CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-585

MEDICAL REVIEW

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

APPLICATION:	NDA 21-585	TRADE NAME:	Mucinex™ D Maximum Strength Mucinex™ D Regular Strength
APPLICANT/SPONSOR:	Adams Laboratories, Inc.	USAN NAME:	Guaifenesin/pseudoephedrine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	CATEGORY:	Expectorant/decongestant
DATE:	3/8/04	ROUTE:	Oral, extended-release tablets

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
10/17/03	10/20/03	N21-585 N000 BM	Safety update, one volume
2/17/04	2/18/04	N21-585 N000 BM	Response to information request

RELATED APPLICATIONS

Document Date	Application Type	Comments
1/31/03	N21-585 N000	Original NDA submission

REVIEW SUMMARY: NDA 21-585, was submitted by Adams Laboratories, Inc. on January 31, 2003. It is a 505(b)(2) application for an extended-release formulation of guaifenesin and pseudoephedrine HCl. The applicant requests approval of two dosage strengths, (1) guaifenesin 600 mg/pseudoephedrine HCl 60 mg tablets, and (2) guaifenesin 1200 mg/ pseudoephedrine HCl 120 mg tablets. The product is an extended-release, bilayer tablet. It is proposed as an over-the-counter (OTC) combination expectorant and nasal decongestant. The proposed labeled indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, and ——— The applicant's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength.

The Division of Pulmonary and Allergy Drug Products and the Division of Over-the-Counter Drug products took an approvable action on November 24, 2003. The NDA had various CMC deficiencies. There was no review and analysis of postmarketing adverse events in the NDA safety update. The applicant submitted the requested review and analysis of postmarketing adverse events on October 17, 2003, too late in the review cycle to review by the action date. The review and analysis of postmarketing adverse events was the only clinical deficiency. The applicant submitted a complete response to the approvable letter on December 19, 2003. This document reviews the requested information and addresses the only clinical deficiency for this application. The applicant provided a safety update that included a summary, analysis, and interpretation of postmarketing safety reports for the period after the cut-off date for their NDA submission. A small number of cases of cerebrovascular accident were associated with the use of pseudoephedrine, but it is not clear if this represents a safety signal. AEs for pseudoephedrine should be monitored in the future for additional evidence of an association with cerebrovascular accident. The applicant's data do not provide evidence of new safety concerns and support the safe OTC marketing in the proposed population. There are no clinical comments on proposed labeling. This reviewer recommends an "approval" action.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	FILEABLE	NOT FILEABLE	
	X—APPROVAL	APPROVABLE	NOT APPROVABLE
OTHER ACTION:			

1. EXECUTIVE SUMMARY

The applicant provided a safety update that included a summary, analysis, and interpretation of postmarketing safety reports for the period after the cut-off date for their NDA submission for guaifenesin and pseudoephedrine extended-release tablets. A small number of cases of cerebrovascular accident were associated with the use of pseudoephedrine, but it is not clear if this represents a safety signal. Adverse events (AEs) for pseudoephedrine should be monitored in the future for additional evidence of an association cerebrovascular accident. The applicant's data do not provide evidence of new safety concerns and support the safe OTC marketing in the proposed population. There are no new clinical comments on proposed labeling. This reviewer recommends an "approval" action.

2. BACKGROUND

NDA 21-585, was submitted by Adams Laboratories, Inc. on January 31, 2003. It is a 505(b)(2) application for an extended-release formulation of guaifenesin and pseudoephedrine HCl. The applicant requests approval of two dosage strengths, (1) guaifenesin 600 mg/pseudoephedrine HCl 60 mg tablets, and (2) guaifenesin 1200 mg/ pseudoephedrine HCl 120 mg tablets. The product is an extended-release, bilayer tablet. It is proposed as an over-the-counter (OTC) combination expectorant and nasal decongestant. The proposed labeled indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, and —— The applicant's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength.

The Division of Pulmonary and Allergy Drug Products and the Division of Over-the-Counter Drug products took an approvable action on November 24, 2003. The NDA had various CMC deficiencies. There was no review and analysis of postmarketing adverse events in the NDA safety update. The applicant submitted the requested review and analysis of postmarketing adverse events on October 17, 2003, too late in the review cycle to review by the action date. The review and analysis of postmarketing adverse events for the safety update was the only clinical deficiency. The applicant submitted a complete response to the approvable letter on December 19, 2003. This document reviews the requested information and addresses the only clinical deficiency for this application.

3. SAFETY UPDATE

3.1. Summary

The applicant provided a safety update that included a summary, analysis, and interpretation of postmarketing safety reports for the period after the cut-off date for the NDA submission for guaifenesin and pseudoephedrine. A small number of cases of cerebrovascular accident were associated with the use of pseudoephedrine, but it is not clear if this represents a safety signal. AEs for pseudoephedrine should be monitored in the future for additional evidence of association with cerebrovascular accident. This

reviewer concurs with the applicant's conclusion that these data do not provide evidence of new safety concerns and support the safe OTC marketing in the proposed population. The safety update is reviewed below.

3.2. Spontaneous adverse event reports from the AERS database

The applicant submitted postmarketing adverse event reports for guaifenesin and pseudoephedrine from the AERS database covering the period from November 4, 2003, until September 15, 2003 [NDA 21-585, N000 BM, 10/17/03, cover letter]. Data from the AERS database support the safety of guaifenesin and pseudoephedrine and do not present new safety issues. A review of the applicant's analyses follows below.

3.2.1. Postmarketing adverse event reports for guaifenesin

The applicant reported that there were 738 AE reports for guaifenesin in the AERS database for the ten month period from November 4, 2003, until September 15, 2003. These 738 reports identified 3313 adverse events. A total of 312 of these AE reports were duplicate reports and 3001 represented unique reports. A total of 33 adverse reactions were associated with guaifenesin as the primary suspect drug. No AE among the 33 AEs associated with guaifenesin as the primary suspect drug were reported more than once [NDA 21-585, N000 BM, 2/17/04, Cover Letter; NDA 21-585, N000 BM, 10/17/03, Cover Letter]. A total of 2968 adverse reactions were associated with guaifenesin as the secondary suspect drug. No AE among the 33 AEs associated with guaifenesin as the primary suspect drug were reported more than once [NDA 21-585, N000 BM, 2/17/04, Cover Letter; NDA 21-585, N000 BM, 10/17/03, Cover Letter and Exhibits A and B].

The most common AEs reported for guaifenesin as secondary suspect drug included cerebrovascular accident (15.9%, 472/2968), hypertension (5.0 %, 147/2968), myocardial infarction (4.5%, 132/2968), and pain NOS (not otherwise specified) (2.1%, 63/2968) NDA 21-585, N000 BM, 10/17/03, Exhibit B]. Associations of guaifenesin as a secondary suspect drug with cerebrovascular accident were noted in spontaneous adverse event reports included in the original NDA submission. This reviewer's search of the AERS database using AERS DataMart showed that the vast majority of cerebrovascular accident and hemorrhagic stroke, myocardial infarction, and hypertension AEs for guaifenesin were also associated with medications containing phenylpropanolamine, a drug that has been withdrawn from the market because of an association with stroke and cardiovascular AEs. The applicant reports that IMS Health data estimates that there were approximately ——— prescriptions for products containing guaifenesin over the period covered by the safety update. The applicant concludes that the postmarketing AE data support the overall safety of guaifenesin do not suggest any deviation from its known safety profile [NDA 21-585, N000 BM, 2/17/04, Cover Letter; NDA 21-585, N000 BM, 10/17/03, Cover Letter].

Reviewer comment:
The association of cerebrovascular accident, myocardial infarction, and hypertension with guaifenesin is likely to be due to concomitant use of phenylpropanolamine. It is not possible to draw conclusions from the small number of AEs associated with guaifenesin

as primary suspect drug. The reviewer concurs with the applicant that these data support the safety of guaifenesin and do not present new safety issues.

3.2.2. Postmarketing adverse event reports for pseudoephedrine

The applicant reported that there were 452 AE reports for pseudoephedrine in the AERS database for the ten month period from November 4, 2003, until September 15, 2003. These 452 reports identified 2561 adverse events. A total of 388 of these AE reports were duplicate reports and 2173 represented unique reports. A total of 52 adverse reactions were associated with pseudoephedrine as the primary suspect drug. The only AE among the 52 AEs associated with pseudoephedrine as the primary suspect drug that was reported more than once was tongue edema, for which there were 3 AEs reported. [NDA 21-585, N000 BM, 2/17/04, Cover Letter; NDA 21-585, N000 BM, 10/17/03, Cover Letter and Exhibits C and D].

The most common AEs reported for pseudoephedrine as secondary suspect drug included cerebrovascular accident (4.2%, 88/2121), pain NOS (not otherwise specified (1.7%, 37/2121), medication error (1.5%, 32/2121), completed suicide (1.4%, 30/2121), hypertension NOS (1.4%, 30/2121), anxiety (1.3%, 28/2121), convulsions NOS (1.3%, 27/2121), vomiting NOS (1.3%, 27/2121), nausea (1.2%, 26/2121), hepatic failure (1.1%, 32/2121), overdose NOS (1.1%, 24/2121), and coma (1.0%, 22/2121) [NDA 21-585, N000 BM, 10/17/03, Exhibit D].

Associations of pseudoephedrine as a secondary suspect drug with hypertension, convulsions, nausea, and overdose were noted in spontaneous adverse event reports included in the original NDA submission. This reviewer performed a search of the AERS database using AERS DataMart with search terms primary ingredient "pseudoephedrine" and reaction "cerebrovascular accident." The search identified 933 adverse event reports. Most of these cerebrovascular accident AEs for pseudoephedrine were associated with medications containing phenylpropanolamine, as was the case with guaifenesin. Most of these were also reported after the removal of phenylpropanolamine-containing drugs from the market, which suggests some reporting bias. However, there were approximately 10 cases of cerebrovascular accident that were associated with pseudoephedrine alone, and not confounded by other medications. Some of these occurred in patients who were as young as 30 to 40 years of age.

Completed suicide and hepatic failure AEs for pseudoephedrine were all also associated with other medications, the most common of which was acetaminophen. The vast majority of coma AEs for pseudoephedrine were also associated with other concomitant medications. The applicant reports that IMS Health data estimates that there were approximately [redacted] prescriptions for products containing pseudoephedrine over the period covered by the safety update. The applicant concludes that the postmarketing AE data support the overall safety of guaifenesin do not suggest any deviation from its known safety profile [NDA 21-585, N000 BM, 2/17/04, Cover Letter; NDA 21-585, N000 BM, 10/17/03, Cover Letter].

Reviewer comment:
As noted above, most of the serious AEs for pseudoephedrine noted above are also associated with use of concomitant medications. The occurrence of rare cases of cerebrovascular accident in younger individuals raises the question of whether this association represents a real safety signal. Articles from the published medical literature have previously suggested an association of stroke and other cardiovascular AEs with phenylpropanolamine and ephedrine-containing compounds.[1], [2] Phenylpropanolamine-containing medications have been withdrawn from the market, and on February 6, 2004, the Agency published a final rule prohibiting sale of dietary supplements containing ephedrine alkaloids because of significant adverse health effects, including heart attack and stroke.

Dr. Lois LaGranade, epidemiologist for the Office of Drug Safety, reviewed cases of cerebrovascular hemorrhagic disorders in patients taking pseudoephedrine-containing products [Office of Drug Safety Review, PID# D000487, 10/31/00]. She identified nine domestic reports potentially associated with pseudoephedrine. She concluded that there was no compelling evidence from AERS data that pseudoephedrine increases the risk of hemorrhagic stroke. More recently another report of an association of stroke with over-the-counter sympathomimetic drugs was published.[3] Of the 22 patients identified in a consecutive stroke registry, four were taking pseudoephedrine. Three were women from 36 to 48 years of age and one was a man 39 years of age. The cases in the AERS database of cerebrovascular accidents in younger individuals who were taking only pseudoephedrine could represent a weak safety signal. Despite these few cases, most of the serious AEs are more likely to be associated with concomitant medications than with pseudoephedrine. AEs for pseudoephedrine should be monitored in the future for additional evidence of a signal for cerebrovascular accident. The applicant's data support the safety of pseudoephedrine and do not present new safety issues.

4. LABELING REVIEW

Proposed package labeling was included in the original NDA submission [NDA 21-585, N000, 1/31/03, Volume 1.1, pages 10-46]. Labeling was later revised to change the proposed dose for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength to 2 tablets every 12 hours, not more than 4 tablets in 24 hours [NDA 21-585 N000 BZ, 4/30/03, Cover Letter]. The applicant changed the dose of the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength because the proposed dose for the 600 mg guaifenesin/60 mg pseudoephedrine product is one-half of the OTC monograph dose of pseudoephedrine for this dosing interval, and is not supported by the studies in this application.

Clinical labeling comments are found in a previous review [NDA 21-585 N000, 1/31/03, Medical Officer Review, Charles E. Lee, M.D.]. The Division of Over-the-Counter Drug Products (DOTDP) completed their labeling review, and the applicant included all of the

[1] Kernan WN, et al. New Engl J Med. 2000; 343(25):1826-1832.
[2] Haller CA and Benowitz NL. New Engl J Med. 2000; 343(25):1833-1838.
[3] Cantu C, et. al. Stroke. 2003; 34(7):1667-1672.

Agency's required and recommended labeling changes [NDA 21-585 N000, 1/31/03, OTC Drug Labeling Review, Cazemiro M. Martin, Regulatory Review Scientist]. There are no new clinical comments on proposed labeling.

Reviewed by:

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Lydia Gilbert-McClain, M.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/McClain/Acting Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Suarez/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-580/Salemme/CMC Reviewer
HFD-570/Bond/Pharmacology Reviewer
HFD-570/C. Jackson/CSO
HFD-560/C. Martin/Regulatory Review Scientist
HFD-560/M. Chang/Team Leader

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/s/

Charles Lee
3/11/04 03:35:44 PM
MEDICAL OFFICER

Lydia McClain
3/16/04 04:05:57 PM
MEDICAL OFFICER
I concur

Clinical Team Leader Review Memorandum

Memorandum to:	NDA 21-585 file
Product:	Mucinex™ D Maximum Strength, and Mucinex™ D Regular Strength
Sponsor:	Adams Laboratories, Inc.
Memo Date:	October 29th , 2003
Memo From:	Lydia I. Gilbert-McClain, MD, Clinical Team Leader (Actg)

This memorandum is to summarize the pertinent findings of the review of NDA 21-585 for Mucinex™ D an extended-release formulation of guaifenesin and pseudoephedrine HCl. The application 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. The regulation allows for a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved reference product. Therefore, this program was fundamentally a bioequivalence program with safety data obtained from the clinical pharmacology studies, the current literature and the U.S. A.E.R.S database.

The sponsor (Adams laboratories, Inc.,) used extended release guaifenesin (Mucinex™) an approved product under NDA 21-282, and extended-release pseudoephedrine (Sudafed 12 hour®), an OTC monograph product as the reference products. The application was submitted seeking approval for Mucinex™ D as an OTC product indicated for the loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, and

The product is proposed for use in adults and children 12 years of age and older. Two dosage strengths are proposed : (1) A maximum strength tablet comprised of 1200 mg guaifenesin and 120 mg of pseudoephedrine, and (2) a regular strength tablet comprised of 600 mg guaifenesin and 60 mg of pseudoephedrine. The proposed dose is 1 maximum strength tablet every 12 hours not to exceed more than 2 tablets in 24 hours, or 2 tablets of the regular strength every 12 hours not to exceed more than 4 tablets in 24 hours. The products are not indicated for children under the age of 12 years.

The maximum strength tablet consists of a white immediate release layer (IR) containing 200 mg guaifenesin and a pink modified release layer (MR) containing 1000 mg of guaifenesin and 120 mg of pseudoephedrine. The regular strength tablet consists of a white immediate release layer (IR) containing 100 mg of guaifenesin and an orange modified release layer (MR) containing 500 mg of guaifenesin and 60 mg of pseudoephedrine, The IR layer in Mucinex™ D is identical to the IR layer used in the approved Mucinex™ product (NDA 21-282). The MR layer in Mucinex™ D is similar to the MR layer used in the approved Mucinex™ tablets with minor adjustments in the polymeric blend to control the release profile of the decongestant and keep the release profile of the expectorant as close to Mucinex™ as possible.

A brief overview of the salient findings in the application is presented below. For further details, please refer to Dr. Charles E. Lee's and Dr. Sandra Suarez-Sharp's excellent reviews.

OVERVIEW

The reference products for this 505(b)(2) application are guaifenesin and pseudoephedrine. Both guaifenesin and pseudoephedrine are considered to be generally recognized as safe and effective (GRASE) for their respective indications at the specified OTC monograph doses.

Given that this application was submitted under Section 505(b)(2) of the FD&C Act and the sponsor's reliance on the Agency's previous findings of efficacy and safety of the approved reference product, no clinical efficacy studies were required and none were submitted with the application.

Clinical pharmacology and Biopharmaceutics

Of the seven clinical pharmacology studies conducted 4 were considered relevant to the NDA. All the studies were conducted in male and female healthy volunteers age 18 or older. The bioavailability of guaifenesin and pseudoephedrine from the proposed extended-release formulation was compared to the reference products in a single and a multiple dose study. In these studies, the mean AUC_{ss} and C_{max} for the proposed product were within 80% - 125% bioequivalence limits compared to the reference standards. In the multiple dose study the C_{min} for guaifenesin for the proposed product was 244% of that of the reference product. However, since this increase represents only 6% of the steady state C_{max} value for guaifenesin the increased C_{min} should not pose a safety concern.

The question of whether the pharmacokinetics of guaifenesin and pseudoephedrine were affected when both were co-administered was addressed in a single dose study that compared the bioavailability of guaifenesin and pseudoephedrine administered alone and co-administered. The results showed that there was no effect on the pharmacokinetics of the two drugs when co-administered.

The dose proportionality of guaifenesin and pseudoephedrine was assessed in a single dose study. The pharmacokinetics of guaifenesin and pseudoephedrine were dose proportional when the dose was doubled from 600 mg guaifenesin/60 mg pseudoephedrine to 1200 mg guaifenesin/120 mg pseudoephedrine. Finally, a single dose study compared the bioavailability of guaifenesin and pseudoephedrine from an experimental extended-release formulation administered under fed and fasted conditions. The C_{max} of guaifenesin was slightly decreased compared to that of the reference product after consumption of a high fat meal however, since the extent of systemic exposure (AUC) was similar this finding is not clinically relevant.

Safety

Safety data in support of this application was provided from the U.S. AERS database, the medical literature, and the safety data from the pivotal bioequivalence studies. A complete safety update with an analysis of post marketing events was not submitted.

From the 7 pharmacology studies a total of 217 subjects received at least one dose of study medication. A total of 36 subjects were exposed to the guaifenesin 600 mg/pseudoephedrine 60 mg combination and 157 subjects were exposed to the 1200 mg guaifenesin/120 mg pseudoephedrine products used in the studies. The adverse events reported were similar to AEs previously reported for guaifenesin and pseudoephedrine and included [in decreasing order of frequency] headache, sleeplessness, nausea, lightheadedness, dry mouth, and loss of appetite. There were no apparent differences in AEs between the test and reference products. One observation of note is a report of one subject who had difficulty swallowing one of the reference products. This was not coded as an AE but it was reported that the subject had to drink approximately 46 ounces of water in order to swallow one of the reference products. Although the approved and marketed Mucinex™ tablet is large (1458 mg in weight) no AEs of swallowing or related events have been reported to the AERS database. Safety data from the published literature did not reveal any new safety signals. The safety update was incomplete in that a review of postmarketing adverse events was not included. Although the medical officer requested the information during the review cycle, the sponsor failed to submit it. Because of this deficiency, a complete safety review could not be done. In addition, there are outstanding CMC issues that would preclude an approval in this cycle therefore the application should receive an approvable action from a clinical standpoint as well.

INTERDISCIPLINARY ISSUES

Chemistry, Manufacturing, and Controls

The most salient CMC issue relates to the sponsor's change to the in –process controls for hardness and friability of the tablets (both strengths). During the review cycle the sponsor changed the controls to improve the friability and hardness of the maximum and regular strength tablets. This change in the manufacturing process of the tablets now require that adequate stability data be provided to establish the stability of the tablets in order to determine the expiration date. Additionally, the sponsor needs to provide *in vitro* dissolution data of the drug batches produced under the new manufacturing process at release and during stability as well as data to link the batches of Mucinex™ D produced under the new manufacturing conditions to the batches of Mucinex™ D used in the pivotal bioequivalence studies.

Clinical Pharmacology and Biopharmaceutics

Already discussed in the overview

Non-clinical Pharmacology and Toxicology

exposure (AUC) was not affected. The safety profile was generally similar for the test and reference products. However, the sponsor failed to submit a complete safety update as required. It is noteworthy to mention that pseudoephedrine is excreted almost exclusively by the kidney and the proposed label does not mention dose adjustments for patients with renal insufficiency. This is not a deficiency on the part of the sponsor given that the monograph labeling for pseudoephedrine products do not contain such a statement. Consideration should be given to addressing this labeling deficiency at the monograph level for all OTC pseudoephedrine. As a precedent, Another pseudoephedrine product loratadine –D (approved under an NDA) has a statement in the label about dose adjustment in patients with renal insufficiency given that loratadine and pseudoephedrine are excreted by the kidney.

RECOMMENDATIONS

I recommend that the drug be given an APPROVABLE action pending satisfactory resolution of the CMC deficiencies and the submission of the complete safety update to the clinical section to allow for a complete safety review.

