CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-282

CORRESPONDENCE

Adams®
LABORATORIES, INC.

July 10, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
HFD-570, Room 10B-03
Attention: Dr. Richard Meyer, Director
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-282

Dear Dr. Meyer:

In additional to the normal stability agreement to place the first three production notices on the stability program, Adams Laboratories, Inc. commits to perform [redacted] studies on the [redacted] of the drug product for commercial production. This will include collection of additional samples of a minimum of [redacted] obtained [redacted] Additional samples will be collected at different times from the regularly scheduled quality assurance and manufacturing samples.

We commit to completing this phase IV commitment within six to twelve months after approval of NDA 21-282.

If you have questions or need further information, please contact me at (817) 786-1243.

Thank you,

D. Jeffrey Keyser
Vice President
Development & Regulatory Affairs

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DRUG ENFORCEMENT
N-000-BC

RECEIVED
MAY 23 2002
HFD-570 / CDER

May 22, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
HFD-570, Room 10B-03
Attention: Dr. Richard Meyer, Director
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-282

Dear Dr. Meyer:

This submission is in response to our teleconference of May 21, 2002. Responses follow for the two questions raised during the teleconference. Dr. Nashed's requests are listed below in bold italics, followed by Adams Laboratories' responses.

1. ***Clarification of page 4-183 and page 4-186 of the stability protocol in the May 8, 2002 submission:***

   Dr. Nashed requested that we put in the stability protocol and in the drug product specification tables a reference which states that any lot exceeding the friability alert limit (specifically, [redacted] for the 600 mg [redacted] products, respectively) will be placed in the stability program and [redacted] conducted. Dr. Nashed wanted this statement added in both the stability protocol and in the drug product release specifications. Additionally, Dr. Nashed requested that a friability and hardness limit be added to the stability protocol (page 4-183 of the May 8, 2002 submission).

   Stability protocol PR02-11-QC has been revised to incorporate a friability limit of NMT [redacted] for [redacted] the 600 mg [redacted] product, including a reference to the specific alert limits for each product (see Exhibit C, page 4-31).

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A hardness limit of [redacted] for the 600 mg product [redacted] has also been added to the specification tables in the stability protocol (see Exhibit C, page 4-31). Additionally, the stability commitment for [redacted] now references the specific values of the corresponding alert limits for the 600 mg [redacted] (see Exhibit C, page 4-34).

The Drug Product Acceptance Specifications for the 600 mg guaifenesin ER tablets (DPS-1003) [redacted] have been amended to clearly indicate a commitment to place any batches exceeding the alert limit into the real-time stability program (see Exhibit A, page 4-1, 4-8, and 4-10 and Exhibit B, page 4-11, 4-18, and 4-20, respectively).

2. ***Dr. Nashed requested a brief history of adjustments to the bi-layer press, specifically with respect to the pilot batches and the validation batches. She asked that a table or time line be provided with dates and lot numbers for the pilot batches, the validation batches, and the post-validation batches manufactured to date. This table should identify where adjustments to the press occurred in order to correct the observed increase in friability.***

The Pilot Batches for the 600 mg guaifenesin ER tablets were compressed in December 1999. At the time the Pilot Batches were compressed, detailed compression parameters had not been established. These Pilot Batches (PB-320, PB-321, and PB-322) were packaged into 2-count bottles, 100-count bottles, and 500-count bottles and were monitored through accelerated and real-time stability studies. During these stability studies, elevated friability results were occasionally observed (see the stability reports included in our 5/8/02 response, Exhibit K, page 4-213 – 4-245).

After compression of the Pilot Batches, optimization studies were undertaken to improve the friability of the tablets. During the studies it was determined that the [redacted] as well as the [redacted], were key variables that needed to be controlled in order to produce a tablet with low friability levels. [redacted] Once these parameters were defined, the appropriate [redacted] were incorporated into the setup instructions of the process validation studies.

All process validation lots (Lots 1E0804, 1G0805, and 1G0806) were manufactured adhering to these press parameters. As can be seen by the friability data (see our 5/8/02 response, Exhibit Q, page 4-422), consistently low friability values were obtained. The process validation lots were packaged for stability studies into 2-count bottles, 20-count bottles, 40-count bottles, and 100-count bottles and were monitored through accelerated and real-time stability studies. During these stability studies, no friability results above — have been observed to date (see the stability reports included in our 5/8/02 response, Exhibit M, page 4-279 – 4-309).

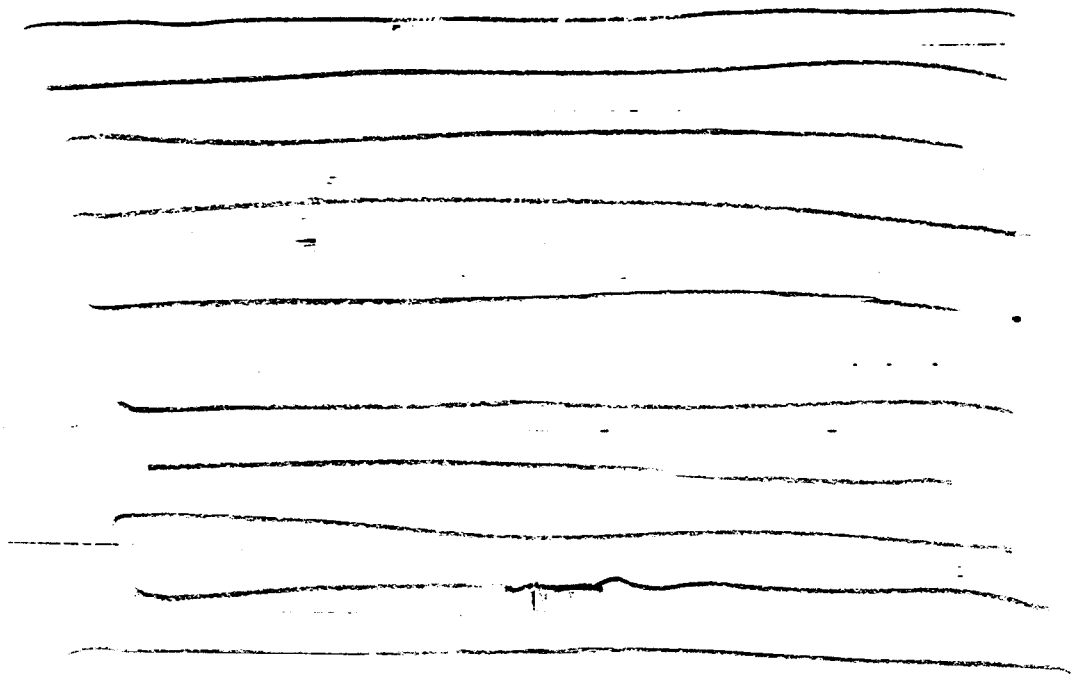
All batches of 600 mg guaifenesin ER tablets manufactured since the process validation lots have utilized the same press parameters. No changes have been made to the validated process.

