CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-282

CHEMISTRY REVIEW(S)

NDA/ANDA 21-282

Mucinex (guaifenesin) Extended-release Tablets

Adams Laboratories, Inc.

Eugenia M. Nashed
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-282

2. REVIEW #: 3

3. REVIEW DATE: 03-July-2002

4. REVIEWER: Eugenia Nashed

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	29-Jun-2000
Amendment	02-Aug-2000
Amendment	10-Nov-2000
AE letter	26-Apr-2001
Amendment AZ	25-Jun-2001
Amendment	23-Jul-2001
Amendment	19-Oct-2001
Amendment	30-Nov-2001
Amendment	04-Dec-2001
AE letter	21-Dec-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	CDER Date	Assigned Date
Amendment AZ	11-Jan-2002	14-Jan-2002	15-Jan-2002
Amendment BL	04-Mar-2002	05-Mar-2002	06-Mar-2002
Amendment BC	08-May-2002	09-May-2002	10-May-2002
Amendment BC	13-May-2002	14-May-2002	15-May-2002
Amendment BC	22-May-2002	23-May-2002	23-May-2002
Amendment BC	23-May-2002	24-May-2002	24-Jun-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Adams Laboratories, Inc.

NDA 21-282 Chemistry Review Data Sheet

Address: 14801 Sovereign Road, Fort Worth, TX 76155

Representative: Jeffrey Keyser, Vice President Development & Reg. Affairs

Telephone: 817-786-1243

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Mucinex Extended-release Tablets
b) Non-Proprietary Name (USAN): Guaifenesin Extended-release Tablets
c) Code Name/# (ONDC only): 93-14-1
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Expectorant

11. DOSAGE FORM: Extended-release Bi-layer Tablets. Each tablet is comprised of smaller white layer (IR) and larger blue (600 mg)

12. STRENGTH/POTENCY: 600 mg white/blue rounded tablet (*ca.* ~ diameter, ~ thick and ~ weight).

13. ROUTE OF ADMINISTRATION: Oral extended-release tablets

14. Rx/OTC DISPENSED: ___Rx X__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X____Not a SPOTS product

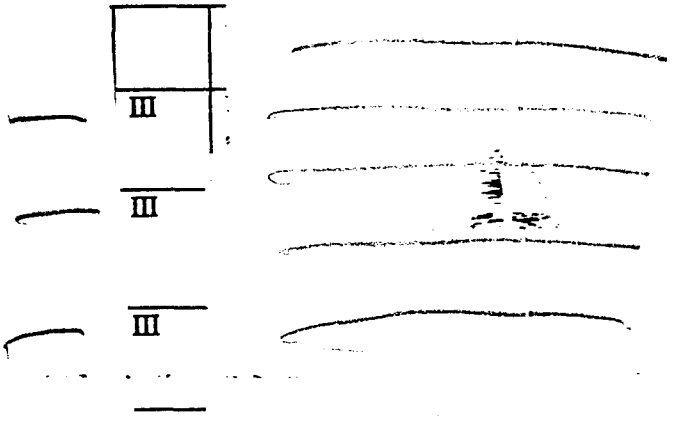
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

[redacted]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	13-May-2002	IR letter sent to the holder (5/23/02)
	II			1	Adequate	15-May-2002	IR letter sent to the holder (5/23/02)
	III			4	N/A		All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001
	III			4	N/A		All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001
	III			4	Adequate	24-Mar-1999 (HFD-160 for tablets)	DMF withdrawn from application and replaced by DMF —— See amendment dated Dec 4, 2001.
	III			4	N/A		All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001
	III			4	Adequate	4-Aug-1999 (HFD-120 for tablets)	All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001
	III			4			DMF withdrawn from application and



	N/A		replaced by DMF ~~ See amend. dated Dec 4, 2001.
4	N/A		All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001
3	Adequate	14-Feb-2001	Reviewed by HFD-540 for use with encapsulated microspheres
1	Adequate	03-Aug-2001	Reviewed by HFD-570 for use with extended-release tablets

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		Guaifenesin tablets by Adams Labs

