CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-282

ADMINISTRATIVE DOCUMENTS

FORM FDA 356h Attachments

13. Patent information on any patent that claims the drug

In the opinion and to the best knowledge of Adams Laboratories, inc., there are no patents 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.

14. A patent certification with respect to any patents that claim the drug

Adams Laboratories, inc. currently has a patent pending on guaifenesin ER 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.

15. Establishment description

Not applicable for this application.

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) or 306(b) of the Federal Food, Drug and Cosmetic Act (21 USC 335a and 335b) in connection with this New Drug Application.

17. Field copy certification

Adams Laboratories, Inc. Certifies that a full copy of the Chemistry, Manufacturing and Controls Section (ITEM 4.0) has been forwarded to the FDA Dallas District Office in accordance with 21 CFR 314.50 (d) (1) (v) and 314.50 (l) (3)

18. User Fee Cover Sheet

See page ___.

19. Categorical exclusion

See page ___.

Certification: Financial interests and arrangements of clinical investigators

See page ___ for FORM FDA 3454.

EXCLUSIVITY SUMMARY for NDA # 21-282 SUPPL # _____
Trade Name Mucinex Generic Name guaifenesin extended release 600 mg tablets_____
Applicant Name Adams Laboratories, Inc. HFD- 570_____
Approval Date July 12, 2002_____

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 questions 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 applicant referred to the monograph ingredient.

      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:

d) Did the applicant request exclusivity?

YES /___/ NO /X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /X___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this 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 /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the

investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any 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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

   (a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

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

_____

_____

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: _____

Ladan Jafari 7.12.02
Signature of Preparer Date
Title: Regulatory Project Manager

Signature of Office or Division Director

7/12/02
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM/L
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

9 pages redacted from this section of the approval package consisted of draft labeling

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-282 Supplement Type (e.g. SE5): _____ Supplement Number:_____

Stamp Date: June 29, 2002 Action Date: July 12, 2002

HFD 570 Trade and generic names/dosage form: Mucinex (guaifenesin) Extended Release 600 mg tablets)

Applicant: Adams Laboratories, Inc. Therapeutic Class: Respiratory

Indication(s) previously approved: Helps loosen phelegm/thin bronchial secretions in patients with chronic bronchitis.

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

Number of indications for this application(s): 1

Indication #1: _____

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

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: X Partial Waiver __Deferred X 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 0 kg_____ mo._____ yr. x Tanner Stage_____
Max 12 kg_____ mo._____ yr. x 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**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other: Age appropriate moiety already exists as immediate release syrup and is legally marketed under the monograph.**

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.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max_ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ **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**
- ☐ **Adult studies ready for approval**
- ☐ **X Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _12___ kg____ mo.____ yr._X___ Tanner Stage____
Max_adult kg____ mo.____ yr.____ Tanner Stage____

Comments:

there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

7.12.02

Regulatory Project Manager

EXCLUSIVITY SUMMARY for NDA # 21-282 SUPPL # _____
Trade Name Mucinex Generic Name guaifenesin extended release 600 mg tablets_____
Applicant Name Adams Laboratories, Inc. HFD- 570_____
Approval Date July 12, 2002_____

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 questions 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 applicant referred to the monograph ingredient.

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:

d) Did the applicant request exclusivity?

YES /___/ NO /X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /X___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this

particular form of the active moiety, e.g., this 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 /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any 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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

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

_____

_____

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: _____

Ladan Jafari
Signature of Preparer Date
Title: Regulatory Project Manager

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM/L
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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
7/12/02 03:45:15 PM

DIVISION DIRECTOR'S MEMORANDUM

DATE: July 12, 2002

TO: NDA 21-282

FROM: Badrul A. Chowdhury, MD, PhD
Acting Director, Division of Pulmonary and Allergy Drug Products

PRODUCT: Mucinex (guaifenesin) Extended-Release Tablets 600mg

APPLICANT: Adams Laboratories, Inc., Fort Worth, Texas

Introduction

Adam Laboratories originally submitted NDA 21-282 on June 29, 2000, for an extended release tablet formulation of guaifenesin 600 mg An approvable action was taken on that application because of various deficiencies, including major chemistry and manufacturing deficiencies. The deficiencies were communicated to the applicant in a letter dated April 26, 2001. The current action is in response to the applicant's second complete response submitted on January 11, 2002. The manufacturing process for the 600 mg product has been revised and validated Other outstanding chemistry deficiencies have largely been resolved. The open application is therefore for the 600 mg dosage strength. The proposed use is as an expectorant.

The regulatory pathway for this application is a 505(b)(2) with a PK program to show equivalent exposure from this product compared to monograph doses of immediate release guaifenesin. The applicant for this product. However, a decision was taken during earlier review cycles that the product should be labeled for over-the-counter marketing because the program supporting this application is based on demonstration of equivalent exposure to monograph doses without any clinical data to support the the sponsor.

Chemistry and Manufacturing

The 600 mg tablets are bilayer, comprised of a smaller white immediate release layer, and a larger blue extended release layer. The tablets are uncoated and rather large, with a diameter of The proposed lower age bound of 12 years for the product is appropriate, because of potential chocking problem for younger children. The proposed packaging configurations include bottles with counts of 2, 20, 40, 100, and 500 tablets.

Clinical Pharmacology and Biopharmaceutics
The applicant submitted results from five studies with the original NDA in support of the application. Two of the studies were considered directly relevant to the application because they were conducted with the to-be-marketed formulation. The studies were a single dose, dose proportionality, and food interaction study (Protocol #99-06), and a multiple-dose bioavailability and bioequivalency study (Protocol #99-05). Office of Clinical Pharmacology and Biopharmacuetics (OCBP) reviewer Dr. Choi reviewed these studies in detail and concluded that the 600 mg guaifenesin extended release tablet meets the AUC criteria for bioequvalence with the reference guaifenesin immediate release (Tussi-Organidin) tablet. The OCBP team has recommended approval of the product and I concur with that recommendation.

Clinical and Statistical
There are no outstanding clinical issues. The , 600 mg tablets are proposed to be administered twice daily. These doses are within the limits of the OTC monograph recommended doses, which has established that guaifenesin is safe and effective as an expectorant in doses of 200 mg to 400 mg every four hours, upto 2400 mg per day. There were also no safety issues identified in review of the literature, and in the PK studies conducted by the applicant, although the PK studies were clearly limited for that purpose.

Pharmacology and Toxicology
There are no outstanding preclinical issues. Dr. Sun in the preclinical review refers to the OTC monographs for immediate release formulation of guaifenesin (CFR 341.18 and 341.78) and has concluded that the proposed drug product is safe and I concur with that conclusion.

Establishment Evaluation
The drug substance manufacturer was inspected on November 21, 2000, and the finished dosage form manufacturer (Adams Laboratories, Fort Worth, TX) was inspected on February 26, 2001. Acceptable decisions were received for both the sites.

Labeling
The applicant has submitted draft carton and container labels, and product label in accordance with the monograph for expectorant drug products (CFR 341.78) and with the over-the-counter drug products (CFR 201.66) in the "Drug Facts" format. The contents of

the label have been reviewed by the various disciplines of this Division and also by the Division of Over-the-Counter drug products, and are found to be acceptable. I concur with the decision.

Product Name
The Office of Drug Safety (ODS) was consulted on the proprietary name Mucinex. The Division of Medication Errors and Technical Support has not identified any additional proprietary or established name that have the potential for confusion with Mucinex and therefore has no objection to the use of Mucinex as the proprietary name.

Pediatric Consideration
The proposed lower age limit for this product is 12 years. This product is not suitable for use in children below 12 years of age because of potential chocking risk. Pediatric study requirement below 12 years of age should be waived because other age appropriate formulations of the moiety already exists as immediate release syrups and are marketed under the monograph.