During a statistical review in May 2002 of all batches of 600 mg guaifenesin ER tablets made to date, a slight upward trend was observed in batches manufactured in late 2001 (specifically, October and November 2001). This observation led to creation of "alert" and "action" levels to provide tighter in-process controls on tablet friability (see our 5/8/02 response, Exhibit Q, page 4-424 – 4-426).

While a slight drift toward higher friability values was noted in some batches, it should be noted that the same press parameters employed during process validation were followed for these batches. The occasional, elevated friability value most likely results from the process of checking the weight of the modified release (MR) layers. In order to determine the weight of the MR layer, a —

This change in — back to the — can cause an occasional, elevated friability result.

All press settings and clarifications determined after production of the Pilot Batches and utilized in the process validation lots remain in effect to this day. All future production of 600 mg guaifenesin ER tablets will be performed under these criteria. In addition, the use of "alert" and "action" levels has been implemented for in-process friability checks. These tightened criteria generate an immediate corrective action or adjustment of the press at the respective "alert" and/or "action" limits. A table summarizing the chronology of the 600 mg ER tablet compression process is attached as Exhibit D, page 39.



If you have any questions regarding this matter, or need additional information, please contact me at (817) 786-1243.

Sincerely,

D. Jeffery Keyser
Vice President
Development & Regulatory Affairs

DUPLICATE N-000BC

Adams®
LABORATORIES, INC.

May 23, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
HFD-570, Room 10B-03
Attention: Dr. Richard Meyer, Director
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
MAY 24 2002
HFD-570 / CDER

RE: NDA 21-282

Dear Dr. Meyer:

This is in response to our teleconference of May 23, 2002. We agreed on the following expiration dating for the Mucinex™ 600 mg tablet packaging configurations.

- Bottles of 2 count.....12 month expiration dating
- Bottles of 20 count.....24 month expiration dating
- Bottles of 40 count.....24 month expiration dating
- Bottles of 100 count.....18 month expiration dating
- Bottles of 500 count.....18 month expiration dating

We commit to submitting a prior approval submission to the Division in order to increase the expiration dating on the above referenced packaging configurations. Attached to this submission you will find the revised stability protocol with the changes agreed to in the teleconference. We have referenced the agreed upon expiration dating to the appropriate packaging configuration on page 12 of 16 in the stability protocol. The commitment to submit a prior approval submission to the Division in order to increase the agreed upon expiration dating for Mucinex™ 600 mg tablets is included on page 15 of 16 in the stability protocol.

As a part of this agreement to move forward with the above referenced expiration dating and approval of NDA 21-282 we agreed to withdrawal without prejudice the [redacted] at this time. We will be [redacted] after NDA approval. We hereby request that the [redacted] be removed from NDA 21-282 at this time.

If you have additional questions related to this matter, please contact me at (817) 786-1243.

Thank you,

D. Jeffrey Keyser
Vice President
Development & Regulatory Affairs

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Adams® LABORATORIES, INC.

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MAY 1 4 2002

HFD-570 / CDER

May 13, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
HFD-570, Room 10B-03
Attention: Dr. Richard Meyer, Director
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-282

Dear Dr. Meyer:

This is in response to your telephone call of May 10, 2002 requesting additional clarification for our submission of May 8, 2002. We provided you with a fax copy of this submission on May 13, 2002.

This is to confirm that Adams Laboratories is not requesting approval of a [redacted] package configuration for Mucinex. We request that any reference to this type of packaging configuration [redacted] be withdrawn from your consideration during the final evaluation of NDA 21-282.

We have requested approval for additional bottle size presentations. Attached you will find a table that describes these package configurations. The new presentations for 600mg guaifenesin are in sizes of 20's and 40's. [redacted] The new presentations are in a 75cc bottle with a [redacted] plastic cap. The table includes the component type, description of the closure system, DMF references, NDA references, vendor compliance statement references and reference to the appropriate supporting stability report. As you can see the new presentations are identical to prior submitted configurations except for size. The same manufacturer, materials and design were used for the new presentations so the DMF references are the same as that referenced and reviewed from prior submissions.

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The Drug Substance Acceptance Specification (Specification No. [redacted] was revised to include the structures omitted on page 4-13 from the May 8, 2002 submission. This was an unintentional omission on our part; the only change from revision 01 contained in this submission from revision 00 submitted on May 8, 2002 is the addition of the chemical structures to the specification.

If you have additional questions please contact me at (817) 737-1243.

Thank you,

D. Jeffrey Keyser
Vice President
Development & Regulatory Affairs

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ORIGINAL ORIG AMENDMENT

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N-000 BZ

RECEIVED
MAY 0 9 2002
HFD-570 / CDER

May 8, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
HFD-570, Room 10B-03
Attention: Dr. Richard Meyer, Director
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-282

Dear Dr. Meyer:

This submission is in response to our teleconference of March 8, 2002. Responses follow the questions as discussed from the approvable letter.

