



Telephone (973) 526-6005

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

WARNING LETTER

April 28, 2004

CERTIFIED MAIL-
RETURN RECEIPT REQUESTED

Mr. Robert E. Caliari
President
Tri-Med Laboratories Inc.
68 Veronica Avenue, Suite #1
Somerset, NJ 07607

File # 04-NWJ-10

Dear Mr. Caliari:

During an October 14 through November 10, 2003 inspection of your drug manufacturing facility located at 68 Veronica Avenue, Suite #1, Somerset, New Jersey, an investigator from this office documented serious deviations from the Current Good Manufacturing Practice (CGMP) regulations in 21 Code of Federal Regulations (CFR), Part 210 and 211, that cause your finished drugs to be **adulterated** within the meaning of Section 501 (a) (2) (B) of the Federal Food, Drug, and Cosmetic Act (the Act). The following are examples of some of the significant CGMP deviations that were found during our inspection of your firm:

- 1. Failure to assure each drug product is free of objectionable microorganisms throughout their expiration dating period. [21 CFR 211. 166 (a)]**

Anti-microbial preservative effectiveness testing conducted on finished drug products are inadequate as it does not assure that the anti-microbial preservatives formulated into your prescription, oral-liquid drug products, are effective in inhibiting the growth of objectionable microorganisms throughout the expiration-dating period of your drug products. In order to demonstrate the effectiveness of the preservatives added to your multi-dose prescription liquid products, appropriate challenge of your preservatives must be conducted.

Our investigator found that in addition to the lack of adequate preservative effectiveness testing, no microbiological testing of stability samples was conducted as required in your firm's stability protocols. The investigator was informed that your

firm is considering removing the microbiological specifications from the protocols. We wish to point out that you are required to conform to the stability testing protocol approved by your quality unit and any deviation from the protocol should be approved by your quality unit and documented with an appropriate scientific rationale. We regard the failure to conduct appropriate preservative or microbiological testing to be a serious CGMP deviation because of the potential hazard microbiologically contaminated drug products can pose to patients.

The failure to adequately conduct preservative effectiveness testing was previously brought to your attention in a Warning Letter, #97-NWJ-28, dated March 26, 1997. You stated in a March 12, 1997 correspondence to this office that you "agree that in some instances the Preservative effectiveness tests carried out by [REDACTED] now out of business, did not strictly follow USP protocol." Additionally, you explained that you plan to redo the parts of the Preservative Effectiveness tests that did not conform to the protocol and provided an estimated time for completion of July 30, 1997. Similarly, in your April 10, 1997 correspondence to this office you committed to "routinely monitor microbiological content of our products as part of our stability program." Now, in your most recent correspondence dated November 26, 2003, you have submitted *the same* 1994 data obtained from [REDACTED] that you previously indicated as being unacceptable in 1997. Please explain why this data should be acceptable now since it was not acceptable in 1997. You have again committed, as per your November 26, 2003 response, to perform microbiological analysis of your products during stability testing. Please provide a timetable for the completion of this testing. We are concerned about your failure to conduct appropriate microbiological or anti-microbial preservative effectiveness testing, as well as to comply with commitments that you previously made to FDA.

- 2. Failure to have scientifically sound and appropriate specifications and test procedures designed to assure that in-process materials and drug products conform to appropriate standards of identity, strength, quality and purity.**
[21 CFR 211.160 (b)]

Our inspection found that procedures for conducting HPLC testing are inadequate because sample run times and retention times for active ingredient and any significant impurity peaks have not been established in your approved test methods. Our investigator found that your laboratory employees routinely stop chromatographic runs immediately after the active peak has eluted, and as a result, any impurity peak that elutes after the active peak will not be detected. There are no procedures or specifications for evaluating any significant impurities or degradation products, or for evaluating foreign peaks in chromatograms generated during in-process, finished product and stability testing of marketed drug products. Our investigator observed that foreign peaks in chromatograms generated during assays of various marketed products and during forced degradation studies were not evaluated.

This issue was also previously brought to your attention in the March 26, 1997 Warning Letter (#97-NWJ-28) issued to your firm. In your March 12, 1997

correspondence to this office, you promised to perform forced degradation studies with an estimated completion date of March 1, 1999. However, you have not performed this necessary analysis on your products.

As stated in your November 26, 2003 correspondence, you now commit to hiring a consultant to “guide and assist” you in evaluating “all drug substances and current finished products for impurities and degradants.” Please submit to this office a timetable in which you will complete this analysis, and please be reminded that you are responsible for the safety and efficacy of marketed products, which have been manufactured at your firm.