Recommendation
The applicant has submitted adequate rationale and data to support the approval of Mucinex (guaifenesin) Extended-Release Tablets 600mg for OTC use as an expectorant in patients 12 years of age and older. The remaining outstanding chemistry and manufacturing issues has been resolved. The applicant has agreed to Phase 4 commitments listed in the Chemistry discipline review and briefly mentioned above. The application is recommended an APPROVAL action.

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/s/

Badrul Chowdhury
7/12/02 03:36:27 PM
MEDICAL OFFICER

Division Director's Memorandum

Date: Thursday, April 26, 2001
NDA: 21-282
Sponsor: Adams Labs
Proprietary Name: Guaifenesin ER (guaifenesin extended-release tablets)

Introduction: This is a new NDA submitted for an extended-release formulation of guaifenesin in [redacted] 600 [redacted] mg. The regulatory pathway is as a 505(b)(2) with a PK program intended to show equivalent exposure from these products compared to monograph doses of IR guaifenesin. Note that although the sponsor [redacted] (to make this product competitive with a number of products marketed outside the regulatory processes without any NDAs), the demonstration of equivalent exposures to monograph doses without any clinical data to support the unapproved indications proposed by the sponsor for this molecule should result in monograph labeling and OTC marketing, not [redacted]. Due to this package being largely CMC and Biopharm. data, this memo will not provide any details of toxicology and few comments on clinical/statistical.

Biopharmaceutics: The OCPB reviewer and office recommends that this submission does support approval, since the main difference in the PK data between these ER formulations and the IR formulations given at their appropriate dosing intervals was in the C_{min} parameter (with the NDA products being lower), but that this level would still be considered efficacious given other data upon which the FDA based its initial finding of efficacy for monograph purposes. Additionally, the two dosage strengths are dose proportional, though the in vitro dissolution testing results do not suggest they should be. This is inferred to be a problem with the test conditions/methods.

Clinical / Stastical: No particular issues were identified, the safety experience in the PK studies, though clearly limited, showed not important signals of concern. Again, the clinical reviewer asserts, and I agree, that given the pathway under which this drug was developed, the labeling and marketing should be based on the monograph.

CMC: There are numerous deficiencies that need to be addressed prior to the approval of these products (please see the CMC review for details). These include inadequate acceptance criteria, unidentified impurities at levels requiring identification, unsuitable dissolution criteria, as well as others. These are enumerated in the action letter.

Conclusions: This application will be an "approvable," seeking the request CMC data, revisions and appropriate labeling.

LST

Robert J. Meyer, MD
Director,
Division of Pulmonary and Allergy Drug Products.

Division of Over-the-Counter Drug Products
Addendum Labeling Review

NDA #: 21-282

Original Submission Date: 06/29/00
Labeling Amendment Dates: 01/07/02, 03/04/02, 06/28/02 and 07/03/02
Review Date: 07/08/02

APPLICANT: Adams Laboratories, Inc

APPLICANT'S REPRESENTATIVE: D. Jeffrey Keyser
Vice President
Development & Regulatory Affairs

DRUG: Mucinex
(Guaifenesin Extended-Release Bi-layer Tablets, 600 mg)

PHARMACOLOGIC CATEGORY: Expectorant

SUBMITTED:
1. Draft carton and container labels for the 2-, 20-, and 40-count package sizes.
2. Draft container labels for the 100- and 500-count package sizes.

BACKGROUND:

On March 4, 2002 the sponsor submitted on paper draft carton and container labels for the 2-count and immediate container labels for the 100- and 500-count package sizes. These labels were reviewed and found acceptable on March 21, 2002.

On June 28, 2002 (an internal meeting) it was reported that on May 8, 2002 the sponsor had submitted on paper draft carton and container labels for the 20- and 40-count **Mucinex Extended-Release Tablets, 600 mg**. Also, in the same submission, the sponsor

On June 28, 2002, in an electronic submission, the sponsor submitted carton and container labels for **Mucinex Extended-Release Tablets, 600 mg** (i.e., 2-, 20-, 40-, 100- and 500- count package sizes).

On July 3, 2002, via telephone communication, the Agency questioned the sponsor regarding the child-resistant packaging requirement as stated in 16 CFR 1700.14 for **Mucinex Extended-Release Tablets, 600 mg**. The sponsor responded that all marketing sizes are packaged in a non-child-resistant container. As stated in it January 11, 2002 submission, it is exempted from the requirements of the Consumer Product Safety

Commission (CPSC) for child-resistant packaging for certain over-the-counter drug products. It confirmed that all container-closure proposed for marketing, are in compliance with 16 CFR part 1700. The Division of Pulmonary Drug Products (HFD-570) also confirmed that the CPSC requirement did not apply to this NDA because it was submitted prior to the effective date (i.e., January 29, 2002).

REVIEWER'S COMMENTS

The 20- and 40-count carton and container labels for **Mucinex Extended-Release Tablets, 600 mg,** are identical to the labels submitted on March 4, 2002 and they are acceptable.

The sponsor resubmitted 2-, 100- and 500-count labels for **Mucinex Extended-Release Tablets, 600 mg.** These labels are identical to the labels submitted on March 4, 2002 and were found acceptable on March 21, 2002.

REVIEWER'S RECOMMENDATION:

1. An approval letter can be sent to the sponsor requesting final printed 2-, 20- and 40-count carton and container labels, and 100- and 500-count container labels for **Mucinex Extended-Release Tablets, 600 mg.** These final printed labels must be identical to the labels submitted on June 28, 2002.

2. Inform the sponsor that for the 2-, 20- and 40-count **Mucinex Extended-Release Tablets, 600 mg** carton labels, the word "NEW" must be deleted from the PDP six months after introduction into the market place.

IDS: Cazemiro R. Martin

Team Leader: Marina Y. Chang, R. Ph.

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/s/

Cazemiro Martin
7/8/02 10:23:04 AM
INTERDISCIPLINARY

Marina Chang
7/8/02 10:32:59 AM
INTERDISCIPLINARY

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NDA Labeling Review: Addendum

NDA # 21-282

Addendum Date : 3/05/02
Review Date : 3/21/02

Applicant: Adams Laboratories, Inc.

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

Drug: Mucinex
Guaifenesin Extended-Release Bi-layer Tablets
600 mg

Pharmacologic Category: Expectorant

Submitted:

Revised draft labeling as follows:

600 mg:

- 500-count bottle labeling (market package)
- 100-count bottle labeling (market package)
- 2-count bottle label (sample package)
- 2-count individual folding carton (sample package)

Background:

In response to a telephone call on February 27, 2002, between the Division of OTC Drug Products and Adams Laboratories, Inc., the sponsor submitted the above-mentioned revised draft labeling. During the telephone call, the Division requested draft labeling for the sponsor's 500-count product and additional information concerning the location of the lot numbers and expiration dates on the 2-, 100-, and 500-count bottle products. The Division recommended that the sponsor increase the type size of the potency declaration (i.e., "600 mg" on the PDP for the 2-, 100-, and 500-count products. The Division also reminded the sponsor that, as stated in 21 CFR 201.66(d)(3), the type style for all Drug Facts information shall be any single, clear, easy-to-read type style, with no more than 39 characters per inch.

Reviewer Comments:

In addition to the revised draft labeling submitted, the sponsor stated the following:

1. The lot number and expiration date will be printed on the bottom of each 2-, 100-, and 500-count bottle.
2. The Drug Facts labeling of all three-size products has been revised to include an additional bulleted statement under the heading "Other information" that states: "see bottom of bottle for lot code and expiration date".