1. ***Discussion on questions 1.a, and 2.a. of the approvable letter:***

Dr. Nashed requested that the specification sheet for the drug substance and the drug product include a method number for each method used. Dr. Nashed stated that the specification table for the drug substance and the drug product should include the effective date, and superceded date.

The specification sheets for the drug substance and the drug product have been revised to include a method number for each method used (see Exhibit A, pages 4-10 – 4-15 and Exhibit B, pages 4-16 – 4-35). In addition, the individual test methods for the drug substance have been included (see Exhibit C, pages 4-36 – 4-49), as well as the test methods for the drug product (see Exhibit D, pages 4-50 – 4-90). The specification tables for the drug substance (Exhibit A, pages 4-10 - 4-11) and the drug product (Exhibit B, pages 4-16 - 4-19 and pages 4-26 – 4-29) have been revised to include the effective date and superceded date.

All other specifications for the inactive ingredients contained in the 600 mg guaifenesin ER tablets have also been revised to include a method number for each method used (see Exhibit E, pages 4-91 – 4-116). The test methods for each of the inactive ingredients are included as Exhibit F, pages 4-117 – 4-172.

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Also, the frequency of "Full Testing" ——— and information on how many times the drug substance can be re-evaluated should be included. In addition, the stability testing should include melting point evaluation.

The frequency of "Full Testing" ——— and information on how many times the drug substance can be re-evaluated have been included in the Drug Substance Acceptance Specification (Exhibit A, page 4-11). Melting point evaluation has also been included in the re-evaluation/stability testing (see Exhibit A, pages 4-10 – 4-11).

For the drug product stability studies, Adams Labs should include the long-term and accelerated study in the same stability protocol. Stability protocols for the 600 mg tablets may be submitted separately or combined together in one protocol with proper explanation on how many batches of each strength were tested.

The long-term and accelerated studies have been included in the same stability protocol (see Exhibit G, pages 4-173 – 4-190). Stability protocols for the 600 —— mg tablets have been combined in one protocol (Exhibit G, pages 4-173 – 4-190). The stability protocol indicates how many batches of 600 mg ——— tablets were tested in accelerated and real time stability studies (see Exhibit G, pages 4-189 – 4-190).

2. *Discussions on questions 1.b. and 2.b.:*

Dr. Nashed asked that the acceptance criteria be tightened and data be provided to reflect it. It is understood that the drug substance stability program is done by ——— however, we would like to see the data from re-evaluation studies performed by Adams. Adams Labs indicated that they do not have the drug substance in storage for more than a few months, therefore, they do not have any data. Dr. Nashed asked that Adams include a statement to clarify that for the drug substance.

The acceptance criteria for impurity ——— and total impurities have been statistically evaluated. The statistical analysis of the impurity level found in 74 lots of drug substance is presented as Exhibit H, page 4-191 - 4-199. This report indicates that the impurity acceptance criteria currently in place are appropriate for the drug substance. Therefore, the impurity acceptance criteria for the drug substance and the drug product have remained unchanged. The acceptance criteria for impurity ——— and total impurities in both the drug substance and drug product specifications can be found in Exhibit A, page 4-10 and Exhibit B, pages 4-17 and 4-27, respectively. All other impurities' acceptance criteria were either equal to the limits suggested by the statistical review or at the required reporting threshold for specified identified impurities.

Further statistical reviews were performed on the drug substance to establish scientifically-based acceptance criteria for the Harrison Whiteness Color test and Particle Size test. Exhibit I, pages 4-200 - 4-202 and Exhibit J, pages 4-203 - 4-212 are statistical reports that suggest confidence limits for the Harrison Whiteness Color and Particle Size tests as determined by the statistical evaluation of the available data. The existing Harrison Whiteness Color limit of NLT [redacted] was found appropriate, but changes were recommended for the Particle Size acceptance criteria. We have tightened the Particle Size limits from [redacted] for the Mean Particle Size, D10 from NMT [redacted] to NMT [redacted] and D90 from NMT [redacted] to NMT [redacted] The specification for the drug substance has been revised to include the Particle Size acceptance criteria changes (see Exhibit A, page 4-11).

As mentioned during the FDA teleconference with Adams Laboratories on March 8, 2002, herein referenced, Adams Laboratories has not generated any stability data for the drug substance, nor has it had the need to retest drug substance lots under the one-year re-evaluation program. As such, Adams Laboratories is not able to provide any data from lots stored over a year.

However, the update of stability data for the drug product should be submitted. Dr. Nashed indicated that the stability program for the drug product is currently under review by the Agency's statistical reviewer and further communications may be necessary as a result of this review. Dr. Nashed inquired as to why the impurities were not tested until 18 months of storage. Adams Labs responded that in their original submission, the impurities and methods were not available, so they used the contract lab's data to develop the impurity profile.

Dr. Nashed stated that Adams Labs should have 24 month stability data at this point and asked that certain parameters such as assay, friability, hardness, loss on drying and individualized and total impurities be evaluated individually and the statistical evaluation reported with confidence limits on the old vs. the new tablet. This data should be prepared in a graph format. Dr. Nashed reminded Adams Labs that the specification requested should be supported by data, and that we will set expiry based on the data provided. Adams Labs asked if they have to report on every impurity, and Dr. Nashed stated that data is required for impurity number [redacted] and total impurities.

Updated stability reports for the [redacted] 600 mg tablets [redacted] packaged in bottles of 2's, 100's, and 500's are presented in Exhibit K, pages 4-213 - 4-245 and Exhibit L, pages 4-246 - 4-278, respectively. Updated stability reports for [redacted] 600 mg tablets packaged in bottles of 2's, 20's, 40's, and 100's and [redacted] are presented in Exhibit M, pages 4-279 - 4-309 and Exhibit N, pages 4-310 - 4-338, respectively.

