

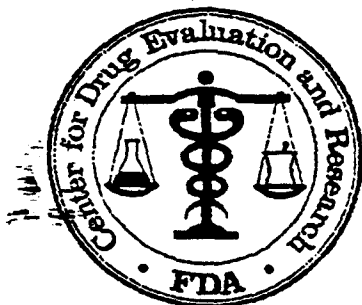
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-282

APPROVAL LETTER

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II**



TO: Mr. Jeff Keyser
Phone Number: 817-545-3629
Fax Number: 817-786-1204
FROM: Ladan Jafari, Project Manager

**DIVISION OF PULMONARY AND ALLERGY DRUG
PRODUCTS**

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 14 Date: July 12, 2002

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-282

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

Attention: D. Jeffrey Keyser
Vice President, Development & Regulatory Affairs

Dear Mr. Keyser:

Please refer to your new drug application (NDA) dated June 29, 2000, received June 29, 2000, submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mucinex (guaifenesin) Extended-Release 600 mg Tablets.

We acknowledge receipt of your submissions dated August 2, September 14, November 8, and 10, 2000, and January 22, and 29, and May 11, June 25, August 29, September 7, October 19, November 30, 2001, and January 4, 7, and 11, and March 4, May 8, 13, 22, and 23, and June 28, and July 3, and 10, 2002.

The January 11, 2002, submission constituted a complete response to our December 20, 2001, action letter.

This new drug application provides for the use of Mucinex (guaifenesin) Extended-Release 600 mg Tablets as an expectorant for patients 12 years and above.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the color mock-up carton and immediate container labels submitted June 28, 2002.

We remind you of your postmarketing commitment dated July 10, 2002. This commitment is listed below.

Chemistry, manufacturing, and controls commitment:

In addition to the normal stability agreement to place the first three production batches on stability program, Adams Laboratories, Inc. commits to perform _____ studies on the _____ of the drug product for commercial production. This will include collection _____

_____ Additional samples will be collected at different times from the regularly scheduled quality assurance and manufacturing samples.

The _____ studies are aimed to assure adequacy and consistency of the drug product manufacturing process controls and increase assurance of the drug product quality.

Upon completion, submit the data and statistical evaluation of the results as a "Supplement-Changes Being ~~Effect~~ected in 0 Days". These reports are due on or before July 15, 2003.

Submit chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of this commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission date, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol," "Postmarketing Study Final Report," or "Postmarketing Study Correspondence."

We also remind you of the following agreements discussed in your submissions dated May 8, 13, 22, and 23, 2002.

1. The extension of the approved expiry period may be attained only by submission and approval of a prior approval supplement. The following are the expiry periods approved for Mucinex (guaifenesin) Extended-Release 600 mg Tablets.

• 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 120 cc	— bottle, 100 bi-layer tablets	18 month expiry
• 600 mg 625 cc	— bottle, 500 bi-layer tablets	18 month expiry
2. Implement Alert Limits _____ as additional in-process, and lot acceptance criteria 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 long-term stability testing program and subjected to enhanced stability testing and withdrawn from the market criteria, as specified in protocol PR02-11QC, page 14, of the amendment dated May 23, 2002.

In addition, we have the following comments.

1. Delete the word "NEW" from the principal display panel (PDP) for the 2-, 20-, and 40-count carton label of Mucinex (guaifenesin) Extended-Release 600 mg Tablets 6 months after approval.

2. Due to safety concerns associated with the size of Mucinex (guaifenesin) Extended-Release 600 mg Tablets, which could pose a choking hazard for young children, we ask you to include child-resistant packaging for all package sizes. We also ask you to include a conspicuous statement "This package for Households Without Young Children" on the principal display panel of the package sizes that will not have child-resistant packaging.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on the information submitted, we conclude the following:

For use as an expectorant:

- We are waiving the pediatric study requirement for this application for patients 0 through 12 years of age.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and one copy to the Division of Over-the-Counter Drug Products.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

In line with Center for Drug Evaluation and Research policy, oversight of this application is being transferred to the Division of Over-the-Counter Drug Products.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

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

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

Enclosure

7

**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 03:44:27 PM

Linda Katz
7/12/02 03:49:12 PM
Linda M. Katz, M.D. signing for Charles J. Ganley, M.D.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-282

