideal
2002-08	Phase II open-label, randomized, 3-way crossover design with 14 day washout period between treatments	Mucinex TM 1200mg and DM 30mg q 6h Mucinex TM 1200mg and DM 20mg q 4h Mucinex TM DM tablets 1200mg/60mg	8 weeks; 3 treatment, 3 period, randomized, crossover design	37 34 34	Healthy, nonsmokers, 18-55 years Weight within 15% of ideal
2002-10	Phase II open-label, multiple dose, randomized, 3-way crossover design with 14 day washout period between treatment	Mucinex TM 1200mg and DM 30mg q 6h Mucinex TM 1200mg and DM 20mg q 4h Mucinex TM DM tablets 1200mg/60mg	8 weeks; 3 treatment, 3 period, randomized, crossover design, multiple doses q12 hours for a total of 11 doses	35 35 35	Healthy, nonsmokers, 18-55 years Weight within 15% of ideal
2002-12	Phase II open-label, single-dose, randomized, 2-way crossover design with 14 day washout period between treatments	Mucinex TM DM tablets 1200mg/60mg, fasted Mucinex TM DM tablets 1200mg/60mg, following high-fat breakfast	4 weeks; 2 treatment, 2 period, randomized, crossover design	35 36	Healthy, nonsmokers, 18-55 years Weight within 15% of ideal

G=Guaifenesin, DM=Dextromethorphan

The sponsor should submit copies of each of the articles identified in their review of the literature. The sponsor should submit a summary of safety by gender, race, in the elderly, and in the pediatric population for guaifenesin and dextromethorphan. There is evidence in the literature about intentional abuse with products containing dextromethorphan (the dextrorotatory isomer of the codeine analog levorphanol) due to its euphoric or psychotropic effects. Dextrorphan, the metabolite of dextromethorphan, can bind to and block N-methyl-D-aspartate (NMDA) resulting in euphoria, dysphoria, hallucinations, or hyperactive behavior similar to those effects found in phenylcyclidine.¹

The abuse potential appears more problematic when using tablets containing 30mg dextromethorphan. The summaries should briefly address relevant information from the literature and from postmarketing reports from the AERS database. The label includes a statement that the product may be taken without regard for timing of meals. This statement will need to be supported by the results of the sponsor's studies.

B. Comments for Sponsor

The following comments are to be communicated to the sponsor.

1. *Please include the appropriate financial disclosure forms from the primary investigator and 3 sub-investigators which were not attached in this submission.*
2. *Adams Laboratories, Inc. identified 19 articles pertaining to guaifenesin and 18 articles for dextromethorphan which support the prescribing precautions for these two drug products. Submit copies of these articles cited in Vol. 1.46, pages 181-182 and Vol. 1.47, pages 140-141. with the exception of the following articles:*
 - *From Volume 1.46, pages 181:*
 - *DHHS, FDA (1989) OTC monograph*
 - *Assimos et al. (1999)*
 - *From Volume 1.47, pages 140*
 - *DHHS, FDA (1989) OTC monograph*
 - *Bern et al. (19920)*
 - *Di Marco et al. (2002)*
 - *Schadel et al. (1995)*
3. *Summarize information regarding guaifenesin and dextromethorphan gleaned from your literature review of the above articles.*
4. *Provide safety information and a more detailed literature review regarding intentional abuse of dextromethorphan.*
5. *You have provided a listing of adverse events that you identified in the AERS database. Provide a tabular summary of the frequencies of these adverse events and a narrative analysis and conclusions based on this summary.*

C. Decision

With the exception of the above noted safety data, the submission is adequate to allow full, in-depth clinical review. The submission is fileable.

VIII. Timeline for Review

Table 2. Timeline for Review of NDA 21-620

Milestone	Target Date for Completion
Stamp Date	June 30, 2003
Filing Meeting	August 15, 2003
Study 00-02	August 29, 2003
Study 2001-04	September 12, 2003
Study 2001-15	October 10, 2003
Study 2002-08	October 24, 2003
Study 2002-10	November 21, 2003
Study 2002-12	December 19, 2003
Supporting Studies	January 12, 2004
Team Meeting	January 2004
ISS, ISE	February 2, 2004
Label Review	March 2004
Draft Review	March 2004
Wrap-up Meeting	March 2004
Division Goal Date	April 16, 2004
PDUFA Date (10 months)	April 30, 2004

IX. References

1. Banerji S, Anderson I. Abuse of Coricidin HBP Cough and Cold tablets: Episodes recorded by a poison center. *Am J Health-Syst Pharm.* 2001 Oct; 58:1811-1814.

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/s/

Katherine Szema
8/29/03 09:42:39 AM
MEDICAL OFFICER

Eugene Sullivan
8/29/03 10:18:36 AM
MEDICAL OFFICER