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	26-Feb-2001	J. D. Ambrogio (HFD-324)
Pharm/Tox and Medical	Acceptable, tighten impurity specifications based on manufacturing capability (Impurities above ICH Q3A and 3B thresholds for qualification)	11-Dec-2001	Joe Sun Mary Puruker Robert Meyer
Statistician	Stability data do not support the proposed expiry periods	03-Jul-02	Ted Guo
Biopharm	Acceptable (Dissolution method and acceptance criteria)	5-Mar-2002	Young Moon Choi
Methods Validation	MV package is prepared for submission		
OPDRA	Acceptable	29-Nov-2001	Nora Roselle (HFD-400)
OTC (labeling)	Acceptable	13-Sep-2001	Cazemiro Martin (HFD-560)

The Chemistry Review for NDA 21-282

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Only the 600 mg extended-release tablet is recommended for APPROVAL, with Phase 4 commitment and additional in-process controls (see below), from the CMC standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Due to the of the original bi-layer tablets applicant provided Phase 4 commitment for on the see item 3b in this review). Also, additional in-process controls for the and additional in this review) for lots exceeding on release the "Alert Limit") are implemented.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This is a 505(b)(2) NDA for of extended release formulation of guaifenesin, USP. Proposed packaging configurations include bottles with counts of 2, 20, 40, 100 and 500 bi-layer tablets per bottle for 600 mg strength The 600 mg tablets are rounded (*ca.* 13 mm diameter, 5 mm thick and 729 mg weight) and are composed of immediate release (IR) white layer and extended release (ER) blue layer.

The proposed maximum daily dose is 2400 mg.

B. Description of How the Drug Product is Intended to be Used

Expectorant extended-release bi-layer tablets. Maximum daily dose: 2400 mg. Not for use in children under 12 years of age. The tablets are relatively large and have no coating.

C. Basis for Approvability or Not-Approval Recommendation

Original NDA was submitted on Jun 29, 2000. Comments resulting from CMC review #1 were forwarded to the applicant in AE letter dated 26-Apr 26-2001. Second CMC review dated 6-Dec-2001 resulted in AE letter dated 20-

Dec-2001. This review (#3) covers the CMC evaluation of applicant's responses submitted up to date (refer to submission dates on the first page of this review). See point by point evaluation of applicant's response to each CMC comment in the Chemistry Assessment section further down in this review. Also, copies of updated drug substance and drug product specifications are reproduced in this review at the end of drug substance and drug product sections, respectively.

Summary of Major CMC isssues:

- **Impurities.** — out of — identified synthetic impurities found in the drug substance (and the drug product) have currently acceptance criteria of NMT · ——— (see item #1b and 2b in this review). These levels are above the qualification threshold limit of 0.05% suggested in the ICH Q3A (drug substance) and 0.10% suggested in the ICH Q3B (drug product) guidelines for drug products with daily dose above 2000 mg. CMC consult dated Oct 17, 2001 was forwarded to PharmTox and Medical reviewers with request to evaluate safety of the proposed limits for these impurities. Based on data submitted by the applicant and on the fact that numerous guaifenesin products (most of them from the same manufacturing source) are in the human use for a long time, the Division recommended to tighten the acceptance criteria for the above impurities to reflect the current manufacturing capabilities.

- **Manufacturing Changes.** During the course of NDA review applicant · ——— removed the — from — 600 mg ——— · tablets. Also, embossing was changed ——— to be consistent with the strength ——— . Data supporting the CMC comparability of the original tablets to the new tablets were submitted on 19-Oct-2001 (manufacturing and release) and on 08-May-2002 (stability). See Chem. Rev. #2 and item 2b in this review.
  Also, changes to the compression process of the bi-layer tablets were implemented due to the excessive friability/separation of layers (see below). Process validation for 600 mg tablets was completed (see item 3a in this review)

  Any lot that exceeds these limits will be placed on stability according to the approved stability protocol. See footnotes on release and stability specification sheets and commitments in the stability protocol, reproduced at the end of the drug product section in this review.

- **Dissolution.** Evaluation of the new dissolution method ——— · and new dissolution acceptance criteria was harmonized with the Biopharm Team (see item #27 in Chem. Rev. #2, item 2i in this review and Biopharm. Rev. dated Mar 5, 2001).