3. In the Drug Facts information, all text and headings are in Helvetica font style; the size and style of the text are the same throughout the labeling; no letters in the labeling are touching; and there are no more than 39 characters per inch of text.
4. The "600 mg" [redacted] potency declaration appearing in the respective PDP have been increased to at least one-half the type size of the letter "M" of the product name "Mucinex".

The sponsor has incorporated all the labeling revisions as required and recommended by the Agency. The labeling revisions are acceptable.

Recommendations:

An approval letter can be sent to the sponsor requesting final printed labeling identical to the labeling submitted on March 5, 2002.

IDS: Cazemiro R. Martin

Team Leader: Marina Chang

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/s/

Cazemiro Martin
3/25/02 06:56:28 AM
INTERDISCIPLINARY

Marina Chang
3/25/02 01:27:47 PM
INTERDISCIPLINARY

NDA Labeling Review: Addendum

NDA # 21-282

Amendment Date : 1/07/02
Review Date : 1/16/02

Applicant: Adams Laboratories, Inc.

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

Drug: Mucinex
Guaifenesin Extended-Release Bi-layer Tablets
600 mg

Pharmacologic Category: Expectorant

Submitted:

Revised draft labeling as follows:

600 mg:

- 100-count bottle labeling (market package)
- 2-count bottle label (sample package)
- 2-count individual folding carton (sample package)

In addition, the sponsor submitted annotated format specifications for all labeling.

Background:

In response to the approvable letter dated December 21, 2001 for OTC Guaifenesin Extended-Release product (NDA 21-282), the sponsor submitted revised labeling on January 7, 2002, that reflects the Agency's required and recommended labeling changes.

Reviewer Comment:

The sponsor has incorporated all the labeling revisions as required and recommended by the Agency in the approvable letter dated 12/21/01. The labeling is acceptable.

Recommendations:

An approval letter can be sent to the sponsor requesting final printed labeling identical to the labeling submitted on 1/7/02.

IDS: Cazemiro R. Martin

Team Leader: Marina Chang

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/s/

Cazemiro Martin
1/17/02 10:44:20 AM
INTERDISCIPLINARY

Marina Chang
1/17/02 11:08:13 AM
INTERDISCIPLINARY

NDA Labeling Review

NDA # 21-282

Submission Date : 6/29/00
Amendment Dates : 8/29/01
Review Date : 9/13/01

Applicant: Adams Laboratories, Inc.

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

Drug: Mucinex
Guaifenesin Extended-Release Bi-layer Tablets
600 mg [redacted]

Pharmacologic Category: Expectorant

Submitted:

600 mg:

- 100-count bottle labeling (market package)
- 2-count bottle label (sample package)
- 2-count individual folding carton (sample package)

[redacted]

Reviewer Comment:

Currently, guaifenesin is available over-the-counter (OTC) as an immediate release ingredient in single- and combination-ingredient cold/cough drug products. There are no approved guaifenesin prescription drug products. The Sponsor originally [redacted] products. An approvable letter was issued on 4/26/01 informing the sponsor that these products are eligible to be marketed as OTC drug products because bioequivalence was based on the comparison to the referenced OTC monograph product. After a meeting with the Agency on 8/26/01, the sponsor is now seeking approval of single-ingredient guaifenesin extended-release, OTC drug products.

On September 7, 2001, the sponsor submitted Drug Facts labeling annotated for type size and font style for the quaifenesin ER 600 mg [redacted] tablets. The specifications provided comply with 21 CFR 201.66.

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

A. Immediate container: 600 [redacted] mg (100-count; "marketed" packages)

NDC #
[600 mg [redacted]

MUCINEX™
[Reviewer comment: This trade name has been referred to the FDA Medication Error Prevention Office of Post-Marketing Drug Risk Assessment for evaluation. No comment is provided at this time until the evaluation of the trade name is completed.]

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/s/

Cazemiro Martin
1/17/02 10:44:20 AM
INTERDISCIPLINARY

Marina Chang
1/17/02 11:08:13 AM
INTERDISCIPLINARY

NDA Labeling Review

NDA # 21-282

Submission Date : 6/29/00
Amendment Dates : 8/29/01
Review Date : 9/13/01

Applicant: Adams Laboratories, Inc.

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

Drug: Mucinex
Guaifenesin Extended-Release Bi-layer Tablets
600 mg ———

Pharmacologic Category: Expectorant

Submitted:

600 mg:

- 100-count bottle labeling (market package)
- 2-count bottle label (sample package)
- 2-count individual folding carton (sample package)

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Reviewer Comment:

Currently, guaifenesin is available over-the-counter (OTC) as an immediate release ingredient in single- and combination-ingredient cold/cough drug products. There are no approved guaifenesin prescription drug products. The Sponsor originally ——— products. An approvable letter was issued on 4/26/01 informing the sponsor that these products are eligible to be marketed as OTC drug products because bioequivalence was based on the comparison to the referenced OTC monograph product. After a meeting with the Agency on 8/26/01, the sponsor is now seeking approval of single-ingredient guaifenesin extended-release, OTC drug products.

On September 7, 2001, the sponsor submitted Drug Facts labeling annotated for type size and font style for the quaifenesin ER 600 mg ——— tablets. The specifications provided comply with 21 CFR 201.66.

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

A. Immediate container: 600 ——— mg (100-count; "marketed" packages)

NDC #
[600 mg or ———

MUCINEX™
[Reviewer comment: This trade name has been referred to the FDA Medication Error Prevention Office of Post-Marketing Drug Risk Assessment for evaluation. No comment is provided at this time until the evaluation of the trade name is completed.]

3 pages redacted from this section of the approval package consisted of draft labeling

[redacted]

Recommendations:

1. Attached is the agency's recommended prototype labeling based on the OTC labeling format and content requirements published in the Federal Register on March 17, 1999 (64 FR 13254).

2. Request that the reviewing chemist verify that the container closure system for the 100- and 2-count packages comply with the Consumer Product Safety Commission's regulation on Child-Resistant Packaging for Certain OTC Drug Products (66 FR 40111).

3. Request that the clinical and bioequivalence reviewers determine the validity of the promotional statement [redacted] that appears on the PDP. However, it is noted that the Division of OTC Drug Products suggests deletion of this phrase because it implies a comparative benefit that is not supported.

4. This initial labeling review serves as guidance for the upcoming scheduled labeling day discussion. It is anticipated that further revision of this review will be necessary following this discussion.

IDS: Cazemiro R. Martin

MO: Linda Hu, M.D.

Team Leader: Marina Chang

Attachments:
A. Agency's recommended prototype labeling
B. Copy of sponsor's draft proposed labeling
C. Specifications for type sizes provided by sponsor
D. Copy of 21 CFR 341.78; Labeling of expectorant drug products

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/s/

Cazemiro Martin
10/11/01 01:18:53 PM
INTERDISCIPLINARY

Marina Chang
10/15/01 02:57:13 PM
INTERDISCIPLINARY

Linda Hu
10/22/01 04:03:20 PM
MEDICAL OFFICER

18 pages redacted from this section of the approval package consisted of draft labeling

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 08/31/01	DUE DATE: 11/30/01	OPDRA CONSULT #: 01-0196

TO: Robert J. Meyer, M.D.
Director, Division of Pulmonary and Allergy Drug Products
HFD-570

THROUGH: Ladan Jafari
Project Manager, Division of Pulmonary and Allergy Drug Products
HFD-570

PRODUCT NAME:	MANUFACTURER: Adams Laboratories, Inc.
Mucinex (Guaifenesin ER tablets) 600 mg NDA#: 21-282	

SAFETY EVALUATOR: Nora Roselle, Pharm.D.

SUMMARY: In response to a consult from the Division of Pulmonary and Allergy Drug Products (HFD-570), OPDRA conducted a review of the proposed proprietary name "Mucinex" to determine the potential for confusion with approved proprietary and established names as well as pending names.