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/s/

Lydia McClain
11/3/03 03:45:13 PM
MEDICAL OFFICER

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

APPLICATION:	NDA 21-585	**TRADE NAME:**	Mucinex™ D Maximum Strength Mucinex™ D Regular Strength
APPLICANT/SPONSOR:	Adams Laboratories, Inc.	**USAN NAME:**	Guaifenesin/Pseudoephedrine
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	Expectorant/Decongestant
DATE:	10/21/03	**ROUTE:**	Oral, extended-release tablets

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
1/31/03	1/31/03	NDA 21-585	Original submission, 86 volumes
4/30/03	5/1/03	NDA 21-585 N000 BZ	IR response, literature and subpopulations
5/21/03	5/23/03	NDA 21-585 N000 C	Safety update
8/18/03	8/18/03	NDA 21-585 N000 BM	IR response, ISS and safety update
9/5/03	9/8/03	NDA 21-585 N000 BM	IR, ISS data

RELATED APPLICATIONS

Document Date	Application Type	Comments
6/29/00	NDA 21-282	NDA submission, Mucinex™, guaifenesin extended-release tablets

REVIEW SUMMARY: This NDA is a 505(b)(2) application for an extended-release formulation of guaifenesin and pseudoephedrine HCl. The reference products for the definitive bioequivalence studies were extended-release guaifenesin (Mucinex™, NDA 21-282) and extended-release pseudoephedrine (Sudafed 12-Hour®, an OTC monograph product). The sponsor requests approval of two dosage strengths—600 mg guaifenesin/60 mg pseudoephedrine HCl and 1200 mg guaifenesin/120 mg pseudoephedrine HCl. The sponsor's definitive clinical pharmacology studies established that the 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength met bioequivalence standards compared to the reference products. The pharmacokinetics of guaifenesin and pseudoephedrine were dose proportional for both dosage strengths. A multiple dose bioequivalence study showed that mean AUC_{ss} and C_{max} values also were within 80% to 125% bioequivalence limits compared to the reference standards. The sponsor demonstrated that the pharmacokinetics of guaifenesin and pseudoephedrine were not affected by the presence of one another. The rate and extent of systemic exposure to pseudoephedrine were not affected by administration of the proposed product after consumption of a high-fat meal. The extent of systemic exposure to guaifenesin was not affected by consumption of a high fat meal. The rate of systemic exposure to guaifenesin was decreased slightly to 74% of the reference when the product was administered after consumption of a high fat meal, but is not expected to be clinically significant because the decrease is small and the extent of systemic exposure was not affected. The sponsor provided data from their clinical pharmacology studies and an evaluation of safety information from the US Adverse Event Reporting System (AERS) database and the clinical literature. Integrated safety data from the sponsor's clinical pharmacology studies show no evidence of new safety signal. Data from the AERS database support the safety of guaifenesin and pseudoephedrine and do not present new safety issues. Even though there were no adverse events (AEs) for dysphagia that were associated with the proposed product in the sponsor's studies, postmarketing reports for the proposed product should still be followed for AEs associated with difficulty in swallowing the tablet because of its large size if it the product is approved. The sponsor's review and summary of the literature do not identify any new safety issue for guaifenesin or pseudoephedrine. The sponsor's safety update provides no evidence of new safety concerns, but did not include a review of postmarketing adverse event reports. The sponsor has succeeded in demonstrating that their product is bioequivalent to approved and OTC monograph reference products. The evidence provided by the sponsor supports the safety of their product. However, the sponsor must still submit a review of postmarketing adverse event reports in their safety update. From a clinical perspective, this reviewer recommends an approvable action because of this deficiency.

OUTSTANDING ISSUES: Review of postmarketing adverse event reports in safety update was not submitted

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	___	FILEABLE	___	NOT FILEABLE	
	___	APPROVAL	X	APPROVABLE	___ NOT APPROVABLE
OTHER ACTION:					

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendations on approvability

The sponsor has succeeded in demonstrating that their product is bioequivalent to approved and over-the-counter (OTC) monograph reference products. The evidence submitted by the sponsor supports the safety of their product. However, the sponsor did not submit a review of postmarketing adverse event reports in their safety update. From a clinical perspective, this reviewer recommends an approvable action because of this deficiency.

1.2. Recommendations on Phase 4 studies and risk management steps

The sponsor's proposed 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength tablet is large in size. There were no adverse events for dysphagia that were associated with the proposed product in the sponsor's studies. However, if the product is approved, postmarketing reports for the proposed product should still be followed for adverse events associated with difficulty in swallowing the tablet.

Pseudoephedrine is largely excreted by the kidney. The current OTC monograph labeling for pseudoephedrine does not include a warning for consumers with kidney disease. Consideration should be given to amending the OTC monograph labeling for pseudoephedrine by adding a warning that instructs consumers with decreased renal function to not take the drug.

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 pseudoephedrine HCl. The sponsor requests approval of two dosage strengths, (1) guaifenesin 600 mg/pseudoephedrine HCl 60 mg tablets, and (2) guaifenesin 1200 mg/ pseudoephedrine HCl 120 mg tablets. The product is an extended-release, bilayer tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and nasal decongestant. The proposed labeled indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, and ——— The sponsor's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength.

Guaifenesin is considered to be generally recognized as safe and effective (GRASE) as an expectorant in age groups and in oral doses specified by the OTC monograph [21 CFR 341.78]. Pseudoephedrine is considered to be generally recognized as safe and effective (GRASE) as a nasal decongestant in age groups and in oral doses specified by the OTC monograph [21 CFR 341.80]. The Combination Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use considers the combination of any single

monograph oral nasal decongestant (such as pseudoephedrine) with any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40]. The sponsor's product is proposed for use in adults and children 12 years of age and older. The sponsor's proposed dose for the 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength is 1 tablet every 12 hours, not more than 2 tablets in 24 hours. The proposed dose for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength is 2 tablets every 12 hours, not more than 4 tablets in 24 hours. Theses doses are within the specified OTC monograph doses for guaifenesin and pseudoephedrine over this dosing interval. The proposed labeling for the both dosage strengths instructs consumers not to use the product in children under 12 years of age.

The sponsor's application 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 and a comparison of the bioavailability and bioequivalence of the proposed new drug to that of the approved reference product. The sponsor's drug development program relied on seven clinical pharmacology studies. Among these seven clinical pharmacology studies, there were four definitive studies. The reference products for the sponsor's definitive clinical pharmacology studies were extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®). The seven studies are listed below:

- Studies 00-01 and Study 00-01A were pilot clinical pharmacology studies that evaluated the bioavailability of two experimental combination extended-release formulations containing both guaifenesin and pseudoephedrine.

- Study 2002-01A was a definitive clinical pharmacology study that compared the bioavailability and dose proportionality of guaifenesin and pseudoephedrine from a combination extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®).

- Study 2002-02A was a clinical pharmacology study conducted under fed conditions that compared the bioavailability of guaifenesin and pseudoephedrine from a combination experimental extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®).

- Study 2002-03 was a definitive multiple dose clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine from a combination experimental extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®) at steady state.

- Study 2002-04 was a clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine when administered alone and upon co-administration.

- Study 2002-11 was a definitive clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine from an experimental combination extended-release formulation administered under both fasting and fed conditions.

The sponsor supported the safety of their product with integrated safety data from the clinical pharmacology studies in the sponsor's 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 pseudoephedrine.

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 and 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 definitive bioequivalence studies were extended-release guaifenesin (Mucinex™, NDA 21-282) and extended-release pseudoephedrine (Sudafed 12-Hour®, an OTC monograph product).

The definitive clinical pharmacology studies in this application confirmed the bioequivalence of their drug product to the reference products. Studies indicated that the pharmacokinetics of guaifenesin and pseudoephedrine were linear over the dose range studied and that the two different proposed dosage strengths were dose proportional. The sponsor's drug interaction study indicated that the pharmacokinetics of guaifenesin and pseudoephedrine were not affected by the presence of one another. The rate and extent of systemic exposure to pseudoephedrine were not affected by administration of the proposed product after consumption of a high-fat meal. The rate, but not the extent, of systemic exposure to guaifenesin was decreased slightly when the product was administered after consumption of a high fat meal. Data from the sponsor's clinical pharmacology studies is sufficient to support the efficacy of their product.

2.3. Safety

The sponsor provided data from their clinical pharmacology studies and an evaluation of safety information from the US AERS database and the clinical literature. Integrated safety data from the sponsor's clinical pharmacology studies shows 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 the test and reference products. Data from the AERS database support the safety of guaifenesin and pseudoephedrine and do not present new safety issues.

The sponsor's 1200 mg guaifenesin/120 mg pseudoephedrine tablet weighs 1587 mg and is large in size. There were no AEs for dysphagia in the sponsor's studies that were associated with the proposed products, and a search of AERS DataMart reveals no AE reports for dysphagia with the currently approved Mucinex™ product. If the product is approved, postmarketing reports for the Mucinex™ D product should still be followed for evidence of AEs associated with difficulty in swallowing the tablet because of its large size.

Pseudoephedrine is largely excreted by the kidney. The current OTC monograph labeling for pseudoephedrine does not include a warning for consumers with kidney disease. Consideration should be given to amending the OTC monograph labeling for pseudoephedrine by adding a warning that instructs consumers with decreased renal function to not take the drug. With this exception, the literature supports the established prescribing precautions of guaifenesin and pseudoephedrine. The sponsor's review and summary of the literature do not identify any new safety issue for guaifenesin or pseudoephedrine in special populations. The sponsor's safety update was incomplete and included only a review of the clinical literature. The sponsor did not submit a review of postmarketing adverse events in the safety update. The sponsor's review of the clinical literature included in the safety update does not provide evidence of new safety concerns and supports the safe OTC marketing of their product in the proposed population.

In summary, the data submitted by the sponsor provide no evidence of a safety signal that has not been previously identified. The sponsor must still a submit a summary, analysis, and interpretation of postmarketing safety reports received since the safety cut-off date for the NDA submission for guaifenesin and pseudoephedrine. Except for this deficiency, the sponsor's integrated review of safety supports the proposed indication of their product.

2.4. Dosing

The sponsor's product is proposed for use in adults and children 12 years of age and older. The sponsor's proposed dose for the 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength is 1 tablet every 12 hours, not more than 2 tablets in 24 hours. The sponsor's proposed dose for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength is 2 tablets every 12 hours, not more than 4 tablets in 24 hours. Both doses are within the specified OTC monograph doses for guaifenesin and pseudoephedrine 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 sponsor's food effect study, Study 2002-11, showed that the rate of guaifenesin absorption from the proposed product is decreased by 26% in the presence of a high fat meal. The extent of guaifenesin absorption and the rate and extent of pseudoephedrine absorption from the proposed product is not affected by a high fat meal. Overall, the rate and extent of absorption of the product in the fasted and fed states is similar. The small decrease in the rate of guaifenesin absorption is not likely

to be clinically significant. The sponsor's claim that the product can be administered without regard to timing of meals is acceptable.

2.5. Special populations

Both guaifenesin and pseudoephedrine are considered to be safe and effective for their respective indications at the specified OTC monograph doses. The OTC monograph labeling for guaifenesin and pseudoephedrine require no special directions or warnings for adults and children 12 years and older, the population for which the sponsor's product is proposed. The sponsor's data do not identify any new safety issue for guaifenesin or pseudoephedrine in special populations.

The sponsor'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 sponsor's proposed labeling appropriately instructs consumers not to use the product in children under 12 years of age. The sponsor's review and summary of the literature identified no articles describing safety issues relevant to gender, for pregnant or lactating women, race or consumer with hepatic disease. The current OTC monograph labeling for pseudoephedrine does not include a warning for consumers with kidney disease. Consideration should be given to amending the OTC monograph labeling for pseudoephedrine by adding a warning that instructs consumers with decreased renal function to not take the drug.

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Introduction

This NDA is a 505(b)(2) application for an extended-release formulation of guaifenesin and pseudoephedrine HCl. The sponsor requests approval of two dosage strength tablets, (1) guaifenesin 600 mg/pseudoephedrine HCl 60 mg tablets, and (2) guaifenesin 1200 mg/ pseudoephedrine HCl 120 mg tablets. The product is a bilayer tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and nasal decongestant. The proposed labeled indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, [redacted]. The sponsor's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength.

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

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

Pseudoephedrine is an orally active sympathomimetic that has a decongestant effect on the nasal mucosa. Pseudoephedrine is considered to be generally recognized as safe and effective (GRASE) as an nasal decongestant in the following age groups at the following oral doses [21 CFR 341.80]:

- Adults and children 12 years of age and older: 60 mg every 4 to 6 hours, NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 to 6 hours, NTE 120 mg in 24 hours
- Children 2 to under 6 years of age: 15 mg every 4 to 6 hours, NTE 60 mg in 24 hours
- 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 nasal decongestant (such as pseudoephedrine) with any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

The proposed labeled indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, and The sponsor's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength.

The sponsor's product is proposed for use in adults and children 12 years of age and older. The proposed dose for the 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength is 1 tablet every 12 hours, not more than 2 tablets in 24 hours [Volume 1.1, pages 40-46]. This dose is within the specified OTC monograph doses for guaifenesin and pseudoephedrine over this dosing interval. The proposed labeling for the 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength instructs consumers not to use the product in children under 12 years of age.

Initially, the sponsor's proposed dose for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength was
[Volume 1.1, pages 40-46]. The proposed dose of for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength is one-half of the OTC monograph dose of pseudoephedrine for this dosing interval, and is not supported by the studies in this application. The proposed dose of 2 tablets every 12 hours for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength is acceptable, as guaifenesin and pseudoephedrine are within OTC monograph doses for this dosing interval. The sponsor was advised that the lower dose is not supported. The sponsor has changed the recommended dose for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength to 2 tablets every 12 hours, not more than 4 tablets in 24 hours [NDA 21-585 N000 BZ, 4/30/03, Cover Letter]. The proposed labeling for the 600 mg guaifenesin/60 mg pseudoephedrine product also instructs consumers not to use the product in children under 12 years of age.

The sponsor's application 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 bioequivalence of the proposed new drug to that of the approved reference product.

1.2. Foreign marketing and regulatory history

Guaifenesin and pseudoephedrine single-ingredient products and guaifenesin/ pseudoephedrine combination products are marketed internationally by many manufacturers. The sponsor reports that they do not make guaifenesin or pseudoephedrine or the trade names Mucinex™ and Mucinex™ D available to foreign markets. The sponsor states that to the best of their knowledge, neither active ingredient has been withdrawn from foreign markets for reasons of safety or effectiveness [Volume 1.1, page 47].

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 dosage strength tablets were approved on July 12, 2002, and the 1200 mg dosage strength tablets were approved on December 18, 2002. The sponsor's

program was based on demonstrating that the exposure of guaifenesin from their product 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 guaifenesin product approved in the US.

The sponsor notes that guaifenesin has been used widely in the United States for over 50 years and is a well-known expectorant. The sponsor also notes that pseudoephedrine is a well know pharmaceutical ingredient used as a decongestant. The proposed Mucinex™ D products were designed by the sponsor to be a line extension to the single-ingredient Mucinex™ 600 mg and 1200 mg products. The sponsor believes that the proposed product would be a more convenient dosage form for combined guaifenesin and pseudoephedrine therapy and would allow for greater consumer compliance. There currently are various combination guaifenesin/pseudoephedrine products that are unapproved and illegally marketed in the United States. [Volume 1.1, page 47]

2. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

2.1. Chemistry, Manufacturing, and Controls

The sponsor's supplier of guaifenesin is [redacted] The application references the supplier's drug master file, DMF [redacted] [Volume 1.1, page 48].

The sponsor's suppliers of pseudoephedrine HCl are [redacted] The application references the suppliers' drug master files, DMF [redacted] respectively [Volume 1.1, page 48].

The drug product is a bi-layer tablet, with a white immediate release layer and a colored modified release layer. All of the pseudoephedrine HCl is contained in the modified release layer. The guaifenesin 1200 mg/pseudoephedrine HCl 120 mg dosage strength tablets (Mucinex™ D Maximum Strength) are pink and white. The guaifenesin 600 mg/pseudoephedrine HCl 60 mg dosage strength tablets (Mucinex™ D Maximum Strength) are orange and white [Volume 1.1, page 48].

The composition of the guaifenesin 1200 mg/pseudoephedrine HCl 120 mg dosage strength tablet is described below in Table 2.1.

Table 2.1. Composition of guaifenesin 1200 mg/pseudoephedrine HCl 120 mg dosage strength tablets, Mucinex™ Maximum Strength [Volume 1.1, page 49].

Component	Amount, mg/tablet
Guaifenesin	
Hydroxypropyl methylcellulose	
Pseudoephedrine HCl	
Microcrystalline cellulose	
Sodium starch glycolate	
Carbomer 934P	
Magnesium stearate	
FD&C Red #40 Aluminum Lake	
Water, purified	
Total Weight	1587.0

The composition of the guaifenesin 600 mg/pseudoephedrine HCl 60 mg dosage strength tablet is described below in Table 2.2.

Table 2.2. Composition of guaifenesin 600 mg/pseudoephedrine HCl 60 mg dosage strength tablets, Mucinex™ Regular Strength [Volume 1.1, page 50].

Component	Amount, mg/tablet
Guaifenesin	
Hydroxypropyl methylcellulose	
Pseudoephedrine HCl	
Microcrystalline cellulose	
Sodium starch glycolate	
Carbomer 934P	
Magnesium stearate	
FD&C Red #40 Aluminum Lake	
Water, purified	
Total Weight	794.1

The to-be-marketed formulation of drug product was used in the definitive bioequivalence, dose-proportionality, and food effect studies in this application [Volume 1.1, cover letter, page 2; Volume 1.1, page 74]. 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 Section 11 of this document, "Appendix, Clinical Studies."

The sponsor made changes during the review cycle to the in-process controls for hardness and friability of the drug product. Details may be found in the Chemistry, Manufacturing, and Controls (CMC) review [CMC review, Jean Salemme, Ph.D.]. The changes represent SUPAC Level 1 or Level 2 changes and must be supported by data from in vitro studies. If the data from these studies indicates a significant difference in the quality or performance of the drug product, then the sponsor may need to perform additional in vitro or in vivo studies.

2.2. Nonclinical pharmacology and toxicology

Guaifenesin is generally recognized as safe and effective (GRASE) as an oral expectorant at the sponsor's proposed doses in adults and children 12 years of age and older. Pseudoephedrine is generally recognized as safe and effective (GRASE) as an oral nasal decongestant at the sponsor's proposed doses in adults and children 12 years of age and older. No nonclinical pharmacology and toxicology data were submitted nor were required.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

This submission refers to seven clinical pharmacology studies. The design of these studies are described in Section 4 of this review, "Description of Clinical Data and Sources" and are reviewed individually in Section 11 of this review, "Appendix, Clinical Studies." Among these seven 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 further below in the review of the individual studies (Section 11, Appendix, Clinical Studies) and in Dr. Suarez's review [Sandra Suarez-Sharp, Ph.D., Clinical Pharmacology and Biopharmaceutics Review, NDA 21-585].

Study 2002-01A was a single dose study that compared the bioavailability and dose proportionality of guaifenesin and pseudoephedrine from the proposed extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®). Mean $AUC_{0\text{-}inf}$ and C_{max} values for the proposed 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength tablet were within 80% to 125% bioequivalence limits compared to the reference standards. The pharmacokinetics of guaifenesin and pseudoephedrine were dose proportional when the dose was doubled from 600 mg guaifenesin/60 mg pseudoephedrine to 1200 mg guaifenesin/120 mg pseudoephedrine.

Study 2002-03 was a multiple dose study that compared the bioavailability of guaifenesin and pseudoephedrine from the proposed 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength tablet to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®) at steady state, after 11 doses given every twelve hours. Mean AUC_{ss} and C_{max} values for the proposed product were within 80% to 125% bioequivalence limits compared to the reference standards. The C_{min} value for guaifenesin for the proposed product was 244% of the reference product.

Reviewer comment:
The increased C_{min} value for guaifenesin is unlikely to create a safety concern, as these values were only 1/17 of the steady state C_{max} value for guaifenesin.

Study 2002-04 was a single dose study that compared the bioavailability of guaifenesin and pseudoephedrine when administered alone and upon co-administration. This study provides evidence that the pharmacokinetics of guaifenesin and pseudoephedrine are not affected by the presence of one another.

Study 2002-11 was a single dose study which compared the bioavailability of guaifenesin and pseudoephedrine from an experimental extended-release formulation administered under both fasting and fed conditions. The rate and extent of systemic exposure to pseudoephedrine were not affected by administration of the proposed product after consumption of a high-fat meal. The rate of systemic exposure to guaifenesin was decreased slightly to of the reference when the product was administered after

consumption of a high fat meal. The extent of systemic exposure to guaifenesin was not affected by consumption of a high fat meal.

Reviewer comment:
The decrease in the rate of systemic exposure to guaifenesin is not expected to be clinically significant because the decrease is small and the extent of systemic exposure was not affected.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

This submission refers to seven clinical pharmacology studies. These studies are summarized in Table 4.1. More detailed descriptions of the design of these studies follow below. There were no clinical efficacy or safety studies in this application.

4.1. Study 00-01

Study 00-01 was a pilot clinical pharmacology study that evaluated the bioavailability of experimental combination extended-release formulations containing both guaifenesin and pseudoephedrine. The two experimental formulations were compared to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and fexofenadine/extended-release pseudoephedrine (Allegra® D). 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. 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 for plasma guaifenesin and pseudoephedrine levels. 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 1.47, pages 6-7; Volume 1.52, page 130]

4.2. Study 00-01A

Study 00-01A was a pilot clinical pharmacology study that evaluated the bioavailability of two combination experimental extended-release formulations containing both guaifenesin and pseudoephedrine. The two experimental formulations were compared to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®). 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. 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 for plasma guaifenesin and pseudoephedrine levels. 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 1.53, pages 7-11; Volume 1.56, page 401]

4.3. Study 2002-01A

Study 2002-01A was a definitive clinical pharmacology study that compared the bioavailability and dose proportionality of guaifenesin and pseudoephedrine from a combination extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®). One group received the sponsor's proposed product containing 1200 mg guaifenesin and 120 mg pseudoephedrine and one group received the proposed product containing 600 mg guaifenesin and 60 mg pseudoephedrine. The third group received the reference treatment. 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 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, 6, 8, 10, 12, 14, 16, and 24 hours for plasma guaifenesin and pseudoephedrine levels. 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. There was one subject who withdrew from the study and did not return for the second study period. [Volume 1.57, pages 7-10; Volume 1.63, pages 423, 433]

4.4. Study 2002-02A

Study 2002-02A was a clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine from a combination experimental extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®) under 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. 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 for plasma guaifenesin and pseudoephedrine levels. 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 1.64, pages 7-9; Volume 1.68, pages 398, 408]

4.5. Study 2002-03

Study 2002-03 was a definitive clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine from a combination experimental extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®) at steady state, after 11 doses given every twelve hours. The study was an open-label, randomized, multiple dose, two period, two-way crossover bioavailability study conducted in 37 healthy male and female subjects. Samples were taken immediately before dosing (0 hours) on Days 1, 4, 5, and 6. On day 6, subjects also had blood samples drawn at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours for plasma guaifenesin and pseudoephedrine levels. 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 seven days

separated each treatment period. Safety endpoints reported included adverse events. [Volume 1.69, pages 7-10, 46; Volume 1.74, pages 324, 336]

4.6. Study 2002-04

Study 2002-04 was a clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine when administered alone and upon co-administration. The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study conducted in 36 healthy male and female subjects. Treatment groups included the proposed guaifenesin 1200 mg/ pseudoephedrine 120 mg product, 1200 mg guaifenesin (Mucinex™), and 120 mg pseudoephedrine (Sudafed 12-Hour®). 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 and pseudoephedrine levels. Subjects were housed at the study site after the 24-hour sample was drawn. A minimum washout period of seven days separated each treatment period. Safety endpoints reported included adverse events. [Volume 1.75, pages 7-10, 46; Volume 1.80, pages 411, 421]

4.7. Study 2002-11

Study 2002-11 was a definitive clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine from a combination experimental 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. 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 for plasma guaifenesin and pseudoephedrine levels. 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 1.81, pages 7-10; Volume 1.86, pages 147, 157]

Table 4.1. Summary of studies, NDA 21-585 [Volume 1.1, pages 53, 67-73].