Statistical evaluations of all the referenced parameters supporting at least a 24-month expiration date are presented in Exhibit R, pages 4-456 - 4-661.

The statistical evaluation of the assay from stability data highlighted statistical differences between the [redacted] tablets. As reported in this evaluation (see Exhibit R, pages 4-456 - 4-485), the significant result appears to result from the substantially reduced assay error from the [redacted] data to the [redacted] data. Significant variations in assay results were highlighted in FDA's approvable letter dated April 26, 2001 and Adams response dated June 25, 2001. In this response Adams Laboratories acknowledged that the stability assay data appeared to indicate variations in assay results from time point to time point. Consequently, certain documentation and procedural activities were strengthened in the laboratory. It is noteworthy that all of the data reported for the [redacted] products were generated after the laboratory enhancements were incorporated, as opposed to all of the [redacted] data reported prior to these enhancements. The statistical evaluation correctly identifies the positive difference these enhancements have made. Whether [redacted] or not, the weight of the material compressed into a tablet is not changed. In these analyses, the effect of [redacted] represents the effect of everything associated with the [redacted] tablets. Therefore, the differences noted in the statistical report between [redacted] tablets are attributed to the laboratory improvements implemented in response to the April 26, 2001 approvable letter.

The statistical evaluation of the assay data from the stability studies for the 600 mg product, [redacted] unscored, conclude that in all the presentations studied, the lot mean potency will remain within [redacted] of label claim for at least 24 months.

[redacted]

The statistical evaluation of the friability results from the stability studies concluded that while elevated results were observed for some of the [redacted] tablets, the results seem to be a function of the tablets themselves rather than an influence of the package size, environmental conditions, or length of storage (see Exhibit R, pages 4-486 - 4-496).

Friability concerns were first identified during the stability studies for the 600 mg product, more specifically lot PB-321.These concerns were also raised by FDA in an approvable letter dated April 26, 2001 and Adams' response dated June 25, 2001. In this response, Adams Laboratories expanded on the types of studies conducted to address the observed high friability values. Data on new batches was also provided to demonstrate that the friability issues had been rectified. Data on the validation batches and subsequent commercial batches were also provided under response dated January 11, 2002 to an approvable letter dated December 21, 2001. Additionally, the [redacted] validation lots have been placed on stability and friability monitored. The data collected to date provide evidence that the optimization of the compression parameters at time of manufacture have corrected the friability concerns and any excursions beyond the established limits are very rare.

The statistical evaluation of the hardness results from the stability studies of the — 600 mg — product concluded that in all the presentations studied, the hardness will remain within the release limits for at least —. As expected, the hardness projections for the unscored tablets are consistent with the —— The data support that hardness will remain within release limits for — — (see Exhibit R, pages 4-581 - 4-661).

The statistical evaluation of the LOD results from the stability studies concluded that lot mean Loss On Drying (LOD) in all the packages proposed for marketing of each strength of the product will remain below the established limit for at least —— (see Exhibit R, pages 4-497 - 4-516). This evaluation also highlighted differences in LOD between the —— unscored tablets. However, given this specific test and the variations in moisture levels from lot to lot of material used to manufacture the tablets, these differences are not considered of significance in practical terms, as evidenced in the referenced report. As expected, the rate of LOD change varied with the various packages, with all values well within the established limits.

The statistical evaluation of the individual and total impurity results from the stability studies concluded that there is no increase in any of the reported impurities regardless of strength or shape, with most of the variation originating from lot to lot or measurement variations (see Exhibit R, pages 4-517 - 4-580).

Adams Laboratories has committed to an ongoing stability program for guaifenesin ER Tablets. Based upon and supported by the submitted data, we are requesting a 24 month expiration date for our product.

Dr. Nashed asked that the stability data be reported with the latest acceptance criteria. Adams Labs should also indicate in a footnote if they are using a new modified method (e.g., new RPM) or revised acceptance criteria.

All stability data reported in Exhibits K, L, M, and N are reported with the latest acceptance criteria. Changes in methods or acceptance criteria throughout the stability studies are denoted using footnotes to indicate the nature of the changes.

3a. Discussion on question 3.b. of the approvable letter.

Dr. Nashed indicated that the data for validation batches were different from those of the full-scale batches. Therefore, we need to know about any manufacturing changes, press operation speed during validation, and how this is reflected in the ——— for the current in-process controls. In addition, Adams should provide numbers for full scale that was used for validation batches and tighten the in-process specifications as appropriate. A revised "Exhibit O" should be submitted.

There have been no manufacturing changes in the manufacture of Mucinex (guaifenesin ER) 600 mg tablets. The tablet manufacturing process was validated at a press speed of — using a ——— . All batches manufactured after the — validation batches have been compressed at a press operating speed of — Any changes to this operating speed will be validated accordingly.

Any batches manufactured using a tablet press with more than [redacted], of the same make, model, and operating principle, will have the tablet speed adjusted accordingly so that the press speed of the press will be equivalent to [redacted] In effect, this will provide the same running RPMs used under the validated conditions.

The friability data for the first three batches, the validation batches, as well as seventeen subsequent full-scale batches, is presented in Exhibit Q, pages 4-420 - 4-455. Of all friability results generated to date, 98.7% of the values are between [redacted] and 99.8% of the values are between [redacted] A slight drift toward higher values was observed during the manufacture of some of the post-validation batches, with rare excursions beyond the established limit. Some of these excursions are attributed to in-process press adjustments that resulted in higher friability values than desired. Overall, the data presented in Exhibit Q, pages 4-420 - 4-455 indicates a controlled process generating tablets within the established acceptance criteria.

A statistical evaluation of all the friability data generated to date is also presented in Exhibit Q, pages 4-420 - 4-455. Based on this statistical evaluation, a [redacted]

The statistical evaluation also highlighted the significance of the friability test as an in-process check to maintain the process at its optimum running conditions. The report also noted that individual values in isolation did not necessarily measure the overall acceptability of the lot. Rather, the values obtained for the lot should be viewed overall to determine the acceptability of the lot. As such, the result reported for the friability test representative of the batch will be the average of all friability results generated during the compression run. This result will become the official friability result for the released batch.

