



DEPARTMENT OF HEALTH & HUMAN SERVICES

New York District

Food & Drug Administration
158-15 Liberty Avenue
Jamaica, NY 11433

WARNING LETTER

May 13, 2003

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: NYK-2003-25

Mr. Muhammed Malik
President
Intermax Pharmaceuticals, Inc.
228 Sherwood Avenue
Farmingdale, NY 11746

Dear Mr. Malik:

During an inspection of your drug manufacturing facility on October 22-24, 28, 30-31 and November 4-7 & 20, 2002, our investigators documented the marketing by your firm of Guaifenesin 1200 mg. sustained release tablets, a single ingredient guaifenesin timed release dosage form.

Guaifenesin is a drug that presently has an established general recognition of safety and effectiveness under the OTC Monograph system as an expectorant (21 CFR 341), but the OTC monograph system does not include provisions for timed release dosage form drug products. The agency has, through rule making procedures, accorded new drug status to certain drugs. Included among these are timed release dosage form drugs. Specifically, Title 21, Code of Federal Regulations part 310.502(a)(14) codifies the new drug status of timed release drug products. Therefore, single ingredient guaifenesin timed release drug products are new drugs and require an approved application for marketing.

Before there was a New Drug Application (NDA) approved for a single ingredient guaifenesin timed release product, FDA did not expend scarce enforcement resources to address such unapproved drugs. However, on July 12, 2002, FDA approved NDA 21-282 covering the marketing of Mucinex 600 mg, a guaifenesin timed release tablet expectorant for patients 12 years and above. Other single ingredient timed release guaifenesin drug products, which are new drugs, must be approved under an NDA or abbreviated new drug application (ANDA) as required by the Federal Food, Drug, and Cosmetic Act (the Act).

There is no approved application under the provisions of Section 505 of the Act on file with the FDA for Guaifenesin 1200 mg. sustained release tablets as marketed by your firm. Therefore,

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marketing of this product without an approved new drug application constitutes a violation of Section 505(a) of the Act.

Our investigators also documented deviations from Current Good Manufacturing Practice (CGMP) for Finished Pharmaceuticals Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211) concerning the manufacture of your drug products Coldec Tablets (Carbinoxamine Maleate, Pseudoephedrine HCl), Crantex Tablets (Phenylephrine HCl and Guaifenesin), Dyphylline & Guaifenesin Tablets, Migrazone (Isometheptene Mucate, Dichloralphenazone and Acetaminophen), Usept Tablets (Methenamine, Phenyl Salicylate, Methylene Blue, Benzoic Acid, Atropine Sulfate and Hyoscyamine Sulfate) and Guaifenesin Sustained Release Tablets. These deviations cause these drug products to be adulterated within the meaning of Section 501(a)(2)(B). The deviations include, but are not limited to, the following:

1. The accuracy, sensitivity, specificity, and reproducibility of test methods employed by your firm are not established and documented as required by 21 CFR 211.165(e) in that:
 - (a) There are no validation data for the methods used to analyze any products. Your firm's SOP for analytical method validation describes the steps your firm must take to validate your methods, but the SOP is not being followed.
 - (b) Your firm uses USP methods to analyze your products, but changes have been made to the USP methods and no validation has been performed. For example, for Migrazone Capsules, the USP uses three different wavelengths to analyze the three active ingredients. Your firm changed the method to use [REDACTED] for all three actives and no validation of the new procedure was performed.
 - (c) Test methods used in validation data for Guaifenesin 1200 mg. S.R. tablets for 2001 were conducted for only two batches and were deficient in that:
 - (i) preparation of the in-house standard failed to identify the actual in-house standard being used;
 - (ii) the solvent used for the preparation of samples was not recorded; and
 - (iii) the HPLC system used is not identified in the logbook.
2. Failure to follow your firm's written stability testing program as required by 21 CFR 211.166(a) in that your firm has no validation data to demonstrate that the method used to analyze products for stability is capable of detecting degradation of the products.

3. Failure to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process materials and drug products as required by 21 CFR 211.110, in that validation studies have not been performed for any products for such operations as blending, tableting, encapsulation, coating, and packaging. Although your firm has a validation protocol requiring that the first three commercial batches of each product to be validated, there is no record of such validation ever having been performed.
4. Laboratory controls fail to include the establishment of written scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity as required by 21 CFR 211.160(a) and (b) in that:
 - (a) Your firm lacks complete written methods that fully describe the procedures, equipment, parameters and specifications to be used in the analysis of individual products.
 - (b) For dissolution of time release products, your firm's specifications are only for average amount released at each specified time period. There are no specifications or the amount released by individual tablets at each specified time period. Further, the specification fails to identify the reviewing and approval individuals for either the original specification or the changed specification.
 - (c) There are no written procedures to address out of specification results. Your current unwritten policy is to retest with a different analyst. If the retest meets specifications, it is considered to meet requirements. There is no procedure to conduct an investigation to determine the cause of the original out of specification result.
5. Failure to document the review and approval of written procedures and changes to such procedures for production, process and laboratory controls by the appropriate organizational unit and quality control as required by 21 CFR 211.100(a), 21 CFR 211.160(a) and 21 CFR 211.22(c). For example:
 - (a) Your two master SOP logs contain SOPs which do not consistently bear the signatures of the persons preparing and/or approving the procedures, i.e. untitled SOPs Q30 and Q32.
 - (b) Written instructions for analyzing products include cross outs and changes to the instructions without any documentation as to why these changes were made.

