CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-585

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-585	Efficacy Supplement Type -	Supplement Number
Drug: Mucinex D (guaifenesin and pseudoephedrine) Tablets		Applicant: Adams Respiratory Therapeutics
RPM: Colette Jackson	HFD-570	Phone # 301-827-9388
Application Type: ( ) 505(b)(1) (x) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): 21-282 Mucinex	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	11/30/2003
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) (x) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	6/8/04
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
[redacted]	
❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	10/20/03
• Applicant proposed	1/31/03, 4/30/03, 10/27/03, 10/30/03, and 2/25/04
• Reviews	OTC on 9/4/03, 11/17/03, and 3/11/04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	4/14/03, 6/9/03 (2), 10/20/03, 1/21/04, and 3/3/04
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Team Leader 11/3/03 Division Director 11/24/03,
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	3/18/03, 3/31/03, and 10/22/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	3/16/04
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	6/8/04
❖ Statistical review(s) *(indicate date for each review)*	None needed
❖ Biopharmaceutical review(s) *(indicate date for each review)*	3/27/03, 10/24/03, and 5/13/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	10/17/03
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	4/1/03, 6/5/03, 10/6/03, and 5/27/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	4/1/03
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	Not needed
❖ Facilities inspection (provide EER report)	Date completed: 4/16/03 **(x)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**(x)** Completed **()** Requested **()** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9/15/03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-585	Efficacy Supplement Type SE-	Supplement Number
Drug: Mucinex D (guaifenesin and pseudoephedrine)	Applicant Adams Laboratores	
RPM: Colette Jackson	HFD- 570	Phone 7-5584
Application Type: ( ) 505(b)(1) (x) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	11/30/2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
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❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
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• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	N/A
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
[illegible]	
❖ Actions	
• Proposed action	( ) AP ( ) TA (X) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
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• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	9/4/2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	None
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
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❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	10/22/2003, 3/31/2003, and 3/18/2003
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❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	3/27/03 and 10/24/2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	4/17/2003
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	4/1/03, 6/5/03, and 10/6/2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	(x) Acceptable ( ) Withhold recommendation
❖ Methods validation	(x) Completed ( ) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9/15/03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

13.0 PATENT INFORMATION ON ANY PATENT THAT CLAIMS THE DRUG

Time Sensitive Patent Information Pursuant to 21 C.F.R 314.53 for NDA # 21-585

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: Mucinex™ D Extended-Release Tablets
Active Ingredient(s): guaifenesin/pseudoephedrine hydrochloride
Strength(s): 600/60 mg and 1200/120 mg
Dosage Form: Extended-Release Tablet
Approval Date:

A. This information should be provided for each individual patent submitted:

U.S. Patent Number: 6,372,252 B1

Expiration Date: April 28, 2020

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient) ____ Y _X_ N
Drug Product (Composition/Formulation) _X_ Y ____ N
Method of Use _X_ Y ____ N

a. **If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:** Expectorant Nasal Decongestant

Name of Patent Owner: Adams Laboratories, Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Not Applicable

B. **The following declaration statement is required by 21CFR 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.**

The undersigned, Adams Laboratories, Inc., declares that the United States Patent Number US 6,372,252 B1 covers the formulation, composition, and/or method of use of Mucinex™ products. Mucinex™ D is the subject of this application for which approval is being sought. This product is:

_____ **currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act**

OR

__X__ **the subject of this application for which approval is being sought.**

Signed:

D J Kuyper 1-31-03

V.P.- Development and Regulatory Affairs

14.0 PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

Adams Laboratories, Inc. certifies to the best of their knowledge, there are no patents other than US 6,372,252B1 and one pending that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Adams Laboratories, Inc. currently has a patent pending on guaifenesin and pseudoephedrine for which patent information must be submitted according to 21 CFR 314.53. Within 30 days of the date of issuance of the patent, Adams Laboratories, Inc. will submit to the FDA the required patent information.

Donald Jeffrey Keyser
VP Regulatory and Development Affairs

1-31-03
Date:

EXCLUSIVITY SUMMARY FOR NDA # 21-585 SUPPL #_____

Trade Name Mucinex D (Extended Release Tablets)

Generic Name guaifenesin and pseudoephedrine

Applicant Name Adams Respiratory Therapeutics (formerly Adams Laboratories) HFD # 570

Approval Date If Known June 22, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /___/ NO /_X_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The application is based on the bioequivalence between Mucinex D and reference guaifenesin and pseudoephedrine drug products based on criteria established by the OTC monograph.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-282 Mucinex (quaifenesin) ER tablets

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant."

reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature Date
Title:

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

/s/

Badrul Chowdhury
6/26/04 05:50:15 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # 21-5850 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: December 22, 2003 Action Date: June 22, 2004

HFD 570 Trade and generic names/dosage form: Mucinex D (guaifenesin and pseudoephedrine)

Applicant: Adams Respiratory Therapeutics Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Expectorant

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ ✓No: Please check all that apply: ✓ Partial Waiver ____Deferred ✓ Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo. 0	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr. <12	Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ ✓There are safety concerns for use of this extended release product in ages <12.
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ ✓Other: There are liquid immediate-release formulations labeled for use in ≥ 2 years of age and for ages <2 the labeling recommends consulting a physician.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Nasal Decongestant

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **✓No: Please check all that apply: ✓ Partial Waiver ___Deferred ✓ Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.** 0	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** <12	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **✓There are safety concerns for use of this extended release product in ages <12.**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **✓Other: : There are liquid immediate-release formulations labeled for use in ≥ 2 years of age and for ages <2 the labeling recommends consulting a physician.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

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

/s/

Sandra Barnes
6/25/04 05:05:51 PM

16. DEBARMENT CERTIFICATION

Adams Laboratories, Inc. certifies that it did not and will not use in any capacity the services of any person debarred under subsection 306(a) and 306(b) of the Federal Food, Drug and Cosmetic Act (21 USC 335a and 335b) in connection with this New Drug Application.

D J Keyser

Donald Jeffrey Keyser
VP Regulatory and Development Affairs

12/17/02

Date:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM:
Colette Jackson
Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 8, 2004		21-585	N	December 19, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Mucinex® D (guaifenesin and pseudoephedrine) Extended Release Tablets	Standard	Expectorant and Nasal Decongestant	May 8, 2004

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for a nomenclature consult to evaluate the acceptability of Mucinex ®D.
The most recent labeling submission is electronic only and is located in the EDR in the submission dated February 25, 2004.

PDUFA DATE: June 22, 2004

CC:
Archival NDA 21-585
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Labeling Review: Addendum

NDA # 21-585

Submission Date : 2/25/04
Review Date : 3/10/04

Applicant: Adams Laboratories, Inc.