A revised Exhibit "O" reflecting the tightening of the press speed (for the validated 600 mg tablet) and the establishment of friability "alert limits" is presented under Exhibit Q and Exhibit P, pages 4-347 - 4-348 and 4-353 - 4-354 and pages 4-397 - 4-398 and 4-400 - 4-401 for the 600 mg [redacted] tablets [redacted].

3b. Discussion on question 3.b. of the approvable letter.

Adams should provide a commitment with more details on the [redacted] with explanation indicating which tests will be carried out during the release and which ones on the stability testing. This commitment will be listed in the action letter.

Adams Laboratories commits to [redacted] each strength of guaifenesin ER Tablets for commercial distribution by the procedure outlined below.

In addition to the hourly samples collected by Quality Assurance (QA) and Manufacturing, QA personnel will also collect [redacted] QC laboratory for testing. These additional samples will be collected at different times from the regularly scheduled QA and Manufacturing samples. These tests will be conducted as part of the release of that batch.

Additional [redacted] during the stability studies has been outlined in stability protocol PR02-11-QC (Exhibit G, page 4-186).

4. ***Discussions on the DMF***

Dr. Nashed indicated that the response to DMF [redacted] is under review, however, no response has been received for DMF [redacted]

[redacted] was contacted regarding the response to DMF [redacted] On April 30th, Adams Laboratories was notified that an update to DMF [redacted] had been submitted to FDA.

5. ***Submit a method validation package preferably listing the drug substance and the drug product methods separately.***

A method validation package listing the drug substance and the drug product methods is presented in volume 3 of 3. Three chemistry copies are included.

As you are aware, per FDA direction, the [redacted] the products has [redacted] since the initial NDA submission, [redacted] to over-the-counter. Therefore, market package sizes should reflect the over-the-counter marketing status. We have already introduced data on the container closure system in the 10, 20, and 40 counts. We request that these sizes be included in the approval. This submission includes draft labels for the 20 and 40 count 600 mg [redacted] bottles and cartons (pages 2-1 - 2-8). The container closure system for the 20 and 40 count for the Mucinex™ 600 mg are identical, except for the volume, to the 2 count and 500 count container closure system. [redacted] On pages 4-1 and 4-2, you will find an update of the comprehensive container closure system table previously submitted November 30, 2001. This table now includes the container closure system for the 10, 20 and 40 count sizes with the appropriate references to suppliers, compliance statements, DMF, and NDA references, including the specifications and Certificates of Compliance included with this submission. Stability data is also included with this submission (see Response 2 above).

We have received two approvable letters and fully responded. In addition, we have responded fully to two telephone requests for additional information. The issues from the approvable letters and telephone requests have been primarily chemistry related. It is our understanding that with the last submission of our labeling, that only finalization of the chemistry review is outstanding. We would like to reach final resolution on any remaining chemistry issues so that we do not have to receive a third approvable letter. I would like to request a meeting with the Division, if any additional chemistry issues remain unresolved for NDA 21-282.

Dr. Charles Kumkumian and Dr. William Fairweather have assisted us with preparing this latest response for Dr. Nashed. If a meeting is required, both Dr. Kumkumian and Dr. Fairweather have agreed to be in attendance.

If you have any questions regarding this matter, or need additional information, please contact me at (817) 786-1243. Also, feel free to contact either [redacted] directly, if you require additional input. Enclosed you will find, as requested, the updated methods validation package.

Thank you,

D. Jeffrey Keyser
Vice President
Development & Regulatory Affairs

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 8, 2002

To: Mr. Jeff Keyser	**From: Ladan Jafari**
Company: Adams	Division of Pulmonary and Allergy Drug Products
Fax number: 817-786-1204	**Fax number:** 301-827-1271
Phone number: 817-545-3629	**Phone number:** 301-827-1084
Subject: Telecon minutes of March 8, 2002	
Total no. of pages including cover: 3	

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-282
Drug: Mucinex (guaifenesin extended release)
Applicant: Adams Labs
Date of Telecon: March 8, 2002

Adams Labs Representatives:

Al Guillem, CMC
Bryan Hill. CMC
Jeff Keyser, Regulatory Affairs

Division of Pulmonary & Allergy Drug Products (DPADP):

Ladan Jafari, Regulatory Project Manager
Eugenia Nashed, CMC Reviewer

Background: The Division requested this telecon to discuss the responses provided by Adams in an amendment dated January 11, 2002, to questions 1.a.,1.b., 2.a., 2.b., and 3.b. of the approvable letter issued on December 20, 2001.

1. Discussion on questions 1.a, and 2.a.of the approvable letter: Dr. Nashed requested that the specification sheet for the drug substance and the drug product include a method number for each method used. Dr. Nashed stated that the specification table for the drug substance and the drug product should include the effective date, and superceded date. Also, the frequency of "Full Testing" [redacted] and information on how many times the drug substance can be re-evaluated should be included. In addition, the stability testing should include melting point evaluation. For the drug product stability studies, Adams Labs should include the long-term and accelerated study in the same stability protocol. Stability protocols for the 600 [redacted] mg tablets may be submitted separately or combined together in one protocol with proper explanation on how many batches of each strength were tested..

2. Discussions on questions 1.b. and 2.b.: Dr. Nashed asked that the acceptance criteria be tightened and data be provided to reflect it. It is understood that the drug substance stability program is done by [redacted] however, we would like to see the data from re-evaluation studies performed by Adams. Adams Labs indicated that they do not have the drug substance in storage for more than a few months, therefore, they do not have any data. Dr. Nashed asked that Adams include a statement to clarify that for the drug substance. However, the update of stability data for the drug product should be submitted. Dr. Nashed indicated that the stability program for the drug product is currently under review by the Agency's statistical reviewer and further communications may be necessary as a result of this review. Dr. Nashed inquired as to why the impurities were not tested until 18 months of storage. Adams Labs responded that in their original submission, the impurities and methods were not available, so they used the contract lab's data to develop the impurity profile.