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

G = guaifenesin, PSE = pseudoephedrine
*Fexofenadine 60 mg/120 mg PSE = Allegra® D
**Prototype chosen for drug development

- Statements of Good Clinical Practice [Volume 1.47, page 6; Volume 1.53, page 2; Volume 1.57, page 2; Volume 1.64, page 2; Volume 1.69, page 2; Volume 1.75, page 2; Volume 1.81, page 2]

The sponsor 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 sponsor 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 sponsor certified that the clinical investigators did not have a proprietary interest in the proposed product or a significant equity in the sponsor. The sponsor certified that no investigator was the recipient of significant payments.

6. INTEGRATED REVIEW OF EFFICACY

As noted above, this application 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 bioequivalence of the proposed new drug to that of the approved reference product. The reference products for the definitive clinical pharmacology studies in this 505(b)(2) application were the sponsor's approved and marketed extended-release single-ingredient guaifenesin product (Mucinex™, NDA 21-282) and an approved and marketed extended-release pseudoephedrine product, (Sudafed 12-Hour®, an OTC monograph product) both at OTC monograph doses. No clinical studies of the efficacy of the product or integrated summary of efficacy were required for to support this application.

The definitive clinical pharmacology studies in this application confirmed the bioequivalence of their drug to the reference products. Studies indicated that the pharmacokinetics of guaifenesin and pseudoephedrine were linear over the dose range studied and that the two different proposed dosage strengths were dose proportional. The sponsor's drug interaction study indicated that the pharmacokinetics of guaifenesin and pseudoephedrine were not affected by the presence of one another. The rate and extent of systemic exposure to pseudoephedrine were not affected by administration of the proposed product after consumption of a high-fat meal. The rate, but not the extent, of systemic exposure to guaifenesin was decreased slightly when the product was administered after consumption of a high fat meal.

Data from the sponsor's clinical pharmacology studies is sufficient to support the efficacy of their product.

7. INTEGRATED REVIEW OF SAFETY

The sponsor's drug development program for Mucinex™ D was based on establishing that their combination guaifenesin/pseudoephedrine 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 pseudoephedrine product. Both reference products are generally recognized as safe and effective for their respective indications by the OTC monograph [21 CFR 341.78 and 21 CFR 341.80].

The focus of this section of this review is on the case that the sponsor has made for the safety of guaifenesin and pseudoephedrine, given this background. A review of the sponsor's Integrated Summary of Safety follows below.

7.1. Summary and conclusions

The sponsor provided data from their clinical pharmacology studies and an evaluation of safety information from the US Adverse Event Reporting System (AERS) database and the clinical literature. Integrated safety data from the sponsor's clinical pharmacology studies shows 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 the test and reference products. Data from the AERS database support the safety of guaifenesin and pseudoephedrine and do not present new safety issues.

The sponsor's 1200 mg guaifenesin/120 mg pseudoephedrine tablet weighs 1587 mg and is large in size. There were no AEs for dysphagia in the sponsor's studies that were associated with the proposed products, and a search of AERS DataMart reveals no AE reports for dysphagia with the currently approved Mucinex™ product. Because of the large tablet size, postmarketing reports for the Mucinex™ D product should still be followed for AEs associated with difficulty in swallowing the tablet, if the product is approved.

Pseudoephedrine is largely excreted by the kidney. The current OTC monograph labeling for pseudoephedrine does not include a warning for consumers with kidney disease. Consideration should be given to amending the OTC monograph labeling for pseudoephedrine by adding a warning that instructs consumers with decreased renal function to not take the drug. With this exception, the literature supports the established prescribing precautions of guaifenesin and pseudoephedrine. The sponsor's review and summary of the literature do not identify any new safety issues for guaifenesin or pseudoephedrine in special populations. The sponsor's safety update was incomplete and included only a review of the clinical literature. The sponsor did not submit a review of postmarketing adverse events in the safety update. The sponsor's review of the clinical literature included in the safety update does not provide evidence of new safety concerns and supports the safe OTC marketing of their product in the proposed population.

In summary, the data submitted by the sponsor provide no evidence of a safety signal that has not been previously identified. The sponsor must still a submit a summary, analysis, and interpretation of postmarketing safety reports received since the safety cut-off date for the NDA submission for guaifenesin and pseudoephedrine. Except for this deficiency, the sponsor's integrated review of safety supports the proposed indication of their product.

7.2. Content

The following are reviewed in this Integrated Review of Safety:

- Integrated safety data from the clinical pharmacology studies in the sponsor's drug development program

- Sponsor's evaluation of spontaneous adverse event reports from the AERS database obtained through the Freedom of Information Act (FOIA)
- Sponsor's review of information related to drug abuse and overdose
- Sponsor's review of the literature for safety information relevant to guaifenesin and pseudoephedrine
- Sponsor's safety update

7.3. Integrated safety data, sponsor's studies

Integrated safety data from the sponsor's clinical pharmacology studies show no evidence of new safety signal. In general, AEs were more frequent in the subjects that received reference treatment single-ingredient guaifenesin 1200 mg plus single-ingredient pseudoephedrine 120 mg than for the sponsor's test products. There were no meaningful differences in AEs between the test and reference products. There were no meaningful differences between the test and the reference products in withdrawals due to AEs or other SAEs. The subject population in this study was not ideal to assess safety in subgroups. There were too few AEs to determine if there was an association of AEs with gender for any of the individual formulations studied. All subjects were from 18 to 54 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.

A detailed review of the integrated safety data from the seven clinical pharmacology studies in this application follows below.

7.3.1. Description of pivotal studies

Brief descriptions of the seven clinical pharmacology studies in the sponsor's drug development plan follow below.

Study 00-01 was a pilot clinical pharmacology study that evaluated two experimental combination extended-release formulations of guaifenesin and pseudoephedrine. The two experimental formulations were compared to a reference treatment consisting of extended-release guaifenesin (Mucinex™) plus fexofenadine/extended-release pseudoephedrine (Allegra® D). The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study conducted in 21 healthy male and female subjects [Volume 1.47, pages 6-7; Volume 1.52, page 130].

Study 00-01A was a pilot clinical pharmacology study that also evaluated two experimental combination extended-release formulations of guaifenesin and pseudoephedrine. The two experimental formulations were compared to a reference treatment consisting of extended-release guaifenesin (Mucinex™) plus extended-release pseudoephedrine (Sudafed 12-Hour®). The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study conducted in 15 healthy male and female subjects [Volume 1.53, pages 7-11; Volume 1.56, page 401].

Study 2002-01A was a definitive clinical pharmacology study that compared the bioavailability and dose proportionality of guaifenesin and pseudoephedrine from a

combination extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) plus extended-release pseudoephedrine (Sudafed 12-Hour®). One group received the sponsor's proposed product containing 1200 mg guaifenesin and 120 mg pseudoephedrine and one group received the proposed product containing 600 mg guaifenesin and 60 mg pseudoephedrine. The third group received the reference treatment. The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study conducted in 36 healthy male and female subjects [Volume 1.57, pages 7-10; Volume 1.63, pages 423, 433].

Study 2002-02A was a clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine from an experimental combination extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®) under 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 [Volume 1.64, pages 7-9; Volume 1.68, pages 398, 408].

Study 2002-03 was a definitive clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine from an experimental combination extended-release formulation to a reference treatment consisting of extended-release guaifenesin (Mucinex™) and extended-release pseudoephedrine (Sudafed 12-Hour®) at steady state, after 11 doses given every twelve hours. The study was an open-label, randomized, multiple dose, two period, two-way crossover bioavailability study conducted in 37 healthy male and female subjects [Volume 1.69, pages 7-10, 46; Volume 1.74, pages 324, 336].

Study 2002-04 was a clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine when administered alone and upon co-administration. The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study conducted in 36 healthy male and female subjects [Volume 1.75, pages 7-10, 46; Volume 1.80, pages 411, 421].

Study 2002-11 was a definitive clinical pharmacology study that compared the bioavailability of guaifenesin and pseudoephedrine 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 [Volume 1.81, pages 7-10; Volume 1.86, pages 147, 157].

7.3.2. Demographics

A total of 217 subjects received at least one dose of study medication. The great majority of subjects were Caucasian (198/217, 91.2%). Small proportions of the study population were Black (8/217, 3.7%), Asian (3/217, 1.4%), Hispanic (1/217, 0.5%) or multiracial (6/217, 2.8%). Males and females were fairly evenly represented, with 59.9% (130/217) of male subjects and 40.1% (87/217) of female subjects. The mean age of subjects in

these studies was 26.1 years, ranging from 18-54 years. [from data, Volume 1.46, pages 152, 155, 158, 166, 174, 180, 185].

Reviewer comment:
Non-Caucasian subjects were underrepresented in these studies. Even though the subject population in this study is not ideal to assess safety in subgroups, both guaifenesin and pseudoephedrine are OTC monograph drugs and are generally recognized as safe at the doses given in this study.

7.3.3. Disposition

A total of 217 subjects received at least one dose of study medication in the sponsor's drug development program. Of these 217 subjects, 210 subjects received all treatments and completed the studies according to protocol [Volume 1.46, page 193]. Of the seven subjects who did not complete the studies, there was one subject who withdrew because of an adverse event. This subject withdrew from study 2002-02A with an upper respiratory infection. There were three subjects who return for the second period of their studies. There was one subject who withdrew because of a class schedule conflict, one subject who was dropped because of a positive drug screen, and one subject who withdrew consent [Volume 1.46, page 194].

7.3.4. Exposure

Exposure to study medication is summarized in Table 7.1. A total of 36 subjects were exposed to the sponsor's guaifenesin 600 mg/pseudoephedrine 60 mg combination product. A total of 157 subjects were exposed to any of the sponsor's three guaifenesin 1200 mg/pseudoephedrine 120 mg combination products used in studies in this application. A total of 177 subjects were exposed to guaifenesin 1200 mg plus pseudoephedrine 120 mg single-ingredient products [from data, Volume 1.46, page 193].

Table 7.1. Exposure in clinical pharmacology studies, NDA 21-585 [from data, Volume 1.46, page 193].

Study Treatments	Subjects exposed* n	Doses taken
Any study treatment	217	Up to 11 doses
Guaifenesin 600 mg/PSE 60 mg	36	Single dose
Guaifenesin 1200 mg/PSE 120 mg, all formulations	157	Up to 11 doses
Guaifenesin 1200 mg	36	Single dose
PSE 120 mg	36	Single dose
Guaifenesin 1200 mg plus PSE 120 mg	177	Up to 11 doses
Guaifenesin 1200 mg plus fexofenadine 60 mg/PSE 120 mg	21	Single dose

*Sum of individual study treatment numbers does not equal the number of subjects exposed to any study treatment because all studies were crossover studies and subjects were exposed to more than one study treatment.

7.3.5. Adverse events

Adverse events (AEs) occurring in the clinical pharmacology studies are integrated and presented in Table 7.2. AEs were more frequent for the guaifenesin 1200 mg plus pseudoephedrine 120 mg single-ingredient reference treatment (28.0%, 44/157) than with guaifenesin 600 mg/pseudoephedrine 60 mg (16.7%, 6/36) or guaifenesin 1200 mg/pseudoephedrine 120 mg (20.3%, 36/177) combination products. Sleeplessness

(3.4%, 6/177) and sore throat (1.7%, 3/177) occurred more frequently with the guaifenesin 1200 mg/pseudoephedrine 120 mg combination product than the guaifenesin 600 mg/pseudoephedrine 60 mg (0%, 0/36 and 0%, 0/36, respectively) combination product. Other AEs occurred more often in the guaifenesin 1200 mg plus pseudoephedrine 120 mg single-ingredient reference treatment group or occurred in two or fewer subjects.

The majority of subjects (59.9%, 130/217) in the clinical pharmacology studies were men, and 40.1% (87/217) were women. Of all AEs noted in these studies, nausea and lightheadedness were more common among women than men (5.7%, 5/87 vs.1.5%, 2/130 and 4.6% , 4/87 vs. 1.5%, 2/130, respectively). There was no evidence of an association of any of the other AEs with gender. There were too few AEs with the individual formulations to determine if there was an association of AEs with gender for any of them. All subjects were from 18 to 54 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 [from data, Volume 1.46, pages 152, 155, 158, 166, 174, 180, 185; from data, NDA 21-585 N000 BZ, 4/30/03, cover letter page 2 and Exhibit 4, all pages].

Reviewer comment:
In general, AEs were more frequent in the subjects that received reference treatment guaifenesin 1200 mg plus pseudoephedrine 120 mg single-ingredient reference treatment than for the combination products. There appear to be no meaningful differences in AEs between the test and reference products.

Although it was not coded as an AE, the sponsor noted that in Study 00-01, one subject drank approximately 46 ounces of tap water in order to swallow one of the reference products, due to its large size [Volume 1.47, page 53-55, 65]. One wonders if the subject needed to drink this large amount of water because the pill was stuck in her throat. The 1200 mg guaifenesin product that is currently approved and marketed (Mucinex™, NDA 21-282) is large, weighing 1458 mg/tablet [CMC review dated 3/20/01 , Dr. Juanita Ross, NDA 21-282, 6/29/00]. The 1200 mg guaifenesin/120 mg pseudoephedrine tablet, at 1587 mg, is also large in size [Volume 1.1, page 49]. A search of AERS DataMart reveals no AE reports for Mucinex™ for the following reactions: "choking, choking sensation, esophageal obstruction, tracheal obstruction, or laryngeal obstruction," despite its large size. If the product is approved, postmarketing reports for the Mucinex™ D product should be followed for AEs related to the large tablet size or for difficulty in swallowing the tablet.

Table 7.2. Adverse events occurring in more than one subject with any formulation in studies in Mucinex D development program, integrated data [compiled from Volume 1.46, pages 193, 195-197].

Adverse event	Guaifenesin 600 mg/ PSE 60 mg N = 36		Guaifenesin 1200 mg/ PSE 120 mg N = 177		Guaifenesin 1200 mg Plus PSE 120 mg N = 157		Guaifenesin 1200 mg N = 36		PSE 120 mg N = 36		Guaifenesin 1200 mg Plus Fexofenadine 60 mg/ PSE 120 mg N = 21	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
All adverse events	6	(16.7)	36	(20.3)	44	(28.0)	4	(11.1)	4	(11.1)	2	(9.5)
Headache	2	(5.6)	6	(3.4)	14	(8.9)	4	(11.1)	1	(2.8)	1	(4.8)
Sleeplessness	0	(0)	6	(3.4)	1	(0.6)	0	(0)	0	(0)	0	(0)
Nausea	1	(2.8)	3	(1.7)	3	(1.9)	0	(0)	0	(0)	0	(0)
Sore throat	0	(0)	3	(1.7)	0	(0)	0	(0)	0	(0)	0	(0)
Lightheadedness	1	(2.8)	2	(1.1)	2	(1.3)	0	(0)	1	(2.8)	0	(0)
Dry mouth	0	(0)	2	(1.1)	7	(4.5)	0	(0)	0	(0)	0	(0)
Nervousness*	0	(0)	2	(1.1)	1	(0.6)	0	(0)	0	(0)	0	(0)
Cough	0	(0)	2	(1.1)	0	(0)	0	(0)	0	(0)	0	(0)
Moodiness	0	(0)	2	(1.1)	0	(0)	0	(0)	0	(0)	0	(0)
Vomiting/emesis	0	(0)	1	(0.6)	3	(1.9)	0	(0)	0	(0)	0	(0)
Drowsiness**	0	(0)	0	(0)	4	(2.5)	0	(0)	0	(0)	0	(0)
Loss of appetite	0	(0)	0	(0)	1	(0.6)	0	(0)	2	(5.6)	0	(0)

*Includes AEs for "edgy" and "restlessness"
**Includes AEs for "sleepiness"

7.3.6. Serious adverse events and deaths

There were no SAEs or deaths in the sponsor's studies [Volume 1.46, page 198].

7.3.7. Withdrawals due to adverse events

There was one subject who withdrew from a study because of an AE. Subject 3 in study 2002-02A experienced an upper respiratory tract infection and withdrew after the first dose of study medication, but before the second period of the study [Volume 1.46, page 198].

7.3.8. Vital signs

Vital signs were not safety endpoints in the sponsor's studies.

7.3.9. Physical examination

Physical examination was not a safety endpoint in the sponsor's studies.

7.3.10. Laboratory studies

Laboratory studies were not safety endpoints in the sponsor's studies.

7.3.11. ECGs

ECGs were not safety endpoints in the sponsor's studies.

7.4. Spontaneous adverse event reports from the AERS database

The sponsor submitted postmarketing adverse event reports for guaifenesin and pseudoephedrine from the AERS database covering the period from November 1, 1997, until November 8, 2002 [Volume 1.46, pages 202-218, 222-273]. These reports were tabulated and analyzed by the sponsor in later submissions [NDA 21-585, N000 BM, 8/18/03 and NDA 21-585, N000 BM, 9/5/03]. Data from the AERS database support the safety of guaifenesin and pseudoephedrine and do not present new safety issues.

A review of the sponsor's analyses follows below.

7.4.1. Postmarketing adverse event reports for guaifenesin

The sponsor reported that there were 222 AE reports for guaifenesin in the AERS database for the five year period November 1, 1997, through November 1, 2002. Of these 222 reports, 21 (9.5%) were associated with guaifenesin as the primary suspect drug. The most common AEs reported for guaifenesin included dizziness (2.7%, 6/222), cerebrovascular accident not otherwise specified (NOS) (2.3%, 5/222), drug interaction NOS, drug toxicity NOS, headache NOS, medication error, nausea, overdose NOS, pneumonia, vomiting (each 1.8%, 4/222) [NDA 21-585, N000 BM, 9/5/03, Exhibit C]. Guaifenesin was a secondary suspect drug for all five patients with reports for cerebrovascular accident and all five patients were taking phenylpropanolamine, a drug that has been withdrawn from the market because of an association with stroke [Volume

1.46, pages 202-218, 222-273]. There were a total of 21 AEs associated with guaifenesin as the primary suspect drug. The most common AEs for guaifenesin as primary suspect drug included completed suicide, drug toxicity, insomnia, nausea, and Stevens Johnson syndrome (9.5% each, 2/21) [NDA 21-585, N000 BM, 9/5/03, Exhibit A]. The sponsor reports that IMS Health data estimates that there were approximately ——— prescriptions annually for guaifenesin. Additionally, the sponsor notes that there are no estimated numbers for over the counter usage for guaifenesin. The sponsor concludes 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 [NDA 21-585, N000 BM, 9/5/03, Cover Letter].

Reviewer comment:
The association of cerebrovascular accident with guaifenesin is likely to be due to concomitant use of phenylpropanolamine. It is not possible to draw conclusions from the small number of AEs associated with guaifenesin as primary suspect drug. These data support the safety of guaifenesin and do not present new safety issues.

7.4.2. Postmarketing adverse event reports for pseudoephedrine

The sponsor reported that there were 781 AE reports for pseudoephedrine in the AERS database for the five year period November 1, 1997, through November 1, 2002. Of these 781 reports, 160 (20.5%) were associated with pseudoephedrine as the primary suspect drug. The most common AEs reported for pseudoephedrine as primary and secondary suspect drug included drug ineffective (3.1%, 24/781), accidental overdose (2.6%, 20/781), insomnia (1.7%, 13/781), overdose NOS (1.3%, 10/781), convulsions NOS (1.2%, 9/781), and non-accidental overdose (1.2%, 9/781) [NDA 21-585, N000 BM, 9/5/03, Exhibit C]. There were a total of 160 AEs associated with pseudoephedrine as the primary suspect drug. The most common AEs for pseudoephedrine as primary suspect drug included drug ineffective (11.9%, 19/160), insomnia (6.9%, 11/160), urticaria NOS (3.1%, 5/160), dermatitis NOS (2.5%, 4/160), blood pressure increased, nausea, and tachycardia (1.9% each, 3/160) [NDA 21-585, N000 BM, 9/5/03, Exhibit B]. The sponsor concludes that the postmarketing AE data support the overall safety of pseudoephedrine as previously concluded by the OTC Monograph Review and do not contain any new information which would change the safety profile of pseudoephedrine [NDA 21-585, N000 BM, 9/5/03, Cover Letter].

Reviewer comment:
Insomnia, increased blood pressure, and tachycardia are AEs known to be associated with pseudoephedrine. These data support the safety of pseudoephedrine and do not present new safety issues.

7.5. Drug abuse and overdose

The sponsor's literature review identifies several cases of abuse related to guaifenesin and pseudoephedrine. Cases of guaifenesin abuse appeared to be related to use of products also containing ephedrine and were associated with the development of renal stones containing a guaifenesin metabolite [Volume 1.46, pages 277-282, 284-286].[1, 2]

Cases of pseudoephedrine overdose identified by the sponsor included children who accidentally received larger than recommended doses. The sponsor identified one case of intentional intravenous use of pseudoephedrine in an adult and case reports of two children, 13 and 15 years of age with psychosis due to intentional use of larger than recommended doses of pseudoephedrine [Volume 1.46, pages 287-289; NDA 21-585 N000 BZ, 4/30/03, Exhibit 3, articles 12 and 13].[3, 4, 5, 6]

The sponsor states that Mucinex™ D is not expected to be subject to abuse. Acute overdose of Mucinex™ D would probably result in symptoms of tremor, restlessness, and insomnia as well as sympathomimetic symptoms such as tachycardia, hypertension, mydriasis, hyperglycemia, and hypokalemia. The sponsor notes that guaifenesin may cause gastrointestinal discomfort, nausea, and vomiting at very large doses [Volume 1.46, page 275].

Reviewer comment:
The literature suggests that there is some potential for abuse of pseudoephedrine-containing products. However, there are relatively few case reports, given the widespread use of the large number of pseudoephedrine-containing products. The sponsor's product does not appear to be at risk for abuse because of its guaifenesin content. This reviewer concurs with the sponsor that there does not appear to be large risk for abuse of their product because of its pseudoephedrine content.

7.6. Evaluation of safety information from the literature

The sponsor conducted extensive searches of the scientific and medical literature for references related to guaifenesin and pseudoephedrine. These searches were performed for the sponsor by [redacted]. Multiple medical and scientific databases were searched [Volume 1.45, pages 178-401; Volume 1.46, pages 1-149, 276-320]. Of the multiple citations retrieved, the sponsor identified 19 articles of interest for guaifenesin and 16 articles for pseudoephedrine.

The sponsor concluded that the literature supports the established prescribing precautions of guaifenesin and pseudoephedrine [Volume 1.45, page 178; Volume 1.46, page 1]. The sponsor's review of the published literature for guaifenesin- and pseudoephedrine-associated adverse events does not provide evidence of new safety concerns. It is known that pseudoephedrine is largely excreted by the kidney, but the current OTC monograph labeling for pseudoephedrine does not include a warning for consumers with kidney disease. Consideration should be given to amending the OTC monograph labeling for pseudoephedrine by adding a warning instructing consumers with decreased renal function to not take the drug. With this exception, this reviewer concurs with the sponsor's conclusion that the literature supports the established prescribing precautions of guaifenesin and pseudoephedrine.