Applicant's Representative: D. Jeffrey Keyser
Vice President
Development & Regulatory Affairs

Drug: Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength Extended-Release Bi-layer Tablets

Guaifenesin 600 mg/Pseudoephedrine HCl 60 mg
- and -
Guaifenesin 1200 mg/Pseudoephedrine HCl 120 mg

Pharmacologic Category: Expectorant/Nasal decongestant

Submitted: Revised draft labeling as follows:

1. Mucinex™ D (Regular Strength)
   Guaifenesin 600 mg/Pseudoephedrine HCl 60 mg
   - 2-, 20-, and 40-count bottle label
   - 20-, and 40-count carton label
   - 2-count tray label

2. Mucinex™ D (Maximum Strength)
   Guaifenesin 1200 mg/Pseudoephedrine HCl 120 mg
   - 2-, 10-, 20-count bottle label
   - 10-, 20-count carton label
   - 2-count tray label

Reviewer comments:

The sponsor has resubmitted the following draft labeling that is identical to the labeling revisions included in its October 30, 2003 submission:

- 20- and 40-count regular strength carton and immediate container label
- 10- and 20-count maximum strength carton and immediate container label
- 2-count regular and maximum strength immediate container label

This reviewer has previously reviewed the sponsor's revised labeling and noted that the sponsor had incorporated all of the Agency's required and recommended labeling changes. (See review dated 11/17/03.)

Recommendation:

1. An approval letter can be issued to the sponsor requesting final printed labeling for the following:
   - 20- and 40-count carton and 2-, 20-, and 40-count bottle labels for the Mucinex D Regular Strength product
   - 10- and 20-count carton and 2-, 10-, and 20-count bottle labels for the Mucinex D Maximum Strength product
   - 2-count tray labeling for the Regular and Maximum Strength products.

   These final printed labeling must be identical to the labeling submitted on February 25, 2004.

2. Inform the sponsor that the word "NEW" must be deleted from the PDP six months after introduction into the market place.

Cazemiro R. Martin
IDS: Reg. Review Scientist

Concur: Marina Chang, R.Ph.
Team Leader

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/s/

Cazemiro Martin
3/11/04 08:46:22 AM
INTERDISCIPLINARY

Marina Chang
3/11/04 08:51:03 AM
INTERDISCIPLINARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-585

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155-2645

Attention: D. Jeffrey Keyser
V.P., Development and Regulatory Affairs

Dear Mr. Keyser

We acknowledge receipt on December 22, 2003, of your December 19, 2003, resubmission to your new drug application for Mucinex ™D (guaifenesin and pseudoephedrine hydrochloride) Extended Release Tablets.

We consider this a complete, class 2 response to our November 24, 2003, action letter. Therefore, the user fee goal date is June 22, 2004.

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-9388.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/ .

Colette Jackson
1/21/04 11:41:17 AM
Signed for S. Barnes.

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/s/

Colette Jackson
3/8/04 03:28:57 PM

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.

3. Submit individual dissolution-time profiles data in a tabulated form for all the batches of Mucinex-D extended release tablets used in the definitive pharmacokinetic studies.

4. The primary stability data you have provided in the NDA, particularly for Maximum Strength Mucinex D tablets, show the tablets often failed to meet the Friability Test acceptance criterion of NMT 1% during stability. In addition, the friability values show significant variability.

   In the NDA you state you have developed process controls to ensure future batches of Maximum Strength tablets will pass the Friability Test acceptance criterion. To demonstrate this, provide available release and stability data for batches of Maximum Strength Mucinex D tablets manufactured with the in-process improvements. Approval of the Maximum Strength tablets will require adequate stability data demonstrating that the drug product meets the friability test acceptance criterion.

   In addition, please explain the reason for the high variability in the friability values observed in the NDA primary stability batches and discuss if the high variability has been eliminated with the in-process improvements.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
4/14/03 11:05:16 AM

DIVISION DIRECTOR'S MEMORANDUM

Date: November 24, 2003

To: NDA 21-585

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Mucinex D (guaifenesin 600 mg/pseudoephedrine hydrochloride 60 mg and guaifenesin 1200 mg/pseudoephedrine hydrochloride 120 mg) Extended Release Tablets

Applicant: Adams Laboratories, Inc.,

Administrative and Introduction

Adams Laboratories submitted NDA 21-585 for an extended release formulation of guaifenesin and pseudoephedrine hydrochloride as a 505(b)(2) application for over-the-counter (OTC) marketing as an expectorant and nasal decongestant. The NDA was received by the Agency on January 31, 2003. The PDUFA due date on this application is November 30, 2003. The applicant is requesting approval of two dosage strength tablets, guaifenesin 600 mg/pseudoephedrine hydrochloride 60 mg tablets, and guaifenesin 1200 mg/pseudoephedrine hydrochloride 120 mg. The Agency recently approved Adams Laboratories two single ingredient extended release tablet formulations of guaifenesin (Mucinex, 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 Mucinex product is the only extended release guaifenesin product that is approved and legally marketed in the United States. The current application is a line extension of Mucinex products that will contain a nasal decongestant. Guaifenesin and pseudoephedrine are both OTC products listed in the final monograph. The clinical program for this application was based on bioequivalence studies with supported safety data. The clinical program supports approval of the application, but there are outstanding chemistry and manufacturing issues that will preclude approval of this application in this cycle.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The Mucinex D drug product is a bi-layer tablet, with a white immediate release layer and a colored modified release layer. The lower strength tablets contain 100 mg guaifenesin in the immediate release layer, and 500 mg guaifenesin and 60 mg pseudoephedrine in an orange modified release layer. The higher strength tablets contain 200 mg guaifenesin in the immediate release layer, and 1000 mg guaifenesin and 120 mg pseudoephedrine in a pink modified release layer. The drug substances guaifenesin and pseudoephedrine have been used in a number of approved products. The DMFs for these two products were reviewed and found to be acceptable by the CMC reviewer.

The major CMC concern with the product is easy friability seen with both the dosage strengths. The batches that were used in the pivotal clinical pharmacology studies and placed in stability had problems with friability that would preclude approval. During the review cycle the applicant changed the manufacturing process to increase the [redacted] of the tablets by increasing the [redacted] to resolve the friability problem, but has not submitted a dissolution profile comparison of the tablets manufactured with the changed process to that of the tablets used in the clinical pharmacology studies. Furthermore, no stability data with tablets manufactured under the changed process is submitted. The CMC reviewer recommended that the applicant will need to provide dissolution data, and release and stability data to support approval of the product manufactured with the new process, and I concur with that recommendation.

Clinical Pharmacology and Biopharmaceutics, and Clinical
The clinical program was based on seven clinical pharmacology studies conducted in healthy male and female volunteers. Five of these studies were considered pivotal and were reviewed in depth by the Office of Clinical Pharmacology Reviewer Dr. Suarez-Sharp, and all submitted studies and additional safety data were reviewed by Medical Officer Dr. Lee. Both disciplines have recommended approval, and I concur with that recommendation. Brief comments on the clinical program are made in the following sections.