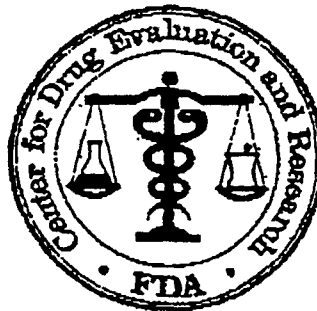
APPROVABLE LETTER

*** TX REPORT ***

TRANSMISSION OK

TX/RX NO	1272
CONNECTION TEL	918177861204
SUB-ADDRESS	
CONNECTION ID	
ST. TIME	12/21 10:17
USAGE T	06'32
PGS.	9
RESULT	OK

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION II



TO: Mr. Jeff Keyser

Phone Number: 817-786-1243

Fax Number: 817-786-1204

FROM: Ladan Jafari, Project Manager

BEST POSSIBLE COPY

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

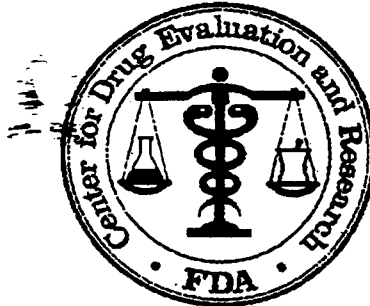
CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet:9 Date: December 21, 2001

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II**



TO: Mr. Jeff Keyser
Phone Number: 817-786-1243
Fax Number: 817-786-1204
FROM: Ladan Jafari, Project Manager

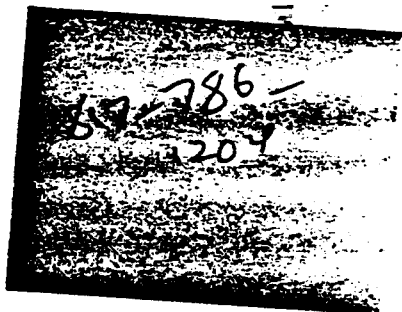
**DIVISION OF PULMONARY AND ALLERGY DRUG
PRODUCTS**

**CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857**

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet:9 Date: December 21, 2001

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.





NDA 21-282

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

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

Dear Mr. Keyser:

Please refer to your new drug application (NDA) dated June 29, 2000, received June 29, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Mucinex (guaifenesin extended release) 600 mg: _____ tablets.

We acknowledge receipt of your submissions dated June 25, July 23, August 29, September 7, October 19, and November 30, and December 4, 2001. Your submission of June 25, 2001, constituted a complete response to our April 26, 2001, action letter.

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

1. The following comments pertain to the drug substance.
 - a. Submit the revised acceptance criteria sheet (Specification number _____) and the revised stability protocol for re-testing of the drug substance. Include a table with a list of all tested attributes, individual method numbers for every analytical method in each document (to allow for tracking of future changes to the method) and the proposed acceptance criteria. Attach a sheet with structures and proper chemical names for all identified impurities. Clearly indicate (e.g., footnotes) which attributes are tested during acceptance and which are tested on reduced-schedule or during stability testing. Specify the responsible party for each test and the frequency of reduced schedule testing, e.g., every second batch. In addition, revise the proposed acceptance criteria and methods as requested in item 1b-c below.
 - b. Tighten the acceptance criteria for impurity _____ and total impurities to reflect the data. Revise the acceptance criteria and data-reporting format to include two significant figures after the decimal point for every impurity attribute. Submit supportive release and stability data, preferably in the revised table format as described in item 1.a. above, i.e., attribute, method, acceptance criteria, and results.