- **Specifications' Format.** The need to submit specifications with individual method numbers for acceptance and re-testing of drug substance and for release and stability testing of drug product was requested in our letter dated Dec, 21 2001. Applicant's response dated Jan 11, 2001 was extensively discussed during teleconference on Mar 8, 2002. The revised drug substance and drug product specifications were submitted on May 8, May 13, May 22 and May 23, 2002, and are reproduced in this review at the end of drug substance and drug product sections, respectively.

- **Container-Closure.** Originally, applicant submitted 6 drug product presentations: 2-, 100-, and 500-count — bottles for each strength. On May 8, 2002, additional four new drug product presentations (600 mg: 20 & 40 tablets ——— · was submitted. Additional information about the new container-closures and supporting DMFs was submitted, upon request on May 13, 2002. See updates to the DMF table on pp.5-6 of this review.

As a result the NDA will be approved with 5 drug product presentations for the 600 mg drug product: 2-, 20-, 40-, 100-, and 500-count bottles.

- **Stability.** 6 months of the accelerated and 6 months of the long-term stability data were submitted for the 600 mg product manufactured with the validated manufacturing process (amendment May 8, 2002). In addition, 24 months of long-term and 6 months accelerated supportive data are available for each strength. The supportive data have limited amount of impurity data points (only 18 and 24 months) due to lack of adequate impurity method and have out-of-specifications results due to changes in compression. Based on the analysis of the submitted data, the Phase 4 commitment for , of the and on the commitment for additional in-process controls the following expiry periods are recommended for approval:

1.	600 mg, 30 cc	bottle, 2 bi-layer tablets	12 month expiry
2.	600 mg, 75 cc	bottle, 20 bi-layer tablets	24 month expiry
3.	600 mg, 75 cc	bottle, 40 bi-layer tablets	24 month expiry
4.	600 mg, 120cc	bottle, 100 bi-layer tablets	18 month expiry
5.	600 mg, 625 cc	bottle, 500 bi-layer tablets	18 month expiry

Commitments:

1. Phase 4 commitment: In addition to the normal stability agreement to place the first three production batches on stability program, Adams Laboratories commits to perform of drug product for commercial distribution. This will include collection of additional samples of minimum tablets obtained Additional samples will be collected at different times from the regularly scheduled quality assurance and manufacturing samples. The are aimed to assure adequacy and consistency of drug product manufacturing process controls and increase assurance of drug product. Upon completion, submit the data and statistical evaluation of the results as a "Supplement - Changes Being Effected in 0 Days" supplement.

2. Agreement: Adams Laboratories has agreed to include Alert Limits as controls as specified in amendment dated May 8, 2002, pages 4-424 to 4-426. Any lot with a release result that exceeds the Alert Limit for 600 mg tablets) must be placed in a and subjected to the market criteria as specified in Protocol page 14, amendment dated May 23, 2002.

3. Agreement: Adams Laboratories agreed that the extension of the approved expiry periods (see below) can be attained only by a prior-approval supplement with appropriate amount of supportive data.

- 600 mg, 30 cc bottle, 2 bi-layer tablets 12 month expiry
- 600 mg, 75 cc bottle, 20 bi-layer tablets 24 month expiry
- 600 mg, 75 cc bottle, 40 bi-layer tablets 24 month expiry
- 600 mg, 120cc bottle, 100 bi-layer tablets 18 month expiry
- 600 mg, 625 cc bottle, 500 bi-layer tablets 18 month expiry

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Eugenia Nashed/03-July-2002
ChemistryTeamLeader: Guirag Poochikian/
ProjectManager: Ladan Jafari/

C. CC Block

Medical reviewer: Mary Puruker
Biopharm reviewer: Emanuel Fadiran
CMC Div Director: Eric Duffy

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/s/

Eugenia Nashed
7/3/02 04:57:22 PM
CHEMIST

Guiragos Poochikian
7/3/02 05:01:29 PM
CHEMIST

NDA/ANDA 21-282

Mucinex (guaifenesin) Extended-release Tablets

Adams Laboratories, Inc.