In the pivotal clinical pharmacology studies extended-release guaifenesin (Mucinex) and extended-release pseudoephedrine (Sudafed 12-Hour) were used as reference products. Mucinex tablets were previously approved by the Agency based on demonstrated equivalence to the OTC monograph doses of immediate release guaifenesin (NDA 21-282). Pseudoephedrine hydrochloride has been approved by the Agency as OTC single ingredient extended release 120 mg and 240 tablet dosage strength. Immediate release guaifenesin and pseudoephedrine 120 mg and 240 mg dosage strengths are also listed in the OTC monograph (21 CFR 341.78, and 21 CFR 341.80).

The aim of the clinical pharmacology studies were to determine in vivo bioequivalence of Mucinex D compared to Mucinex and Sudafed 12-Hour, to establish dose proportionately of the two strengths of Mucinex D, to assess the effect of food on the bioavailability of guaifenesin and pseudoephedrine delivered from Mucinex D, to assess possible drug-drug interaction between guaifenesin and pseudoephedrine in the Mucinex D formulation, and to characterize the pharmacokinetic parameters of Mucinex D at steady state. The clinical pharmacology program has demonstrated that Mucinex D was bioequivalent to Mucinex and Sudafed 12-Hour, the two strengths of Mucinex D were dose proportional, food did not have any significant effect on the pharmacokinetic parameters, there were no interactions between the two active ingredients of Mucinex D, and Mucinex D was bioequivalent to Mucinex and Sudafed 12-Hour at steady state under fasted conditions. The data supporting these conclusions are reviewed in depth in Dr. Suarez-Sharp's excellent review.

Safety of the Mucinex D product is supported from the submitted clinical pharmacology studies, and review of other database submitted by the applicant. The applicant has not

submitted summary of post-marketing adverse events reports in the safety update. The applicant will be asked to include such a summary in the complete response. Another potential concern is the size of the higher strength Mucinex D tablets. The tablet weighs 1587 mg and is rather large in size. Although in the clinical pharmacology program no problem was reported by the study participants with regard the tablet size, the applicant will be asked to maintain post-approval vigilance for problem related to the tablet size.

Pharmacology and Toxicology
The applicant did not conduct any new preclinical data for this application because the two active components of Mucinex are approved OTC monograph listed products.

Data Quality, Integrity, and Financial Disclosure
There was one study center and one analytical site for all clinical pharmacology studies. The DSI audited the principal investigator of the study site and did not note any irregularities. During review of the studies no issues with data quality and integrity were seen. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues are present.

Pediatric Consideration
The applicant is proposing indication down to the age of 12 years and is not proposing to go further down on age. This is acceptable because the fixed dose combination would not be suitable for children younger than 12 years of age. The lower age limit also conforms to the proposed doses in the OTC monograph.

Product Name
The proposed trade names for the two strength products are Mucinex D Regular Strength and Mucinex D Maximum Strength, for guifenesin 600mg/pseudeophedrine Hydrochloride 60mg and guifenesin 1200mg/pseudeophedrine Hydrochloride 120mg products, respectively. The trade name Mucinex is used by the same company for the marketed single ingredient guifenesin product. Addition of the D suffix is customary for products containing a decongestant. The proposed product name is reasonable.

Labeling
Adams Laboratories has submitted labeling that generally conforms to the OTC product label for such products. The label has been reviewed by the Division of over-the-counter Drug Products and by this Division. Detail language of the label will be negotiated with the applicant during a later review cycle when the product will be closer to approval.

Action

The clinical pharmacology and clinical safety data support approval of the application. There are outstanding CMC issues that need to be resolved before the application can be approved. Therefore, the action on this application will be APPROVABLE.

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/s/

Badrul Chowdhury
11/24/03 10:43:38 AM
MEDICAL OFFICER
Division Director Memorandum

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Labeling Review: Addendum

NDA # 21-585

Submission Date : 10/27/03; 10/30/03
Review Date : 11/17/03

Applicant: Adams Laboratories, Inc.

Applicant's Representative: D. Jeffrey Keyser
Vice President
Development & Regulatory Affairs

Drug: Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength Extended-Release Bi-layer Tablets

Guaifenesin 600 mg/Pseudoephedrine HCl 60 mg
- and -
Guaifenesin 1200 mg/Pseudoephedrine HCl 120 mg

Pharmacologic Category: Expectorant/Nasal decongestant

Submitted: Revised draft labeling as follows:

1. Mucinex™ D (Regular Strength)
   Guaifenesin 600 mg/Pseudoephedrine HCl 60 mg
   - 2-, 20-, and 40-count bottle label
   - 20-, and 40-count carton label
   - 2-count tray label

2. Mucinex™ D (Maximum Strength)
   Guaifenesin 1200 mg/Pseudoephedrine HCl 120 mg
   - 2-, 10-, 20-count bottle label
   - 10-, 20-count carton label
   - 2-count tray label

Background:

On October 20, 2003, the Agency sent by fax its recommended labeling revisions of the sponsor's proposed Mucinex D regular and maximum strength SKUs. On October 27, 2003 and October 30, 2003, the sponsor submitted the above-mentioned revised draft labeling. The sponsor mentioned that it had redesigned the carton labeling of the 2-count Mucinex D regular and maximum strength to be a tray which will contain twelve 2-count bottles of the regular and maximum strength product. The sponsor also submitted draft labeling for the tray for both product strengths.

Reviewer comments:

The sponsor incorporated all of the Agency's required and recommended labeling changes for the following:

- 20- and 40-count regular strength carton and immediate container label
- 10- and 20-count maximum strength carton and immediate container label
- 2-count regular and maximum strength immediate container label

The sponsor has also included draft labeling for the proposed 2-count regular and maximum strength tray that includes the phrase "Physician Sample Not To Be Sold" on the tray PDP along with the complete "Drug Facts" labeling and annotated specifications. The labeling of the trays for both strengths is acceptable.

Recommendation:

1. An approval letter can be issued to the sponsor requesting final printed labeling for the following:
   - 20- and 40-count carton and 2-, 20-, and 40-count bottle labels for the Mucinex D Regular Strength product
   - 10- and 20-count carton and 2-, 10-, and 20-count bottle labels for the Mucinex D Maximum Strength product
   - 2-count tray labeling for the Regular and Maximum Strength products.

   These final printed labeling must be identical to the labeling submitted on October 30, 2003.

2. Inform the sponsor that the word "NEW" must be deleted from the PDP six months after introduction into the market place.

