



DEPARTMENT OF HEALTH & HUMAN SERVICES

M906N

Public Health Service
Mid-Atlantic Region

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (201) 331-2906

May 12, 1997

WARNING LETTER

John Gruen
President
Glenwood-Palisades
P.O. Box 369
One New England Avenue
Piscataway, New Jersey 08855

RELEASE
REVIEWED BY DCE
CQ. 5/13/97
DATE

Dear Mr. Gruen:

File No: 97-NWJ-33

This is in regard to an inspection of your facility located at One New England Avenue, Piscataway, New Jersey between the dates of March 24 and April 3, 1997. During the inspection our investigator documented serious deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Parts 210 & 211) in conjunction with your firm's manufacture, processing, packing, and holding of various drug products.

These deviations were noted on the FDA-483 presented to your firm at the close of the inspection on April 3, 1997. These CGMP deficiencies cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

The significant observations are as follows:

Process validation was not completed for marketed products, such as Carbiset Tablets, Carbiset TR Tablets, and Potaba Tablets. In addition, your firm has not established manufacturing procedures with set parameters for these products. Batch to batch variations include additional processing steps, tablet specification changes, changes in blending instructions and variations in batch sizes. These changes were made without formal evaluation through a change control system and could not be evaluated against a standard as these processes have not been defined and validated.

The batch record for Carbiset Tablet lot 49596 was adjusted to account for the lack of an adequate amount of Microcrystalline Cellulose by reducing the theoretical quantities of the remaining excipients. During compression, target hardness and thickness specifications were changed in order to achieve acceptable results for friability. Finished tablets failed content uniformity during laboratory testing. The tablets

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were milled into granules, blended with magnesium stearate and compressed. The investigation into the content uniformity failures was attributed to the blending stage not being validated. This lot was released on 12/20/96.

Twenty lots of Potaba tablets have been manufactured and released, however process validation has not been completed. Changes were made in manufacturing procedures and specifications without documentation justifying the change or showing evaluation of the change on product quality.

Analytical methods used during stability have not been shown to be stability indicating. There are no procedures for assuring stability samples are analyzed at their appropriate stations and results are reviewed in a timely manner. It was observed that many stability stations have been missed since the firm moved to Piscataway.

Process deviations were not investigated or evaluated from a quality standpoint. Your corrective actions achieved a product passing specifications however there was little or no evaluation on the overall effect on product quality.

Carbiset lot 49526 and Carbiset TR lot 49525 both contained lumps in the blend after blending. The corrective action was to screen the material and then blend for an additional three minutes. There was no investigation into the cause of the lumpy blend, or whether other batches would be affected. It appears that this change was made by production personnel and was not reviewed by quality assurance.

For Potaba Tablet lot 49586 the deviation report indicates hardness ranges were widened in order to meet acceptable friability results for finished tablets. There was no investigation into the cause of the unacceptable friability results. Lot 49592 manufactured immediately after lot 49586 produced acceptable friability results using the original hardness specifications.

Laboratory investigations were not conducted and/or did not fully document laboratory investigations and deviations. There is no system for tracking investigations performed or using this information in evaluating analyst performance.

We have reviewed your letter dated April 23, 1997 in response to the list of Inspectional Observations (FDA-483) issued to your firm at the close of the inspection. We have the following comments regarding your response.

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Observation 1A) What is your proposed time frame for establishing and implementing stability indicating methods?

Observation 3) What is your proposed time frame for validating manufacturing processes? Do you intend to continue marketing these products without completing validation? How will you ensure the quality, purity and safety of these drug products?

It is obvious from the examples cited above that planned deviations were not processed via change control procedures and were not subject to validation prior to being released for distribution.

Shortage of a non-active ingredient does not justify downsizing by 33% in order to produce a batch. The fact that this change was reviewed and approved by senior production and quality assurance personnel is disturbing. This batch was produced using a non-validated manufacturing process which failed initial content uniformity testing. Based on this failure the tablets were milled, compressed and released. The final content uniformity results, as cited in the response, provide little assurance regarding the quality of this batch, since it was obviously manufactured without regard for good manufacturing practices. Monitoring without stability indicating methods provides minimal assurance that this lot will meet quality, safety and purity characteristics through its expiration date. What is your basis for the continued marketing of this batch?

Changing specifications/master batch records must be reviewed and approved prior to implementation and must be applied to all batches. These specifications should be based on prior knowledge of the product. It is not appropriate to alter hardness specifications to achieve proper friability. The conditions for producing tablets with acceptable friability need to be established and validated. If a situation arises where unacceptable tablets are being produced an investigation needs to be conducted to determine the cause. It is not acceptable to alter specifications to bring a batch into compliance.

You indicate that tablet specification changes referred to minor hardness and thickness changes. What data do you have to support that these changes do not effect the quality of the product? The fact that the batches met all requirements of compendial testing does not assure the quality of the product through out the shelf life. Quality cannot be assessed by finished product testing alone. Without a validated process to use as a standard it is difficult to predict the acceptability of lots which deviate from established specifications.

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Observation 4d) All unknown peaks need to be investigated. If the source is unknown what information do you have to assure you that the cause was not due to accelerated aging? Since you have not demonstrated that your assay methods are stability indicating we do not agree that the lack of abnormal peaks in the assay indicates a stable product.

Observation 7) Are stability indicating methods being used to evaluate raw materials?

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted 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 the delay and the time needed to complete the corrections.

Please submit your response to Attention: Diane Edson, Compliance Officer, Food and Drug Administration, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054.

Sincerely,

Charles B. Thorne

CHARLES B. THORNE
Acting District Director
New Jersey District

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

DCE:np