Eugenia Nashed
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-282

2. REVIEW #: 2

3. REVIEW DATE: 04-Dec-2001

4. REVIEWER: Eugenia Nashed

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	29-Jun-2000
Amendment	02-Aug-2000
Amendment	10-Nov-2000
AE letter	26-Apr-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment AZ	25-Jun-2001
Amendment	23-Jul-2001
Amendment	19-Oct-2001
Amendment	30-Nov-2001
Amendment	04-Dec-2001

7. NAME & ADDRESS OF APPLICANT:

Name: Adams Laboratories, Inc.

Address: 14801 Sovereign Road, Fort worth, TX 76155

Representative: Jeffrey Keyser, Vice President Development & Reg. Affairs

Telephone: 817-786-1243

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Mucinex Extended-release Tablets
b) Non-Proprietary Name (USAN):	Guaifenesin Extended-release Tablets
c) Code Name/# (ONDC only):	93-14-1
d) Chem. Type/Submission Priority (ONDC only):	
• Chem. Type:	3
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Expectorant

11. DOSAGE FORM: Extended-release Bi-layer Tablets. Each tablet is comprised of smaller white layer (IR) and larger blue (600 mg)

12. STRENGTH/POTENCY: 600 mg white/blue rounded tablet (*ca.* —— diameter, —— thick and —— weight)

Maximum daily dose: 2400 mg

13. ROUTE OF ADMINISTRATION: Oral extended-release tablets

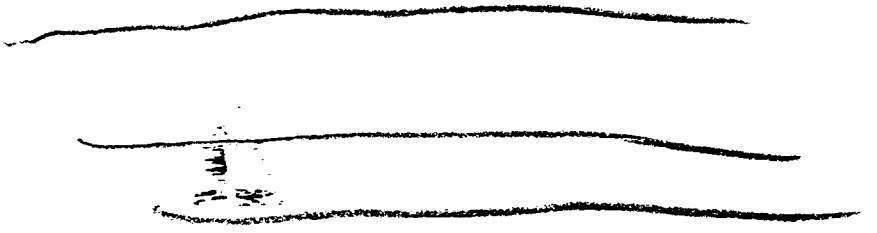
14. Rx/OTC DISPENSED: ___Rx X__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

X____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	4-Dec-2001	IR letter dated Dec, 2001sent to the holder
	II			1	Adequate	4-Dec-2001	IR letter dated Dec, 2001 sent to the holder
	III			4	N/A		All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001
	III			4	N/A		All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001
	III			4	Adequate	24-Mar-1999 (HFD-160 for tablets)	DMF withdrawn from application and replaced by DMF — See — amendment dated Dec 4, 2001.
	III			4	N/A		All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001
	III			4	Adequate	4-Aug-1999 (HFD-120 for tablets)	All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001
	III			4	N/A		DMF withdrawn from application and replaced by DMF — See amend. dated Dec 4, 2001.
	III			4	N/A		All parts comply with food additive regs.: see amend dated Nov 30, and Dec 4, 2001

III		3	Adequate	14-Feb-2001	Reviewed by HFD-540 for use with encapsulated microspheres
III		1	Adequate	03-Aug-2001	Reviewed by HFD-570 for use with extended-release tablets

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		Guaifenesin tablets by Adams Labs

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	26-Feb-2001	J. D. Ambrogio (HFD-324)
Pharm/Tox and Medical	Pending, (impurities above ICH Q3A and 3B thresholds for qualification)	Pending	Joe Sun Mary Puruker
Biopharm	Dissolution method and acceptance criteria need revision	Pending	Young Moon Choi
Methods Validation	Will be submitted upon complete method submission		
OPDRA	Acceptable	29-Nov-2001	Nora Roselle (HFD-400)
OTC (labeling)	Acceptable	13-Sep-2001	Cazemiro Martin (HFD-560)

The Chemistry Review for NDA 21-282

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is APPROVABLE from the CMC standpoint. See list of comments (end of this review) that need to be adequately addressed by applicant before the approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Currently none. Phase 4 commitment about [redacted]) is expected due to the [redacted] of the original bi-layer tablets.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This is a 505(b)(2) NDA for [redacted] extended release formulation of guaifenesin. Proposed packaging configurations include [redacted] bottles with counts of 2, 100 and 500 tablets per bottle for each strength, 600 mg [redacted] see first page of this review for detail description). Drug product is intended for over-the-counter (OTC) marketing. The proposed maximum daily dose is 2400 mg.