Cazemiro R. Martin
IDS: Reg. Review Scientist

Concur: Marina Chang, R.Ph.
Team Leader

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/s/

Cazemiro Martin
11/17/03 09:52:56 AM
INTERDISCIPLINARY

Marina Chang
11/17/03 10:49:05 AM
INTERDISCIPLINARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-585

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155-2645

Attention: D. Jeffrey Keyser
V.P., Development and Regulatory Affairs

Dear Mr. Keyser:

Please refer to your new drug application (NDA) dated January 31, 2003, received January 31, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mucinex ™D (guaifenesin and pseudoephedrine hydrochloride) Extended Release Tablets.

We acknowledge receipt of your submissions dated April 29 and 30, May 21, June 30(2), July 14, August 18(2), September 5 and 19, October 27, and November 4, 2003.

We also acknowledge receipt of your submission dated October 17, 2003. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

1. The following interim dissolution specifications are recommended for guaifenesin and pseudoephedrine HCl from the Mucinex-D regular and maximum strengths:

Maximum Strength

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

Regular Strength

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

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

3. Provide the appropriate information (refer to principles of SUPAC-MR guidance for industry) to link the batches of Mucinex-D produced under new manufacturing conditions to the batch of Mucinex-D used in the pivotal Bioequivalence study.

4. While you have provided preliminary information stating that manufacturing changes have been made that have improved the friability characteristics of Mucinex D tablets, you have not provided release and stability data for batches manufactured with the proposed manufacturing changes.

   a. Provide adequate release and stability data from batches manufactured with the proposed manufacturing improvements. Include all release and stability attributes including hardness, friability, moisture content, and dissolution profile. Provide individual and mean values for each test.

   b. Demonstrate with adequate data and appropriate analysis that the dissolution profiles of the batches manufactured with the proposed manufacturing improvements are comparable to the dissolution profiles of the biobatch for each strength.

   c. Provide a summary of the tablet process parameters (e.g moisture content) used in the manufacture of these batches and those proposed for commercial batches, with the corresponding hardness, friability, and dissolution data.

   d. Tighten the proposed tablet hardness acceptance and release criteria (individual and mean). Additionally, provide dissolution profiles of tablets at the extreme ends of the hardness acceptance criteria to demonstrate that the tablets are comparable at both extremes of the proposed hardness test acceptance criteria.

   e. Comments on dissolution acceptance criteria are withheld pending receipt and evaluation of adequate release and stability data (see 4a and 4b).

   f. For the stability data provided in the original application to be considered as supporting data, provide a comparison of the dissolution profiles from the original

stability batches to batches made with the latest manufacturing changes proposed for commercial batches.

g. Comments regarding the proposed drug product stability commitment and any revisions to the stability protocol are being withheld pending resolution of the issues raised in this letter.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b) for the period from November 4, 2002, the safety cut off date for the NDA submission, to the safety cut off date for the resubmission. You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend this application notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

NDA 21-585
Mucinex ™D (guaifenesin and pseudoephedrine hydrochloride) Extended Release Tablets

We are currently reviewing your application dated January 31, 2003, and we have the following preliminary labeling comments and/or recommendations.

1. Revise the *2-count* Mucinex D *Regular Strength* and *Maximum Strength* products carton labels as follows:

   Left side-panel:

   a. Relocate the phrase "Physician Sample Not To Be Sold". The Agency encourages that this information conspicuously appear on the PDP.

   b. Relocate the web site and the US patent information to either before or after the Drug Fact box or similar enclosure. According to 21 CFR 201.66(d)(7), such information must not appear in or in any way interrupt the information included in the Drug Facts box.

2. Revise the carton **Drug Facts** labeling for the *Regular Strength* and *Maximum Strength* products as follows:

   a. Under the "Uses" section, delete the sub-bulleted indication

   Accordingly, FDA no longer considers this indication appropriate for an OTC nasal decongestant drug product.

   b. Under the "Directions" section, the letter "C" in the word "Children" should appear in lower case letter.

3. Revise the immediate container label for the *Regular Strength* (20- and 40-count) and *Maximum Strength* (10- and 20-count) of the following: If the "Drug Facts" labeling appears on the outside container or wrapper as required in 21 CFR 201.66, this information does not need to also appear on the immediate container label. However, if you choose to use the "Drug Facts" labeling, the content, format, and graphical specifications must be in accordance with 21 CFR 201.66.

4. If the "Drug Facts" title and subsequent information appear on the immediate container labels, the annotated specifications for the Drug Facts graphical features must be submitted for review.

Please submit revised mock-up carton and container labels and the annotated specifications for the Drug Facts graphical features for the immediate container labels so that we can complete our review.

We remind you that we have not yet received a summary, analysis, and interpretation of postmarketing safety reports for guaifenesin and pseudoephedrine received since the safety cut-off date for the NDA submission, as requested in our information request dated June 9, 2003. This information is needed in order to complete our review of your application.

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-5584.

cc:

HFD-570/Lee
HFD-570/Gilbert-McClain
HFD-560/Abraham
HFD-560/Chang
HFD-560/Cazemiro

Drafted: October 9, 2003

Initialed:

Barnes/October 20, 2003
Lee/ October 20, 2003
Gilbert-McClain/ October 20, 2003
Abraham/ October 17, 2003
Chang/ October 17, 2003

Finalized: CCJ/ October 20, 2003

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/s/

Colette Jackson
10/20/03 01:22:05 PM
CSO

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

NDA Labeling Review

NDA # 21-585

Submission Date : 1/31/03, 4/30/03
Review Date : 9/04/03

Applicant: Adams Laboratories, Inc.

Applicant's Representative: D. Jeffrey Keyser
Vice President
Development & Regulatory Affairs

Drug: Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength Extended-Release Bi-layer Tablets

Guaifenesin 600 mg/Pseudoephedrine HCl 60 mg
- and -
Guaifenesin 1200 mg/Pseudoephedrine HCl 120 mg

Pharmacologic Category: Expectorant/Nasal decongestant

Submitted:

1. Mucinex™ D (Regular Strength)
   Guaifenesin 600 mg/Pseudoephedrine HCl 60 mg

   - 2-, 20-, and 40-count bottle label
   - 2-, 20-, and 40-count carton label

2. Mucinex™ D (Maximum Strength)
   Guaifenesin 1200 mg/Pseudoephedrine HCl 120 mg

   - 2-, 10-, 20-count bottle label
   - 2-, 10-, 20-count carton label

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. The sponsor's proposed trade names are Mucinex™ D Regular Strength and Mucinex™ D Maximum Strength.

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 extended release tablet formulation was based on demonstrating that exposures of

guaifenesin were achieved from their product that were equivalent to the OTC nasal decongestant final monograph doses of immediate release guaifenesin. Currently, the Mucinex™ product is the only extended release guaifenesin product that is approved in the United States.