7.6.1. Review of literature, guaifenesin

Of note among the 19 articles of interest for guaifenesin are two articles describing an association of renal stones with chronic use of excessive amounts of guaifenesin. In both

articles, the stones consisted of metabolites of guaifenesin. The dosages taken, as reported by patients, ranged from 600 to 24,000 mg of guaifenesin per day. Both authors conclude that patients taking large amounts of guaifenesin may be at risk for development of stones derived from guaifenesin metabolites [Volume 1.46, pages 278-282, 284-286].[1, 2]

Reviewer comment:
Although renal stones are not noted in the OTC monograph labeling for guaifenesin, the OTC monograph labeling instructs the consumer not to exceed 400 mg every 4 hours or 2400 mg in 24 hours. The OTC monograph label also instructs the consumer to consult a doctor if cough persists longer than one week [21 CFR 341.78(c)]. It is likely that the patient who reported taking 600 mg per day was underreporting the dosage taken. As the association of renal stones with guaifenesin appear to be related to chronic use in much greater amounts than the labeled dose, the current OTC monograph labeling is appropriate.

7.6.2. Review of literature, pseudoephedrine

There are seven articles of note among the 16 articles of interest for pseudoephedrine. These articles are briefly reviewed below.

The sponsor identified a case report of pseudoephedrine accumulation in a patient with chronic renal failure due to renal artery stenosis, with BUN values in the 80-100 mg/dL range. Shortly after beginning pseudoephedrine 60 mg QID daily for nasal congestion, the patient developed myoclonic jerking and bizarre behavior, both of which ceased with cessation of pseudoephedrine and initiation of hemodialysis. Pseudoephedrine plasma levels were elevated to 1425 ng/mL, which fell to the expected concentration of approximately 1000 ng/mL within the first two days after discontinuation of the drug [Volume 1.45, pages 136-138].[7]

Reviewer comment:
The OTC monograph labeling instructs consumers not to take pseudoephedrine if they have heart disease, high blood pressure, thyroid disease, diabetes, difficulty in urination due to enlargement of the prostate gland unless directed by a doctor [21 CFR 341.80(c)]. Labeling for the prescription product Allegra-D (fexofenadine 60 mg/pseudoephedrine 120 mg) notes that pseudoephedrine is known to be substantially excreted by the kidney and that the risk of toxic reactions may be greater in patients with impaired renal function. The Allegra-D label recommends a reduced dose in patients with decreased renal function. Labeling for OTC products Claritin-D 24 Hour (loratadine 10 mg/pseudoephedrine 240 mg) and Claritin-D 12 Hour (loratadine 5 mg/pseudoephedrine 120 mg) includes warnings to consumers with kidney disease advising them to ask a doctor before use. Consideration should be given to amending the labeling for pseudoephedrine in the OTC monograph for decongestant drug products to include a warning for consumers with kidney disease.

The sponsor identified four articles describing case reports of psychosis and/or hallucinations associated with pseudoephedrine use. One case was an 18-year old adult

who intentionally injected himself with 60 mg of pseudoephedrine intravenously [Volume 1.46, pages 287-289].[3] Two cases of psychosis were in children 2 and 3 years of age and were associated with unintentional ingestion of larger than recommended doses of pseudoephedrine [NDA 21-585 N000 BZ, 4/30/03, Exhibit 3, articles 12 and 13].[4, 5] These patients had resolution of symptoms after hospitalization for observation and/or treatment with antipsychotic medications. One article described case reports of two children, 13 and 15 years of age, with acute psychosis from intentional use of larger than recommended doses of pseudoephedrine. This article also described a case report of a 10-year old who had irritability, hallucinations, and paranoia with recommended doses of pseudoephedrine in conjunction with a prednisone burst of 120 mg per day tapered to 5 mg per day at presentation [NDA 21-585 N000 BZ, 4/30/03, Exhibit 3, article 14].[6]

Reviewer comments:
All but one of these cases were associated with intentional or unintentional exposure to larger than recommended doses of pseudoephedrine. The last case is confounded by the recent use of large doses of prednisone. OTC monograph labeling instructs the consumer not to exceed the recommended dosage, and to discontinue use if nervousness, dizziness, or sleeplessness occurs.

One article describes the results of a double blind, randomized, placebo controlled, crossover study in 20 hypertensive patients designed to assess the effect of a single dose of 60 mg pseudoephedrine on blood pressure. Statistically significant increases in mean values for systolic blood pressure (+2.9 mm Hg) and heart rate (+3.4 bpm) were noted. Smaller increases in diastolic BP (+ 1.1 mm Hg) and mean arterial pressure (+1.5 mm Hg) were noted but these were not statistically significant [NDA 21-585 N000 BZ, 4/30/03, Exhibit 3, article 2].[8]

Reviewer comments:
Pseudoephedrine is a sympathomimetic drug, and changes in blood pressure and pulse are a manifestation of its activity. The OTC monograph labeling includes a warning that instructs consumers not to take the product if they have heart disease or high blood pressure [21 CFR 341.80(c)].

The sponsor identified one reference describing intracranial hemorrhage in a 17-year old girl who intentionally ingested 1200 mg of pseudoephedrine in a suicide attempt. She presented with headache, drowsiness, a right hemiparesis with sensory deficit, and had a CT scan that showed a hematoma in the left frontal area. She recovered with supportive care and six months later was reported to be normal except for a small residual cavity at the site of the previous hematoma [NDA 21-585 N000 BZ, 4/30/03, Exhibit 3, article 9].[9]

7.6.3. Special populations

Two articles in the sponsor's literature review described a registry for toxicology data in children 15 years of age or younger. There were fifteen cases in which toxicology samples identified serum levels of pseudoephedrine in children. All cases were in children less than 6 months of age and all cases were deaths. The most common cause of death was Sudden Infant Death Syndrome (SIDS). Pseudoephedrine concentrations in

these cases ranged from 0.07 mg/L to 13.0 mg/L. The author concluded that the data do not allow definitive statements about the toxicity of pseudoephedrine at given concentrations [NDA 21-585 N000 BZ, 4/30/03, cover letter, page 2 and Exhibit 3, articles 6 and 7].[10, 11] The sponsor also noted that the terminal elimination half-life for pseudoephedrine in a study of children 6 to 12 years of age was 3.1 hours, which was significantly shorter than values for adults [NDA 21-585 N000 BZ, 4/30/03, cover letter, page 2 and Exhibit 5, article 1].[12]

As noted above, the sponsor identified a case report of pseudoephedrine accumulation in a patient with chronic renal failure due to renal artery stenosis, with BUN values in the 80-100 mg/dL range [Volume 1.45, pages 136-138].[7] Elderly consumers are more likely to have decreased renal function, but OTC monograph labeling includes no warnings for consumers ≥65 years of age.

The sponsor's review and summary of the literature identified no articles describing safety issues relevant to gender or race [NDA 21-585 N000 BZ, 4/30/03, cover letter, page 2].

In this reviewer's opinion, the sponsor's review and summary of the literature do not identify any new safety issue for guaifenesin or pseudoephedrine in special populations.

7.7. Safety update

The sponsor provided a safety update that included a review of the clinical literature from September 30, 2002, the sponsor's cut-off date for the NDA submission, until August 13, 2003. The sponsor did not submit a summary, analysis, and interpretation of postmarketing safety reports for the period after the cut-off date for the NDA submission for guaifenesin and pseudoephedrine. The sponsor concluded that the review of the clinical literature did not identify any new safety concerns for guaifenesin or pseudoephedrine [NDA 21-585, N000 BM, 8/18/03, Cover Letter]. This reviewer concurs with the sponsor's conclusion that the review of the clinical literature does not provide evidence of new safety concerns and supports the safe OTC marketing of their product in the proposed population. The sponsor must a submit a summary, analysis, and interpretation of postmarketing safety reports received since the safety cut-off date for the NDA submission for guaifenesin and pseudoephedrine.

The safety update is reviewed below.

7.7.1. Updated literature review

The sponsor used RetroSearch to conduct searches for references from September 30, 2002 until August 13, 2003 that were relevant to guaifenesin and pseudoephedrine. The sponsor identified 32 titles relevant to guaifenesin and 55 titles relevant to pseudoephedrine. Many of these are veterinary or chemistry articles. Although the sponsor stated that they did not identify any new safety concern for either drug, the searches identified one article addressing the illicit use of pseudoephedrine and two articles addressing the use of pseudoephedrine to illegally manufacture

methamphetamine [NDA 21-585, N000 BM, 8/18/03, Cover Letter and Exhibit B, pages 27, 32-33].

Reviewer comment:
As noted earlier in this review, the literature suggests that there is some potential for abuse of pseudoephedrine-containing products. This potential has previously been recognized and does not represent a new safety concern. This reviewer searched the AERS database with AERS DataMart for reports of abuse associated with pseudoephedrine. Search terms were "drug abuser NOS, polysubstance abuse, chemical abuser, drug addict, and maternal use of illicit drugs." The search identified eight case reports with pseudoephedrine as primary suspect drug and 15 reports with pseudoephedrine as primary or secondary suspect drug. Most of these reports are associated with concomitant use of drugs of abuse such as cocaine, codeine, heroin, oxycodone, and ethanol. It is unlikely that the sponsor's product is more likely to be abused than any other extended-release pseudoephedrine products. One would expect single-ingredient pseudoephedrine products to have a higher potential for illegally manufacturing methamphetamine than multiple-ingredient products.

The sponsor's largest proposed package sizes, 20 tablets of the guaifenesin 1200 mg/pseudoephedrine 120 mg product and 40 tablets guaifenesin 600 mg/pseudoephedrine 60 mg product, would limit the potential for abuse of these products and their use in the illegal manufacture of methamphetamine.

This reviewer concurs with the sponsor that the literature review reveals no new safety signal.

7.7.2. Updated review of postmarketing AE reports for guaifenesin and pseudoephedrine

The sponsor did not submit a review and analysis of AEs associated with guaifenesin and pseudoephedrine covering the time since the safety cut-off date for the NDA submission.

Reviewer comment:
The sponsor must a submit a summary, analysis, and interpretation of postmarketing safety reports received since the safety cut-off date for the NDA submission for guaifenesin and pseudoephedrine.

7.8. References

1. Pickens CL, et. al. Urology. 1999; 54(1):23-27.
2. Assimos DG, et. al. J Endourol. 1999; 13(9):665-667.
3. Sullivan G. J Psychopharmacol. 1996; 10(4):324-325.
4. Roberge RJ, et. al. J Emerg Med. 1999; 17(2):285-288.
5. Sauder KL, et. al. Am J Emerg Med. 1997; 15(5):521-525.
6. Soutullo CA, et. al. J Am Acad Child Adolesc Psychiatry. 1999; 38(12):1471-1472.
7. Sica DA, Comstock TJ. Am J Med Sci 1989; 298(4):261-263.
8. Chua SS, et. al. Br J Pharmacol. 1989; 28(3):369-372.

9. Loizou LA, et. al. J Neurol Neurosurg Psychiatry. 1982; 45(5):471-2.
10. Hanzlick R. Toxicology. 1996; 107(2):153-158.
11. Hanzlick R. Am J Forensic Med Pathol. 1995; 16(4):270-277.
12. Simons FER, et. al. J Pediatr 1996; 129(5):729-734.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The sponsor's product is proposed for use in adults and children 12 years of age and older. The proposed dose for the 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength is —— every 12 hours, not more than 2 tablets in 24 hours [Volume 1.1, pages 40-46]. This dose is within the specified OTC monograph doses for guaifenesin and pseudoephedrine over this dosing interval. The proposed labeling for the 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength instructs consumers not to use the product in children under 12 years of age.

Initially, the sponsor's proposed dose for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength was ——— ; [Volume 1.1, pages 40-46]. The proposed dose of ——— for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength is — of the OTC monograph dose of pseudoephedrine for this dosing interval, and is not supported by the studies in this application. The sponsor was advised that the lower dose was not supported. The sponsor changed the recommended dose for the 600 mg guaifenesin/60 mg pseudoephedrine product to 2 tablets every 12 hours, not more than 4 tablets in 24 hours [NDA 21-585 N000 BZ, 4/30/03, Cover Letter]. The revised dose is acceptable, as guaifenesin and pseudoephedrine are within OTC monograph doses for the dosing interval. The proposed labeling for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength also instructs consumers not to use the product in children under 12 years of age.

Initially, the sponsor's proposed labeling instructed consumers to ——— ——— [Volume 1.1, pages 40-46]. The clinical pharmacology studies in this application do not support this claim. The sponsor was advised that clinical studies would be necessary if they wished to pursue this claim. The sponsor deleted this claim from the proposed labeling [NDA 21-585 N000 BZ, 4/30/03, Cover Letter].

The proposed labeling includes text that states that the product can be administered without regard to timing of meals. The sponsor's food effect study, Study 2002-11, showed that the rate of guaifenesin absorption from the proposed product is decreased by 26% in the presence of a high fat meal. The extent of guaifenesin absorption and the rate and extent of pseudoephedrine absorption from the proposed product is not affected by a high fat meal. Overall, the rate and extent of absorption of the product in the fasted and fed states is similar. The small decrease in the rate of guaifenesin absorption is not likely to be clinically significant. The sponsor's claim that the product can be administered without regard to timing of meals is acceptable.

9. USE IN SPECIAL POPULATIONS

Both guaifenesin and pseudoephedrine are considered to be safe and effective for their respective indications at specified OTC monograph doses. The OTC monograph labeling for guaifenesin and pseudoephedrine require no special directions or warnings for adults and children 12 years and older, the population for which the sponsor's product is proposed. The sponsor's data do 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 and pseudoephedrine require no special recommendations or instructions for elderly consumers [21 CFR 341.78; 21 CFR 341.80]. All subjects in the sponsor's clinical pharmacology studies were from 18 to 54 years of age, so no subgroup analysis of AEs for subjects ≥65 years of age was possible [from data, Volume 1.46, pages 152, 155, 158, 166, 174, 180, 185; from data, NDA 21-585 N000 BZ, 4/30/03, cover letter page 2 and Exhibit 4, all pages]. The sponsor's review of the literature identified no new safety signal specific to elderly consumers.

9.2. Pediatric population

All subjects were from 18 to 54 years of age, so no subgroup analysis of AEs for pediatric subjects was possible [from data, Volume 1.46, pages 152, 155, 158, 166, 174, 180, 185; from data, NDA 21-585 N000 BZ, 4/30/03, cover letter page 2 and Exhibit 4, all pages]. The sponsor's review of the literature identified no new safety signal specific to the pediatric subpopulation.

The sponsor'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 [Volume 1.1, pages 10-46]. 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. The sponsor did not provide a request for waiver of pediatric studies. Such a waiver is not required now that the court has struck down the Pediatric Rule and ruled that it may not be enforced.

9.3. Gender

There were too few AEs noted in the sponsor's clinical pharmacology studies to determine if there was an association of AEs with gender for any of the individual formulations studied. The sponsor's review and summary of the literature identified no articles describing safety issues relevant to gender [NDA 21-585 N000 BZ, 4/30/03, cover letter, page 2].

9.4. Pregnancy and lactation

The OTC monograph labeling for guaifenesin and pseudoephedrine requires no warning for pregnant or lactating women. The sponsor's proposed labeling includes no special labeling or warnings for pregnant or lactating women [Volume 1.1, pages 10-46].

9.5. Race

There were too few non-Caucasian subjects in the sponsor's clinical pharmacology studies to perform a subgroup analysis of AEs by race [from data, Volume 1.46, pages 152, 155, 158, 166, 174, 180, 185; from data, NDA 21-585 N000 BZ, 4/30/03, cover letter page 2 and Exhibit 4, all pages]. The sponsor's review and summary of the literature identified no articles describing safety issues relevant to race [NDA 21-585 N000 BZ, 4/30/03, cover letter, page 2].

9.6. Hepatic disease

The OTC monograph labeling for guaifenesin and pseudoephedrine does not specify special recommendations or precautions for consumers with hepatic disease. The sponsor's review and summary of the literature identified no articles describing safety issues relevant to consumers with hepatic disease [NDA 21-585 N000 BZ, 4/30/03, cover letter, page 2].

9.7. Kidney disease

The sponsor identified a case report of pseudoephedrine accumulation in a patient with chronic renal failure due to renal artery stenosis, with BUN values in the 80-100 mg/dL range [see Reference 7, Section 7.8 of this review and Volume 1.45, pages 136-138]. Pseudoephedrine is largely excreted by the kidney. The current OTC monograph labeling for pseudoephedrine does not include a warning for consumers with kidney disease. Consideration should be given to amending the OTC monograph labeling for pseudoephedrine by adding a warning that instructs consumers with kidney disease not to take the drug.

10. CONCLUSIONS AND RECOMMENDATIONS

The sponsor's definitive clinical pharmacology studies established that the proposed 1200 mg guaifenesin/120 mg pseudoephedrine product met bioequivalence standards compared to the reference products. The pharmacokinetics of guaifenesin and pseudoephedrine were dose proportional when the dose was doubled from 600 mg guaifenesin/60 mg pseudoephedrine to 1200 mg guaifenesin/120 mg pseudoephedrine. Mean AUC_{ss} and C_{max} values for the proposed product also were within 80% to 125% bioequivalence limits compared to the reference standards. The C_{min} value for guaifenesin for the proposed product was 244% of the reference product, but is unlikely to create a safety concern, as this value is only 1/17 of the steady state C_{max} value for guaifenesin. The sponsor demonstrated that the pharmacokinetics of guaifenesin and pseudoephedrine are not affected by the presence of one another. The rate and extent of systemic exposure to pseudoephedrine were not affected by administration of the proposed product after consumption of a high-fat meal. The rate of systemic exposure to guaifenesin was decreased slightly to 74% of the reference when the product was administered after consumption of a high fat meal, but is not expected to be clinically significant because the decrease is small and the extent of systemic exposure was not affected. The extent of systemic exposure to guaifenesin was not affected by consumption of a high fat meal.

The sponsor's integrated review of safety supports the proposed indication of their product. Safety data came from the clinical pharmacology studies and an evaluation of safety information from the US AERS database and the clinical literature. Integrated safety data from the clinical pharmacology studies shows no evidence of new safety signal. There were no meaningful differences in AEs, withdrawals due to AEs, or SAEs between the test and reference products. Data from the AERS database support the safety of guaifenesin and pseudoephedrine and do not present new safety issues.

The sponsor's proposed 1200 mg guaifenesin/120 mg pseudoephedrine dosage strength tablet is large in size. Even though there were no AEs for dysphagia that were associated with the proposed product in the sponsor's studies, postmarketing reports for the proposed product should still be followed for AEs associated with difficulty in swallowing the tablet if the product is approved.

Pseudoephedrine is largely excreted by the kidney. The current OTC monograph labeling for pseudoephedrine does not include a warning for consumers with kidney disease. Consideration should be given to amending the OTC monograph labeling for pseudoephedrine by adding a warning that instructs consumers with decreased renal function to not take the drug. The sponsor's review and summary of the literature do not identify any new safety issue for guaifenesin or pseudoephedrine. The sponsor's safety update was incomplete and included only a review of the clinical literature. The sponsor did not submit a review of postmarketing adverse events in the safety update. The sponsor's review of the clinical literature included in the safety update does not provide evidence of new safety concerns and supports the safe OTC marketing of their product in the proposed population.

The sponsor has succeeded in demonstrating that their product is bioequivalent to approved and over-the-counter (OTC) monograph reference products. The evidence submitted by the sponsor supports the safety of their product. However, the sponsor did not submit a review of postmarketing adverse event reports in their safety update. From a clinical perspective, this reviewer recommends an approvable action because of this deficiency.

11. APPENDIX, CLINICAL STUDIES

11.1. Study 00-01

Title: A pilot study designed to examine the bioavailability of two different experimental controlled release formulations of guaifenesin and pseudoephedrine in normal healthy volunteers compared to reference controlled released guaifenesin and pseudoephedrine products

Date of protocol: 8/21/00
Study initiated: 10/17/00
Study completed: 11/12/00
Date of study report: 10/11/02

Study 00-01 was an open-label, randomized, single dose, three-way crossover study designed to examine the relative bioavailability of guaifenesin and pseudoephedrine from two experimental sustained release formulations containing both guaifenesin and pseudoephedrine as compared to reference controlled release guaifenesin and pseudoephedrine products in normal, healthy male and female volunteers. The study was conducted at Bio-Kinetic Clinical Applications, Inc. in Springfield, MO [Volume 1.47, pages 6, 11].

There was a washout period of at least 7 days between study periods [Volume 1.47, page 11]. The study enrolled 21 healthy, adult male and female subjects, ages 18-55 years of age and within 15% of ideal weight. [Volume 1.47, pages 44, 48].

Subjects were confined to the study center from the evening before dose administration until after the final blood draw, 24 hours after dosing. Subjects fasted overnight before dosing and for at least 4 hours afterwards. Water was allowed ad libitum after the 2-hour post-dose blood sample was drawn. A standardized lunch and dinner was given approximately 4 and 10 hours after dosing, respectively. A light snack was allowed at approximately 10 PM. The meals were the same for each study period [Volume 1.47, pages 47, 48].

Blood samples were collected prior to dosing with study treatment (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 measurement of guaifenesin and pseudoephedrine concentrations [Volume 1.47, page 11]. The total volume of blood drawn per subject for guaifenesin and pseudoephedrine samples was 450 mL [Volume 1.47, page 11].

The formulations studied are displayed in Table 11.1.1. The experimental formulations and the reference guaifenesin for this study were supplied by Adams Laboratories, Inc. [Volume 1.47, page 43-44, 54].

Table 11.1.1. Study treatments, Study 00-01 [Volume 1.47, page 54].

Treatment A **Reference Product**	Guaifenesin 1200 mg tablet Lot Number PB-304A plus Fexofenadine 60 mg/pseudoephedrine 120 mg (Allegra-D Tablets) Lot number 1026307
Treatment B **Experimental formulation**	Guaifenesin 1200 mg/pseudoephedrine 120 mg Lot number CB00-02A
Treatment C **Experimental formulation**	Guaifenesin 1200 mg/pseudoephedrine 120 mg Lot number CB00-01A

Each subject received a medical history, vital signs, physical examination, and clinical laboratory tests on blood and urine, and ECGs at screening, within 14 days of study drug administration [Volume 1.47, pages 46, 47]. Adverse events were to be recorded for any clinically significant changes in physical examination of vital signs, or upon subject report of any complaint relative to well-being. Adverse events were to be recorded on source documents and transcribed to the case report form [Volume 1.47, pages 46, 48].

All 21 subjects completed the study. Pharmacologic and statistical analyses were performed on data from these subjects [Volume 1.47, pages 15-19].

All subjects were Caucasian. Most were males (71%, 15/21) with a mean age of 27.3 years [range 19 - 46 years]. [Volume 1.47, pages 15, 17].

Reviewer comment:
Non-Caucasian subjects were underrepresented in this study. This is less than ideal. Even though the subject population in this study is not ideal to assess safety in subgroups, both guaifenesin and pseudoephedrine are OTC monograph drugs and are generally recognized as safe at the doses given in this study.