- c. Provide a validated quantitative method and a data-based acceptance criteria for color and particle size distribution. Submit the release and stability data (preferably in a revised table format, i.e., attribute, method, acceptance criteria and results) to show comparability of your results to the results obtained by the drug substance manufacturer as a justification for the reduced-schedule testing. The proposed acceptance criteria for particle size distribution (mean) and color seem exceedingly wide. Tighten the acceptance criteria to reflect the test results.
2. The following comments pertain to the drug product release and stability testing.
- a. Submit the revised specification tables for release (Specification numbers _____) and stability (Protocol _____) testing. Include a list of all tested attributes, individual method numbers for each analytical method in the tables (to allow for tracking of future changes to the method) and the proposed acceptance criteria. Also, list all impurities present in the drug substance on the drug product specification sheets. If you have adequate data demonstrating that some of the listed impurities do not increase during manufacturing or storage, they do not need to be routinely tested, but need to be listed as supportive information. In such cases, provide explanatory footnotes and references to the submitted supportive data. Attach a sheet with structures and proper chemical names for all identified impurities to each specification table. In addition, revise the proposed acceptance criteria and methods as requested in item 2b-i below.
- b. Tighten the acceptance criteria for impurity _____ and total impurities to reflect the data (refer to comments 1b and 2a above). Submit an update on the pending stability studies for the original and the new tablets to support the proposed expiry period of 24 months. The revised format (i.e., a table listing all tested attributes, methods, acceptance criteria and results) is highly recommended (refer to item 2a above).
- c. Explain how the Total Degradation Products are determined and provide supportive data to justify the proposed acceptance criteria of NMT _____. Include a short description of the Total Degradation Products in the table to indicate what is included in this attribute.
- d. Increase the accuracy of reporting data for impurities to include two significant figures after the decimal point. Revise the acceptance criteria and methods for every impurity attribute accordingly to avoid reporting "Total Unspecified Impurities" as _____, whereas individual unspecified impurities are present at _____ levels (refer to page 4 of October 19, 2001 amendment).
- e. Tighten the release and stability acceptance criteria for assay to improve the mass balance. Provide supportive data and revise the analytical method as necessary.
- f. Specify which variant of the method described in USP <905> is used for the determination of content uniformity. Provide acceptance criteria consistent with the results. Include appropriate revisions on the drug product specification sheets.

- g. Modify the acceptance criteria for description to reflect the new shape of the tablets. Note that "conforms" (refer to the stability specifications) is not an acceptable entry for the acceptance criteria.
- h. Revise the stability commitments (refer to stability protocol page 4-443 of your June 25, 2001, amendment) to clarify that each of the 2-, 100- and 500-count presentations for drug product (600 mg) will be placed into the stability program.
- i. The following dissolution method and specifications are recommended for the 600 mg guaifenesin extended release formulations.

Recommended Dissolution Method and Specification for 600 mg ER

Apparatus:

Medium:

Recommended specification:

Time (Hour)	600 mg ER
—	NMT —
—	—
—	—
—	NLT —

- 3. The following comment pertains to the history of the high friability of the bi-layer tablets. (Refer to you response to item #33 of our letter dated April 26, 2001).
 - a. Provide a short summary of the process validation for the bi-layer tablet compression and a copy of the current in-process compression controls (maximum number of strokes, etc.) for the full scale manufacturing batches.
 - b. Provide a _____ regarding the _____ for the first _____ of the bi-layer tablets.

- c. Provide the revised acceptance criteria _____ to include at least _____ significant figure after the decimal point. Tighten the proposed acceptance criteria to reflect the results from full scale manufacturing batches.
4. Letters dated December 13, 2001, have been issued to the holder of the Drug Master File (DMF) _____. Adequate status of each supporting DMF is necessary before this application is approved.
5. Confirm that the container closures proposed for marketing comply with the Consumer Product Safety Commission's Regulation on Child-Resistant Packaging for Certain OTC Drugs.
6. Submit revised draft carton (2 counts) and container labels (2 and 100 counts) incorporating the following comments:
- (1) Immediate container labels for 100 counts
 - (a) Relocate the word "Bi-layer" from the _____ to be part of the declaration of net content (i.e. "Guaifenesin Extended-Release Tablets" and "100 Bi-layer Tablets"), where applicable. The net quantity should appear away from the product strength and have less prominence.
 - (b) Use the attached prototype "Drug Facts" to revise the "Drug Facts" section of the carton label.
 - (2) Immediate container label for 2 counts
 - (a) Relocate the word "Bi-layer" from the _____ to be part of the declaration of net content (i.e. "Guaifenesin Extended-Release Tablets" and "100 Bi-layer Tablets"), where applicable. The net quantity should appear away from the product strength and have less prominence.
 - (b) Revise _____ "SEE CARTON FOR COMPLETE INFORMATION".
 - (c) Revise the "DIRECTIONS" section in accordance to the "DIRECTIONS" in the "Drug Facts" prototype labeling.
 - (3) Carton labels for 2 counts
 - (a) Relocate the word "Bi-layer" from the _____ to be part of the declaration of net content (i.e. "Guaifenesin Extended-Release Tablets" and "100 Bi-layer Tablets"), where applicable. The net quantity should appear away from the product strength and have less prominence.
 - (b) Revise the phrase ' _____ ' to " _____ " because it implies a comparative benefit that is not supported.