6. Failure to record complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays in official laboratory records as required by 21 CFR 211.194(a) in that:
 - (a) Raw data, such as, sample and standard weights, dilutions, calculations, etc. have been found to be recorded in a "non-official" spiral notebook. For example, only after the analysis is completed and the results calculated is the raw data transcribed to the official laboratory bound notebook. Examination of the spiral notebook revealed data for two analyses (Guaifenesin 1200 mg. SR Tablets, lot #A0105 and Migrazone Capsules, lot #G0201) that were labeled failing and had not yet been entered into the official notebook.
 - (b) Review of chromatograms revealed that, in certain instances, out of specification results which were recorded on the chromatograms had no corresponding reference or raw data recorded in the official laboratory bound notebook. In these cases, the data was recorded in the notebook only when the sample was retested and results found to be within limits. For example:
 - (i) For Crantex tablets, lot #H0206, chromatograms for the dissolution analysis conducted on 8/26/02 yielded out of specification results for phenylephrine HCl. The analysis was repeated on 8/28/02 and passing results were obtained. The laboratory notebook does not contain any raw data or reference to the out of specification analysis conducted on 8/26/02. The only recorded data is for the analysis conducted on 8/28/02.
 - (ii) For Coldec Tablets, stability lot #s C0207 and E0102, original analysis conducted on 9/17/02 yielded out of specification results for both lots. Lot #C0207 was reassayed on 9/17/02 and found within limits. On 9/18/02, lot #E0102 was reassayed and found to be within limits. The official laboratory notebook fails to reference or contain raw data corresponding to the out of specification assay performed on 9/17/02.
 - (iii) An original content uniformity analysis was conducted on Migrazone capsules, lot #E0202 on 5/29/02 which yielded one tablet outside the [REDACTED] limit. No data corresponding to this analysis is in the official laboratory notebook. Additional 10 tablets were tested on 5/30/02 and all were within the [REDACTED] limit. The only data in the official laboratory notebook is for the analysis conducted on 5/30/02.
 - (c) There are no other signatures or initials indicating a check of the data as was noted with laboratory records for Crantex tablets, lot # A0203 which had failed dissolution specifications for guaifenesin.

- (d) Corrections made on ambient stability study reports for Migrazone capsules, lot # J-00002, 3 month station, and accelerated stability study for Migrazone capsules, batch A00003 are not initialed or dated by the individual making the corrections.
7. Failure to conduct a thorough investigation of unexplained discrepancies or the failure of a batch of any of its components to meet any of its specifications as required by 21 CFR 211.192. For example:
- (a) Your firm has released products purporting to meet USP requirements when, in certain cases, they fail to meet such requirements. For example:
- (i) (Crantex Tablets, lot #H0212) Your firm tested two sets of ten tablets for uniformity of dosage units. Two tablets out of twenty tested were outside the [REDACTED] limit for phenylephrine HCl. The certificate of analysis for this lot claims that it meets USP requirements for uniformity of dosage units even though the USP specification states that no more than one tablet can be outside the [REDACTED] limit.
- (ii) (Crantex Tablets, lot #H0206) For the uniformity of dosage test, one tablet was outside the [REDACTED] limit for guaifenesin. The USP requires that additional 20 tablets be tested to determine if the product meets the requirement. Your firm did not test the additional 20 tablets and the certificate of analysis claims that this lot meets USP requirements based on only the 10 tablets tested.
- (iii) (Crantex tablets, lot #G0204) For the uniformity of dosage unit test, one tablet in the first 10 tested was outside the [REDACTED] limit for phenylephrine HCl. Your firm tested additional 10 tablets, then averaged the two sets of results and reported the results as meeting requirements.
- (b) For Crantex Tablets, lot # A0203, package size 100's, the six month ambient, stability dissolution results for guaifenesin were out of specification, yet no investigation was conducted and no action was taken.
- (c) The ambient stability study report for Migrazone Capsules, lot # B99001, 500 tablet package, has two sets of data reported for 18 and 24 months. A failing assay result for dichloralphenazone at the 24-month station was reported on this report without any explanation or investigation.
8. Failure to verify the suitability of all testing methods under actual conditions of use as required by 21 CFR 211.194(a)(2). For example:

- (a) The relative standard deviation of standard injections is not calculated to ensure the reproducibility of the chromatographic system.
 - (b) Resolution solutions are not prepared and the resolution factor is not calculated as required by certain USP methods (i.e., Dyphilline and Guaifenesin tablets).
9. Your firm fails to have an appropriate laboratory determination of satisfactory conformance to final specifications for each batch of drug product in accordance with 21 CFR 211.165(a) in that Usept lot# C0206 was shipped to a customer on 4/12/01 without having received a Certificate of Analysis from your contract laboratory.
10. Your firm does not have a SOP describing calibration procedures to be used for your firm's liquid chromatographs, nor is there a SOP for the calibration of the disintegration apparatus. Further, these pieces of equipment have not been calibrated and documented as required by 21 CFR 211.160(b)(4) and 211.194(d).