Dr. Nashed stated that Adams Labs should have 24 month stability data at this point and asked that certain parameters such as assay, friability, hardness, loss on drying and individualized and total impurities be evaluated individually and the statistical evaluation reported with confidence limits on the old vs. the new tablet. This data should be prepared in a graph format. Dr. Nashed reminded Adams Labs that the specifications requested should be supported by data, and that we will set expiry based on the data provided. Adams Labs asked if they have to report on every impurity, and Dr. Nashed stated that the data is required for impurity number ——— and total impurities. Dr. Nashed asked that the stability data be reported with the latest acceptance criteria. Adams Labs should also indicate in a footnote if they are using a new modified method (e.g., new RPM) or revised acceptance criteria.

3. Discussion on question 3.b. of the approvable letter.

   a. Dr. Nashed indicated that the data for validation batches were different from those of the full-scale batches. Therefore, we need to know about any manufacturing changes, press operation speed during validation, and how this is reflected in the ——— for the current in-process controls. In addition, Adams should provide numbers for full scale that was used for validation batches and tighten the in-process specifications as appropriate. A revised "Exhibit O" should be submitted.

   b. Adams should provide a commitment with more details on the ——— with explanation indicating which tests will be carried out during the release and which ones on the stability testing. This commitment will be listed in the action letter.

4. Discussions on the DMF. Dr. Nashed indicated that the response to DMF ——— is under review, however, no response has been received for DMF ———

5. Submit a method validation package preferably listing the drug substance and the drug product methods separately.

Action: Adams Labs stated that they will try to get the requested information to the Division in the near future.

Initialed by: Nashed/4-5-02

Filename: Adams Marchtcon

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

/s/

Ladan Jafari
4/8/02 09:10:10 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research

Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: September 10, 2001

To: Mr. Jeff Keyser	**From:** **Ladan Jafari**
Company: Adams Labs	Division of Pulmonary and Allergy Drug Products
Fax number: 817-786-1151	**Fax number:** 301-827-1271
Phone number: 817-545-3629	**Phone number:** 301-827-5584

Subject: Meeting minutes of August 16, 2001

Total no. of pages including cover: 6

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-282
August 16, 2001
Applicant: Adams Laboratories, Inc.
Drug: Guaifenesin (600 mg [redacted]) Extended Release Tablets
Page 1

Adams Representatives:

Mr. John Adams, Jr., Vice President
Mr. John Adams, Sr., President
Mr. Jeff Keyser, Vice President, Development & Regulatory Affairs

Division of Pulmonary & Allergy Drug Products (DPADP)

Dr. Emmanuel Fadiran, Clinical Pharmacology & Biopharmaceutics Team Leader
Ms. Ladan Jafari, Regulatory Project Manager
Dr. Marianne Mann, Deputy Director
Dr. Robert Meyer, Director
Dr. Mary Purucker, Clinical Team Leader

Division of Over the Counter Drug Products (OTC)

Ms. Marina Chang, Team Leader, Interdisciplinary Scientist
Dr. Charles Ganley, Director
Dr. Linda Hu, Medical Officer
Mr. Cazemiro Martin, Interdisciplinary Scientist
Ms. Babette Merritt, Regulatory Project Manager

Office of Drug Evaluation II (ODE II):

Dr. John Jenkins, Director

Office of Drug Evaluation V (ODE V):

Dr. Jonca Bull, Acting Director

Office of Regulatory Policy (ORP)

Mr. David Read, Supervisory Regulatory Counsel
Mr. Mitchell Weitzman, Regulatory Counsel

Background: The Division of Pulmonary & Allergy Drug Products (DPADP) issued an approvable letter to Adams Laboratories on April 26, 2001, for their Guaifenesin Extended Release (600 mg [redacted] Tablets. Although, this approvable letter cited deficiencies from various disciplines, Adams Labs requested this meeting to discuss the following issue raised in the approvable letter.

- *The determination of approvability of [redacted] Guaifenesin 600 ER was based upon a filing of adequate bioequivalence as compared to the referenced OTC monograph product. [redacted] and Guaifenesin 600 ER are therefore eligible to be marketed as OTC products, and should be labeled as OTC products.*

➢ Adams Labs indicated that they were very pleased that they had received an approvable letter from the Agency, and hoped that they could correct all the deficiencies cited in the approvable letter as soon as possible. Adams Labs also indicated that they would like to [redacted] the Guaifenesin Extended Release Tablets as [redacted] to assure that any potential issues are captured in a more controlled environment. Adams Labs indicated that since the 600 mg tablet in the form of extended release has already been in the market and that the size of the [redacted] was a concern to the Division, they would agree to market the 600 mg tablet as OTC and keep the [redacted] Adams Labs believed that any adverse events would be identified by a [redacted]

- The Division (DPADP) reiterated the point raised in the approvable letter that the approvability of this application was based upon the bioequivalence of this drug to the monograph dosing, and that we do not have information to [redacted] Therefore, we have to refer to the monograph labeling and add a couple of statements with regard to the professional labeling. The Division (DPADP) also explained that there was no [redacted], nor data to support [redacted] The Division (DPADP) asked for clarification for observing this drug in a more controlled environment and inquired if Adams Labs had any particular concerns with these tablets (e.g., size or any other issues). The Division reminded Adams Labs that since this is an NDA product, it is subject to adverse event reporting whether or not it is marketed as OTC [redacted]

➢ Adams Labs indicated that they are not aware of any problems with size or otherwise

with this drug. They did have one incident where the subject had a hard time swallowing the ——— tablet, and had to drink more water to swallow.