11.1.1. Clinical pharmacology outcomes

Plasma guaifenesin and pseudoephedrine levels were analyzed using a validated LC method at [redacted]. The validated analytical ranges used were [redacted] for guaifenesin and [redacted] for pseudoephedrine [Volume 1.47, pages 15, 81, 105; Volume 1.48, page 9].

The pharmacokinetic and statistical analyses were conducted on data from the 21 subjects, all of whom completed the three study periods [Volume 1.47, page 14]. Pharmacokinetics results comparing the proposed product and the reference product when given under fasting conditions are presented in Table 11.1.2.

$AUC_{0\text{-}inf}$ for guaifenesin for experimental treatment B (6799 ng.hr/mL) was 99.1% of the value for the reference product. $AUC_{0\text{-}inf}$ for guaifenesin for experimental treatment C (6388 ng.hr/mL) was 93.2% of the value for the reference product. C_{max} for guaifenesin for experimental treatment B (1437 ng/mL) was 95.8% of the value for the reference

product. C_{max} for guaifenesin for experimental treatment C (968.6 ng/mL) was 63.2% of the value for the reference product. $T_{1/2}$ for guaifenesin for treatment B (2.57 h) and treatment C (2.92 h) were less than that for reference (3.43 h). T_{max} for guaifenesin for treatment B (0.99 h) was slightly less than that of reference (1.01 h) and T_{max} for guaifenesin for treatment C (1.32 h) was greater than that of reference [Volume 1.47, pages 19-29].

$AUC_{0\text{-}inf}$ for pseudoephedrine for experimental treatment B (4684 ng.hr/mL) was 116.2% of the value for the reference product. $AUC_{0\text{-}inf}$ for pseudoephedrine for experimental treatment C (4440 ng.hr/mL) was 107.6% of the value for the reference product. C_{max} for pseudoephedrine for experimental treatment B (299.6 ng/mL) was 130.2% of the value for the reference product. C_{max} for pseudoephedrine for experimental treatment C (244.9 ng/mL) was 106.2% of the value for the reference product. $T_{1/2}$ for pseudoephedrine for treatment B (6.1 h) and treatment (6.7 h) were less than that for reference (8.0 h). T_{max} for pseudoephedrine for treatment B (6.0 h) and for treatment C (6.5 h) were greater than that of reference (5.6 h) [Volume 1.47, pages 19-29].

Table 11.1.2. Mean pharmacokinetics parameters for guaifenesin and pseudoephedrine, fasting conditions, Study 00-01 [Volume 1.47, pages 19-29].

PK Parameter	Guaifenesin 1200 mg plus Fexofenadine 60 mg/ Pseudoephedrine 120 mg Fasting conditions Reference Treatment A N = 21	Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Fasting conditions Experimental Treatment B N = 21	Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Fasting conditions Experimental Treatment C N = 21	Mean of ratios for individual subjects, B/A, %	Mean of ratios for individual subjects, C/A, %
Guaifenesin					
$AUC_{(0\text{-}inf)}$, ng.hr/mL	6728	6799	6388	99.1	93.2
C_{max}, ng/mL	1579	1437	968.6	95.8	63.2
$T_{1/2}$, hr	3.43	2.57	2.92	89.0	113.0
T_{max}, hr	1.01	0.99	1.32	119.0	154.8
Pseudoephedrine					
$AUC_{(0\text{-}inf)}$, ng.hr/mL	4171	4684	4440	116.2	107.6
C_{max}, ng/mL	231.8	299.6	244.9	130.2	106.2
$T_{1/2}$, hr	8.0	6.1	6.7	78.7	86.3
T_{max}, hr	5.6	6.0	6.5	111.1	126.2

Detailed statistical analysis was not performed because it was clear to the sponsor that neither experimental formulation appeared ideal for bioavailability of both guaifenesin and pseudoephedrine [Volume 1.47, page 14].

Reviewer comment:
The sponsor abandoned both of the two experimental formulations used in this study because bioavailability was not acceptable.

11.1.2. Safety outcomes

[There were four adverse events (AEs) experienced by three subjects in this study - groin pain experienced by a reference-treated subject, and diarrhea, headache, and vomiting reported by subjects who were taking experimental treatment C [Volume 1.52, page 128]. The subject's groin pain was due to a kidney stone, which was passed without sequelae. There were no serious adverse events and no withdrawals from this study. [Volume 1.47, page 11; Volume 1.52, pages 120, 130]. The sponsor notes that one subject drank approximately 46 ounces of tap water in order to swallow a tablet, due to its large size. This subject was taking the reference Mucinex™ and Allegra-D® products [Volume 1.47, pages 53-55, 65].

Reviewer comment:
There were few AEs noted in this single dose crossover study. Kidney stones have been noted with chronic dosing of guaifenesin, however, it is unlikely that this subject's kidney stone was related to study treatment in this single dose study.

Although it is true that, as the sponsor states in the sponsor's benefit/risk section that "no subjects were observed to have difficulty swallowing any test medication," there was one subject who had difficulty with one of the reference products [Volume 1.1, page 81]. One wonders if the subject who needed to drink this large amount of water had the pill stuck in her throat. If so, this event should have been recorded as an AE. The 1200 mg guaifenesin product that is currently approved and marketed (Mucinex™, NDA 21-282) is large, weighing 1458 mg/tablet [CMC review dated 3/20/01, Dr. Juanita Ross, NDA 21-282, 6/29/00]. The 1200 mg guaifenesin/120 mg pseudoephedrine tablet, at 1587 mg, is also large in size [Volume 1.1, page 49]. A search of AERS DataMart reveals no AE reports for Mucinex™ for the following reactions: "choking, choking sensation, esophageal obstruction, tracheal obstruction, or laryngeal obstruction," despite its large size. If the product is approved, postmarketing reports for the Mucinex™ D product should be followed for evidence of AEs related to the large tablet size or difficulty in swallowing the tablet.

11.2. Study 00-01A

Title: A pilot study designed to examine the bioavailability of two different experimental controlled release formulations of guaifenesin and pseudoephedrine in normal healthy volunteers compared to reference controlled released guaifenesin and pseudoephedrine products

Date of protocol: 9/25/01
Study initiated: 10/16/01
Study completed: 11/14/01
Date of study report: 10/11/02

Study 00-01A was an open-label, randomized, single dose, three-way crossover study designed to examine the relative bioavailability of guaifenesin and pseudoephedrine from two experimental sustained release formulations containing both guaifenesin and pseudoephedrine as compared to reference controlled release guaifenesin and pseudoephedrine products in normal, healthy male and female volunteers. The study was conducted at Bio-Kinetic Clinical Applications, Inc. in Springfield, MO [Volume 1.53, pages 2, 9].

There was a washout period of at least 7 days between study periods [Volume 1.53, page 7]. The study enrolled 15 healthy adult male and female subjects, ages 18-55 years of age within 15% of ideal weight. [Volume 1.53, pages 11, 49].

Reviewer comment:
The design of this study was the same as for Study 00-01, with the exception of the reference and experimental treatments and the number of subjects enrolled. Study 00-01 enrolled 21 subjects.

Subjects were confined to the study center from the evening before dose administration until after the final blood draw, 24 hours after dosing. Subjects fasted overnight before dosing and for at least 4 hours afterwards. Water was allowed ad libitum after the 2-hour post-dose blood sample was drawn. A standardized lunch and dinner was given approximately 4 and 10 hours after dosing, respectively. A light snack was allowed at approximately 10 PM. The meals were the same for each study period [Volume 1.53, pages 43, 44].

Blood samples were collected prior to dosing with study treatment (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 measurement of guaifenesin and pseudoephedrine concentrations [Volume 1.53, page 10]. The total volume of blood drawn per subject for guaifenesin and pseudoephedrine samples was 450 mL [Volume 1.53, page 10].

The formulations studied are displayed in Table 11.2.1. The experimental formulations and the reference guaifenesin for this study were supplied by Adams Laboratories, Inc.

[Volume 1.53, page 50]. Treatment B was the same formulation as the to-be-marketed product [Volume 1.1, cover letter, page 2; Volume 1.1, page 74].

Table 11.2.1. Study treatments, Study 00-01A [Volume 1.53, page 50].

Treatment A **Reference Product**	Guaifenesin 1200 mg tablet (Mucinex) Lot Number PB-304A plus Pseudoephedrine HCl 120 mg (Sudafed® 12-Hour Tablets) Lot number 12171V
Treatment B **Experimental formulation**	Guaifenesin 1200 mg/pseudoephedrine 120 mg Lot number PB01-K61
Treatment C **Experimental formulation**	Guaifenesin 1200 mg/pseudoephedrine 120 mg Lot number CB00-01A2

A medical history, vital signs, physical examination, and clinical laboratory tests on blood and urine, and ECGs were conducted at screening, within 14 days of study drug administration [Volume 1.53, page 43]. Adverse events were to be recorded on source documents and transcribed to the case report form for any clinically significant changes in physical examination of vital signs, or upon subject report of any complaint relative to well-being. [Volume 1.53, pages 42, 45].

The majority of subjects were Caucasian (87%, 13/15). The remainder of the subjects in the study were multiracial (13%, 2/15). Subjects were evenly divided by gender. Seven subjects were males (47%, 7/15) and eight were women (53%, 8/15). The mean age for subjects in this study was 26.4 years [range 18 -50 years]. [Volume 1.53, pages 11, 13].

11.2.1. Clinical pharmacology outcomes

Plasma guaifenesin and pseudoephedrine levels were analyzed using a validated LC method at [redacted] The validated analytical ranges used were [redacted] for guaifenesin and [redacted] for pseudoephedrine [Volume 1.53, pages 10, 75, 96; Volume 1.54, page 23].

The pharmacokinetic and statistical analyses were conducted on data from the 15 subjects, all of whom completed the three study periods [Volume 1.53, page 11]. PK results comparing the proposed product and the reference product when given under fasting conditions are presented in Table 11.2.2.

$AUC_{0\text{-}inf}$ for guaifenesin for experimental treatment B (7602 ng.hr/mL) was 108.7% of the value for the reference product. $AUC_{0\text{-}inf}$ for guaifenesin for experimental treatment C (7128 ng.hr/mL) was 99.8% of the value for the reference product. C_{max} for guaifenesin for experimental treatment B (1784 ng/mL) was 102.9% of the value for the reference product. C_{max} for guaifenesin for experimental treatment C (1154 ng/mL) was 64.6% of the value for the reference product. $T_{1/2}$ for guaifenesin for treatment B (1.59 h) and treatment C (2.40 h) were less than that for reference (3.60 h). T_{max} for guaifenesin for

treatment B (0.82 h) and for treatment C (1.22 h) were greater than that of reference (0.78 h) [Volume 1.53, pages 15-25].

$AUC_{0\text{-}inf}$ for pseudoephedrine for experimental treatment B (4449 ng.hr/mL) was 99.9% of the value for the reference product. $AUC_{0\text{-}inf}$ for pseudoephedrine for experimental treatment C (4444 ng.hr/mL) was 96.8% of the value for the reference product. C_{max} for pseudoephedrine for experimental treatment B (285.3 ng/mL) was 99.3% of the value for the reference product. C_{max} for pseudoephedrine for experimental treatment C (256.4 ng/mL) was 86.4% of the value for the reference product. $T_{1/2}$ for pseudoephedrine for treatment B (5.40 h) and treatment C (5.39 h) were less than that for reference (5.98 h). T_{max} for pseudoephedrine for treatment B (5.80 h) was less than that for reference (6.00) and for T_{max} for pseudoephedrine for treatment C (8.27 h) were greater than that of reference [Volume 1.53, pages 15-25].

Table 11.2.2. Mean PK parameters for guaifenesin and pseudoephedrine, fasting conditions, Study 00-01A [Volume 1.53, pages 15-25].

PK Parameter	Guaifenesin 1200 mg plus Pseudoephedrine 120 mg Fasting conditions Reference Treatment A N = 15	Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Fasting conditions Experimental Treatment B N = 15	Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Fasting conditions Experimental Treatment C N = 15	Mean of ratios for individual subjects, B/A, %	Mean of ratios for individual subjects, C/A, %
Guaifenesin					
$AUC_{(0\text{-}inf)}$, ng.hr/mL	7302	7602	7128	108.7	99.8
C_{max}, ng/mL	1847	1784	1154	102.9	64.6
$T_{1/2}$, hr	3.60	1.59	2.40	66.5	79.6
T_{max}, hr	0.78	0.82	1.22	112.8	179.9
Pseudoephedrine					
$AUC_{(0\text{-}inf)}$, ng.hr/mL	4710	4449	4444	99.9	96.8
C_{max}, ng/mL	300.3	285.3	256.4	99.3	86.4
$T_{1/2}$, hr	5.98	5.40	5.39	93.4	94.0
T_{max}, hr	6.00	5.80	8.27	101.1	151.1

Detailed statistical analysis was not performed because it was clear to the sponsor that experimental treatment B appeared ideal for bioavailability of both guaifenesin and pseudoephedrine [Volume 1.53, page 10].

The sponsor states that the formulation used for Treatment B (lot number PB01-K61) was used for the subsequent studies in the development program [Volume 1.1, page 53].

Reviewer comment:
Based on the results of this study, the sponsor chose the formulation used for experimental treatment B for the remaining clinical pharmacology studies. It is the same formulation as the to-be-marketed product [Volume 1.1, cover letter, page 2; Volume 1.1, page 74].

11.2.2. Safety outcomes

There were no adverse events (AEs) experienced by subjects in this study [Volume 1.56, page 399] and no withdrawals from this study [Volume 1.53, page 7; Volume 1.56, pages 392, 401].

11.3. Study 2002-01A

Title: A definitive study designed to examine the bioavailability of an experimental controlled release formulation of 1200 mg guaifenesin and 120 mg pseudoephedrine hydrochloride and to examine the dose proportionality of pseudoephedrine in normal healthy volunteers compared to reference controlled released guaifenesin and pseudoephedrine hydrochloride products

Date of protocol: 1/21/02
Study initiated: 1/28/02
Study completed: 2/24/02
Date of study report: 9/30/02

Study 2002-01A was an open-label, randomized, single dose, three-way crossover study designed to examine the relative bioavailability of guaifenesin and pseudoephedrine from an experimental sustained release formulation containing both guaifenesin and pseudoephedrine as compared to reference controlled release guaifenesin and pseudoephedrine products in normal, healthy male and female volunteers. The study also was designed to examine the dose-proportionality of pseudoephedrine. The study was conducted at Bio-Kinetic Clinical Applications, Inc. in Springfield, MO [Volume 1.57 pages 2, 7, 9].

There was a washout period of at least 7 days between study periods [Volume 1.57, page 7]. The study enrolled 36 healthy, adult male and female subjects, ages 18-55 years of age within 15% of ideal weight. [Volume 1.57, pages 7, 9, 46].

Reviewer comment:
The design of this study was similar to that for Studies 00-01 and 00-01A, with the exception of the reference and experimental treatments and the number of subjects enrolled.

Subjects were confined to the study center from the evening before dose administration until after the final blood draw, 24 hours after dosing. Subjects fasted overnight before dosing and for at least 4 hours afterwards. Water was allowed ad libitum after the 2-hour post-dose blood sample was drawn. A standardized lunch and dinner was given approximately 4 and 10 hours after dosing, respectively. A light snack was allowed at approximately 10 PM. The meals were the same for each study period [Volume 1.57, pages 49, 50].

Blood samples were collected prior to dosing with study treatment (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 measurement of guaifenesin and pseudoephedrine concentrations [Volume 1.57, pages 7, 43]. The total volume of blood drawn per subject for guaifenesin and pseudoephedrine samples was 450 mL [Volume 1.57, pages 7, 10].

The formulations studied are displayed in Table 11.3.1. The experimental formulations and the reference guaifenesin for this study were supplied by Adams Laboratories, Inc. The reference pseudoephedrine was manufactured by [Volume 1.57, pages 59, 62, 63]. Treatments B and C are same formulation as the to-be-marketed products [Volume 1.1, cover letter, page 2; Volume 1.1, page 74].

Table 11.3.1. Study treatments, Study 2002-01A [Volume 1.57, pages 62, 63].

Treatment A **Reference Product**	Guaifenesin 1200 mg tablet (Mucinex) Lot Number PB-01-H34A plus Pseudoephedrine HCl 120 mg (Sudafed® 12-HourTablets) Lot number 12171V
Treatment B	Guaifenesin 1200 mg/pseudoephedrine 120 mg Lot number PB01-M65A2
Treatment C	Guaifenesin 600 mg/pseudoephedrine 60 mg Lot number PB02-A12A

A medical history, vital signs, physical examination, and clinical laboratory tests on blood and urine, and ECGs were conducted at screening, within 14 days of study drug administration [Volume 1.57, page 49]. Adverse events were to be recorded for any clinically significant changes in physical examination of vital signs, or upon subject report of any complaint relative to well-being. Adverse events were to be recorded on source documents and transcribed to the case report form [Volume 1.57, pages 48, 50].

There were 36 healthy adult men and women enrolled in this study and 35 completed the study. One subject did not return for the second study period and was dropped from the study. [Volume 1.57, pages 12, 45, 75].

The majority of subjects were Caucasian (89%, 32/36). The remainder of the subjects in the study were Black (8%, 3/36) or multiracial (3%, 1/36). The majority of subjects were males (67%, 24/36). There were twelve women in the study (33%, 12/36). The mean age for subjects in this study was 23.0 years [range 18- 48 years]. [Volume 1.57, pages 12, 15].

11.3.1. Clinical pharmacology outcomes

Plasma guaifenesin and pseudoephedrine levels were analyzed using a validated LC method at The validated analytical ranges used were for guaifenesin and for pseudoephedrine [Volume 1.57, pages 10, 111; Volume 1.58, page 23].

The pharmacokinetic and statistical analyses were conducted on data from the 35 subjects who received reference product, and the experimental treatment B, and the 36 subjects who received experimental treatment C [Volume 1.57, pages 16-27]. PK results for the proposed products and the reference product when given under fasting conditions are presented in Table 11.3.2.

Mean $AUC_{0\text{-}inf}$ values for guaifenesin were 8061 ng.hr/mL for the reference product (1200 mg guaifenesin), 8124 ng.hr/mL for experimental treatment B (1200 mg guaifenesin) product, and 3565 ng.hr/mL for experimental treatment C (600 mg guaifenesin). Mean C_{max} values for guaifenesin were 1940 ng/mL for the reference product (1200 mg guaifenesin),1813 ng/mL for experimental treatment B (1200 mg guaifenesin), and 920 ng/mL for experimental treatment C (600 mg guaifenesin). Mean $T_{1/2}$ values for guaifenesin were 4.74 h for reference product, 2.21 h for experimental treatment B, and 1.76 h for experimental treatment C. Mean T_{max} values for guaifenesin were 0.77 h for reference product, 1.04 h for experimental treatment B, and 0.99 h for experimental treatment C [Volume 1.57, pages 16-27].

Mean $AUC_{0\text{-}inf}$ values for pseudoephedrine were 3847 ng.hr/mL for the reference product (120 mg pseudoephedrine), 3884 ng.hr/mL for experimental treatment B (120 mg pseudoephedrine) product, and 1968 ng.hr/mL for experimental treatment C (60 mg pseudoephedrine). Mean C_{max} values for pseudoephedrine were 250 ng/mL for the reference product (120 mg pseudoephedrine), 263 ng/mL for experimental treatment B (120 mg pseudoephedrine), and 141 ng/mL for experimental treatment C (60 mg pseudoephedrine). Mean $T_{1/2}$ values for pseudoephedrine were 5.75 h for reference product, 5.22 h for experimental treatment B, and 5.57 h for experimental treatment C. Mean T_{max} values for pseudoephedrine were 6.29 h for reference product, 5.11 h for experimental treatment B, and 4.94 h for experimental treatment C [Volume 1.57, pages 16-27].

Table 11.3.2. Mean PK parameters for guaifenesin and pseudoephedrine, fasting conditions, Study 2002-01A [Volume 1.57, pages 28-31].

PK Parameter	Guaifenesin 1200 mg plus Pseudoephedrine 120 mg Fasting conditions Reference Treatment A N = 35	Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Fasting conditions Experimental Treatment B N = 35	Guaifenesin 600 mg/ Pseudoephedrine 60 mg Fasting conditions Experimental Treatment C N = 36
Guaifenesin			
$AUC_{(0\text{-}inf)}$, ng.hr/mL	8061	8124	3565
C_{max}, ng/mL	1940	1813	920
$T_{1/2}$, hr	4.74	2.21	1.76
T_{max}, hr	0.77	1.04	0.99
Pseudoephedrine			
$AUC_{(0\text{-}inf)}$, ng.hr/mL	3847	3884	1968
C_{max}, ng/mL	250	263	141
$T_{1/2}$, hr	5.75	5.22	5.57
T_{max}, hr	6.29	5.11	4.94

Detailed statistical analysis was performed to compare the bioavailability of Treatment B with the reference and to compare the dose proportionality of Treatments B and C. These data are presented in Table 11.3.3. The sponsor states that for guaifenesin, the comparison of dose-adjusted $AUC_{(0\text{-}inf)}$ and C_{max} values for Treatment B (1200 mg guaifenesin/120 mg pseudoephedrine) with Treatment A (1200 mg guaifenesin plus 120 mg pseudoephedrine) were entirely contained within the 80% to 125% bioequivalence limits. The comparison of dose adjusted $AUC_{(0\text{-}inf)}$ and C_{max} values for Treatment B with

Treatment C (600 mg guaifenesin/60 mg pseudoephedrine) were also entirely contained within the 80% to 125% bioequivalence limits. The sponsor states that for pseudoephedrine, the comparisons of dose-adjusted $AUC_{(0\text{-}inf)}$ and C_{max} values for Treatment B (1200 mg guaifenesin/120 mg pseudoephedrine) with Treatment A (1200 mg guaifenesin plus 120 mg pseudoephedrine) were entirely contained within the 80% to 125% bioequivalence limits. The comparisons of dose-adjusted $AUC_{(0\text{-}inf)}$ and C_{max} values for Treatment B with Treatment C (600 mg guaifenesin/60 mg pseudoephedrine) were also entirely contained within the 80% to 125% bioequivalence limits.

The sponsor concludes, based on these data, that the experimental formulation containing 1200 mg guaifenesin and 120 mg pseudoephedrine (Treatment B) is bioequivalent to the reference formulations. The sponsor also concludes that the pharmacokinetics of guaifenesin and pseudoephedrine are linear for Treatment B (1200 mg guaifenesin/120 mg pseudoephedrine) and Treatment C (600 mg guaifenesin/60 mg pseudoephedrine) [Volume 1.57, pages 13, 14, 28-31].

Table 11.3.3. Statistical analysis of PK parameters for guaifenesin and pseudoephedrine, fasting conditions, Study 2002-01A [Volume 1.57, pages 28-31].