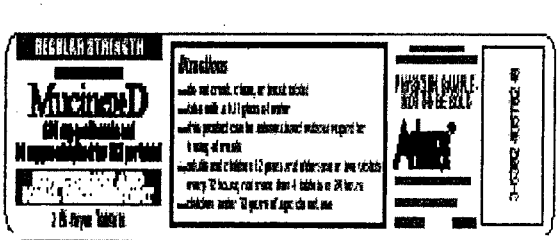
Pseudoephedrine hydrochloride in oral dosage form has been approved by the agency as an OTC single-ingredient extended-release 120 mg and 240 mg tablet dosage strength. Pseudoephedrine sulfate is also approved as an OTC single-ingredient extended release 120 mg tablet.

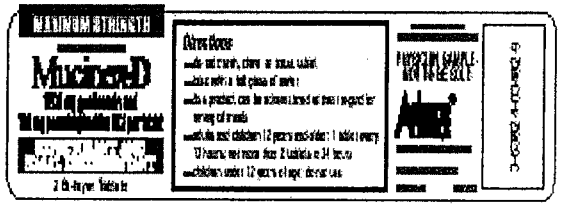
In response to the Agency's Filing Review Letter of April 14, 2003, the sponsor submitted revised Drug Facts labeling for the regular and maximum strength Mucinex D products. The following labeling review is based on the original labeling submitted on January 31, 2003 and the revised Drug Facts labeling submitted on April 14, 2003.

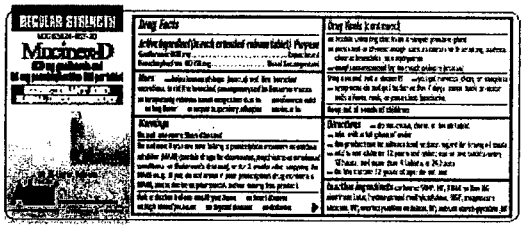
Reviewer Comment:
Reviewer recommended additions are identified by "redlining" (shaded text) and deletions are identified by "strike out."

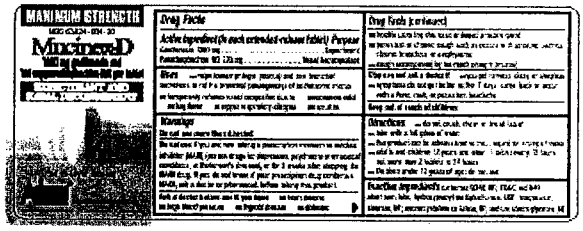
1. Immediate container labeling:

2-, 20-, and 40-count Regular Strength *(Guaifenesin/PSE: 600 mg/60 mg)*; and 2-, 10-, and 20-count Maximum Strength *(Guaifenesin/PSE: 1200 mg/120 mg)*:









A. **Drug Facts labeling:** (Regular Strength 20- and 40-count immediate container label; Maximum Strength 10- and 20-count immediate container label)

[Reviewer comment: If the sponsor intends to include the Drug Facts title in the labeling of the immediate container, the entire Drug Facts information must appear in the same standardized content and format as it appears on the outside carton labeling (i.e., as set forth in 21 CFR 201.66). We will reserve comments on these labels until the sponsor has an opportunity to response to our comment. If the sponsor wants to include "Drug Facts" labeling, the same revisions that apply to the carton label are applicable on this immediate container labeling. In the final revision, the content and format must be must identical to the carton label's "Drug Facts."]

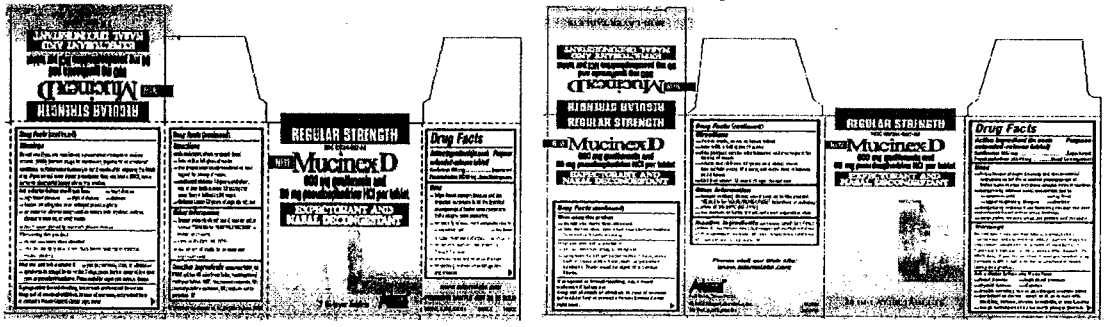
B. Directions section: [2- count Regular and Maximum Strength]

- this product can be administered without regard for timing of meals

[Reviewer comment: The Biopharm reviewer needs to verify the validity of this statement. Please note that this statement appears in the "Directions" section of the Drug Facts labeling for the guaifenesin extended-release tablet product (NDA #21-282).]

2. Carton container labeling:

2-, 20-, and 40-count Regular Strength *(Guaifenesin/PSE: 600 mg/60 mg)*; and 2-, 10-, and 20-count Maximum Strength *(Guaifenesin/PSE: 1200 mg/120 mg)*:



A. PDP:

(i) 2-count Regular *and* Maximum Strength:

Physician Sample Not To Be Sold
[Reviewer comment: The Agency encourages that this statement conspicuously appear on the PDP for clarity.]

(ii) 2-, 20-, and 40-count Regular Strength; and 2-,10-, and 20-count Maximum Strength:

NEW
[Reviewer comment: This promotional flag must be removed six months after introduction into the market place.]

B. Top and Back panels: 2-, 20-, 40-count Regular *and* 2-, 10-, 20-count Maximum Strengths:

NEW
[Reviewer comment: This promotional flag must be removed six months after introduction into the market place.]

C. Left side-panel: 2-count Regular *and* Maximum Strength:

[Reviewer comment: The web site, sample statement, and patent information must be relocated to either before the Drug Facts box begins or after the entire Drug Facts box concludes on the left side-panel, as it is done on the 20- and 40-count regular strength and 10- and 20-count maximum strength carton labeling. According to 21 CFR 201.66(d)(7), graphical images and information must not appear in or in any way interrupt the information included in the Drug Facts box or similar enclosure. However, we encourage the sponsor to include the statement "Physician Sample Not To Be Sold" on the PDP.]

D. Drug Facts information panels: (2-, 20-, and 40-count Regular Strength; and 2-, 10-, and 20-count Maximum Strength)

(i) [interrupting text: 2-count Regular Strength and Maximum Strength]
[Reviewer comment: See previous 2-C comment above.]

(ii) "**Uses**" section:

[Reviewer comment: ——— may be a symptom of a more serious condition. Accordingly, the agency no longer considers this indication appropriate for an OTC nasal decongestant drug product.]

