



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Mid-Atlantic Region
D1294B

Telephone (201) 331-2906

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

March 26, 1997

WARNING LETTER

Robert E. Callari
President
Tri-Med Laboratories, Inc.
68 Veronica Avenue
Somerset, New Jersey 08873

RELEASE
REVIEWED BY: D.E. C.O.
3/31/97
DATE

Dear Mr. Callari:

File No: 97-NWJ-28

This is in regard to an inspection of your facility located at 68 Veronica Avenue, Somerset, New Jersey between the dates of January 6 and 22, 1997. During the inspection our investigators 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 January 22, 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:

There is a lack of justification for the overages used to manufacture Tri-vitamin Drops with Fluoride .25mg, Supplement for Infants. The current formulation contains a [redacted] excess of vitamin A, a [redacted] excess of vitamin D and a [redacted] excess of ascorbic acid. No upper limits have been set for the assay of vitamins A, D, and ascorbic acid therefore quality assurance is not notified of possible manufacturing problems associated with this product. For example, Lot F502 was released with a vitamin D assay value of 202% of label claim. No investigation was conducted to determine the cause of this high result.

The agency has conducted a health hazard evaluation of Tri-vitamin Drops with Fluoride .25mg, Supplement for Infants. This evaluation was based on an infant consuming infant formula containing the maximum amount of vitamin A and vitamin D allowable by the Code of Federal Regulations in conjunction with 1mL of Tri-vitamin Drops. Although the daily intakes of each vitamin would be below levels generally associated with chronic toxicity, signs of toxicity have been more frequently observed at lower intake levels for supplements containing both vitamin A and vitamin D than when

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either vitamin is given alone. Some risk of permanent effects is possible, although not highly probable, in formula-fed infants consuming additional vitamin A and vitamin D at levels present in Tri-vitamin Drops with Fluoride from birth through two years of age. Please address this issue in your written response.

Production and control records were not always reviewed and approved by the quality control unit to determine compliance with established procedures prior to the release of a batch. Reviews that were conducted did not assure investigations were conducted when batch records contained unexplained discrepancies or specification failures. For example, management reviewed the Certificate of Analysis and released Tri-vitamin Drops with Fluoride .25mg lot L404 with a pH value of 5.43. The pH specification is [REDACTED]. No investigation was conducted into this out of specification result.

Your firm lacks control procedures to assure the consistent manufacture of product meeting quality attributes for non-sterile oral solution products.

Mixing times were not evaluated and holding times were not established to assure uniformity and homogeneity.

Batch sizes for oral solution products varied. Tri-vitamin Drops with Fluoride .25mg ranged from [REDACTED]. Gas Relief ranged from [REDACTED] and Tri-Care liquid ranged from [REDACTED]. Not all batch sizes were validated.

Tri-vitamin Drops with Fluoride .25mg were retrospectively validated however there was no indication of batch size for the 20 lots reviewed (1992-1994). The following batch sizes were observed for product manufactured during 1995 and 1996: [REDACTED] and [REDACTED].

No validation was available for Tri-vitamin drops with Fluoride .5mg which is manufactured by reserving some of a .25mg batch and adding extra Fluoride.

There is a lack of assurance that a consistent amount of water is added during the final Q.S. of oral solutions. The method of volumetrically adding water was not evaluated during process validation.

No evaluation is made of batch to batch variability.

The SOP/Protocol for Process Validation in effect since 1993 which requires a final report is not followed. No validation

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reports were available, only chromatograms and laboratory notebooks.

The following was observed regarding analytical methods:

Analytical methods used for stability testing have not been shown to be stability indicating. No attempt is made to identify or evaluate degradation products during routine stability testing. The HPLC recorder is turned off as soon as the analyte peak elutes.

Assay peaks with shoulders and unresolved peaks were observed on release and stability for Tri-vitamin Drops with Fluoride .25mg. and Tri-Care Syrup. These chromatographic problems were not documented in available method validation data.

The method for integrating HPLC peaks of the same product was inconsistent. Computer generated peak heights were used to calculate the assay for Phenylpropanolamine and Phenylephrine in Tri-Tex Liquid lot P603. Manual integration was used for these ingredients in lot P604.

Method Validation has not been completed for all analytical methods for all products. Drug substance monographs used for release of various combination products have not been shown to be suitable for their intended use.

Accuracy, sensitivity, specificity, and reproducibility has not been established for all analytical test methods and in-house methods have not been shown to be equivalent to USP methods.

Analytical methods used for cleaning validation studies have not been validated for Limit of Detection or Limit of Quantitation.

The method for calculating potency of Simethicone has not been shown to be equivalent to the USP calculation.

Preservative effectiveness tests on finished products did not assure the adequacy of the preservative system. The test method (USP Antimicrobial Preservative Effectiveness Challenge Test) was not followed and all test results did not meet USP criteria.

Evaluation of the preservative system is not a part of routine stability. The method used to assay Sodium Benzoate and Methyl Paraben was not validated for this use.

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We have reviewed your letter (undated) received on March 24, 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.

1. Accuracy, sensitivity, specificity and reproducibility of test methods must be established and documented. Your firm needs to establish that analytical methods meet proper standards for accuracy and reliability as applied to the product tested. A validated method for an active ingredient does not assure the ability of that method to function properly when testing the finished product. In addition, the suitability of a method must be evaluated for each finished product and can not be based on the analysis of a different finished product.

2. Please provide more information regarding the products that still need to be validated. What is the basis of your estimated time frame?

Has batch to batch variability been evaluated for all your products?

3. All batch sizes need to be evaluated to determine the extent of validation necessary. Please provide the basis for your estimated time frame.

4. Your time frame of March 1, 1999 seems excessive. Please provide detailed information on how you intend to complete this project and the basis for your time frame. How will you evaluate products that are currently on stability?

5. Please provide the justification for the original pH specification of [REDACTED]. What data do you have to support the pH specification of [REDACTED]. How will adjusting the specification to meet the average pH effect the quality of the product?

Are you modifying your procedures to require documented QA approval of batch records?

8. & 9. What assurance do you have that the cleaning method currently used for Gas Relief Drops is adequate? Please provide a schedule for evaluating your analytical methods.

10. What data do you have to support your method of calculating Simethicone assay results is equivalent to the USP calculation?

11. How do you intend to "clean up" the sample before analysis. Your method of determining peak heights should be evaluated during

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method validation and should remain consistent whenever the method is performed.

12. Please provide the upper limits for each vitamin in your vitamin preparations. What is the basis for these limits?

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,

Ray Abrahams

RAY ABRAHAMS
Acting District Director
New Jersey District

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

DCE:np