PK Parameter	Ratio B/A, %	(90% C I)	Ratio B/C, %	(90% C I)
Guaifenesin				
$AUC_{(0\text{-}inf)}$, ng.hr/mL/dose*	99.2	(93.8, 105)	112	(106, 119)
C_{max}, ng/mL/dose*	92.3	(83.7, 102)	98.0	(88.8, 108)
$T_{1/2}$, hr**	54.0	(44.6, 65.3)	123	(102, 149)
Pseudoephedrine				
$AUC_{(0\text{-}inf)}$, ng.hr/mL/dose*	101	(96.8, 106)	100	(96, 105)
C_{max}, ng/mL/dose*	105	(101, 109)	94.0	(90.3, 97.9)
$T_{1/2}$, hr**	90.9	(86.7, 95.3)	94.2	(89.9, 98.7)

Treatment A = Guaifenesin 1200 mg plus pseudoephedrine 120 mg reference
Treatment B = Guaifenesin 1200 mg/pseudoephedrine 120 mg
Treatment C = Guaifenesin 600 mg/pseudoephedrine 60 mg
*Dose-adjusted values, log transformed
**log transformed values

Reviewer comment:
$AUC_{(0\text{-}inf)}$ and C_{max} values for guaifenesin and pseudoephedrine both fell within 80% to 125% limits, indicating that the rate and extent of exposure to both ingredients for the proposed products were bioequivalent to the reference products. This study also demonstrated the dose proportionality of the proposed products.

11.3.2. Safety outcomes

[Volume 1.57, page 50]. There were ten adverse events (AEs) experienced by seven subjects in this study [Volume 1.63, page 431]. AEs in this study are summarized below in Table 11.3.4. Headache was the only AE that occurred more than once and in more than one subject. There were no serious adverse events and no subjects withdrew from the study because of AEs [Volume 1.57, pages 7, 12; Volume 1.63, page 433].

Table 11.3.4. Adverse events occurring in Study 2002-01A [compiled from Volume 1.63, page 431].

Adverse event	Guaifenesin 1200 mg plus Pseudoephedrine 120 mg Reference Treatment A N = 35		Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Treatment B N = 35		Guaifenesin 600 mg/ Pseudoephedrine 60 mg Treatment C N = 36	
	n	(%)	n	(%)	n	(%)
All adverse events	1	(2.8)	3	(8.6)	6	(16.7)
Headache	1	(2.8)	0	(0)	2	(5.6)
Cough	0	(0)	1	(2.9)	0	(0)
Lightheadedness	0	(0)	0	(0)	1	(2.8)
Sore throat	0	(0)	1	(2.9)	0	(0)
Postnasal drip	0	(0)	1	(2.9)	0	(0)
Pelvic pain	0	(0)	0	(0)	1	(2.8)
Nausea	0	(0)	0	(0)	1	(2.8)
Stomach cramps	0	(0)	0	(0)	1	(2.8)

Reviewer comment:
There were few AEs noted in this study. There was no association with dose for headache, the only AE that occurred more than once.

11.4. Study 2002-02A

Title: A definitive study designed to examine the effect of a high fat breakfast on the bioavailability of an experimental controlled release formulation of 1200 mg guaifenesin and 120 mg pseudoephedrine hydrochloride in normal healthy volunteers compared to reference controlled released guaifenesin and pseudoephedrine hydrochloride products

Date of protocol: 1/15/02
Study initiated: 2/5/02
Study completed: 2/24/02
Date of study report: 9/30/02

Study 2002-02A was an open-label, randomized, single dose, two-way crossover study designed to examine the relative bioavailability of guaifenesin and pseudoephedrine from an experimental sustained release formulation containing both guaifenesin and pseudoephedrine as compared to reference controlled release guaifenesin and pseudoephedrine products in normal, healthy male and female volunteers in the fed condition. The study was conducted at Bio-Kinetic Clinical Applications, Inc. in Springfield, MO [Volume 1.64 pages 2, 7].

There was a washout period of at least 7 days between study periods [Volume 1.64, page 7]. The study enrolled 36 healthy, adult male and female subjects, ages 18-55 years of age within 15% of ideal weight. [Volume 1.64, pages 7, 39, 42].

Reviewer comment:
The design of this study was similar to that of studies in the drug development program previously reviewed, with the exception of the reference and experimental treatments, the number of subjects enrolled, and dosing under fed conditions.

The choice of study treatments is somewhat unusual. Normally, one compares the rate and extent of absorption of a single experimental formulation taken under fasting and fed conditions. In this study, the sponsor compared the experimental formulation with a reference treatment, both given under fed conditions. This study does not provide information to determine if there is a food effect on absorption of the experimental formulation.

Subjects were confined to the study center from the evening before dose administration until after the final blood draw, 24 hours after dosing. Subjects were fasted overnight. Subjects were consumed a high fat breakfast 30 minutes before dosing. The high fat breakfast consisted of 2 eggs cooked in butter, 2 strips of bacon, 2 pieces of buttered toast, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. No further food was consumed until after the collection of the 4 hour blood sample. Water was allowed ad libitum after the 2-hour post-dose blood sample was drawn. A standardized lunch and dinner was given approximately 4 and 10 hours after dosing, respectively. A light snack was allowed at approximately 10 PM [Volume 1.64, pages 45, 46].

Blood samples were collected prior to dosing with study treatment (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 measurement of guaifenesin and pseudoephedrine concentrations [Volume 1.64, pages 7, 9, 44]. The total volume of blood drawn per subject for guaifenesin and pseudoephedrine samples was 300 mL [Volume 1.64, pages 7, 10, 44].

The formulations studied are displayed in Table 11.4.1 [Volume 1.64, pages 57, 62, 63]. Treatment B is the same formulation as the to-be-marketed product [Volume 1.1, cover letter, page 2; Volume 1.1, page 74].

Table 11.4.1. Study treatments, Study 2002-02A [Volume 1.64, pages 51, 57, 63].

Treatment A Reference	Guaifenesin 1200 mg tablet (Mucinex) Lot Number PB-314A2 plus Pseudoephedrine HCl 120 mg (Sudafed®-12 Hour Tablets) Lot number 12171V
Treatment B	Guaifenesin 1200 mg/pseudoephedrine 120 mg Lot number PB01-M65

Each subject received a medical history, vital signs, physical examination, and clinical laboratory tests on blood and urine, and ECGs at screening, within 14 days of study drug administration [Volume 1.64, page 45]. Adverse events were to be recorded for any clinically significant changes in physical examination of vital signs, or upon subject report of any complaint relative to well-being. Adverse events were to be recorded on source documents and transcribed to the case report form [Volume 1.64, pages 44, 46].

There were 36 healthy adult men and women who were enrolled in this study. Thirty-three of the 36 subjects completed the study. Two subjects did not return for the second study period and were dropped from the study. One subject withdrew from the study before the second study period because of an adverse event, an upper respiratory infection. Pharmacologic and statistical analyses were performed on data from the subjects completing each study period [Volume 1.64, pages 7, 8, 11].

The majority of subjects enrolled in this study were Caucasian (92%, 33/36). The remainder of the subjects in the study were of Black race (8%, 3/36). The majority of subjects in this study were males (69%, 25/36). There were 11 women in the study (31%, 11/36). The mean age for subjects in this study was 24.9 years. Subjects ranged from 18 to 54 years of age [Volume 1.64, pages 11, 15].

11.4.1. Clinical pharmacology outcomes

Plasma guaifenesin and pseudoephedrine levels were analyzed using a validated LC method at [redacted]. The validated analytical ranges used were [redacted] for guaifenesin and [redacted] for pseudoephedrine [Volume 1.64, pages 9, 101; Volume 1.65, page 9].

The pharmacokinetic and statistical analyses were conducted on data from the 35 subjects who received reference product and the 34 subjects who received the experimental treatment [Volume 1.64, pages 17-27, 55]. Pharmacokinetics results for the proposed products and the reference product when given under fed conditions are presented in Table 11.4.2.

Mean $AUC_{0\text{-}inf}$ values for guaifenesin were 8067 ng.hr/mL for reference and 7663 ng.hr/mL for experimental treatment B. Mean C_{max} values for guaifenesin were 2207 ng/mL for reference and 1649 ng/mL for experimental treatment B. Mean $T_{1/2}$ values for guaifenesin were 1.22 h for reference product and 1.40 h for experimental treatment B. Mean T_{max} values for guaifenesin were 1.85 h for reference and 1.84 h for experimental treatment B [Volume 1.64, pages 17-23].

Mean $AUC_{0\text{-}inf}$ values for pseudoephedrine were 3636 ng.hr/mL for reference and 3528 ng.hr/mL for experimental treatment B. Mean C_{max} values for pseudoephedrine were 268 ng/mL for reference and 274 ng/mL for experimental treatment B. Mean $T_{1/2}$ values for pseudoephedrine were 5.28 h for reference and 5.26 h for experimental treatment B. Mean T_{max} values for pseudoephedrine were 6.38 h for reference product and 4.80 h for experimental treatment B [Volume 1.64, pages 17-23].

Table 11.4.2. Mean PK parameters for guaifenesin and pseudoephedrine, fed conditions, Study 2002-02A [Volume 1.64, pages 17-23].

PK Parameter	Guaifenesin 1200 mg plus Pseudoephedrine 120 mg Fed conditions Reference Treatment A N = 35	Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Fed conditions Experimental Treatment B N = 34
Guaifenesin		
$AUC_{(0\text{-}inf)}$, ng.hr/mL	8067	7663
C_{max}, ng/mL	2207	1649
$T_{1/2}$, hr	1.22	1.40
T_{max}, hr	1.85	1.84
Pseudoephedrine		
$AUC_{(0\text{-}inf)}$, ng.hr/mL	3636	3528
C_{max}, ng/mL	268	274
$T_{1/2}$, hr	5.28	5.26
T_{max}, hr	6.38	4.80

Detailed statistical analysis was performed to compare the bioavailability of Treatment B with the reference. These data are presented in Table 11.4.3. For guaifenesin, the lower 90% confidence interval for C_{max} for Treatment B (1200 mg guaifenesin/120 mg pseudoephedrine) fell below bioequivalence limits. The sponsor states that for guaifenesin, the comparison of $AUC_{0\text{-}inf}$ values for Treatment B (1200 mg guaifenesin/120 mg pseudoephedrine) with reference (1200 mg guaifenesin plus 120 mg pseudoephedrine) were entirely contained within the 80% to 125% bioequivalence limits.

The sponsor states that for pseudoephedrine, the comparison of Treatment B (1200 mg guaifenesin/120 mg pseudoephedrine) with reference (1200 mg guaifenesin plus 120 mg

pseudoephedrine) for both C_{max} and $AUC_{0\text{-}inf}$ were entirely contained within the 80% to 125% bioequivalence limits.

The sponsor concluded that the extent of absorption of guaifenesin from the experimental formulation is bioequivalent to the reference formulation in the presence of a high fat meal. The sponsor concluded that the rate of absorption of guaifenesin from the experimental formulation is not bioequivalent to the reference formulation in the presence of a high fat meal. The sponsor concluded that the rate and extent of pseudoephedrine absorption was bioequivalent to the reference formulation in the presence of a high fat meal [Volume 1.64, pages 12-14, 17-23].

Table 11.4.3. Statistical analysis of PK parameters for guaifenesin and pseudoephedrine, fed conditions, Study 2002-02A [Volume 1.64, pages 24-25].

PK Parameter*	Ratio B/A, %	(90% C I)
Guaifenesin		
$AUC_{(0\text{-}inf)}$, ng.hr/mL	92.2	(87.8, 96.8)
C_{max}, ng/mL	74.5	(67.9, 81.8)
$T_{1/2}$, hr	113	(95.5, 134)
Pseudoephedrine		
$AUC_{(0\text{-}inf)}$, ng.hr/mL	95.8	(92.4, 99.3)
C_{max}, ng/mL	102	(99.2, 105)
$T_{1/2}$, hr	99.8	(94.9, 105)

Treatment A = Guaifenesin 1200 mg plus pseudoephedrine 120 mg
Treatment B = Guaifenesin 1200 mg/pseudoephedrine 120 mg
*log transformed values

Reviewer comment:
Although this study shows that under fed conditions, guaifenesin in the experimental formulation has a lower rate of absorption than guaifenesin from the reference guaifenesin tablet plus pseudoephedrine tablet, it does not provide information to determine if absorption of guaifenesin and pseudoephedrine in the experimental formulation is affected by food. To answer this question, the sponsor should have measured the rate and extent of absorption from the experimental formulation when given under fed conditions and compare them with values for the experimental formulation when given in the fasting state.

11.4.2. Safety outcomes

There were 15 adverse events (AEs) experienced by five subjects in this study [Volume 1.68, page 406]. AEs in this study are summarized below in Table 11.4.4. Headache and dry mouth were the only AEs that occurred more than once and in more than one subject. One subject had nine AEs and two subjects had two AEs. There were no serious adverse events. One subject (#003) withdrew from the study because of an upper respiratory infection before the second study period. [Volume 1.64, pages 7, 11; Volume 1.68, page 398, 406, 408]

Table 11.4.4. Adverse events occurring in Study 2002-02A [compiled from Volume 1.68, page 431].

Adverse event	Guaifenesin 1200 mg plus Pseudoephedrine 120 mg Reference Treatment A N = 35		Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Treatment B N = 34	
	n	(%)	n	(%)
All adverse events	11	(31.4)	4	(11.8)
Headache	2	(5.7)	1	(2.9)
Dry mouth	2	(5.7)	0	(0)
Dry nose	1	(2.9)	0	(0)
Dizziness	1	(2.9)	0	(0)
Diarrhea	1	(2.9)	0	(0)
Sleepiness	1	(2.9)	0	(0)
Loss of appetite	1	(2.9)	0	(0)
Nausea	1	(2.9)	0	(0)
Emesis	1	(2.9)	0	(0)
Feverish	0	(0)	1	(2.9)
Upper respiratory infection	0	(0)	1	(2.9)
Lightheadedness	0	(0)	1	(2.9)

Reviewer comment:
AEs were more common in this study than in previous studies, however, the majority of AEs noted were from one subject.

11.5. Study 2002-03

Title: A definitive study designed to compare the steady state pharmacokinetics of guaifenesin and pseudoephedrine from an experimental controlled release formulation of 1200 mg guaifenesin and 120 mg pseudoephedrine hydrochloride in normal healthy volunteers compared to reference controlled released guaifenesin and pseudoephedrine hydrochloride products

Date of protocol: 1/15/02
Study initiated: 2/26/02
Study completed: 3/31/02
Date of study report: 9/30/02

Study 2002-03 was an open-label, randomized, multiple dose, two-way crossover study designed to determine the steady state pharmacokinetics of guaifenesin and pseudoephedrine from an experimental sustained release formulation containing both guaifenesin and pseudoephedrine as compared to reference controlled release guaifenesin and pseudoephedrine products in normal, healthy male and female volunteers. The study was conducted at Bio-Kinetic Clinical Applications, Inc. in Springfield, MO [Volume 1.69 pages 2, 7].

There was a washout period of at least 7 days between study periods [Volume 1.69, page 7]. The study was to enroll 36 healthy, adult male and female subjects, ages 18-55 years of age and within 15% of ideal weight. However, 37 healthy adult male and female subjects were enrolled, and 36 subjects completed the study. One subject left the clinic after the first dose due to a class schedule conflict [Volume 1.69, pages 7, 9, 12, 41, 42].

Reviewer comment:
The design of this study was similar to that of studies in the drug development program previously reviewed, with the exception of the number of subjects enrolled and the administration of multiple doses of test and reference study treatments.

Subjects were confined to the study center the evening before administration of the first dose. After administration of the first dose, subjects were allowed to leave the study center and to return to the study center for the morning and evening doses on study days 2 to 5. Subjects were to fast overnight prior to coming in for each of their morning doses. On study day 5, subjects remained at the study center following their evening dose and were confined to the study center until after the final blood sample was drawn, 24 hours after the final dose of study treatment was administered.

While subjects were confined to the study center, water was allowed ad libitum after the 2-hour post-dose blood sample was drawn, and a standardized lunch and dinner was given approximately 4 and 10 hours after dosing, respectively. A light snack was allowed at approximately 10 PM. The meals were the same during each period of the study [Volume 1.69, pages 9, 46, 47].

Pre-dose blood samples were obtained before the morning dose on Days 1, 4, 5, and 6. On day 6, additional blood samples were collected at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours after the last dose for measurement of guaifenesin and pseudoephedrine concentrations [Volume 1.69, pages 7, 9, 44]. The total volume of blood drawn per subject for guaifenesin and pseudoephedrine samples was 380 mL [Volume 1.69, pages 7, 9, 44].

The formulations studied are displayed in Table 11.5.1. Adams Laboratories, Inc. supplied the test compounds [Volume 1.69, pages 7, 9, 56]. Treatment B is same formulation as the to-be-marketed product [Volume 1.1, cover letter, page 2; Volume 1.1, page 74].

Table 11.5.1. Study treatments, Study 2002-03 [Volume 1.69, pages 7, 9, 56].

Treatment A **Reference**	Guaifenesin 1200 mg tablet (Mucinex) Lot Number PB-01-H34A2 plus Pseudoephedrine HCl 120 mg (Sudafed®-12 Hour Tablets) Lot number 12171V
Treatment B **Test**	Guaifenesin 1200 mg/pseudoephedrine 120 mg Lot number PB01-M65A3

Each subject received a medical history, vital signs, physical examination, and clinical laboratory tests on blood and urine, and ECGs at screening, within 14 days of study drug administration [Volume 1.69, page 45]. Adverse events were to be recorded for any clinically significant changes in physical examination of vital signs, or upon subject report of any complaint relative to well-being. Adverse events were to be recorded on source documents and transcribed to the case report form [Volume 1.69, pages 44, 47].

There were 37 healthy adult men and women who were enrolled in this study. Thirty-six of the 37 subjects completed the study. One subject withdrew from the study after the first dose of study medication because of a class schedule conflict. Pharmacologic and statistical analyses were performed on data from the subjects completing the study [Volume 1.69, pages 7, 9, 12].

The majority of subjects enrolled in this study were Caucasian (89%, 33/37). The remainder of the subjects in the study were of Asian race (5%, 2/37), Black race (3%, 1/37), or were multiracial (3%, 1/37). The majority of subjects in this study were males (62%, 23/37). There were 14 women in the study (38%, 14/37). The mean age for subjects in this study was 24.2 years. Subjects ranged from 18 to 48 years of age [Volume 1.69, pages 12, 16].

11.5.1. Clinical pharmacology outcomes

Plasma guaifenesin and pseudoephedrine levels were analyzed using a validated LC method at [redacted] The validated analytical ranges used were [redacted] for guaifenesin and [redacted] for pseudoephedrine [Volume 1.69, pages 10, 105; Volume 1.70, page 23].

The pharmacokinetic and statistical analyses were conducted on data from the 36 subjects who completed the study [Volume 1.69, pages 18-23]. PK results for the proposed products and the reference product when given under fed conditions are presented in Table 11.5.2.

Mean AUC_{ss} values for guaifenesin were 7209 ng.hr/mL for reference and 8183 ng.hr/mL for experimental treatment B. Mean C_{min} values for guaifenesin were 52.0 ng/mL for reference and 117 ng/mL for experimental treatment B. Mean C_{max} values for guaifenesin were 1960 ng/mL for reference and 1983 ng/mL for experimental treatment B. Mean T_{max} values for guaifenesin were 120.8 h for reference and 121.0 h for experimental treatment B [Volume 1.69, pages 18-23].

Mean $AUC_{0\text{-}inf}$ values for pseudoephedrine were 3528 ng.hr/mL for reference and 3550 ng.hr/mL for experimental treatment B. Mean C_{min} values for pseudoephedrine were 182 ng/mL for reference and 173 ng/mL for experimental treatment B. Mean C_{max} values for pseudoephedrine were 361 ng/mL for reference and 365 ng/mL for experimental treatment B. Mean T_{max} values for pseudoephedrine were 124.9 h for reference product and 124.1 h for experimental treatment B [Volume 1.69, pages 18-23].

Table 11.5.2. Mean steady state PK parameters for guaifenesin and pseudoephedrine, Study 2002-03 [Volume 1.69, pages 18-23].

PK Parameter	Guaifenesin 1200 mg plus Pseudoephedrine 120 mg Fed conditions Reference Treatment A N = 36	Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Fed conditions Experimental Treatment B N = 36
Guaifenesin		
$AUC_{(ss)}$, ng.hr/mL	7209	8183
C_{min}, ng/mL	52.0	117
C_{max}, ng/mL	1960	1983
T_{max}, hr	120.8	121.0
Pseudoephedrine		
$AUC_{(ss)}$, ng.hr/mL	3528	3550
C_{min}, ng/mL	182	173
C_{max}, ng/mL	361	365
T_{max}, hr	124.9	124.1

Detailed statistical analysis was performed to compare the bioavailability of Treatment B with the reference. These data are presented in Table 11.5.3.

The sponsor states that for the comparison of Treatment B with the reference, the 90% confidence intervals for log-transformed values for AUC_{ss} and C_{max} for guaifenesin were entirely contained within 80% to 125% bioequivalence limits. For the comparison of Treatment B with the reference, the upper 90% confidence interval for log-transformed C_{min} values for guaifenesin was above the 80% to 125% bioequivalence limits. The sponsor states that for pseudoephedrine, the comparison of Treatment B (1200 mg guaifenesin/120 mg pseudoephedrine) with reference (1200 mg guaifenesin plus 120 mg

pseudoephedrine) for log-transformed values for AUC_{ss}, C_{max}, and C_{max} were entirely contained within the 80% to 125% bioequivalence limits [Volume 1.69, page 14].

The sponsor concludes that for guaifenesin, the experimental formulation is bioequivalent to the reference formulation in terms of AUC_{ss} and C_{max}. The sponsor notes that for guaifenesin, the higher C_{min} for Treatment B is without clinical significance because it would result in at least equal efficacy and it is unlikely to cause safety concern because the value is less than 10% of that for the C_{max}. The sponsor concludes that for pseudoephedrine, the experimental formulation is bioequivalent to the reference formulation in terms of AUC_{ss}, C_{max}, and C_{min} [Volume 1.69, pages 13-14].

Table 11.5.3. Statistical analysis of steady state PK parameters for guaifenesin and pseudoephedrine, Study 2002-03 [Volume 1.69, pages 26-27].

PK Parameter*	Ratio B/A, %	(90% C I)
Guaifenesin		
C_{max}, ng/mL	99.0	(90.9, 108)
C_{min}, ng/mL	244	(155, 383)
$AUC_{(ss)}$, ng.hr/mL	111	(102, 119)
Pseudoephedrine		
C_{max}, ng/mL	101	(95.3, 107)
C_{min}, ng/mL	95.4	(86.0, 106)
$AUC_{(ss)}$, ng.hr/mL	101	(95.7, 106)

Treatment A = Guaifenesin 1200 mg plus pseudoephedrine 120 mg
Treatment B = Guaifenesin 1200 mg/pseudoephedrine 120 mg
*log transformed values

Reviewer comment:
This reviewer concurs with the sponsor that the steady state C_{min} value for guaifenesin noted with Treatment B are unlikely to produce a safety concern and is not likely to impact the efficacy of the product. The steady state C_{min} value is only 1/17 of the steady state C_{max} value and the AUC_{ss} is within 80% to 125% bioequivalence limits.