- The Division (OTC) also asked if there were any concerns with this drug, and stated that there are adverse event reporting for OTC products, however, since some are reported by consumers, they don't know how much of that is accurate information. The Division (OTC) asked about the tradename (Aquatab) that was proposed by Adams Labs and inquired if Adams Labs was planning on having a container label as well as a label for the outer package. The Division (OTC) stated that upon cursory review of the labeling submitted, they noticed several content and formatting discrepancies between Adams proposed labeling and the required OTC drug monograph labeling for expectorant drug products. The Division (OTC) reminded Adams Labs that any OTC labeling for guaifenesin should follow 21 CFR 341.78 for labeling of OTC expectorant drug products and 21 CFR 201.66 for format and font/type size specifications. Specific font/type size for each labeling component must be submitted with the proposed labeling. The Division (OTC) stated that they would work closely with Adams Labs to assist them with their proposed OTC labeling.

➢ Adams Labs reconfirmed that there are no known concerns, and they are just anxious to try this drug ——— Adams Labs stated that they would consider the Agency's recommendations regarding the ——— this application. Adams Labs indicated that they have decided on a different name for this drug product (Mucinex ——— 600 mg) Tablets, and indicated that they have submitted a request to that effect to the Division (DPADP) on August 2, 2001. Adams Labs indicated that they had referred to the CFR, but also used language from labeling of other guaifenesin drug products that are currently on the market. Adams Labs believed it is best to have more information on the labeling. At this point, they are only planning on having container label only, but may consider a box label as well. Adams Labs stated that they would welcome the Agency's input regarding the proposed OTC labeling.

——— representing Adams Labs stated that they also wanted to discuss the issue of other extended-release guaifenesin drug products (Rx) that are currently being

marketed without an approved application and requested that upon approval of the Adams Labs application, the Agency act to remove all unapproved modified-release guaifenesin drug products that are on the market. Adams Labs provided a list of companies (see attachment 1) that are currently marketing guaifenesin extended release formulations without an NDA (though they gave the caveat that it might not be complete). Mr. Hutt gave an example of a similar situation, where all firms marketing Rx wart remover, were given warning letters to discontinue marketing in 1992. Adams Labs also discussed the guaifenesin market and stated that they have the capacity to manufacture this drug so that there would not be any shortage issues.

- The Agency stated that we note Adams Labs is adhering to the law in applying for an NDA for this drug product, and stated that we would consult with the Office of Compliance regarding this request. It is not clear at this point, however, if the Office of Compliance will have enough resources to act upon this request. The Agency stated that upon approval of this drug, we recommend that Adams Labs contact the Office of Compliance, but indicated that we would also bring this matter to the attention of Office of Compliance immediately.

➢ Adams Labs inquired about the status of the review, and the Division (DPADP) responded that we follow PDUFA time lines and will take an action on or before December 26, 2001. The Division (DPADP) noted that there are other deficiencies involved with this application, and until all deficiencies are satisfactorily resolved, an approval letter would not be issued.

Action: Adams Labs stated that they would submit a letter to the Division (DPADP) to inform us about their decision to go forward with their application as OTC.

Attachment 1:

LIST OF CURRENTLY MARKETED GUAIFENESIN EXTENDED RELEASE FORMULATIONS

GUAIFENESIN – SINGLE ENTITY

	COMPANY	PRODUCT NAME	NDC
2.	Sidmak	Guaifenesin ER	
		600 mg	50111-0535-01 50111-0535-02
3.	[redacted]		
4.	Mutual Pharmaceuticals	600 mg	53489-0423-05 53489-0423-01
5.	Martec Pharmaceuticals	600 mg	52555-0628-05
6.	UCB Pharmaceuticals	Duratuss G	
		1200 mg	50474-0620-50
7.	[redacted]		
8.	Duramed Pharmaceuticals, Inc.	Tabs	
		600 mg	51285-0417-02
		1200 mg	51285-0857-02
9.	Amide Pharmaceutical	Amibid L.A.	
		600 mg	52152-0106-02 52152-0106-04
10.	[redacted]		

11.	Allscrips	Guaifenesin	
		600 mg	54569-1489-01
12.	Ethex	Guaifenex G	
		1200 mg	58177-0205-08
		Guaifenex L.A.	
		600 mg	58177-0205-04
13.	Caraco Pharmaceuticals	Guaifenesin L.A.	
		600 mg	57664-0152-13
			57664-0152-08
14.	Wakefield/Ivax	Muco-Fen	
		1200 mg	59310-0120-10
15.	MCR/American Pharm	All Fen	
		1000 mg	58605-0509-01
16.	———	———	
17.	Alphagen Labs	Guaifenesin SR	
		600 mg	59743-0018-05
		1200 mg	—
18.	Respa Pharmaceuticals	Respa-GF	
		600 mg	60575-786-19
19.	———	———	
20.	Boca Pharmaceuticals	Guaifenesin L.A	
		600 mg	64376-0501-01
			64376-0501-05
21.	Capellon	Liquibid SR	
		1200 mg	64543-0131-05
		Liquibid Tab	
		600 mg	64543-0131-01
22.	Biovail Corp.	Fenesin	
		600 mg	64455-0009-01
23.	CellTech	Humibid L.A.	
		600 mg	53014-0012-10
			53014-0012-50

cc: HFD-570/Div.files
HFD-570/Rosebrough
HFD-570/Purucker
HFD-570/Choi
HFD-570/Sun
HFD-570/Nashed
HFD-570/Poochikian
HFD-570/Jafari

Initialed by: Mann/9-4-01
Meyer/9-4-01
Purucker/9-4-01
Ganley/9-5-01
Jenkins/9-10-01
Martin/9-5-01
Hu/9-5-01
Bull/9-5-01
Chang/9-5-01
Merritt/9-5-01
Weitzman/9-5-01
Read/9-5-01

Filename:Adamsmeeting8-16-01

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/s/

Ladan Jafari
9/12/01 11:50:06 AM

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*** TX REPORT ***
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TX/RX NO	0547
CONNECTION TEL	918177861151
SUB-ADDRESS	
CONNECTION ID	ADAMS LABS
ST. TIME	09/01 09:17
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PGS.	2
RESULT	OK

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Mr. Jeff Keyser

Phone Number: 817-786-1243

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: 2 Date: September 1, 2000

FOOD AND DRUG ADMINISTRATION
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TO: Mr. Jeff Keyser

Phone Number: 817-786-1243

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Total number of pages, including cover sheet: 2 Date: September 1, 2000

NDA 21-282

We are reviewing the Clinical Pharmacology and Biopharmaceutics portion of your submission and have the following questions and request for additional information.