- (c) Use the attached prototype "Drug Facts" to revise the "Drug Facts" section of the carton label.
- (4) Others:
 - (a) The term "NEW" may not appear on the carton labeling more than six months from the date of approval.
 - (b) 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.
 - (c) We have concerns regarding the ease of swallowing in relation to the size of the tablets, especially in children. Thus, we are limiting these products to adults and children over 12 years of age only. The "Direction" section has been revised to limit the dose instructions to "adults and children 12 years of age and over" only.

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

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-5584.

Sincerely,

(See appended electronic signature page)

Robert J. Meyer, M.D.

Director

Division of Pulmonary and Allergy Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Charles Ganley, M.D.

Director

Division of Over the Counter Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

Enclosure: Prototype "Drug Facts" labeling for Guaifenesin Extended-release Tablets

***Prototype:* Drug Facts Labeling**

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

Drug Facts

<i>Active ingredient (in each extended-release tablet)</i>	<i>Purpose</i>
Guaifenesin [insert "600 mg"]	Expectorant

Uses helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus and make coughs more productive

Warnings

Do not use ■ for children under 12 years of age

Ask a doctor before use if you have

- persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema
 - cough accompanied by too much phlegm (mucus)
-

Stop use and ask a doctor if

- cough lasts more than 7 days, comes back, or occurs with fever, rash, or persistent headache. These could be signs of a serious illness.
-

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

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

Directions

- do not crush, chew, or break tablet
 - take with a full glass of water
 - this product can be administered without regard for the timing of meals
 - adults and children 12 years of age and over: [For the 600 mg product insert "one or two tablets"; _____ every 12 hours. Do not exceed [For the 600 mg product, insert "4 tablets"; _____ in 24 hours.
 - children under 12 years of age: do not use
-

Other information

- tamper evident: do not use if neckband is broken
 - store between 20-25°C (68-77°F)
 - see bottom of bottle for lot code and expiration date
-

Inactive ingredients carbomer 934P, NF; dyes; hydroxypropyl methylcellulose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF

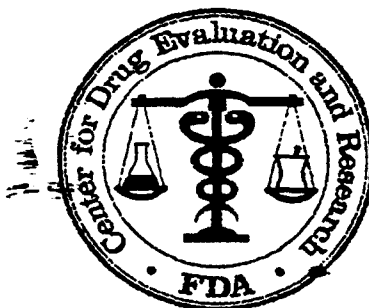
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Marianne Mann
12/20/01 03:27:17 PM

Charles Ganley
12/20/01 05:02:42 PM

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II**



TO: Mr. Jeffrey Keyser
Phone Number: 817-545-3629
Fax Number: 817-786-1151
FROM: Ladan Jafari, Project Manager

**DIVISION OF PULMONARY AND ALLERGY DRUG
PRODUCTS**

**CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857**

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 9 Date: April 27, 2001

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

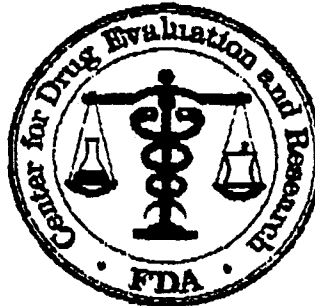
MESSAGE CONFIRMATION

04/27/01 07:12
ID=PULMONARY DIV FDA

NO.	MODE	BOX	GROUP
329	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
04/27	07:09	02'54"	8177861151	009/009	OK	0000

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION II



TO: Mr. Jeffrey Keyser
Phone Number: 817-545-3629
Fax Number: 817-786-1151
FROM: Ladan Jafari, Project Manager

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 9 Date: April 27, 2001
THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED
AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM



NDA 21-282

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

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

Dear Mr. Keyser:

Please refer to your new drug application (NDA) dated June 29, 2000, received June 29, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Guaifenesin 600 mg Extended Release Tablets.

We acknowledge receipt of your submissions dated August 2, September 14, November 8 and 10, 2000, and January 22, and 29, and March 30, 2001.