OPDRA RECOMMENDATION:
OPDRA has no objection to the use of the proprietary name, Mucinex. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 29, 2001

NDA NUMBER: 21-282

NAME OF DRUG: Mucinex (guaifenesin ER) tablets 600 mg

NDA HOLDER: Adams Laboratories, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570) for assessment of the tradename "Mucinex", regarding potential name confusion with other proprietary/generic drug names. This is the second tradename review for this drug product. OPDRA previously approved the name "Aquatab" for this drug product. In addition, the applicant previously and now they have agreed with the Agency that this is an over-the-counter medication.

PRODUCT INFORMATION

Mucinex contains the active ingredient guaifenesin. Guaifenesin is an expectorant used to help loosen mucus and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive. Mucinex is to be marketed as an over-the-counter drug product. Each extended release tablet contains 600 mg of guaifenesin. The daily dose of Mucinex 600 mg is one to two tablets every six hours in adults and children 12 years of age and older. . Mucinex should be used with caution in patients with persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema or with coughs accompanied by excessive phlegm. Mucinex will be supplied in 100-count bottles, as well as 2-count physician sample packages.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to Mucinex to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS)[4] was also conducted. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Mucinex". This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Two product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Mucinex. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage. Several other products also thought to have potential for confusion are also included in the table.

DDMAC did not comment on the name Mucinex. Mucinex is to be marketed as an over-the-counter product, and DDMAC is not responsible for the marketing and advertising of over-the-counter drug products.

---

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[2] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[3] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at http://www.thomson-thomson.com.

TABLE 1

Product Name	Dosage form(s), Generic Name	Usual adult dose*	Other**
Mucinex (OTC)	Guaifenesin ER tablets, 600 mg (100 tablets, 2 tablet physician samples)	*600 mg tablets*: 1-2 tablets every 12 hrs, not to exceed 4 tablets in 24 hrs	
Mycelex (various OTC and Rx products)	Clotrimazole, vaginal cream 1%; vaginal tablet 100 mg, 500 mg; topical solution 1%; troche 10 mg	*Cream*: 1 applicatorful intravaginally daily for 7 days *Topical*: Apply to affected area twice daily for 7 days *Troche*: slowly dissolve by mouth 5x/day for 14 days *Vaginal Tablets*: Two 100 mg tabs x 3 nights; or one 100 mg tab x 7 nights; or one 500 mg tab x 1 night	S/A per OPDRA
Mucomyst (Rx)	Acetylcysteine sodium, solution as 10% (100mg/mL) (4 mL, 10 mL, 30 mL); 20 % (200 mg/mL) (10 mL, 30 mL, 100 mL)	*Oral*: 140 mg/kg followed by 17 doses of 70 mg/kg every 4 hours *Inhalation*: use in infants, children, and adolescents	S/A per OPDRA
Melanex (Rx)	Hydroquinone 3% topical solution (30 mL)	Apply a thin layer and rub in twice daily to affected area on skin	L/A per OPDRA
Mesnex (Rx)	Mesna 100 mg/mL injection (10 mL)	*IV bolus*: 20% of ifosfamide dosage (w/w) at the times of ifosfamide administration, and 4 and 8 hrs after each dose of ifosfamide	L/A per OPDRA
Mucilax (OTC)	Various types of psyllium laxatives	Use as directed	S/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

Three separate studies were conducted within FDA, to determine the degree of confusion of Mucinex with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 112 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote one inpatient and one outpatient order, each consisting of a combination of marketed and unapproved drug products and prescriptions for Mucinex. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal

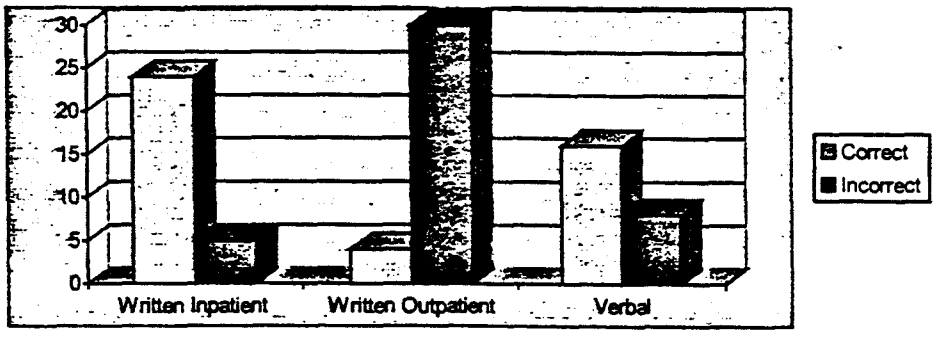
outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Inpatient Sample: Mucinex 600 mg q12	*Outpatient*: Mucinex 600 mg Take one tablet by mouth every 12 hours Dispense #20 with no refills
Outpatient Sample: Mucinex 600 mg 1 po q12h #20 Refills: 0	

2. Results

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted Mucinex	Incorrectly Interpreted
Written: Inpatient	39	29 (74%)	24 (83%)	5 (17%)
Outpatient	38	34 (89%)	4 (12%)	30 (88%)
Verbal: Outpatient	35	24 (69%)	16 (67%)	8 (33%)
Total	112	87 (78%)	44 (51%)	43 (49%)



Among participants in the written prescription studies, 28 of 63 respondents (44%) interpreted the name correctly. Many of the incorrect name interpretations were misspelled variations of "Mucinex" such as Mucenex, Muconex, and Mucunex. Other responses included Mucurex, Micronex, Micurex, Mucivax, and Mucirex. One respondent's interpretation of the inpatient written prescription was "Mucomax" and in her email she also stated that the "name is too close to Mucomyst".

Among verbal prescription study participants, 16 of 24 (67%) of the study participants interpreted the name correctly. All except one of the incorrect name interpretations were phonetic variations of "Mucinex" including: Musinex, Musonex, Mucenex, and Musinix. One individual misinterpreted the name to be Businex.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Mucinex, the primary concerns raised were related to a couple of sound-alike, look-alike names that already exist in the U.S. marketplace. Two products, Mycelex and Mucomyst, were believed to be the most problematic in terms of potential medication error. Through further evaluation the following names were also believed to be of concern: Melanex, Mesnex, Mucilax.

We conducted prescription studies to simulate the prescription ordering process. *In this case, there was no confirmation that Mucinex could be confused with Mycelex or Mucomyst.* Yet, one respondent from the inpatient order stated in the email response that the "name is too close to Mucomyst". The results of the verbal and written analysis studies demonstrate that 44 of 87 (51%) participants interpreted the proprietary name Mucinex correctly. The majority of the incorrect responses from the verbal and written studies were misspelled/phonetic variations of the drug name. These responses did not overlap with any existing approved drug products.

Mycelex (clotrimazole) is marketed as both a prescription and over-the-counter drug product. Clotrimazole is an antifungal drug that is effective against a broad spectrum of fungi. Clotrimazole is available for oral, topical, and vaginal use. Mycelex is indicated in the treatment of vulvovaginal candidiasis (vaginal tablets), oral and esophageal candidiasis in immunosuppressed patients (oral troches), and in dermatomy cases (topical). Mycelex and Mucinex can sound similar when pronounced, both tradenames contain three syllables, and each product is available as in tablet form. However, there are distinguishing factors between Mycelex and Mucinex that may decrease the potential risk of medication errors. Differences between the two products include variations in indications, dosing schedules, and strengths. Likewise, Mycelex is available in various product formulations while Mucinex is available in a tablet preparation only. Also, there are differences in the product names when they are written. Mucinex does not contain any upstroke or downstroke letters other than the letter "M". Mycelex, on the other hand, contains two letters, a "y" (downstroke) and "l" (upstroke), each of which differentiates Mycelex and Mucinex when they are written.