1. Clarify whether the to-be-marketed formulation is to be produced at the same manufacturing site using the same manufacturing process as lots PB304 and PB322 that were used in studies 99-05 and 99-06.

2. The dissolution data currently submitted only provide mean values and ranges of 6 tablet units per time point. Provide data that include at least 12 units per time point, for the 600 mg strength tablets. Use the same batches as those employed in studies 99-05 and 99-06. Provide individual and mean values of the percentage dissolved for each sampling time in table format, as well as multi-point dissolution profiles.

3. The current data indicate an unsatisfactory dissolution of the biobatch tablets, especially the strength. The tablets appear to dissolve only up to about after using as the medium. Include a wider range of media than the two currently submitted Include a sufficient number of sampling times in the dissolution profiles (e.g.) and sample sufficiently long so that the plateau phase is clearly reached. Submit additional dissolution data in the format as stated under item 2.

4. With regard to study 99-06, it appears that 90% confidence intervals were provided for the food-interaction "arm" of the study, but not for the dose proportionality between the 600 mg and 1200 mg tablet. Provide 90% confidence intervals for the ratios of the (geometric) averages of C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the two tablet strengths. Include a printout of the statistical analyses.

If you have any questions please contact me at 301-827-5584.

/S/

Ladan Jafari, Project Manager

Memorandum of Telephone Facsimile Correspondence

Date: February 11, 1999

To:Mr. Jeff Keyser
Fax no. 817-283-0611

From: Ladan Jafari
Project Manager

Through: Cathie Schumaker
Chief, Project Management Staff

Subject: Comments from OCPB

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

Ladan Jafari
Project Manager

COMMENTS:

1. There is no information provided on the composition, batch sizes/Nos. and date/site of manufacture of the modified-release (MR) guaifenesin 600 mg tablets to be used in protocol Nos. 99-01 and 99-02. Therefore, You should provide such information in the future protocol submissions.

2. For the food effect study (No. 99-01), the highest strength of the to-be-marketed dosage form/formulation should ~~be used~~ and a high fat (stressed) meal should be employed, e.g., two fried eggs, two slices of toast with butter, two strips of bacon, 4-8 oz. of hash brown potato, and 8 oz. of whole milk. The high fat meal should be consumed within 30 min and the study medication should be administered immediately after the meal. Please refer to the draft guidance on "food-effect bioavailability and bioequivalence studies" for details. According to the draft guidance, the Groups 1 and 2 (for a lower strength in this food effect study) could be omitted provided that the MR 600 mg tablet formulation is compositionally the same as and dose-proportionally similar to the ——— tablet formulation. Subjects should be confined at the study site for 24 hr on study day and additional blood samples be obtained, i.e., at 16 and 24 hr post dose. In addition, the Agency's 90% confidence interval using two one-sided test procedure on log-transformed C_{max} and AUC should be calculated for assessing food effects. Please also refer to the Agency's guidance for details.

3. As proposed in study No. 99-02, too much blood needs to be drawn from this study (around 750 ml per subject). In order to reduce excessive blood drawing, the study Group 2 [for a lower strength/dose of the immediate-release (IR) tablet] might be omitted provided that data is available to show linear PK for the IR guaifenesin tablet doses between 600 ——— mg. **1)** additional blood samples should be obtained, i.e., at 16 and 24 hr post dose on Days 1 and 6, **2)** single dose PK as well as steady-state PK [e.g., C_{max}, T_{max}, C_{min}, C_{avg}, AUC, accumulation ratio, and fluctuation index; $(C_{max}-C_{min})/C_{avg}$] be analyzed, and **3)** gender effects on guaifenesin PK be assessed. In addition, for both single dose and for steady state, 90% confidence interval using two one-sided test procedure on log-transformed C_{max}, C_{min}, and AUC should be calculated comparing the MR tablet product to the IR tablet product, as appropriate.

4. For the above pivotal PK studies to be conducted, the to-be-marketed MR tablet formulation(s) manufactured at the site for commercial production (with at least 1/10 of proposed production lot size) should be used. If the formulations to be used in the pivotal PK studies are not the to-be-marketed formulation(s) or the manufacturing site is changed, a bioequivalence (BE) study will be needed to link these formulations to the to-be-marketed one made at the commercial site.

5. In the December 17,1998 submission (Serial No. 005), the mean plasma profile of guaifenesin obtained from 2 x 200 mg immediate-release tablets every 4 hrs for 3 doses (Study 98-01) showed that mean peak plasma levels were decreasing after repeated dosing which may imply nonlinear PK. Please provide the reason(s) for the nonlinear PK.

6. For the basis of future approval of guaifenesin MR tablet product, ideally comparable steady-state PK profiles, C_{max}, C_{min}, and AUC after multiple dosing of MR tablet product and those obtained from the IR tablet products (Study No. 99-02) should be demonstrated. As indicated in the January 7, 1999 telecon, simulation of steady-state PK profiles and prediction of PK parameters should be based on guaifenesin pilot PK study prior to conducting the pivotal PK studies. Please provide any available information on PK and pharmacodynamic relationships for guaifenesin.

7. Finally, the assay method(s) to be used in these PK pivotal studies is/are not stated in the protocols. Therefore, the assay method(s) to be used should be specified and the summary of assay validation report should be provided in the future protocol submissions.