Calibration deficiencies were documented with other equipment as well.

11. Failure to adequately clean and maintain equipment at appropriate intervals to prevent malfunctions or contamination as required by 21 CFR 211.67(a). Our inspection found your firm to [REDACTED] several times before discarding. Cleaning procedures have not been validated to assure the adequacy of this cleaning procedure in preventing contamination. Further, your firm does not have written procedures describing the methods for use in cleaning operations as required by 21 CFR 211.67(b).
12. Failure to provide employee training on a continuing basis to assure their knowledge and understanding of the drug CGMP regulations as they relate to their assigned functions as required by 21 CFR 211.25. Although your firm has a written procedure for training, it was found that these procedures are not followed. For example, the procedures require training to be conducted six times annually, but only one record of GMP training was available dated August 5, 2002. The procedures also require documentation by supervisors of CGMP training for all new employees as they relate to each department, but no such documentation was available.
13. Failure to identify each lot as to its status (i.e., quarantined, approved, or rejected) as required by 21 CFR 211.80(d) in that the only designation made for raw materials is that for approved components. This designation is made verbally from the Quality Control lab to Quality Assurance which applies "approved" labels to each container.

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14. Failure to limit access to the label storage area to authorized personnel in accordance with 21 CFR 211.122(d) in that the room was observed to be unlocked with access to all personnel.
15. Failure to document each significant step in the manufacture, processing, packing, or holding of a batch in the batch production and control records as required by 21 CFR 211.188(b) in that:
 - (a) Batch records fail to identify individual pieces of major equipment used as required by 21 CFR 211.188(b)(2) since there is no designation identifying multiple units of the same equipment, i.e., the batch record for Guaifenesin 1200 mg., lot # J0205.
 - (b) Laboratory control results are not included in batch records as required by 21 CFR 211.188(b)(5). Analytical results are only maintained in laboratory notebooks.
16. Failure to establish written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, cleaning and sanitizing agents as required by 21 CFR 211.56(c).

Neither the above identification of violations nor the inspectional observations (Form FDA 483)(copy enclosed) presented to you at the conclusion of the inspection is intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence with each requirement of the Act and its implementing regulations. Federal agencies are advised of the issuance of all warning letters about drug products so that they may take this information into account when considering the award of contracts.

As you may be aware, in October 2002, FDA issued warning letters to the marketers of single ingredient guaifenesin extended-release drug products for marketing the product without approved applications. Subsequently, on February 25, 2003, the Agency sent follow-up letters to the October 2002 warning letter recipients granting them a grace period for continued manufacture and distribution of their products (copy enclosed). We are extending to you the opportunity to obtain the same grace period as was given to marketers of single ingredient guaifenesin extended release if you commit in writing in a letter to FDA within 10 days of receipt of this letter to the following conditions:

- You shall cease manufacturing unapproved single ingredient guaifenesin extended release products no later than May 21, 2003, and shall not resume that manufacturing until FDA approves an application covering the manufacture of the particular products.
- Distribution of unapproved single ingredient guaifenesin extended release products may continue

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until October 23, 2003. Distribution of single ingredient guaifenesin extended release products shall not resume after that date unless and until an approved application covers such products. The FDA expects that, with reasonable advance inventory planning by retailers, this action will result in no further sales of such products past November 2003.

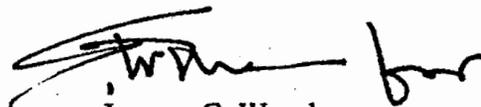
Please be advised this temporary conditional exercise of enforcement discretion on the part of the Agency applies only to the new drug requirements and does not in any way eliminate the requirements for your correction of the cGMP violations.

Failure to promptly correct the violations cited in this letter and/or failure to comply with the above conditions regarding your guaifenesin product may result in regulatory action without further notice. Possible regulatory actions include seizure and/or injunction.

You should notify this office upon receipt of this letter to arrange for a meeting to discuss the specific steps you have taken to correct the noted cGMP violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for delay and the time within which corrections will be completed.

Please send your reply to the attention of Lillian C. Aveta, Compliance Officer, Food and Drug Administration, 158-15 Liberty Avenue, Jamaica, NY 11433. If you have questions regarding any issues in this letter, please contact Ms. Aveta at (718) 662-5576.

Sincerely,



Jerome G. Woyshner
District Director
New York District

Enclosure: Form FDA 483 dated November 20, 2002