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

The determination of approvability of _____ and Guaifenesin 600 ER was based upon a finding of adequate bioequivalence as compared to the referenced OTC monograph product. _____

Guaifenesin 600 ER are therefore eligible to be marketed as OTC products, and should be labeled as OTC products.

Submit revised draft labeling incorporating the following comments.

1. Revise the labeling as specified in 21 CFR 330.1 and according to the final monograph for expectorant drug products, guaifenesin, 21 CFR 341.78 (d). [54 FR 8509, Feb. 28, 1989]
Additional labeling comments will be provided when this and the following issues have been resolved.
2. Under the *Directions* section of the product monograph, include dosing information appropriate to the strength and modified release characteristics of _____ Guaifenesin 600 ER.
3. Under the *Directions* section of the product monograph, include the following statements.
 - a. Do not chew or break.
 - b. Guaifenesin ER can be administered without regard for the timing of meals.

4. List all the excipients on the container and carton labels.

The following comments pertain to the drug substance.

5. Provide a quantitative test for color in the Description Test.
6. Provide appropriate acceptance criteria for particle size distribution. The proposed acceptance criteria of NMT _____ retained on a _____ in the _____ does not assure batch-to-batch consistency of the drug product.
7. The acceptance criterion for guaifenesin _____ is unjustified. Provide appropriate acceptance criterion to reflect actual data. In addition, qualify any impurity with the acceptance criterion _____
8. Identify and qualify with appropriate supportive data, any "Unidentified Individual Impurity" when the proposed acceptance limit is _____
9. Revise the acceptance criteria for "Unidentified Total Impurities" to reflect actual data.
10. Submit a comprehensive stability protocol that also includes storage conditions, test parameters such as assay, moisture content, specified and unspecified impurities, and total impurities (specified and unspecified impurities), and the appropriate stability commitment statement.
11. Provide the following additional information in the stability studies.
- a. Report the Related Impurities individually.
 - b. Monitor and report Guaifenesin _____

The following comments pertain to the manufacture of the drug product.














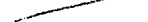
12. Provide better defined distribution criteria for particles using the Sieve Analysis Test or other alternatives for the following.
- a. Sub-lots (A, B, C, and D) of Guaifenesin _____
 - b. Blended material, Guaifenesin _____
13. Provide appropriate acceptance criteria for particle sizing in the _____ used in the immediate release blend and modified release blend to assure batch-to-batch consistency.
14. Clarify why the numbers _____ are proposed to be embossed on the 600 mg _____ tablets _____. The use of 600 _____ notations _____ will be less confusing.

15. Remove _____ of the extended release tablets, or fully justify that the _____ of the tablets does not affect the dissolution characteristics and/or bioavailability.
16. Identify the DMF holder and a DMF number for the proposed _____
In addition, provide a letter of the authorization from the DMF holder.
17. Revise the master batch record to clearly state that no reprocessing will be performed, and to include the modifications listed above.

The following comments pertain to drug product specifications.

18. Provide the description of the proposed sampling plans, [i.e., number of samples selected, how they are used (i.e. as individual or composite samples), number of replicate analysis per sample].
19. Provide dissolution profile data of tablets (600 mg : _____ when the hardness values are at the limits (_____ for the 600 mg _____
Alternatively, tighten the acceptance criteria significantly to reflect data.
20. Provide the following information pertaining to the _____ Assay method.
 - a. Resolution factor between potentially closest eluting peaks with supportive data.
 - b. Limit of detection (LOD) and limit of quantitation (LOQ) for impurities and degradation products.
 - c. Criteria for Tailing Factor for all peaks.
 - d. Chromatograms of samples that include guaifenesin, related substances, and degradants with peaks Identified.
 - e. Description of Standard Impurities Solution.
 - f. Description of Sample Preparation Solution for the drug substance.
 - g. Formula for calculating impurities.

h. Identification of the following peaks (Source: Vol. 1.3, pages 5 and 22):

	(RRT)		(RRT)
Peak 1		Peak 8	
Peak 2		Peak 9	
Peak 3		Peak 10	
Peak 4		Peak 11	
Peak 5		Peak 12	
Peak 6		Peak 13	
Peak 7		Peak 14	
		Peak 15	