(iii) "**Directions**" section: Regular Strength (2-, 20-, and 40- count) and Maximum Strength (2-, 10-, and 20- count)

a. "■ this product can be administered without regard for timing of meals"
[Reviewer comment: As previously noted, the Biopharm reviewer needs to verify the validity of this statement. Please note that this statement appears in the "Directions" section of the Drug Facts labeling for the guaifenesin extended-release tablet product (NDA #21-282).

b. "■ children under 12 years of age: do not use"
[Reviewer comment: For labeling consistency, the letter "C" in the word "Children" should appear in lower case letter.]

E. [Lot number and Expiration date] [all SKU packages]
[Reviewer comment: Provision for Lot number and expiration data are included.]

3. Annotated labeling:

[Reviewer comment: The annotated "Drug Facts" specifications for the Mucinex-D regular and maximum strength carton labels are acceptable. However, if the sponsor intends to include the title Drug Facts on the immediate container labels, the annotated specifications of the graphical features must be submitted for review.]

Recommendations:

1. Inform the sponsor to revise the *2-count* Mucinex D *Regular Strength* and *Maximum Strength* products carton labels as follows:

   Left side-panel:
   A. Relocate the phrase "Physician Sample Not To Be Sold". The Agency encourages that this information conspicuously appear on the PDP.
   B. Relocate the web site and the US patent information to either before or after the Drug Fact box or similar enclosure. According to 21 CFR 201.66(d)(7), such information must not appear in or in any way interrupt the information included in the Drug Facts box.

2. Inform the sponsor to revise the carton **Drug Facts** labeling for the *Regular Strength* and *Maximum Strength* products as follows:
   A. Under the "Uses" section, delete the subbulleted indication ——— Accordingly, FDA no longer considers this indication appropriate for an OTC nasal decongestant drug product.
   B. Under the "Directions" section, the letter "C" in the word "Children" should appear in lower case letter.

3. Inform the sponsor to revise the immediate container label for the *Regular Strength* (20- and 40-count) and *Maximum Strength* (10- and 20-count) of the following: If the "Drug Facts" labeling appears on the outside container or wrapper as required in 21 CFR 201.66, this information does not need to also appear on the immediate container label. However, if the sponsor chooses to use the

"Drug Facts" labeling, the content, format, and graphical specifications must be in accordance with 21 CFR 201.66.

4. Inform the sponsor to delete the flag "New" wherever it appears on the carton labeling of the various size packages six months after introduction into the market place.

5. Inform the sponsor that if the "Drug Facts" title and subsequent information appear on the immediate container labels, the annotated specifications for the Drug Facts graphical features must be submitted for review.

6. **Biopharm reviewer:** Need to verify the validity of the statement in the Directions section: "This product can be administered without regard for timing of meals". If no data are available to support this statement, it needs to be deleted from the labeling.

7. **Project Management Staff:** After the Biopharm reviewer has verified the validity of the Directions statement, the following revision of the labeling may need to be conveyed to the sponsor, in addition to the above recommended revisions: Under the "Drug Facts" Direction section for all SKUs, delete the bulleted statement "this product can be administered without regard for timing of meals".

Cazemiro R. Martin
IDS: Reg. Review Scientist

Concur: Marina Chang, R.Ph.
Team Leader

Attachment:
Prototype "Drug Facts" labeling for guaifenesin and pseudoephedrine HCl

A. Prototype: Drug Facts Labeling[±]

Drug Facts

Active ingredient (in each extended-release tablet) ***Purpose***

Guaifenesin [insert "600 mg" or "1200 mg", whichever is applicable].....Expectorant

Pseudoephedrine HCl [insert "60 mg" or "120 mg", whichever is applicable].....Nasal decongestant

Uses

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

Warnings

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains a MAOI, ask a doctor or pharmacist before taking this product

Ask a doctor before use if you have

- heart disease
- high blood pressure
- thyroid disease
- diabetes
- trouble urinating due to an enlarged prostate gland
- persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema
- cough accompanied by too much phlegm (mucus)

When using this product • do not use more than directed

Stop use and ask a doctor if

- you get nervous, dizzy, or sleepless
- symptoms do not get better within 7 days, come back or occur with a fever, rash, or persistent headache. These could be signs of a serious illness.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- do not crush, chew, or break tablet
- take with a full glass of water
- ***[Biopharm reviewer will comment on the appropriateness of the following statement: • this product can be administered without regard for timing of meals]***
- adults and children 12 years and older: [*For the 600mg/60mg product, insert* "two tablets every 12 hours; not more than 4 tablets in 24 hours"]

  [*For the 1200mg/120mg product, insert* "one tablet every 12 hours; not more than 2 tablets in 24 hours"]
- children under 12 years of age: do not use

Drug Facts (continued)

Other information

- tamper evident: do not use if seal on bottle printed "SEALED for YOUR PROTECTION" is broken or missing
- store at 20-25°C (68-77°F)
- see bottom of bottle for lot code and expiration date

Inactive ingredients carbomer 934P, NF; FD&C yellow #6 aluminum lake; hydroxypropyl methylcellulose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF

± The sponsor should follow this Drug Facts label **in content only**. The font sizes for title, headings, subheadings, condensed text, and other graphic features must be in accordance as set forth in 21 CFR 201.66.

[Lot number and Expiration Date]

cc: NDA 21-585
HFD-560:CGanley/CRosebraugh/LHu
HFD-560:MChang/CMartin/EAbraham
HFD-570: LJafari (PM)

R/D: CMartin: 7/31/03
rev: MChang: 8/7/03; CMartin: 8/11/03
(rev: based on sponsor's 4/30/03 correspondence forwarded to HFD-560 on 9/3/03)
rev: MChang/CMartin: 9/4/03
dfs: 9/4/03

(CM: word/21585mucinDrev5.doc)

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/s/

Cazemiro Martin
9/4/03 11:12:27 AM
INTERDISCIPLINARY

Marina Chang
9/4/03 12:28:43 PM
INTERDISCIPLINARY

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June, 2003

To: Jeff Keyser	**From:** Colette Jackson
Company: Adams Laboratories	Division of Pulmonary and Allergy Drug Products
Fax number: 817-786-1204	**Fax number:** 301-827-5586
Phone number: 817-545-3629	**Phone number:** 301-827-5584
Subject: NDA 21-585	
Total no. of pages including cover: 3	

Comments:

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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NDA 21-585
Mucinex ™D (guaifenesin and pseudoephedrine hydrochloride) Extended Release Tablets

Upon review of your submissions dated January 31, and May 21, 2003, we have the following comments:

1. In your submission dated January 31, 2003, you provided line listings of spontaneous adverse event drug reports associated with guaifenesin and pseudoephedrine [Volume 1.46, pages 199-274]. However, you did not provide a summary, analysis, or interpretation of these data. Provide a summary of these data for guaifenesin and pseudoephedrine by the type of each adverse event reported. Provide an analysis and conclusions regarding the safety of guaifenesin and pseudoephedrine based on your summary.