Mucomyst (acetylcysteine) is an intravenous product used in the treatment of moderate to severe acetaminophen overdose. The loading dose is 140 mg/kg orally followed by 70 mg/kg orally every 4 hours for 17 additional doses. Mucomyst is usually administered to patients in hospitals under the direct supervision and monitoring of a physician, often in conjunction with a poison center. Mucomyst and Mucinex have similar sounds when pronounced verbally. However, there are differences between the two that may decrease the risk for potential error. Mucinex is available as a tablet, while Mucomyst is available only as a solution. Both of the drug products also have different strengths and dosing regimens. Mucinex is available as a 600 mg tablet. Mucomyst, on the other hand, is available as a 10% or 20% oral solution to be dosed according to patient weight. Another difference between the two products is that Mucomyst is a prescription medication that is administered under the direct supervision of a doctor, while Mucinex is an over-the-counter medication. Similarly, Mucomyst and Mucinex have completely different indications for use.

Melanex (hydroquinone) is indicated in the temporary depigmentation of hyperpigmented skin conditions such as chloasma, melasma, freckles, and other forms of melanin hyperpigmentation. Melanex is a prescription strength topical solution that is supplied in 30 mL bottles. Melanex is applied to affected areas twice daily, in the morning and before bedtime. Melanex and Mucinex can look alike when written. Yet, there are differences between the two products that may decrease the potential for error and thus patient harm. Melanex and Mucinex have different indications, dosage forms, and routes of administration thus decreasing the potential risk for error.

Mesnex (mesna) is indicated for use in the prophylaxis of ifosfamide-induced hemorrhagic cystitis thus, protecting the bladder from harmful effects caused by some chemotherapy products. Mesnex is also effective in the management of cyclophosphamide-induced urothelial toxicity. Mesnex is available as a 100 mg/mL intravenous injection and is supplied in 2 mL, 4 mL, and 10 mL vials. The usual dosage is dependent on individual patient protocols. Mesnex and Mucinex can look similar when scripted because the two names share similar combinations of letters. However, there are distinguishing factors between Mesnex and Mucinex which may decrease the potential risk for medication errors. Mesnex and Mucinex have different indications for use, dosage forms, routes of administration, and strengths. Likewise, Mesnex is a prescription product administered in conjunction with a scheduled chemotherapy protocol while Mucinex is an over-the-counter expectorant.

Mucilax is an over-the-counter laxative that is currently marketed through Australia and New Zealand. Mucilax and Mucinex can sound alike when pronounced. According to the Saegis[1] database, the drug has low sales with the last recorded date of sales in the United States in 1991.

The Labeling and Nomenclature Committee reviewed

The proprietary name does not contain any USAN stems.

Even though there are existing tradenames that look and sound similar to Mucinex, there are distinguishing factors among the existing tradenames and Mucinex that decrease the potential for confusion.

[1] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at http://www.thomson-thomson.com.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels and carton labeling of Mucinex, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container labels and carton labeling and has identified several areas of possible improvement, which may minimize potential user error. Professional package insert labeling was not submitted for review.

A. GENERAL COMMENTS:

1. We are unable to identify from the submitted materials, but the product packages should include Child Resistant Closures (CRC).

2. We recommend that the term "bi-layer" not be included in the established name.

3. We recommend that the term "NEW" not appear on the carton labeling more than six months from the date of approval.

4. We are unable to identify from the submitted materials, but as per 21 CFR 211.132 there should be one or more distinctive barriers to entry into the package. Tamper-evident packaging of OTC drug products will improve the security of OTC drug packaging and help assure the safety and effectiveness of OTC drug products.

5. As per 21 CFR 201.63(a), the labeling for all over-the-counter (OTC) drug products that are intended for systemic absorption, unless specifically exempted, shall contain a general warning under the heading "Warnings" as follows: "**If pregnant or breast-feeding**, ask a health professional before use."

6. In the "Directions" section of each of the packages, the first bullet should address the usual daily dose. We suggest moving the daily dosing information to the front of this section in order to provide more prominent, quick information to the patient.

7. As per 21 CFR 341.78(c)(2), expectorant drug products labeled for adults or for adults and children under 12 years of age should include the following: "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema, or where cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

B. CONTAINER LABEL: (600 mg, 100 tablets; 600 mg, 2 tablets;

1. The net quantity (100 tablets or 2 tablets) should appear away from the product strength and have less prominence.

C. CARTON LABELING: (600 mg, 2 tablets:

1. The strength should be increased in font size so that it is more prominent and appears away from the net quantity statement.

D. INSERT LABELING: Professional labeling was not submitted for review.

IV. RECOMMENDATIONS

OPDRA has no objections to the use of the proprietary name, Mucinex. This is considered a tentative decision and the firm should be notified that this must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

OPDRA recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer. Package insert labeling should be submitted for review.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, Project Manager, at 301-827-3242.

Nora Roselle, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

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

/s/

Nora L. Roselle
11/29/01 10:58:04 AM
CSO

Jerry Phillips
11/29/01 12:44:11 PM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Adams Laboratories, Inc.	07/10/02
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
817-786-1200	817-786-1204
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
14801 Sovereign Road Fort Worth, Texas 76155 - 2645 United States of America	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-282

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
guaifenesin ER	Mucinex

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
1,2-propanediol,3-(2-methoxyphenoxy)-3-(0-methoxyphenoxy)-1,2-propanediol

CODE NAME *(If any)* N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	600 mg	Oral

(PROPOSED) INDICATION(S) FOR USE: Expectorant

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Amendment

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Adams Laboratories, Inc., 14801 Sovereign Road, Fort Worth, Texas 76155 - 2645
DMF: N/A
Drug Registration #: 063824 This facility has been inspected.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF #

This application contains the following items: *(Check all that apply)*

- ☐ 1. Index
- ☐ 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
  - ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(k)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER *(Specify)* Phase IV Commitment

CERTIFICATION

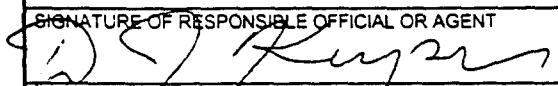
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	D. Jeffrey Keyser, Vice President Development & Regulatory Affairs	07/10/02

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
14801 Sovereign Road, Fort Worth, Texas 76155	817-786-1243

NDA 21-282

MEMORANDUM OF TELECON

DATE: July 27, 2000

APPLICATION NUMBER: NDA 21-282

BETWEEN:

Name:	Jeff Keyser, Vice President, Development and Regulatory Affairs
	Al Guillen, General Manage of Operations
	Brian Hill, Director, QA, QC
Phone:	817-786-7243
Representing:	Adams Labs

AND

Name:	Ladan Jafari, Project Manager
	Sue Johnson, Medical Reviewer
	Juanita Ross, Chemistry Reviewer
	Division of Pulmonary and Allergy Drug Products

SUBJECT: Request for additional chemistry information required for filing of NDA 21-282.

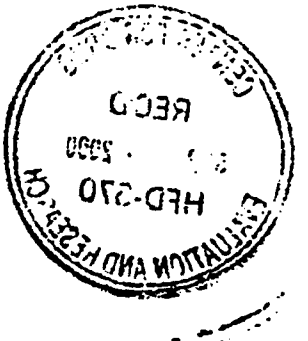
Background: The Division requested this telecon to request for additional chemistry information. Submission of this information was pertinent to the filing of this application.

cc:

NDA 21-282
HFD-570/Div.files
HFD-570/Wakelkamp-Barnes
HFD-570/Choi
HFD-570/Jafari
HFD-570/Johnson
HFD-570/Purucker
HFD-570/Ross
HFD-570/Poochikian
HFD-570/Wilson
HFD-570/Sun

Initialed by: Barnes/8-30-00
Wakelkamp-Barnes/8-31-00
Choi/8-31-00

Filename: Biopharmir1



Summary: The Division requested that Adams Labs submit the following information in an amendment to the NDA.