11.5.2. Safety outcomes

Safety endpoints included adverse events [Volume 1.69, pages 44, 47]. There were 53 adverse events (AEs) experienced by 20 subjects in this study [Volume 1.74, pages 332-334]. AEs in this study are summarized below in Table 11.5.4. AEs occurred at fairly similar frequencies for Treatment B (77.8%, 28/36) and reference (69.4, 25/36). Sleeplessness and nausea appeared to be more frequent with Treatment B than for reference. Headache appeared to be more frequent for reference than for treatment. Other AEs occurred at lower frequencies and in smaller numbers. There were no serious adverse events. There were no subjects who withdrew from the study because of AEs [Volume 1.69, pages 7, 12; Volume 1.74, pages 324, 336].

Table 11.5.4. Adverse events occurring in Study 2002-03 [compiled from Volume 1.74, pages 332-335].

Adverse event	Guaifenesin 1200 mg plus Pseudoephedrine 120 mg Reference Treatment A N = 36		Guaifenesin 1200 mg/ Pseudoephedrine 120 mg Treatment B N = 36	
	n	(%)	n	(%)
All adverse events	25	(69.4)	28	(77.8)
Sleeplessness	1	(4.0)	6	(21.4)
Headache	8	(32.0)	5	(17.9)
Nausea	1	(4.0)	3	(10.7)
Dry mouth	5	(20.0)	2	(7.1)
Moodiness	0	(0)	2	(7.1)
Sore throat	0	(0)	2	(7.1)
Lightheadedness	2	(8.0)	1	(3.6)
Head rush	0	(0)	1	(3.6)
Hot flash	0	(0)	1	(3.6)
Nervousness	0	(0)	1	(3.6)
Runny nose	0	(0)	1	(3.6)
Thirsty	0	(0)	1	(3.6)
Cough	0	(0)	1	(3.6)
Edginess	0	(0)	1	(3.6)
Drowsiness	2	(8.0)	0	(0)
Lethargy	1	(4.0)	0	(0)
Feverishness	1	(4.0)	0	(0)
Restlessness	1	(4.0)	0	(0)
Vomiting	1	(4.0)	0	(0)
Chest pain	1	(4.0)	0	(0)
Chills	1	(4.0)	0	(0)

Reviewer comment:

AEs were more common in this multiple dose study. It is difficult to draw firm conclusions based on these data because of the small number of AEs. Sleeplessness appeared to occur at higher frequency for Treatment B. This may be a chance finding because the PK parameters for pseudoephedrine for Treatment B were quite similar to those for the reference. There is no evidence of new safety signal in this study.

11.6. Study 2002-04

Title: A study designed to test the interaction potential of 1200 mg guaifenesin and 120 mg pseudoephedrine hydrochloride in normal healthy volunteers

Date of protocol: 12/31/01
Study initiated: 1/8/02
Study completed: 2/10/02
Date of study report: 9/30/02

Study 2002-04 was an open-label, randomized, single dose, three-way crossover study designed to determine the relative bioavailability of guaifenesin and pseudoephedrine when administered alone or upon co-administration. The study was conducted at Bio-Kinetic Clinical Applications, Inc. in Springfield, MO [Volume 1.75 pages 2, 7, 8].

There was a washout period of at least 7 days between study periods [Volume 1.75, page 7]. Initially, the study was to enroll 24 healthy, adult male and female subjects, ages 18-55 years of age and within 15% of ideal weight. The protocol was amended to enroll 36 subjects on January 15, 2002 because statistical analysis of a previous study indicated that 33 completed subjects would be needed to have sufficient statistical power to make the desired comparisons. Thirty-six subjects were actually enrolled in the study [Volume 1.75, pages 8, 11, 35, 47].

Reviewer comment:
The design of this study was similar to that of previous studies, with the exception of the reference and experimental treatments and the number of subjects enrolled.

Subjects were confined to the study center from the evening before dose administration until after the final blood draw, 24 hours after dosing. Subjects fasted overnight before dosing and for at least 4 hours afterwards. Water was allowed ad libitum after the 2-hour post-dose blood sample was drawn. A standardized lunch and dinner was given approximately 4 and 10 hours after dosing, respectively. A light snack was allowed at approximately 10 PM. The meals were the same for each study period [Volume 1.75, page 52].

Blood samples were collected prior to dosing with study treatment (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 measurement of guaifenesin and pseudoephedrine concentrations [Volume 1.75, pages 7, 9, 50]. The total volume of blood drawn per subject for guaifenesin and pseudoephedrine samples was 450 mL [Volume 1.75, pages 7, 9, 50].

The formulations studied are displayed in Table 11.6.1. The experimental formulations and the reference guaifenesin for this study were supplied by Adams Laboratories, Inc. [Volume 1.75, pages 7, 9, 61].

Table 11.6.1. Study treatments, Study 2002-04 [Volume 1.75, pages 7, 9, 61].

Treatment A Reference	Guaifenesin 1200 mg tablet (Mucinex) Lot Number PB315A2
Treatment B Reference	Pseudoephedrine 120 mg (Sudafed 12-Hour) Lot number 12171V
Treatment C **Test**	Guaifenesin 1200 mg tablet (Mucinex) Lot number PB02-A12A Plus Pseudoephedrine 120 mg (Sudafed 12-Hour) Lot number 12171V

Each subject received a medical history, vital signs, physical examination, and clinical laboratory tests on blood and urine, and ECGs at screening, within 14 days of study drug administration [Volume 1.75, pages 50, 51]. Adverse events were to be recorded for any clinically significant changes in physical examination of vital signs, or upon subject report of any complaint relative to well-being. Adverse events were to be recorded on source documents and transcribed to the case report form [Volume 1.75, pages 50, 52].

There were 36 healthy adult men and women who were enrolled in this study. Thirty-six subjects completed the study. Pharmacologic and statistical analyses were performed on data from these 36 subjects [Volume 1.75, pages 7, 8, 11].

The majority of subjects enrolled in this study were Caucasian (89%, 32/36). The remainder of the subjects in the study were of Hispanic race (6%, 2/36), Asian race (3%, 1/36), or were multiracial (3%, 1/36). The majority of subjects in this study were males (58%, 21/36). There were 15 women in the study (42%, 15/36). The mean age for subjects in this study was 31.06 years. Subjects ranged from 18 to 53 years of age [Volume 1.75, pages 11, 60].

11.6.1. Clinical pharmacology outcomes

Plasma guaifenesin and pseudoephedrine levels were analyzed using a validated LC method at [redacted]. The validated analytical ranges used were [redacted] for guaifenesin and [redacted] for pseudoephedrine [Volume 1.75, pages 9, 118; Volume 1.76, page 23].

The pharmacokinetic and statistical analyses were conducted on data from the 36 subjects completed the study [Volume 1.75, pages 16-22]. PK results for the proposed products and the reference product when given under fasting conditions are presented in Table 11.6.2.

Mean $AUC_{0\text{-}inf}$ values for guaifenesin were 8138 ng.hr/mL for 1200 mg guaifenesin alone, and 8052 ng.hr/mL for 1200 mg guaifenesin co-administered with 120 mg pseudoephedrine. Mean C_{max} values for guaifenesin were 2009 ng/mL for 1200 mg

guaifenesin alone, and 1989 ng/mL for 1200 mg guaifenesin co-administered with 120 mg pseudoephedrine. Mean $T_{1/2}$ values for guaifenesin were 4.0 h for 1200 mg guaifenesin alone and 3.41 h for 1200 mg guaifenesin co-administered with 120 mg pseudoephedrine. Mean T_{max} values for guaifenesin were 0.89 h for 1200 mg guaifenesin alone and 0.84 h for 1200 mg guaifenesin co-administered with 120 mg pseudoephedrine [Volume 1.75, pages 16-22].

Mean $AUC_{0\text{-}inf}$ values for pseudoephedrine were 4505 ng.hr/mL for 120 mg pseudoephedrine alone, and 4396 ng.hr/mL for 1200 mg guaifenesin co-administered with 120 mg pseudoephedrine. Mean C_{max} values for pseudoephedrine were 295.8 ng/mL for 1200 mg pseudoephedrine alone and 289.3 ng/mL for 1200 mg guaifenesin co-administered with 120 mg pseudoephedrine. Mean $T_{1/2}$ values for pseudoephedrine were 6.05 h for 1200 mg pseudoephedrine alone and 6.04 h for 1200 mg guaifenesin co-administered with 120 mg pseudoephedrine. Mean T_{max} values for pseudoephedrine were 6.17 h for 1200 mg pseudoephedrine alone and 5.75 h for 1200 mg guaifenesin co-administered with 120 mg pseudoephedrine [Volume 1.75, pages 16-22].

Table 11.6.2. Mean PK parameters for guaifenesin and pseudoephedrine, fasting conditions, Study 2002-04 [Volume 1.75, pages 16-22].

PK Parameter	Guaifenesin 1200 mg Fasting conditions Reference Treatment A N = 36	Pseudoephedrine 120 mg Fasting conditions Reference Treatment B N = 36	Guaifenesin 1200 mg plus Pseudoephedrine 120 mg Fasting conditions Experimental Treatment C N = 36
Guaifenesin			
$AUC_{(0\text{-}inf)}$, ng.hr/mL	8138	NA*	8052
C_{max}, ng/mL	2009	NA	1989
$T_{1/2}$, hr	4.0	NA	3.41
T_{max}, hr	0.89	NA	0.84
Pseudoephedrine			
$AUC_{(0\text{-}inf)}$, ng.hr/mL	NA*	4505	4396
C_{max}, ng/mL	NA	295.8	289.3
$T_{1/2}$, hr	NA	6.05	6.04
T_{max}, hr	NA	6.17	5.75

*NA: Not applicable

Detailed statistical analysis was performed to compare the pharmacokinetics of guaifenesin co-administered with pseudoephedrine with that of guaifenesin and pseudoephedrine administered alone. These data are presented in Table 11.6.3. $AUC_{(0\text{-}inf)}$, C_{max}, $T_{½}$, and T_{max} values for guaifenesin co-administered with pseudoephedrine were similar to values for guaifenesin alone. The 90% confidence intervals were within 80% to 125% bioequivalence limits. $AUC_{(0\text{-}inf)}$, C_{max}, $T_{½}$, and T_{max} values for pseudoephedrine co-administered with pseudoephedrine were similar to values for pseudoephedrine alone. The 90% confidence intervals were within 80% to 125% bioequivalence limits [Volume 1.75, pages 12-13, 23-24].

The sponsor concludes, based on these data, that the pharmacokinetics of guaifenesin and pseudoephedrine are unaffected by the presence of one another [Volume 1.75, page 13].

Table 11.6.3. Statistical analysis of PK parameters for guaifenesin, pseudoephedrine, and co-administered guaifenesin and pseudoephedrine under fasting conditions, Study 2002-04 [Volume 1.75, pages 23-24].

PK Parameter	Ratio C/A, %	(90% C I)	Ratio C/B, %	(90% C I)
Guaifenesin				
$AUC_{(0-inf)}$, ng.hr/mL*	99.2	(93.8, 105)	NA	
C_{max}, ng/mL*	98.4	(93.6, 103)	NA	
$T_{1/2}$, hr**	104	(85.0, 126)	NA	
Pseudoephedrine				
$AUC_{(0-inf)}$, ng.hr/mL*	NA		97.3	(93.5, 101)
C_{max}, ng/mL *	NA		97.6	(94.2, 101)
$T_{1/2}$, hr**	NA		99.9	(92.6, 107)

Treatment A = Guaifenesin 1200 mg
Treatment B = Pseudoephedrine 120 mg
Treatment C = Guaifenesin 1200 mg plus pseudoephedrine 120 mg
*log transformed values

Reviewer comment:
This reviewer concurs with the sponsor that the pharmacokinetics of guaifenesin and pseudoephedrine are unaffected by the presence of one another.

11.6.2. Safety outcomes

There were 14 adverse events (AEs) experienced by 11 subjects in this study [Volume 1.80, page 419]. AEs in this study are summarized below in Table 11.6.4. Headache and appetite loss were the only AEs that occurred more than once and in more than one subject. Headache was more common for guaifenesin 1200 mg than for guaifenesin 1200 mg plus pseudoephedrine 120 mg or pseudoephedrine 120 mg alone. There were no serious adverse events or withdrawals from the study because of AEs. [Volume 1.75, pages 7, 11; Volume 1.80, page 411, 421]

Table 11.6.4. Adverse events occurring in Study 2002-04 [compiled from Volume 1.80, page 419].

Adverse event	Guaifenesin 1200 mg Reference Treatment A N = 36		Pseudoephedrine 120 mg Reference Treatment B N = 36		Guaifenesin 1200 mg Plus Pseudoephedrine 120 mg Treatment C N = 36	
	n	(%)	n	(%)	n	(%)
All adverse events	5	(13.9)	4	(11.1)	5	(13.9)
Headache	5	(13.9)	1	(2.8)	2	(5.6)
Nausea	0	(0)	0	(0)	1	(2.7)
Drowsiness	0	(0)	0	(0)	1	(2.7)
Rash	0	(0)	0	(0)	1	(2.7)
Appetite loss	0	(0)	2	(5.6)	0	(0)
Lightheadedness	0	(0)	1	(2.7)	0	(0)

Reviewer comment:
There were few AEs noted in this study. It is difficult to draw conclusions on these data because of the small number of AEs noted.

11.7. Study 2002-11

Title: A definitive study designed to examine the effect of a high fat breakfast on the bioavailability of an experimental controlled release formulation of 1200 mg guaifenesin and 120 mg pseudoephedrine hydrochloride in normal healthy volunteers

Date of protocol: 3/14/02
Study initiated: 4/22/02
Study completed: 5/20/02
Date of study report: 9/30/02

Study 2002-11 was an open-label, randomized, single dose, two-way crossover study designed to determine the effect of the consumption of a high-fat meal on the bioavailability of guaifenesin and pseudoephedrine from an experimental formulation. The study was conducted at Bio-Kinetic Clinical Applications, Inc. in Springfield, MO [Volume 1.81 pages 2, 7].

There was a washout period of at least 7 days between study periods [Volume 1.81, page 7]. The study enrolled 36 healthy, adult male and female subjects, ages 18-55 years of age and within 15% of ideal weight. [Volume 1.81, pages 7, 10, 39, 47].

Reviewer comment:
The design of this study was similar to that of studies previously reviewed in the drug development program with the exception of the reference and experimental treatments, the number of subjects enrolled, and the dosing of study treatment under both fasting and fed conditions. Unlike the previous food effect study, Study 2002-02A, this study provides sufficient information to determine if there is a food effect on absorption of the experimental formulation.

Subjects were confined to the study center from the evening before dose administration until after the final blood draw, 24 hours after dosing. Subjects were fasted overnight. Subjects were consumed a high fat breakfast 30 minutes before dosing. The high fat breakfast consisted of 2 eggs cooked in butter, 2 strips of bacon, 2 pieces of buttered toast, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. No further food was consumed until after the collection of the 4 hour blood sample. Water was allowed ad libitum after the 2-hour post-dose blood sample was drawn. A standardized lunch and dinner was given approximately 4 and 10 hours after dosing, respectively. A light snack was allowed at approximately 10 PM. Meals were the same for each study period [Volume 1.81, page 43].

Blood samples were collected prior to dosing with study treatment (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 measurement of guaifenesin and pseudoephedrine concentrations [Volume 1.81, pages 7, 9, 41]. The total volume of blood drawn per subject for guaifenesin and pseudoephedrine samples was 300 mL [Volume 1.81, pages 7, 9, 41].

The formulations studied are displayed in Table 11.7.1. Adams Laboratories, Inc. supplied the study medication [Volume 1.81, pages 7-9, 52]. Treatments A and B are same formulation as the to-be-marketed product [Volume 1.1, cover letter, page 2; Volume 1.1, page 74].

Table 11.7.1. Study treatments, Study 2002-11 [Volume 1.81, pages 7-9, 52].

Treatment A **Reference**	Guaifenesin 1200 mg/pseudoephedrine HCl 120 mg tablet Lot number PB01-M65A4 Fasting conditions
Treatment B **Test**	Guaifenesin 1200 mg/pseudoephedrine 120 mg tablet Lot number PB01-M65A4 Fed conditions

Each subject received a medical history, vital signs, physical examination, and clinical laboratory tests on blood and urine, and ECGs at screening within 14 days of study drug administration [Volume 1.81, page 41-42]. Adverse events were to be recorded for any clinically significant changes in physical examination of vital signs, or upon subject report of any complaint relative to well-being. Adverse events were to be recorded on source documents and transcribed to the case report form [Volume 1.81, pages 41, 43].

There were 36 healthy adult men and women in this study. Thirty-four subjects completed the study. One subject was dropped from the study before the second study period because of a positive drug screen and a second subject withdrew her consent prior to the second study period. Pharmacologic and statistical analyses were performed on data from the subjects completing each study period [Volume 1.81, pages 7, 8, 10].

The majority of subjects were of Caucasian race (94%, 34/36). The remainder of the subjects in the study were Black (3%, 4/36) or were multiracial (3%, 1/36). The majority of subjects in were females (58%, 21/36). There were 15 males in the study (42%, 15/36). The mean age for subjects in this study was 26.2 years [range 18-54] . [Volume 1.81, pages 10, 11, 14].

11.7.1. Clinical pharmacology outcomes

Plasma guaifenesin and pseudoephedrine levels were analyzed using a validated LC method at [redacted]. The validated analytical ranges used were [redacted] for guaifenesin and [redacted] for pseudoephedrine [Volume 1.81, pages 9, 98; Volume 1.82, page 9].

The pharmacokinetic and statistical analyses were conducted on data from the 36 subjects who received test and reference study treatment [Volume 1.81, pages 7, 8, 14, 16-21]. Pharmacokinetics results for the proposed product when given under fasting and fed conditions are presented in Table 11.7.2.

Mean $AUC_{0\text{-}inf}$ values for guaifenesin were 8142 ng.hr/mL for reference and 7469 ng.hr/mL for experimental treatment B. Mean C_{max} values for guaifenesin were 1857

ng/mL for reference and 1364 ng/mL for experimental treatment B. Mean $T_{1/2}$ values for guaifenesin were 1.82 h for reference product and 1.39 h for experimental treatment B. Mean T_{max} values for guaifenesin were 1.06 h for reference and 2.06 h for experimental treatment B [Volume 1.81, pages 16-21].

Mean $AUC_{0\text{-}inf}$ values for pseudoephedrine were 3746 ng.hr/mL for reference and 3660 ng.hr/mL for experimental treatment B. Mean C_{max} values for pseudoephedrine were 283 ng/mL for reference and 301 ng/mL for experimental treatment B. Mean $T_{1/2}$ values for pseudoephedrine were 5.01 h for reference and 4.64 h for experimental treatment B. Mean T_{max} values for pseudoephedrine were 4.60 h for reference product and 5.77 h for experimental treatment B [Volume 1.81, pages 16-21].

Table 11.7.2. Mean PK parameters for guaifenesin and pseudoephedrine, fed conditions, Study 2002-11 [Volume 1.81, pages 16-21].

PK Parameter	Gualfenesin 1200 mg plus Pseudoephedrine 120 mg Fasted conditions Reference Treatment A N = 35	Gualfenesin 1200 mg/ Pseudoephedrine 120 mg Fed conditions Experimental Treatment B N = 35
Guaifenesin		
$AUC_{(0\text{-}inf)}$, ng.hr/mL	8142	7469
C_{max}, ng/mL	1857	1364
$T_{1/2}$, hr	1.82	1.39
T_{max}, hr	1.06	2.06
Pseudoephedrine		
$AUC_{(0\text{-}inf)}$, ng.hr/mL	3746	3660
C_{max}, ng/mL	283	301
$T_{1/2}$, hr	5.01	4.64
T_{max}, hr	4.60	5.77

Detailed statistical analysis was performed to compare the study treatment under fasting and fed conditions. These data are presented in Table 11.7.3. $AUC_{0\text{-}inf}$ values for guaifenesin administered under fed conditions were 90.2% of values for study treatment administered under fasting conditions. C_{max} values for guaifenesin for study treatment administered under fed conditions were 74.0% of those for study treatment administered under fasting conditions. $AUC_{0\text{-}inf}$ values for pseudoephedrine administered under fed conditions were 98.6% of values for study treatment administered under fasting conditions. C_{max} values for pseudoephedrine for study treatment administered under fed conditions were 106% of those for study treatment administered under fasting conditions. The sponsor concludes that the rate, but not the extent of guaifenesin absorption from the proposed product is decreased in the presence of a high fat meal. The rate and extent of pseudoephedrine absorption from the proposed product is not affected by a high fat meal [Volume 1.81, pages 11-12, 23-24].

Table 11.7.3. Statistical analysis of PK parameters for guaifenesin and pseudoephedrine, fasting and fed conditions, Study 2002-11 [Volume 1.81, pages 23-24].

PK Parameter*	Ratio B/A, %	(90% C I)
Guaifenesin		
$AUC_{(0\text{-}inf)}$, ng.hr/mL	90.2	(84.7, 96.0)
C_{max}, ng/mL	74.0	(65.9, 83.2)
$T_{1/2}$, hr	70.1	(59.6, 82.5)
Pseudoephedrine		
$AUC_{(0\text{-}inf)}$, ng.hr/mL	98.6	(93.6, 104)
C_{max}, ng/mL	106	(101, 112)
$T_{1/2}$, hr	93.7	(88.9, 98.6)

Treatment A = Guaifenesin 1200 mg plus pseudoephedrine 120 mg, fasting conditions
Treatment B = Guaifenesin 1200 mg/pseudoephedrine 120 mg, fed conditions
*log transformed values

Reviewer comment:
The rate of guaifenesin absorption from the proposed product is decreased somewhat in the presence of a high fat meal. The extent of guaifenesin absorption and the rate and extent of pseudoephedrine absorption from the proposed product is not affected by a high fat meal. This is a similar pattern to that noted in food effects study 2002-02A. The small decrease in C_{max} for guaifenesin with a high fat meal is not likely to be clinically significant.

11.7.2. Safety outcomes

There was only one adverse event (AE) experienced among the subjects in this study. This subject had vomiting in the period of the study when study treatment was administered during fasting conditions [Volume 1.86, page 155].

12. APPENDIX, BRIEF LABEL REVIEW

Proposed package labeling was included in the submission [Volume 1.1, pages 10-46]. Labeling was later revised to change the proposed dose for the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength [redacted] to 2 tablets every 12 hours, not more than 4 tablets in 24 hours [NDA 21-585 N000 BZ, 4/30/03, Cover Letter]. The sponsor changed the dose of the 600 mg guaifenesin/60 mg pseudoephedrine dosage strength because the proposed dose [redacted] for the 600 mg guaifenesin/60 mg pseudoephedrine product is one-half of the OTC monograph dose of pseudoephedrine for this dosing interval, and is not supported by the studies in this application.