2. We noted in your May 21, 2003, submission that there have been no clinical studies initiated since the original submission. To complete the required 4-month safety update, submit the following information:

    a. A review of the medical literature of any new safety information relevant to guaifenesin and pseudoephedrine since the safety cut-off date for the NDA submission

    b. A summary, analysis, and interpretation of postmarketing safety reports for guaifenesin and pseudoephedrine received since the safety cut-off date for the NDA submission

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-5584.

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/s/

Colette Jackson
6/9/03 05:34:40 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-585

DISCIPLINE REVIEW LETTER

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155-2645

Attention: D. Jeffrey Keyser
V.P., Development and Regulatory Affairs

Dear Mr. Keyser:

Please refer to your January 31, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mucinex ™D (guaifenesin and pseudoephedrine hydrochloride) Extended Release Tablets.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Provide a revised specification for guaifenesin that lists the impurities by name. A footnote listing the names will be acceptable. Similarly, provide a revised specification for pseudoephedrine hydrochloride that lists the impurities by name. A footnote listing the names will be acceptable.

2. On the specification sheet for guaifenesin, the acceptance criteria you propose for the _____, that of "Meets USP requirements," is not correct as testing is not done. Provide a revised specification sheet for guaifenesin that indicates that no organic solvents are used in the synthesis of guaifenesin.

3. Provide a revised specification sheet for pseudoephedrine hydrochloride that lists the organic solvents used in the synthesis of pseudoephedrine HCl with appropriate acceptance criteria. The latter should be based on actual data. This information should match the manufacturer's specifications.

4. Since no reprocessing of the drug product is being performed, the master batch record should clearly indicate this. Modify and submit the master batch record to indicate that no reprocessing operations will be performed.

5. The information you provide to support the use of the ___ dye, and the ___ dye, is not adequate. For each dye, provide the composition of the dye, a brief manufacturing description, and a certificate of analysis including the results for heavy metals. A reference to a DMF with a Letter of Authorization will be acceptable.

6. The limit for blend assay for in-process specification of ___ for the Immediate Release Blend, and the Modified Blend, both Maximum and Regular Strength, is too

broad. Tighten the acceptance criterion to ensure better batch to batch consistency of the drug product.

7 We have reviewed the Friability Developmental Report (volume 1.4) that discusses changes made to the tableting process to address friability failures. As stated to you in the 74-day letter of April 14, 2003, the approval of the maximum strength tablet will require satisfactory release and stability data. At this time, no data have yet been received. We request that you provide adequate stability data (accelerated and long-term conditions) to establish the stability of the tablets. The expiry that will be granted will be determined by available stability data.

8. The proposed acceptance criteria for hardness, — SCU for maximum strength tablets and — SCU for regular strength tablets, as shown on the specification sheet for each strength, are not justified. Since you have claimed in your Friability Development Report (Volume 1.4) that hardness values of — SCU for maximum strength tablets and — SCU for regular strength tablets rectify high friability concerns, please modify the acceptance criteria for Hardness to reflect the results from the Friability Development Report.

9. The dissolution acceptance criteria proposed in the Specification for the Maximum and the Regular Strength Tablets do not agree with the release data presented in the dissolution discussion. Modify the dissolution acceptance criteria to reflect values obtained at release and during stability for the primary stability batches.

10. Additional comments regarding the proposed drug product stability commitment and any revisions are being withheld pending resolution of the issues raised in this letter.

11. The following are preliminary comments regarding labeling:

    a. The box on the label containing either the words "Regular Strength" or "Maximum Strength" should be removed.

    b. The established names should be increased in size and prominence.

    c. In accordance with 21 CFR for the use of yellow dye #6 in pharmaceutical products, the label for regular strength tablets should state the product contains Yellow Dye #6.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Colette Jackson, Project Manager, at 301-827-5584.

Sincerely,

{See appended electronic signature page}

Guirag Poochikian, Ph.D.
Chemistry Team Leader,
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Guiragos Poochikian
6/9/03 04:37:25 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-585

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155-2645

Attention: D. Jeffrey Keyser
V.P., Development and Regulatory Affairs

Dear Mr. Keyser

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Mucinex ™D (guaifenesin and pseudoephedrine hydrochloride) Extended Release Tablets

Review Priority Classification: Standard (S)

Date of Application: January 31, 2003

Date of Receipt: January 31, 2003

Our Reference Number: NDA 21-585

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 1, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 30, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Colette Jackson
4/14/03 12:02:12 PM
Signed for S. Barnes

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: April 7, 2003

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

FROM: Colette Jackson, Project Manager, HFD-570

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 21-585
Mucinex D (guaifenesin and pseudoephedrine HCl) Extended Release Tablets

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
2002-01A	Dennis N. Morrison, DO BIO-KINETIC Clinical Applications, Inc. 1816 West Mount Vernon Springfield, MO 65802	

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **October 1, 2003**. We intend to issue an action letter on this application by **November 14, 2003**.

Should you require any additional information, please contact Colette Jackson, at 301-827-5584.

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/s/

Colette Jackson
4/7/03 11:13:06 AM

NDA FILEABILITY CHECKLIST

NDA Number: 21-585 **Applicant:** Adams Labs **Stamp Date:** 31-Jan-2003

Drug Name: Mucinex D (guaifenesin and pseudoephedrine HCl)

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes_X_

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		The Table of Contents shows that volume 1.4 is the methods validation package. The methods validation volume submitted is numbered as volume 1.1, volume 1 of 1.
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?			No, however, sites have been inspected previously for other NDAs.
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?		X	[redacted]; real-time/[redacted] accelerated stability data have been provided for each strength Maximum strength tablets fail Friability Acceptance Criterion.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?		X	
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	Not applicable for tablets

Review Chemist: J. Salemme, Ph. D. Date: 26-Mar-2003
Team Leader: G. Poochikian, Ph.D. Date: 26-Mar-2003

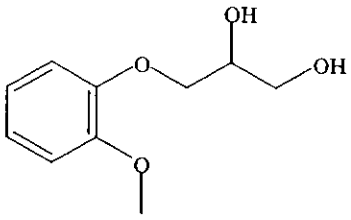
Notes

DMFs for this NDA:

DMF Number	Item
	Drug Substance Mfr: Guaifenesin
	Drug Substance Mfr: Pseudoephedrine HCl
	Drug Substance Alternate Mfr: Pseudoephedrine HCl

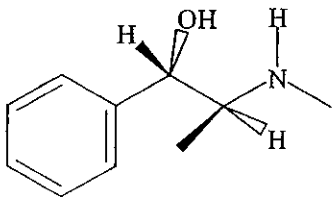
DRUG SUBSTANCES

Guaifenesin USP



guaifenesin

Pseudoephedrine HCl USP (PSE)



HCl

Manufacturer/tester/packager for guaifenesin:

Manufacturer/tester/packager for PSE:

Comment: The DMF has been recently reviewed and found to be adequate.