1. Data from testing the drug substance by Adams Labs.

2. Data from testing the drug product by Adams Labs.

3. Drug Product assay data from the stability studies expressed as mg/tablet.

The Division reminded Adams of the outstanding chemistry comments cited in the Agency's letter to ——— dated August 4, 1998. Specifically, the Division requested the following.

4. Limits should be developed for each specified identified impurity (at or above —, each specified unidentified impurity at or above — , any unspecified impurity (limit of not more than —), total impurities, residual solvents and inorganic impurities in the drug substance (refer to comment 7 of the deficiency letter to —

   - The Division noted that Adams Labs' responses to these deficiencies were not satisfactory, and requested that Adams Labs propose limits (as indicated above) based on appropriate data and provide that data.

5. Degradation products in the drug product should be individually reported at or above the level of — , and identified at or above the level of — In addition, there should be a limit on total degradation products (refer to comment 8.c of the deficiency letter to ———

   - The Division stated that the response provided by Adams Labs was not satisfactory, and stated that real values should be reported for identified individual impurities, unidentified individual impurities, and total impurities.

6. We recommend that moisture content also be evaluated on stability (refer to comment 8.d of the deficiency letter to ——— dated August 4, 1998).

   - The Division stated that Adams Labs did not include the test methods, and the moisture content evaluation in the stability testing.

The Division reminded Adams Labs of the importance of submitting the above requested information in a timely manner to avoid any filability issues.

Action: Adams Labs stated that they would provide the data requested to the Division in a timely manner.

cc:
Archival NDA 21-282
HFD-570/Division Files
HFD-570/Ross
HFD-570/Poochikian
HFD-570/Johnson
HFD-570/Jafari

Drafted by: Jafari/8-4-00

Initialed by: Ross/8-22-00
Johnson/8-15-00
Schroeder/8-25-00

Filename: Telecon1

TELECON

TELECON RECORD

Date: February 22, 2000

Product: Guaifenesin Modified Release Tablets

FDA Participant: J. Lindsay Cobbs, Regulatory Project Manager
Albert Chen, Clinical Pharmacology & Biopharmaceutics Reviewer
Ramana Uppoor, Clinical Pharmacology & Biopharmaceutics Team Leader

Sponsor: Jeff Keyser, VP Regulatory & Development Affairs
Adams Laboratory

Background: A brief teleconference was held to discuss the following issues regarding protocol 99-06 entitled: A Study Designed to Examine the Relative Bioavailability of Two Different Dosage Strengths of Modified Release (MR) Guaifenesin and Test for any Food Effect in Normal Healthy Volunteers.

1. The Division noted concerns with not having a MR 600 mg strength (at the 600 mg dose) specifically studied in the proposed protocol that Adams and the Agency previously agreed upon. The Division previously recommended a 3x3 crossover study using both the MR 600 and 1200 mg strengths (to look at the pharmacokinetics of guaifenesin in the proposed dose range, after administration of the 600 and 1200 mg MR products). The sponsor then suggested that they are willing to remove the 2 x 600 mg strength arm and replace this with the 1 x 600 mg strength arm. The Division noted that while this is useful to compare the pharmacokinetics in the dose range proposed (600 to 1200 mg bid), bioequivalence between strengths can only be compared after dose normalization. If the data could not conclude that 2 MR 600 mg strength tablets are bioequivalent to one MR 1200 mg strength tablet then the labeling would be reflective of the data.

2. Adams stated that the MR 600 mg tablet formulation was identical to the MR 1200 mg tablet formulation in composition (the MR600 mg tablet is half the MR 1200 mg tablet).

3. After discussion, the Division agreed that Adams could revise the protocol 99-06 by removing the 2 (600 mg) strength arm and replacing it with the single 600 mg strength arm under fasting conditions and that dose-proportionality issue could be addressed to cover the proposed dose range.

4. Several other comments on the protocol (such as blood sampling for adequate period of time) were also conveyed to Adams and Adams agreed to incorporate them into the revised protocol.

5. Adams agreed to submit the revised protocol immediately.

HFD-570/Division File
HFD-570/Cobbs
HFD-570/ UPPOOR/3-24-00
HFD-570/CHEN/3-24-00
HFD-570/JAFARI
DRAFTED BY:LCOBBS/3-22-00
N:/MY DOCUMENTS/ L00-02-22.DOC

TELECON RECORD

Date: March 7, 2000

Product: Guaifenesin ER Tablets

FDA Participant: J. Lindsay Cobbs, Regulatory Project Manager

Sponsor: Adams Laboratories
Jeff Keyser
Vice President, Regulatory and Development Affairs

1. Adams submitted a correspondence dated February 24, 2000, and requested feedback from the Chemist regarding the stability data that will be submitted for review in the NDA. Please see the aforementioned correspondence for details.

2. Dr. Schroeder reviewed the correspondence and noted that without reviewing the data, which must be provided in the NDA, he could not give more specific comments and that the proposal regarding the submission of stability data seemed reasonable.

HFD-570/Division File
HFD-570/Cobbs
HFD-570/ SCHROEDER
HFD-570/JAFARI
DRAFTED BY:LCOBBS/3-21-00
N:/MY DOCUMENTS/ —— L00-03-07.DOC

Adams Laboratories, Inc.
Guaifenesin Extended Release Tablets

September 20, 1999

Memorandum of Telephone Facsimile Correspondence

Date: December 16, 1999

To: Donald Jeffrey Keyser
Vice President
Development and Regulatory Affairs
817-786-1151

From: J. Lindsay Cobbs, R.Ph.
Project Manager

Subject: Meeting minutes.

Reference is made to the meeting held between representatives of your company and this Division on September 20, 1999, and the follow-up teleconference dated October 8, 1999. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

Thank you.

LCDR James Lindsay Cobbs
Project Manager
Division of Pulmonary & Allergy Drug Products

Date

Adams Laboratories, Inc. General Guidance Meeting

IMTS # 4776

Representing **Division of Pulmonary & Allergy Drug Products (DPADP)**

Albert Chen, Clinical Pharmacology & Biopharmaceutics Reviewer
Lindsay Cobbs, Project Manager
Sue Johnson, Clinical Reviewer
Bob Meyer, Director DPADP
Ramana Uppoor, Clinical Pharmacology & Biopharmaceutics Team Leader

Representing **Adams Laboratories**

Jeff Keyser, VP, Development and Regulatory Affairs

Background/History

Adams developed bi-layered modified-release (MR) 600 , , tablets for twice daily dosing that consist of a layer of immediate release blend and modified release blend of guaifenesin. Adams studied several variations of the bi-layered tablet and plan to select one formulation for the multiple dose trial (# 99-05). Adams requested a meeting for guidance on the proposed multiple dose trial before proceeding with their drug development. Please see the meeting request (including a request of review for protocol #99-05) dated August 18, 1999, for details.

The Agenda of the meeting follows.

AGENDA

Introduction	Lindsay Cobbs	5 min
Discussion		55 min
Conclusion		5 min

1. The Division noted concerns regarding the large variation in the 0-12 hour mean plasma profile of the immediate release (IR) guaifenesin tablet (2 x 200 mg tablets given every 4 hours) i.e., the peak levels after each dose are quite variable and apparently unpredictable, with the C_{max} after the first dose being the highest in one study vs. C_{max} after the second dose being highest in another study.