The Division of Over-the-Counter Drug Products (DOTDP) has completed their labeling review [NDA 21-585, OTC Drug Labeling Review, Cazemiro M. Martin, Regulatory Review Scientist]. Mr. Martin notes that the "Uses" section of "Drug Facts" states that the product temporarily relieves nasal congestion due to common cold, hay fever, respiratory allergies, [redacted] The Agency no longer considers [redacted] an appropriate indication for an OTC decongestant drug product. The OTC review team recommends that the sponsor delete the reference to [redacted] from the label.

Clinical comments on labeling are noted below.

1. This reviewer was concerned that the sponsor's proposed product names, "Mucinex™ D Maximum Strength," and "Mucinex™ D Regular Strength," were misleading in that the recommended dose of both dosage strengths provide the same amounts of guaifenesin and pseudoephedrine—1200 mg and 120 mg, respectively. However, DOTCDP does not consider the names to be misleading, and notes that there is precedent for other OTC drugs to be labeled similarly. Both Extra Strength Tylenol® Adult Liquid Pain Reliever and Maximum Strength Tylenol® Sore Throat Adult Liquid contain 1000 mg acetaminophen in each 30 mL and are both dosed 2 tablespoons every 4 to 6 hours, not to exceed 8 tablespoons in 24 hours.

2. Initially, the proposed labeling instructed consumers to [redacted] [Volume 1.1, pages 40-46]. The clinical pharmacology studies in this application did not support this claim and the sponsor deleted this claim from the proposed labeling [NDA 21-585 N000 BZ, 4/30/03, Cover Letter].

3. The labeling states that the product may be administered without regard for timing of meals. The sponsor's food effect study, Study 2002-11, supports this labeling claim.

4. Pseudoephedrine is largely excreted by the kidney. The current OTC monograph labeling for pseudoephedrine does not include a warning for consumers with kidney disease. Consideration should be given to amending the OTC monograph labeling for pseudoephedrine by adding a warning that instructs consumers with kidney disease not to take the drug.

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

13. COMMENTS FOR THE SPONSOR

The following comment is to be communicated in the action letter to the sponsor:

Submit a summary, analysis, and interpretation of postmarketing safety reports from the AERS database for guaifenesin and pseudoephedrine. This report should cover the period since the safety cut-off date for the NDA submission.

Reviewed by:

_____

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

_____

Lydia Gilbert-McClain, M.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/McClain/Acting Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Suarez/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-580/Salemme/CMC Reviewer
HFD-570/Bond/Pharmacology Reviewer
HFD-570/C. Jackson/CSO
HFD-560/C. Martin/Regulatory Review Scientist
HFD-560/M. Chang/Team Leader

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

/s/

Charles Lee
10/22/03 08:46:34 AM
MEDICAL OFFICER

Lydia McClain
10/22/03 03:17:26 PM
MEDICAL OFFICER
I concur

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

APPLICATION:	NDA 21-585	**TRADE NAME:**	Mucinex™ D
APPLICANT/SPONSOR:	Adams Laboratories, Inc.	**USAN NAME:**	Guaifenesin/pseudoephedrine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	Expectorant/decongestant
DATE:	3/27/03	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
1/31/03	1/31/03	NDA 21-585	89 volumes

RELATED APPLICATIONS

Document Date	Application Type	Comments
6/29/00	NDA 21-282	NDA for Mucinex™, guaifenesin extended release tablets

REVIEW SUMMARY:

This NDA is a 505(b)(2) application for an extended release formulation of guaifenesin and pseudoephedrine HCl (PSE). The sponsor is Adams Laboratories, Inc. The sponsor requests approval of two dosage strengths, (1) guaifenesin 600-mg/PSE 60-mg tablets, and (2) guaifenesin 1200-mg/PSE-120 mg tablets. The product is an extended release, bilayer tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and nasal decongestant. The proposed indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, and [redacted] The sponsor's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength. There are seven clinical pharmacology studies submitted in support of this application. A filing and planning review by the clinical reviewer has been completed. This addendum to that review outlines additional issues identified and discussed at the filing and planning meeting held on March 26, 2003.

The proposed dose [redacted] e 600-mg guaifenesin/60-mg PSE product is one-half of the OTC monograph dose of PSE for this dosing interval. The studies in this submission do not provide support [redacted] for the 600-mg guaifenesin/60-mg PSE product. The efficacy of this dose must be supported by clinical studies as this dosage represents less than the OTC monograph dose for PSE over this dosing interval. The proposed dose of 1 tablet every 12 hours for the 1200-mg guaifenesin/120-mg PSE tablets is acceptable and is within OTC monograph doses for guaifenesin and PSE over this dosing interval. The sponsor has proposed a dose of 1 or 2 tablets every 12 hours for the 600-mg guaifenesin/60-mg PSE product. The proposed dose of 2 tablets every 12 hours for the 600-mg guaifenesin/60-mg PSE product is acceptable, as guaifenesin and PSE are within OTC monograph doses for this dosing interval. The proposed labeling instructs patients to [redacted] The biopharmaceutics studies in this application are not the type of studies necessary to support this claim. Clinical studies will be necessary if the sponsor wishes to pursue this claim.

The sponsor will be notified that the [redacted] is not supported for the 600-mg guaifenesin/60-mg PSE product. The sponsor should also be advised that the claim regarding [redacted] supported. The sponsor should be advised that clinical studies will be necessary to support this dosage and this claim. The submission is fileable.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	**SAFE TO PROCEED**	___	**CLINICAL HOLD**	
NDA/SUPPLEMENTS:	X	**FILEABLE**	___	**NOT FILEABLE**	
	___	**APPROVAL**	___	**APPROVABLE**	___ **NOT APPROVABLE**
OTHER ACTION:					

1. COMMENTS FOR THE SPONSOR

The following comments are to be communicated to the sponsor, in addition to the comments included in the previous filing and planning review:

1. *You have proposed a dose of 2 tablets every 12 hours for the 600-mg guaifenesin/60-mg pseudoephedrine product. The dose of [redacted] 600-mg guaifenesin/60-mg pseudoephedrine product provides one-half of the OTC monograph dose of pseudoephedrine over this dosing interval. The studies in this submission do not provide support for this dosage regimen. The efficacy of this dosage regimen must be supported by clinical studies, as the dose of pseudoephedrine over this dosing interval is less than that specified by the OTC monograph.*

2. *Your proposed labeling instructs patients to [redacted] The biopharmaceutics studies in this application are not the type of studies necessary to support this claim. Clinical studies are necessary if you wish to pursue this claim.*

Reviewed by:

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Lydia Gilbert-McClain, M.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/McClain/Acting Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Suarez/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-580/Salemme/CMC Reviewer
HFD-570/Bond/Pharmacology Reviewer
HFD-570/C. Jackson/CSO
HFD-560/Chang/Supervisory CSO

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/s/

Charles Lee
3/31/03 08:45:09 AM
MEDICAL OFFICER

Lydia McClain
3/31/03 08:49:58 AM
MEDICAL OFFICER

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

APPLICATION:	NDA 21-585	TRADE NAME:	Mucinex™ D
APPLICANT/SPONSOR:	Adams Laboratories, Inc.	USAN NAME:	Guaifenesin/pseudoephedrine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	CATEGORY:	Expectorant/decongestant
DATE:	3/17/03	ROUTE:	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
1/31/03	1/31/03	NDA 21-585	89 volumes

RELATED APPLICATIONS

Document Date	Application Type	Comments
6/29/00	NDA 21-282	NDA for Mucinex™, guaifenesin extended release tablets

REVIEW SUMMARY:

This NDA is a 505(b)(2) application for an extended release formulation of guaifenesin and pseudoephedrine HCl (PSE). The sponsor is Adams Laboratories, Inc. The sponsor requests approval of two dosage strengths, (1) guaifenesin 600 mg/PSE 60 mg tablets, and (2) guaifenesin 1200 mg/PSE 120 mg tablets. The product is an extended release, bilayer tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and nasal decongestant. The proposed indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, and [redacted] The sponsor's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength. The sponsor has provided a paper submission. There are seven clinical pharmacology studies submitted in support of this application. These studies are appropriately indexed and organized to allow review.

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 pseudoephedrine. The summaries should briefly address relevant information from the literature and from postmarketing reports from the AERS database. Preliminary review of proposed product labeling reveals discrepancies with the labeling specified by the OTC cough and cold monograph. 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.

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

OUTSTANDING ISSUES: The sponsor should submit the above noted information.

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	SAFE TO PROCEED	___	CLINICAL HOLD		
NDA/SUPPLEMENTS:	X	FILEABLE	___	NOT FILEABLE		
	___	APPROVAL	___	APPROVABLE	___	NOT APPROVABLE
OTHER ACTION:						

1. GENERAL INFORMATION AND BACKGROUND

This NDA is a 505(b)(2) application for an extended release formulation of guaifenesin and pseudoephedrine HCl (PSE). The sponsor requests approval of two dosage strength tablets, (1) guaifenesin 600 mg/PSE 60 mg tablets, and (2) guaifenesin 1200 mg/PSE 120 mg tablets. The product is an extended release, bilayer tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and nasal decongestant. The proposed labeled indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies, ~~~~. The sponsor's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength. The sponsor has provided a paper submission.

Guaifenesin is considered to be generally recognized as safe and effective (GRASE) as an expectorant in the following age groups at the following oral doses [21 CFR 341.78]:

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

PSE is an orally active sympathomimetic that has a decongestant effect on the nasal mucosa. PSE is considered to be generally recognized as safe and effective (GRASE) as an nasal decongestant in the following age groups at the following oral doses [21 CFR 341.80]:

- Adults and children 12 years of age and older: 60 mg every 4 to 6 hours, NTE 240 mg in 24 hours
- Children 6 to under 12 years of age: 30 mg every 4 hours, NTE 120 mg in 24 hours
- Children 2 to under 6 years of age: 15 mg every 4 hours, NTE 60 mg in 24 hours
- 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 nasal decongestant (such as PSE) with any single expectorant (such as guaifenesin) to be a permitted combination [21 CFR 341.40].

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 were 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 guaifenesin product that is approved in the US.

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

The sponsor's application includes reports of seven PK and bioavailability studies [Volume 1.1, page 53]:

1. Protocol 00-01, a pilot single dose study designed to examine the relative bioavailability of two different experimental formulations of the proposed product in healthy men and women
2. Protocol 00-01A, a second pilot single dose study designed to examine the relative bioavailability of two different experimental formulations of the proposed product in healthy men and women
3. Protocol 2002-01A, a definitive single dose study designed to examine the relative bioavailability of the product and dose proportionality of the individual component drugs
4. Protocol 2002-03, a definitive multiple dose study designed to examine the steady state bioavailability of the product in healthy men and women
5. Protocol 2002-02A, a single dose study designed to examine the effect of a high-fat breakfast on the bioavailability of the product in healthy men and women
6. Protocol 2002-11, 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
7. Protocol 2002-04, a single dose study designed to examine the potential for interaction of the component drugs in healthy men and women

Individual studies are described in greater depth in a later section of this filing and planning review.

2. FOREIGN MARKETING AND REGULATORY HISTORY

Guaifenesin and PSE single ingredient products and guaifenesin/PSE combination products are marketed internationally by many manufacturers. The sponsor reports that they do not make guaifenesin or PSE or the trade names Mucinex™ and Mucinex™ D available to foreign markets. The sponsor states that to the best of their knowledge, neither active ingredient has been withdrawn from foreign markets for reasons of safety or effectiveness [Volume 1.1, page 47].

3. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [Volume 1.1, page not numbered]
- Debarment certification [Volume 1.1, page 95]

- Financial disclosure statement [Volume 1.1, pages 89-90]
- Statements of Good Clinical Practice [Volume 1.47, page 6; Volume 1.53, page 2; Volume 1.57, page 2; Volume 1.64, page 2; Volume 1.69, page 2; Volume 1.75, page 2; Volume 1.81, page 2]
- Integrated Summary of Efficacy [Volume 1.46, pages 150-191]
  - This application relies on the support of clinical pharmacology studies to demonstrate bioequivalence of the new drug to the test product. No clinical studies of the efficacy of the product or integrated summary of efficacy were required
- Integrated Summary of Safety (ISS) [Volume 1.46, pages 192-274] included the following:
  - Summary of safety information from clinical pharmacology studies in this application [Volume 1.46, pages 192-198]
  - Spontaneous adverse event reports from the AERS database obtained through the Freedom of Information Act (FOIA) [Volume 1.46, pages 199-274]
  - Drug abuse and overdose information [Volume 1.46, pages 275-320]
  - Review of the literature for safety information relevant to guaifenesin and PSE [Volume 1.45, pages 178-401; Volume 1.46, pages 1-149, 276-320]
    - The sponsor has identified 19 articles of interest for guaifenesin and 16 articles for PSE, but provided copies of only three articles for guaifenesin and two articles for PSE. The sponsor should submit copies of each of the identified articles noted in Volume 1.45, pages 178-179 and Volume 1.46, pages 1-2, with the following exceptions. The sponsor does not need to submit the following articles:
      - From Volume 1.45, pages 178-179:
        - DHHS, FDA (1989) OTC monograph
        - Assimos DG, et. al. (1999)
        - Pickens CL et. al. (1999)
      - From Volume 1.46, pages 1-2
        - DHHS, FDA (1989) OTC monograph
        - Sica DA, et. al. (1989)
  - The sponsor did not address safety by gender, race, in the elderly, or in the pediatric population
- Proposed labeling and annotated labeling [Volume 1.1, pages 10-46].
- Case report forms for patients with SAEs or discontinuing studies [Volume 1.89, pages 359-375]
- List of referenced DMFs [Volume 1.1, page 47]
- Environmental assessment [Volume 1.1, page 50]
  - The sponsor has requested a categorical exclusion from this requirement because approval of this NDA would not increase the amount of the active moieties because they are in current use at the same total daily levels, 2400 and 240 mg, respectively [Volume 1.1, page 50].
- Request for waiver of pediatric studies
  - The dose of active drugs in the product and its formulation are not appropriate for use in children less than 6 years of age. A suitable pediatric dosage form currently exists. The sponsor did not, however, provide a request for waiver of

pediatric studies. However, such a waiver is not required given that the court has struck down the Pediatric Rule and ruled that it may not be enforced.

4. CLINICAL PHARMACOLOGY STUDIES

This submission refers to seven clinical pharmacology studies. The studies are appropriately indexed to allow review. The studies are summarized in Table 1. More detailed descriptions of these studies follow below.

4.1. Study 00-01

Study 00-01 was a pilot clinical pharmacology study that compared the bioavailability of guaifenesin and PSE from two experimental extended release formulations containing both guaifenesin and PSE. The two experimental formulations were compared to a reference consisting of extended release guaifenesin (Mucinex™) and fexofenadine/extended release PSE (Allegra® D). 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. 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 for plasma guaifenesin and PSE 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. Safety endpoints reported included adverse events. There were no withdrawals from the study. There were no SAEs [Volume 1.47, pages 6-7; Volume 1.52, page 130].

4.2. Study 00-01A

Study 00-01A was a pilot clinical pharmacology study that compared the bioavailability of guaifenesin and PSE from two experimental extended release formulations containing both guaifenesin and PSE. The two experimental formulations were compared to a reference consisting of extended release guaifenesin (Mucinex™) and extended release PSE (Sudafed 12-Hour®). 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. 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 for plasma guaifenesin and PSE 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. Safety endpoints reported included adverse events. There were no withdrawals from the study. There were no SAEs [Volume 1.53, pages 7-11; Volume 1.56, page 401].

4.3. Study 2002-01A

Study 2002-01A was a definitive clinical pharmacology study that compared the bioavailability and dose proportionality of guaifenesin and PSE from an extended release formulation to a reference consisting of extended release guaifenesin (Mucinex™) and extended release PSE (Sudafed 12-Hour®). One group received the sponsor's proposed product containing 1200-mg guaifenesin and 120 mg PSE and one group received the proposed product containing 600-mg guaifenesin and 60 mg PSE. The third group

received the reference treatment. 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 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, 6, 8, 10, 12, 14, 16, and 24 hours for plasma guaifenesin and PSE 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. Safety endpoints reported included adverse events. There was one patient who withdrew from the study and did not return for the second study period. There were no withdrawals from the study because of AEs. There were no SAEs [Volume 1.57, pages 7-10; Volume 1.63, pages 423, 433].

4.4. Study 2002-02A

Study 2002-02A was a clinical pharmacology study that compared the bioavailability of guaifenesin and PSE from an experimental extended release formulation to a reference consisting of extended release guaifenesin (Mucinex™) and extended release PSE (Sudafed 12-Hour®) under 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. 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 for plasma guaifenesin and PSE 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. Safety endpoints reported included adverse events. There were three patients who withdrew from the study, including one who withdrew from the study because of an AE coded as URI. There were no SAEs [Volume 1.64, pages 7-9; Volume 1.68, pages 398, 408].

4.5. Study 2002-03

Study 2002-03 was a definitive clinical pharmacology study that compared the bioavailability of guaifenesin and PSE from an experimental extended release formulation to a reference consisting of extended release guaifenesin (Mucinex™) and extended release PSE (Sudafed 12-Hour®) at steady state, after 11 doses given every twelve hours. The study was an open-label, randomized, multiple dose, two period, two-way crossover bioavailability study conducted in 37 healthy male and female subjects. Samples were taken immediately before dosing (0 hours) on Days 1, 4, 5, and 6. On day 6, patients also had blood samples drawn at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours for plasma guaifenesin and PSE levels. 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. A minimum washout period of seven days separated each treatment period. Safety endpoints reported included adverse events. There was one patient who withdrew from the study because of a schedule conflict, but there were no patients who withdrew from the study because of an AE. There were no SAEs [Volume 1.69, pages 7-10, 46; Volume 1.74, pages 324, 336].

4.6. Study 2002-04

Study 2002-04 was a clinical pharmacology study that compared the bioavailability of guaifenesin and PSE when administered alone and upon co-administration. The study was an open-label, randomized, single dose, three period, three-way crossover bioavailability study conducted in 36 healthy male and female subjects. Treatment groups included the proposed guaifenesin 1200 mg/PSE 120 mg product, 1200 mg guaifenesin (Mucinex™), and 120 mg PSE (Sudafed 12-Hour®). 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 and PSE levels. Patients were housed at the study site after the 24-hour sample was drawn. A minimum washout period of seven days separated each treatment period. Safety endpoints reported included adverse events. There were no patients who withdrew from the study. There were no SAEs [Volume 1.75, pages 7-10, 46; Volume 1.80, pages 411, 421].

4.7. Study 2002-11

Study 2002-11 was a definitive clinical pharmacology study that compared the bioavailability of guaifenesin and PSE from an experimental 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. 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 for plasma guaifenesin and PSE 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. Safety endpoints reported included adverse events. There were two patients who withdrew from the study, but no patients who withdrew from the study because of an AEs. There were no SAEs [Volume 1.81, pages 7-10; Volume 1.86, pages 147, 157].

Table 1. Summary of studies, NDA 21-585 [Volume 1, pages 53, 67-73].

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

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

5. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission [Volume 1.1, pages 10-46]. A brief review of proposed labeling was performed. Labeling concerns are noted below.

1. 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' studies.

2. The "Uses" section of "Drug Facts" states that the product temporarily relieves nasal congestion due to common cold, hay fever, respiratory allergies, and . However, the sub-bullets are arranged in such a way that one might conclude that the product is indicated for treatment of these conditions, and not just nasal congestion due to these conditions

3. The "Uses" section of "Drug Facts" states that the product temporarily relieves nasal congestion due to common cold, hay fever, respiratory allergies, and The regulation specifies that this statement should state: "Temporarily relieves nasal congestion due to: *the* common cold," "hay fever *or other* upper respiratory allergies", or "*associated with* sinusitis" [21 CFR 341.80].

4. 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.

6. DSI REVIEW/AUDIT

DSI clinical audit will not be requested because no efficacy or safety studies were included in the development program for this drug product.

7. SUMMARY

This NDA is a 505(b)(2) application for an extended release formulation of guaifenesin and pseudoephedrine HCl (PSE). The sponsor is Adams Laboratories, Inc. The sponsor requests approval of two dosage strengths, (1) guaifenesin 600 mg/PSE 60 mg tablets, and (2) guaifenesin 1200 mg/PSE 120 mg tablets. It is an extended release 12-hour bilayer tablet formulation. It is proposed as an over-the-counter (OTC) combination expectorant and nasal decongestant drug product. The proposed indication is loosening of phlegm and bronchial secretions and temporary relief of nasal congestion due to the common cold, hay fever, upper respiratory allergies. The sponsor's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength. The sponsor has provided a paper submission. There are seven clinical pharmacology studies submitted in support of this application. These studies are appropriately indexed and organized to allow review.

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 pseudoephedrine. The summaries should briefly address relevant information from the literature and from postmarketing reports from the AERS database. Preliminary review of proposed product labeling reveals discrepancies with the labeling specified by the OTC cough and cold monograph. 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.

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

8. TIME LINE FOR REVIEW

Write-up will be concomitant with the review process. The schedule for review is displayed in Table 2. Clinical review will focus primarily on safety and will be performed for each study before moving to the next study. The review of the safety review and ISS will take place next and will be complete by 10/3/03. Label review will be complete by 10/17/03. Draft review will be complete by 10/31/03, four weeks before the action date.

Table 2. Proposed schedule for review of NDA 21-375.

Milestone	Target Date for Completion
Pilot studies 00-01, 00-01A	7/18/03
Studies 2002-01A, 2002-02A	8/14/03
Studies 2002-03, 2002-04, 2002-11	9/4/03
Safety review and ISS	10/3/03
Label Review	10/17/03
Draft Review Complete	10/31/03
Action Date, 10 months	11/30/03

9. COMMENTS FOR THE SPONSOR

The following comments are to be communicated to the sponsor:

1. *You identified 19 articles of interest for guaifenesin and 16 articles for pseudoephedrine in your review of the literature, but provided copies of only three for guaifenesin and two for pseudoephedrine. Submit copies of each of the articles noted in Volume 1.45, pages 178-179 and Volume 1.46, pages 1-2, with the following exceptions. You do not need to submit the following articles:*
   - *From Volume 1.45, pages 178-179:*
     - *DHHS, FDA (1989) OTC monograph*
     - *Assimos DG, et. al. (1999)*
     - *Pickens CL et. al. (1999)*
   - *From Volume 1.46, pages 1-2*
     - *DHHS, FDA (1989) OTC monograph*
     - *Sica DA, et. al. (1989)*

2. *Submit a summary of safety by gender, race, in the elderly, and in the pediatric populations for guaifenesin and pseudoephedrine. These summaries should briefly address any relevant information from the application's clinical pharmacology studies, from the medical literature, and from postmarketing reports from the AERS database.*

Reviewed by:

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Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

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Lydia Gilbert-McClain, M.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/McClain/Acting Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Suarez/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-580/Salemme/CMC Reviewer
HFD-570/Bond/Pharmacology Reviewer
HFD-570/C. Jackson/CSO

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

/s/

Charles Lee
3/17/03 01:36:44 PM
MEDICAL OFFICER

Lydia McClain
3/18/03 07:15:08 AM
MEDICAL OFFICER