Alternate manufacturer /tester/packager for PSE: may be used for future supplies

Comment: The DMF was reviewed in 2000 and found to be acceptable. Recently, an October 2002 memorandum to the DMF from Art Shaw, of ONDC, states the DMF holder has notified the Agency that the manufacturing site of

DRUG PRODUCT

Dosage form: Extended Release Tablet

Two Strengths: 1200 mg guaifenesin/ 120 mg PSE (maximum strength)
600 mg guaifenesin/ 60 mg PSE (regular strength)

Description:
A bi-layer tablet with a white immediate release layer and a colored modified release layer.

Components and composition

Table: Batch Formula for Mucinex D Maximum Strength and Regular Strength Tablets

Component	1200 mg Gua / 120 mg PSE Amount (mg/tablet)	600 mg Gua / 60 mg PSE Amount (mg/tablet)

Guaifenesin DC (direct compression) [redacted]	[redacted]	[redacted]
Hydroxypropyl methylcellulose		
Pseudoephedrine HCl		
Microcrystalline cellulose		
Sodium starch glycolate		
Carbomer 934P		
Magnesium stearate		
FD&C Red #40 Aluminum Lake (14-16%)		
FD&C Yellow #6 Aluminum Lake (15-18%)	None	
Water	[redacted]	
TOTAL WEIGHT	1587.0	794.1

Manufacturing Process

Two granulations are used: one is an immediate release (IR) and one is a modified release MR

- The same IR granulation is used for either strength tablet. This is the IR formulation is that same as that used in 21-282.
- The same MR granulation is used for either strength with the exception that a different dye is used for each strength. *The same components, except for the colorants, are used in the approved product, Mucinex. The amounts of hydroxypropylmethyl cellulose, carbomer 934P, magnesium stearate, and colorants are greater in this formulation.*

Manufacturers of Drug Product

Manufacturer/tester/packager

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155

Additional Packagers

[redacted]

Additional Stability Storage Site

[redacted]

SPECIFICATIONS

Description; identification of guanifenesin by HPLC retention time and by color; identification of PSE by assay retention time and by IR: average tablet weight; average tablet thickness; average tablet hardness; friability; loss on drying; dose uniformity; assay for each drug substance; degradation products unspecified, and total degradation; and dissolution

Dissolution

Container/Closures:

Materials are described. DMF references and LOAs are provided.

Stability Information

Three pilot batches of Mucinex D maximum strength and three pilot batches of Mucinex D regular strength have been manufactured and placed on stability as shown in table below:

Tablet Strength Gua / PSE	Container/Closure in Stability	Batch ID/ Batch Size	Mfg Date
1200 mg/ 120 mg		M65	20-Dec-2001
1200 mg/ 120 mg		M68	02-Jan-2002
1200 mg/ 120 mg		M71	02-Jan-2002
600 mg/ 60 mg		A12	29-Jan-2002
600 mg/ 60 mg		B13	29-Jan-2002
600 mg/ 60 mg		B1	30-Jan-2002

Stability conditions:

The sponsor requests a month expiry based on The sponsor was informed during pre-NDA that they could submit the month data in April 2003 and the month data in October 2003 for consideration.

Comments:

The primary stability data provided for the 1200 mg/120 mg strength show that the three batches often failed to meet the friability acceptance criterion at accelerated and real-time conditions. The data for the 600mg/60 mg strength showed that the friability acceptance criterion was met at all but one time interval at real-time conditions of the stability program to months.

For example:
1200/120 in 75-mL bottles:
Batch 65: at

Batch 68:
Batch 71:

The sponsor provides a study report that describes how parameters for setup and tablet hardness have been developed that improve the friability.

Comments to Convey to Sponsor for 74-Day Comments:

The primary stability data you have provided in the NDA, particularly for Maximum Strength Mucinex D tablets, show the tablets often failed to meet the Friability Test acceptance criterion of NMT 1% during stability. In addition, the friability values show significant variability.

In the NDA you state you have developed process controls to ensure future batches of Maximum Strength tablets will pass the Friability Test acceptance criterion. To demonstrate this, please provide available release and stability data for batches of Maximum Strength Mucinex D tablets manufactured with the in-process improvements. Approval of the Maximum Strength tablets will require adequate stability data demonstrating that the drug product meets the friability test acceptance criterion.

In addition, please explain the reason for the high variability in the friability values observed in the NDA primary stability batches and discuss if the high variability has been eliminated with the in-process improvements.

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/s/

Jean Salemme
4/1/03 04:08:16 PM
CHEMIST

Guiragos Poochikian
4/1/03 05:27:16 PM
CHEMIST

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 3, 2004

To: Jeff Keyser	**From:** Colette Jackson
Company: Adams Laboratories	Division of Pulmonary and Allergy Drug Products
Fax number: 817-786-1204	**Fax number:** 301-827-1271
Phone number: 817-545-3629	**Phone number:** 301-827-9388

Subject: NDA 21-585

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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NDA 21-585
Mucinex ™D (guaifenesin and pseudoephedrine hydrochloride) Extended Release Tablets

Upon review of your submission dated December 19, 2003, we have the following request:

Provide the [redacted]-month 25°C stability data for the following batches:

Maximum Strength:	PB02-M31
	PB02-M32
	PB02-M33
Regular Strength:	PB02-M28
	PB02-M29
	PB02-M30

If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-827-9388.

cc:

HFD-570/Lostritto

Drafted: February 25, 2004

Initialed:

Barnes/February 27, 2004
Lostritto/February 27, 2004

Finalized: CCJ/March 3, 2004

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/s/

Colette Jackson
3/3/04 12:37:28 PM
CSO

18. USER FEE COVER SHEET

A copy of Form FDA 3397 follows this cover page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the rse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155

2. TELEPHONE NUMBER *(Include Area Code)*

(817) 786-1243

3. PRODUCT NAME

Mucinex D Bi-Layer Tabletas

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NO21585

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4467

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
D. Jeffrey Keyser	Vice President, Development and Regulatory Affairs	January 31, 2003

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

19. FINANCIAL INFORMATION

In accordance with 21 CFR, Part 54, Financial disclosure was collected for principal and subinvestigators listed on the signed FDA form 1572 for all studies conducted in support of this New Drug Application.

List of investigators:
Dennis N. Morrison, D.O. – Principal Investigator

Subinvestigators:

Form FDA 3454 follows this cover page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

— (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Dennis N. Morrison, D.O.	

— (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

— (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
D. JEFFREY KEYSER	Vice President, Development and Regulatory Affairs
FIRM / ORGANIZATION: Adams Laboratories, Inc., Fort Worth, Texas 76155	
SIGNATURE: DJ Keyser	DATE: 1/31/03

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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4 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative-_____