B. Description of How the Drug Product is Intended to be Used

Expectorant extended-release bi-layer tablets. Maximum daily dose: 2400 mg. [redacted] Labeling was revised to indicate that the tablets be taken with a full glass of water.

C. Basis for Approvability or Not-Approval Recommendation

Original NDA was submitted on Jun 29, 2000. Comments resulting from CMC review #1 were forwarded to the applicant in AE letter dated Apr 26, 2001. This review covers CMC evaluation of applicant's response submitted up to date. See below point by point evaluation of applicant's response to each CMC comment, followed by copies of updated drug substance and drug product specifications after each section. All outstanding CMC issues were summarized in a draft letter at the end of this review.

Summary of major CMC isssues:

- During the course of this review applicant [redacted] removed the [redacted] rom [redacted] 600 mg [redacted] tablets. Also, embossing was changed [redacted] to be consistent with the strength of each tablet. Data on CMC comparability of the original tablets to the new

tablets were submitted on Oct 19, 2001. Stability study of the new tablets is pending – update should be submitted in Nov 2001.

- Evaluation of new dissolution method [redacted] and new dissolution acceptance criteria is pending by the Biopharm team (see item #27 in this review).

- [redacted] out of [redacted] identified synthetic impurities found in the drug substance have currently acceptance criteria of NMT [redacted] item #7 in this review). These levels are above the qualification threshold limit of 0.05% suggested in the ICH Q3A (drug substance) and 0.10% suggested in the ICH Q3B (drug product) guidelines for drug product with daily dose above 2000 mg. Consult to evaluate safety of these levels was forwarded to PharmTox and Medical reviewers and review is pending.

- Letters to the holder (BI) of both type II DMFs [redacted]) for [redacted] are in preparation.

Commitments:

- [redacted]) was observed in certain batches of the original bi-layer tablets. Applicant attributed this to the [redacted] of the MR layer and proposed the following actions (see comment #3 in the List of Deficiencies at the end of this review).
  - Process validation of [redacted] will be performed on full scale production batches prior to commercialization of [redacted] the 600 mg [redacted]
  - In-process controls on the [redacted] will be validated and included in the batch record
  - [redacted] from each processing shift, in addition to the testing for release) will be implemented for [redacted]

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Eugenia Nashed/4-Dec-01-2001
ChemistryTeamLeader: Guirag Poochikian/
ProjectManager: Ladan Jafari/

C. CC Block

Medical reviewer: Mary Puruker
Biopharm reviewer: Young Moon Choi
CMC Div Director: Eric Duffy

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/s/

Eugenia Nashed
12/5/01 12:18:19 PM
CHEMIST

Guiragos Poochikian
12/6/01 05:16:10 PM
CHEMIST

DIVISION OF PLUMONARY AND ALLERGY PRODUCTS (HFD-570)

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-282 **DATE REVIEWED:** Mar. 16, 2001

REVIEW #: 1 **REVEWER:** Juanita Ross

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-JUN-00	29-JUN-00	06-JUL-00
AMENDMENT	02-AUG-00	03 -AUG-00	04-AUG-00
AMENDMENT	10-NOV-00	14-NOV-00	16-NOV-00

NAME & ADDRESS OF APPLICANT: Adams Laboratories, Inc.
14801 Sovereign Road
Fort Worth, TX 76155

DRUG PRODUCT NAME

Proprietary: None Provided

Established: Guaifenesin Extended Release Tablets (Bilayer Tablet)

Code Name/#:

Chem.Type/Ther.Class:

PHARMACOL. CATEGORY/INDICATION: Expectorant

DOSAGE FORM: Tablet

STRENGTHS: 600 mg
2400 mg per day/Maximum Dosage

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: __ Rx _X_ OTC

SPECIAL PRODUCTS: Yes X No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR

SUPPORTING DOCUMENTS:

TYPE/ NUMBER	SUBJECT	HOLDER	STATUS	REVIEW DATE	LETTER DATE
—	—	Adams Laboratories		7/8/98	8/4/98
DMF —	—		Inadequate Juanita Ross	12/7/00	12/19/ 00
DMF —	—		Adequate J.Clark Richard Adams	9/14/94 1/10/95	
DMF —	—		Adequate Donald Klein	9/15/00	
DMF —	—		Adequate Ravis Harapanhall	3/23/99	
DMF —	—		Adequate Chen/Duffy	9/03/97	
DMF —	—		Inadequate James Fan	7/20/94	8/15/94
DMF —	—		Inadequate Vibhakar Shah	11/4/96 1/21/97	11/7/96 1/24/97
DMF —	—		Adequate Mike Adams	12/4/00	

DMF	Adequate Ravi Harapanhalli	3/24/99	
DMF	Adequate Jeanne Taborsky Susan Rosencrance	5/26/93 1/3/00	
DMF	Adequate J. Taborsky	8/2/94	

DMF	Adequate James D. Vidra	8/13/99	
DMF	Inadequate Peri Prasad	3/14/00	3/17/00
DMF	Inadequate Peri Prasad	3/14/00	3/17/00
DMF	Inadequate J.Ross No information on	3/15/01	
DMF	Adequate Robert Permisohn	11/20/91	
DMF	Inadequate V. Sayeed	10/31/97	11/4/97

DMF	No Chemist Review		
DMF	No Chemist 'eview		
DMF	No Chemist Review		
DMF	No Chemist Review		

Evaluation:

There were drug master files, namely where there was no information submitted; thus letters will be written to the DMF holders.

There were no chemist reviews found in DMFs which described the excipients used in the drug formulation. As I reviewed these drug master files, it was noted that the suppliers were testing these excipients as compendial monographs and the applicant was also following the compendial monographs. Even the supplier's Certificate of Analysis in the NDA listed the testing as found in the compendium; therefore I see no need for an actual review.

RELATED DOCUMENTS (if applicable): None

CONSULTS: 1. Biometrics consult is deferred due to absence of adequate stability data.

2. Once reasonable acceptance criteria and corresponding methods are provided, they need to be consulted to pharmacology/toxicologists for evaluation.

REMARKS: After reviewing this application deficiencies were noted in regard to specifications for the drug substance, and its impurities, missing information for the — assay method and deficient stability information. In addition deficiencies were noted in regard to the drug product as to the Manufacturing process, specification limits, the — assay method and stability.

The applicant indicated in an amendment dated Nov. 10, 2000; that [redacted] performed — packaging during development. However, the applicant's current plans do not include data on — packages. If their plan changes, then the NDA would be supplemented.

CONCLUSIONS & RECOMMENDATIONS:

- From a chemist viewpoint this application is deficient and not approvable. See deficiency comments to applicant, pages 52 – 55.

Juanita Ross, Review Chemist

cc:
Org. NDA 21-282
HFD-570/Division File
HFD-570/RossJ/Mar. 16, 2001
HFD-570/Jafari
HFD-570/Poochikian
R/D Init by:
F/T by: Rossj
filename: **NDA21282.doc**

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/s/

Juanita Ross
3/20/01 10:18:35 AM
CHEMIST

The dates listed include the original submission and its amendments

Guiragos Poochikian
3/20/01 06:32:55 PM
CHEMIST

21 CFR 314.50 (d) (1) (iii) ENVIRONMENTAL IMPACT

CATEGORICAL EXCLUSION

This submission of an NDA for guaifenesin ER includes the claim of categorical exclusion for an Environmental Assessment.

The active moiety is currently marketed.

Current approved products on the market are for total daily doses of 2400 mg, for which the proposed will not increase.

In accordance with 21 CFR 25.31 (a), this action is a categorical exclusion. Approval of this NDA would not increase the use of the active moiety (guaifenesin) because it is currently in use at the same total daily levels, 2400 mg.

An applicant is eligible to file a claim of categorical exclusion from the requirement to submit an EA if the action meets the criteria or at least one categorical exclusion. Guaifenesin ER 600 mg meet the criteria to file a claim of categorical exclusion.