2. The Division also noted that the low plasma concentrations in the last four hours after administration of the ——— tablet during the 12-hour post-dosing period is of particular concern. There appears to be little drug left in systemic circulation after 8 hours and the Division inquired as to why Adams was pursuing a 12-hour formulation rather than a 8 hour dosing (i.e., rationale as to how the MR formulation could provide clinical efficacy during the 8 to 12 hours post dosing).

    a. Adams referred to the Final Monograph that stipulates a maximum 2400 mg of guaifenesin per 24 hours and their goal for twice daily dosing for this product. Adams also stated that with the bi-layered tablet they could vary the amount the controlled release layer up to 2400 mg in an attempt to cover the 8 to 12 hour period.

    b. The Division stated that for a switch from an IR to an MR formulation, demonstration of comparable C_{max}, C_{min}, and AUC_{0-12} between the two products is recommended and it should be based on the Agency's current acceptance criteria for equivalency using the two-one-sided test procedures and 90% confidence intervals. After the discussion and an agreement on the

equivalency requirement for C_{min} and AUC, the Division agreed to get back to the sponsor regarding the requirement specific for showing equivalency in C_{max}.

c. The Division recommended that in order to minimize variability for the IR product (protocol # 99-05), Adams consider using guaifenesin syrup and that the feeding times be standardized (e.g., 1 hour before and 2 hours after meal) to generally assure that all doses are administered under similar conditions.

Note: A teleconference dated September 9, 1999 was held for further discussion between Adams and the Division. The Division indicated that regarding the demonstration of equivalency in C_{max} following the standard procedures is recommended (90% confidence intervals be within 80-125%). If the criteria for C_{max}, C_{min}, and AUC are not met at steady state, Adams will need to provide PK/PD data to justify that the PK differences seen have no clinically meaningful impact on safety and efficacy. If such data are not available, Adams may consider reformulating the product. In addition to meeting these requirements, it is also equally important that the MR product provides meaningful guaifenesin concentrations throughout the dosing interval. Adams indicated that the initiation of protocol # 99-05 would be postponed for bi-layered MR tablet reformulation.

3. Questions from the meeting request package dated August 18, 1999.

a. Given the plasma data generated in 99-01 on guaifenesin, we are not planning to conduct another single dose study (dose dumping trial) with the bi-layer tablet. A dose dumping formulation would achieve a C_{max} of approximately 7000 ng/ml. The C_{max} obtained in 99-04 and those expected to be evidenced in the multiple dose trial (99-05) will likely provide around 200-2500 ng/ml plasma level. Do you agree with our position?

- The Division stated that this approach is not acceptable, and a further single dose data on the final formulation are warranted.

b. We have determined that guaifenesin has linear kinetics. As such, we are conducting a multiple dose trial with a 600 mg bi-layer tablet and a 1200 mg bi-layer tablet compared to only a 400 mg immediate release formulation. We [redacted] Do you agree with this approach?

(1) The Division stated that this product does appear to have linear kinetics and agreed that this approach is acceptable.

(2) The Division agreed that single-dose PK profiles for IR and MR guaifenesin tablets should be characterized on Day 1 (first dose only) and their PK profiles following multiple-dosing (twice daily dosing beginning Day 2) should be obtained on Day 6 as proposed for protocol # 99-05. Additional samples at trough should be obtained, as proposed, to determine whether steady state has been achieved by Day 6.

c. We have studied the food-effect of guaifenesin in trial 99-01. The formulation studied was comparable but not identical to the bi-layer tablet formulation. We plan on adding a food effect statement into our labeling based upon 99-01. We do not plan on conducting another food-effect study on the bi-layer tablet formulation. Do you agree with this position?

- The Division stated that this approach is not acceptable and noted that food effect study should be performed with the to-be-marketed bi-layered product. The Division stated that the reason for the food effect study is to observe dose dumping and the effects of food on the bi-layered MR product as finally formulated.

4. The Division proposed a single-dose, 3-way cross-over study (with an appropriate washout period) to address Comments 3.a. and 3.c. above and the equivalency concern for the MR tablet strengths (2 x 600 mg vs. 1 x1200 mg).

a. 1x 1200 mg MR tablet, fasting.
b. 1 x1200 mg MR tablet with food (a high fat meal).
c. 2x 600 mg MR tablets, fasting.

5. Adams inquired about the Division's thoughts on the product's linearity.

- The Division stated that a conclusion of linearity, based on the data, looks reasonable.

6. The Division reminded Adams that a complete characterization of the PKs of the to-be-marketed product is essential for submission of the NDA.

7. Adams noted their timeline for submission of the application for the first quarter of 2000.

8. Adams noted that they would request a meeting with the Chemists soon.

CC: ORIGINAL
DIVISION FILE
HFD-570/COBBS
HFD-570/UPPOOR/11-12-99/12-13-99/12-15-99
HFD-570/CHEN/11-12-99
HFD-570/JOHNSON/detailed
HFD-570/MEYER/12-16-99

DRAFT BY:LCOBBS/OCTOBER 1, 1999
MY DOCUMENTS/ :ams.DOC

CORRESPONDENCE

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

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

2. TELEPHONE NUMBER *(Include Area Code)*

(817) 786-1243

3. PRODUCT NAME

guaifenesin ER

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. NO

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).

5. USER FEE I.D. NUMBER

3966

6. LICENSE NUMBER / NDA NUMBER

21-282

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. NO

☐ 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)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
D. Jeffrey Keyser	Vice President-Development and Regulatory Affairs	6-21-00

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21282/000
Org Code : 570
Priority : 3S

Sponsor: ADAMS LABS
14801 SOVEREIGN RD
FORT WORTH, TX 761552645

Stamp Date : 29-JUN-2000
PDUFA Date : 14-JUL-2002
Action Goal :
District Goal: 28-FEB-2001

Brand Name : MUCINEX
Estab. Name:
Generic Name: GUAIFENESIN ER 600MG, TABLETS
Dosage Form: (EXTENDED-RELEASE TABLET)
Strength : 600 MG

FDA Contacts:			
L. JAFARI	Project Manager	(HFD-570)	301-827-1050
E. NASHED	Review Chemist	(HFD-570)	301-827-1066
G. POOCHIKIAN	Team Leader	(HFD-570)	301-827-1050

Overall Recommendation: ACCEPTABLE on 26-FEB-2001by J. D AMBROGIO(HFD-324) 301-827-0062

Establishment : CFN : 1640689 FEI : 1640689
ADAMS LABORATORIES INC
14801 SOVEREIGN RD
FORT WORTH, TX 761552645

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-FEB-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-NOV-00
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21282/000
Stamp: 29-JUN-2000 Regulatory Due: 29-APR-2001
Applicant: ADAMS LABS
14801 SOVEREIGN RD
FORT WORTH, TX 761552645

Priority: 1S Org Code: 570
Action Goal: District Goal: 28-FEB-2001
Brand Name: GUAIFENESIN ER 600MG [redacted] TABLETS
Established Name:
Generic Name: GUAIFENESIN ER 600MG/ [redacted] TABLETS
Dosage Form: EXT (EXTENDED-RELEASE TABLET
Strength: 600 MG [redacted]

FDA Contacts:			
	L. JAFARI	(HFD-570)	301-827-1050 , Project Manager
	J. ROSS	(HFD-570)	301-827-1066 , Review Chemist
	G. POOCHIKIAN	(HFD-570)	301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 26-FEB-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1640689
ADAMS LABORATORIES INC
14801 SOVEREIGN RD
FORT WORTH, TX 761552645

DMF No:
AADA No:

Profile: TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 26-FEB-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 21-NOV-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21282/000
Stamp: 29-JUN-2000
Regulatory Due: 29-APR-2001
Applicant: ADAMS LABS
14801 SOVEREIGN RD
FORT WORTH, TX 761552645
Priority: S
Org Code: 570

Action Goal:
District Goal: 28-FEB-2001
Brand Name: GUAIFENESIN ER 600MG, [redacted] TABLETS
Estab. Name:
Generic Name: GUAIFENESIN ER 600MG [redacted] TABLETS