21. Tighten the release acceptance criteria for assay of the active ingredient : _____
22. Provide appropriate validation data that include limit of detection (LOD), limit of quantitation (LOQ), accuracy, precision, resolution factor, etc. for impurities. Refer to ICH guidance entitled, "Validation of Analytical Procedures: Methodology".
23. The acceptance criterion for guaifenesin _____ of NMT _____ is not justified. Tighten the acceptance criterion to reflect actual data. In addition, the proposed limit is beyond the qualification threshold of _____
24. The proposed acceptance criteria for the Unidentified Individual Impurity of NMT _____ and the Total Unidentified Impurities of NMT _____ are not justified. Identify and qualify any unidentified degradation product _____ with appropriate supportive data.
25. Revise the acceptance criterion for Unidentified Total Impurities to reflect actual data. In addition, since the specification limit of "to be determined" for Total Degradation Products is not acceptable, include appropriate acceptance criterion for "Total Degradation products".
26. Submit actual Content Uniformity data for the clinical lots PB304 and PB322.
27. The proposed dissolution specifications are inadequate and should be tightened significantly to reflect the data. Alternatively, provide available bioavailability data to establish and validate appropriate dissolution acceptance criteria ranges.
28. Identify the supplier of each component of the container closure system, (e.g. bottles, caps, seals, blister, cotton coil, desiccant, etc), and provide corresponding specifications and test results (properly identified).

The following comments pertain to stability studies and stability protocol.

29. Revise the stability protocol to identify and list the impurities and degradants individually and as total.

- The specifications should include guaifenesin _____, unidentified individual, unidentified total, etc. In addition, provide corresponding acceptance criteria to reflect actual data.
30. Explain the reported results for Total Degradation of _____ and the apparent discrepancy in balance since the Assay results have decreased over a six months period by more than _____. Provide supportive data for mass balance. Also, see comments 20, 22, and 31.
 31. Identify the compounds that were reported in the stability studies, indicated under Related Substances, specifically:
 - a. Result _____ reported for lot PB322-OB at three months for bottles of 2's at 40°C/75%RH.
 - b. Result _____ reported for lot PB-314S at three months for bottles of 2's at 5°C/60%RH.
 - c. Result _____ reported for lot PB315S at three months for bottles of 2's at 25°C/60%RH.
 32. Monitor and report in the stability studies, all degradation products: _____
 33. The following comments pertain to friability of the tablets.
 - a. Describe in detail the types of studies that were conducted to address the observed high values over _____ for friability.
 - b. Provide data on new batches to demonstrate that friability issues have been rectified.
 34. Include Photostability Testing in your stability studies describing conditions, duration of studies and data. Refer to "Guidelines for Photostability Testing of New Drug Substances and New Products" (ICH Q1B), for details.
 35. Provide stability data for each potency of the 500 count bottles.
 36. Specify the type of closures and type of seals used in the stability studies and those intended to be used for marketing.
 37. Provide a comprehensive stability protocol that includes all the pertinent information. Refer to the draft stability guidance for additional information.
 38. In the stability protocol, include the requisite stability commitment as well as information pertaining to annual stability batches. Refer to guidance entitled "Stability Testing of Drug Substance and Drug Products" (ICH Q1A).
 39. DMFs _____ are inadequate and the DMF holders have been notified.

The following comments pertain to clinical and biopharmaceutical issues.

40.

41. The _____ of the 600 mg _____ tablets _____ that these products can be or ought to be _____ prior to oral ingestion. For this reason, the _____ of these tablets should be _____ or, alternatively, data on the effects of _____ the tablet on the modified release characteristics of the 600 mg _____ tablets should be provided. Submit comparative data on the strength and the profile dissolution data of each of the _____ and whole tablet using your proposed assay and dissolution condition.

42.

For the 600 mg ER tablet, _____ appeared not an appropriate medium since the dissolution did not reach plateau and is less than _____ at _____ hour. Change the dissolution medium to _____

The following is recommended dissolution method and specification for the 600 mg Guaifenesin Extended Release Tablets.

Apparatus: USP type II (Paddle) 50 rpm

Medium: _____

Recommended specification:

Time (Hour)	600 mg ER
_____	_____
_____	_____
_____	_____
_____	NLT _____

You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

NDA 21-282

Page 7

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Robert Meyer

4/26/01 05:13:30 PM