Dosage Form: (EXTENDED-RELEASE TABLET)
Strength: 600 MG [redacted]

Application Comment: AS PER THE APPLICANTS LETTER OF NOV. 10,2000: MEDEVA PLC OFN LONDON ENGLAND PURCHASED ADAMS LABS. IN 1991 AND USED IT AS THEIR N. AMERICAN HEADQUARTERS. IN 1996 MEDEVA PURCHAED FISONS PHARMACEUTICALS OF ROCHESTER NY AND TRANSFERRED ITS HEADQUARTERS THERE. THEN IN 1997,MEDEVA OFFERED THE FORT WORTH PLANT FOR SALE(INCLUDING THE NAME ADAMS LABS.IT WAS BOUGHT BY THE ORIGINAL OWNERS OF ADAMS LABS. INC. IN 1997. THE MANUFACTURING DIVISION OF AHAMS LAB. GOES BY THE NAME LONE STAR.USING THE SAME FORT WORTH ADDRESS. (on 21-NOV-2000 by J. ROSS (HFD-570) 301-827-1066)

FDA Contacts:

L. JAFARI	(HFD-570)	301-827-1050	, Project Manager
J. ROSS	(HFD-570)	301-827-1066	, Review Chemist
G. POOCHIKIAN	(HFD-570)	301-827-1050	, Team Leader

Overall Recommendation: ACCEPTABLE on 26-FEB-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1640689
ADAMS LABORATORIES INC
14801 SOVEREIGN RD
FORT WORTH, TX 761552645

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TTR OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-NOV-2000				ROSSJ
SUBMITTED TO DO	21-NOV-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	21-NOV-2000	PS			JMARTIN1
INSPECTION SCHEDULED	22-FEB-2001		16-FEB-2001		JMARTIN1
INSPECTION PERFORMED	22-FEB-2001		16-FEB-2001		JMARTIN1

DALLAS DISTRICT CONDUCTED A PAI/GMP INSPECTION AT ADAMS LABS. MINOR DEFICIENCIES WERE OBSERVED AND A FDA-483 WAS ISSUED. CORRECTIVE ACTION HAS BEEN IMPLEMENTED OR HAS BEEN INITIATED. THE PAI WILL BE CLASSIFIED ACCEPTABLE FOR PROFILE CLASS - "TTR". DALLAS DISTRICT WILL RECOMMEND APPROVAL OF THIS NDA.

DO RECOMMENDATION	22-FEB-2001		ACCEPTABLE INSPECTION	JMARTIN1

DALLAS DISTRICT RECOMMENDS APPROVAL OF THIS NDA BASED ON THE PAI/GMP INSPECTION CONDUCTED AT ADAMS LABS ON 2/12-16/2001 THAT WAS CLASSIFIED ACCEPTABLE FOR PROFILE CLASS - "TTR". A PROFILE SAMPLE WAS COLLECTED.

OC RECOMMENDATION	26-FEB-2001		ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]

[redacted]

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

AADA:

Responsibilities:

Profile: CSN OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-NOV-2000				ROSSJ
OC RECOMMENDATION	21-NOV-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Document Information Page

This page is for FDA internal use only. Do NOT send this page with the letter.

Application #(s):	NDA 21-282
Document Type:	NDA Letter
Document Group:	Approvable Letters
Document Name:	Approvable letter - Misc. deficiencies and FPL identical to enclosed/submitted labeling text.
Letter Code:	NDA-H5
COMIS Decision:	AE: APPROVABLE
Drafted by:	LJ/December 10, 2001
Revised by:	
Initialed by:	Barnes/12-/18-01 Nashed/12-10-01 Poochikian/12-10-01 Choi/12-18-01 Fadiran/12-18-01 Purucker/12-18-01 Sun/12-18-01 Mann/12-18-01, 12-20-01 Hilfiker/12-13-01 Hu/12-13-01 Chang/12-13-01 Katz/12-13-01 Ganley/12-13-01, 12-20-01
Finalized:	
Filename:	N21282AE
DFS Key Words:	
Notes:	
Linking Instructions:	If this is the first action on the application, link the outgoing letter to the N, RS, AR, or FO coded incoming document, as appropriate. Otherwise, the outgoing letter must be linked to the major amendment submitted in response to the previous action letter. In addition, the outgoing document should also link to all associated amendments and correspondences included in the action. Do NOT link this letter to any amendments that were not reviewed for this review cycle (i.e., amendments where the review was deferred to the next review cycle).

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

Document Information Page

This page is for FDA internal use only. Do NOT send this page with the letter.

Application #(s):	NDA 21282
Document Type:	NDA Letter
Document Group:	Approvable Letters
Document Name:	Approvable letter - Misc. deficiencies and labeling revisions listed in letter.
Letter Code:	NDA-H4
COMIS Decision:	AE: APPROVABLE
Drafted by:	LJ/April 16, 2001
Revised by:	
Initialed by:	Barnes/4-19-01 & 4-25-01 Ross/4-20-01 Poochikian/4-20-01 & 4-26-01 Choi/4-20-01 Fadiran/4-20-01 Purucker/4-20-01 & 4-26-01 Sun/4-19-01 Huff/4-19-01 Meyer/4-26-01
Finalized:	
Filename:	N 21282ae
DFS Key Words:	
Notes:	
Linking Instructions:	If this is the first action on the application, link the outgoing letter to the N, RS, AR, or FO coded incoming document, as appropriate. Otherwise, the outgoing letter must be linked to the major amendment submitted in response to the previous action letter. In addition, the outgoing document should also link to all associated amendments and correspondences included in the action. Do NOT link this letter to any amendments that were not reviewed for this review cycle (i.e., amendments where the review was deferred to the next review cycle).

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA
Document Type:	NDA Letters
Document Group:	NDA Approval Letters
Document Name:	Approval Letter – FPL acceptable
Shortcut ID Code:	NDA-I2
COMIS Decision Code	AP
Drafted by:	LJ/7-5-02
Revised by:	
Initialed by:	Barnes/7-9-02 Purucker/7-9-02 Sun/7-9-02 Guo/7-10-02 Kammerman/7-10-02 Fadiran/7-10-02 Nashed/7-10-02 Poochikian/7-10-02 Martin/7-11-02 Chang/7-11-02 Abraham/7-11-02 Hilfiker/7-11-02 Katz/7-12-02 Chowdhury/7-12-02
Finalized:	
Filename:	N21282AP.doc
DFS Key Words:	
Notes:	

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-282	Efficacy Supplement Type SE-	Supplement Number
Drug: Mucinex (guaifenesin extended release tablets)	Applicant: Adams Laboratories, Inc.	
RPM: Ladan Jafari	HFD-570	Phone # 301-827-1084
Application Type: ( ) 505(b)(1) (X) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): Monograph Ingredient	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	July 14, 2002
❖ 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) ( ) (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	See attached
• 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, ~~A~~DRA) *(indicate date of each review)*	January 15, 2002
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE/26-April 2001, AE/20-December 2001
• 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	( ) 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)	N/A
• Most recent applicant-proposed labeling	See attached
• Original applicant-proposed labeling	See attached
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	~~N/A~~ See reviews
• 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)	N/A
• Applicant proposed	See attached
• Reviews	See labeling reviews attached
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	See CMC review
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See attached
❖ Memoranda and Telecons	See attached
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	See attached

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)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	December 12, 2001
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	See attached
❖ Statistical review(s) *(indicate date for each review)*	7.3.02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	March 5, 2002
❖ 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	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	7.3.02
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See CMC review 7.3.02
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: 2-26-01 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(~~X~~) Completed (~~X~~) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	April 10, 2001
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

WITHHOLD 4 PAGE (S)