3. Expiration dating assigned to marketed lots of prescription PSE Carbinoxamine DM Syrup and PDM GG Drops have not been determined by appropriate stability testing. [21 CFR 211.137 and 211.166]

Your firm failed to conduct appropriate stability testing to justify the two-year expiration dating assigned to PSE Carbinoxamine DM Syrup. Stability testing has not been conducted on samples of lots representing the current formulation and manufacturing process. Your firm indicated that the two-year expiration dating is based on stability testing conducted on one pilot batch of Carbodex DM Syrup. However, our investigator noted there are significant differences between the quantitative formulations and manufacturing processes utilized for the two products, and your firm lacks scientific basis for asserting that the Carbodex stability data is applicable to PSE Carbinoxamine DM Syrup.

Our inspection also found that your firm failed to conduct appropriate stability testing to justify the two-year expiration dating assigned to PDM GG Drops packaged into 1-ounce HDPE containers. Our investigator noted that no stability testing had been conducted on samples of lots representing the current commercial formulation and manufacturing process. The investigator was advised that the two-year expiration dating is based on stability testing conducted on PDM GG Syrup, however, it was noted that there are significant differences between the quantitative formulations and manufacturing processes as well as the size of the container-closures utilized for the two products. Consequently, your firm lacked a scientific basis for asserting that the stability testing conducted on PDM GG Syrup is applicable to PDM GG Drops.

Your November 26, 2003, FDA 483 response includes a stability report showing that three-month accelerated stability testing was conducted on October 26, 2003, on PDM GG Drops, lot F316, in support of tentative two-year expiration-dating. Based on the October 26, 2003, three-month accelerated testing referenced in the stability report, this testing was completed during the course of our inspection. It is unclear to us why this data was not shown to our investigator, when the lack of adequate stability data for PDM GG Drops was documented during the inspection. Additionally, we note that your stability reports do not include documentation of the temperature conditions utilized for room temperature and accelerated stability sample storage conditions. According to the stability report, accelerated testing was

conducted at one time-point only after three-months, which may not provide sufficient data to establish tentative expiration dating.

4. Failure to establish written procedures for the reprocessing of failing batches to insure that reprocessed batches will conform with all established standards, specifications and characteristics. [21 CFR 211.115(a)]

Your firm reworked a failing lot of Pediahist DM syrup, lot #F312, a prescription pediatric drug, into three smaller sized lots after it was determined that the manufacturing order for Pediahist lot F312 contained the quantitative formulation for a different product. There were no written procedures for this reprocessing and the reformulation was not documented.

Your investigation report for failing Pediahist lot F312 indicates that the batch was formulated superpotent because the manufacturing order sheet was reproduced from another product format on a computer, hence the incorrect amounts of ingredients were carried forward. Although, the Pediahist lot F312 manufacturing order includes the signatures of yourself and another individual who prepared and reviewed the manufacturing order prior to manufacturing, the error was not found until the batch was compounded and a portion of the batch was filled. We are extremely concerned by the apparent lack of appropriate master production records and systems to prevent such errors from occurring. The corrective action documented in your firm's investigation report states that in the future utmost care would be taken for preparation and review of the documents for formulations and bulk manufacturing. However, there is no mention of any specific measures that will be taken to prevent a recurrence of such an error. Moreover, there is no indication that your investigation of this error was extended to other lots and products that have been manufactured by your firm. Considering that your operations allowed for such an error, it is critical that appropriate measures be taken to ensure that similar formulation errors have not occurred in other products marketed by your firm.

In the reworking of lot F312, your firm used the incorrectly formulated blend that was assumed to be superpotent for the manufacture of three new batches. Your firm failed to assay the blend to confirm the strength of the four active ingredients before using the blend to manufacture the three new batches. There was no written reprocessing procedure and no documentation of the calculations used to formulate the three new batches with the blend material from lot F312.

Your FDA 483 response states that a master production record (MPR) for the Pediahist 900 liter batch size had been established prior to the manufacture of the three 900 liter reprocessed batches. However, the copy of the MPR submitted with your response does not contain rework or reprocessing procedures and does not include signatures or dates of review and approval of the MPR by the quality control unit. Lastly, the "Protocol for Reprocessing" dated June 23, 2003, submitted with your response, states that "principally" lot F312 may not be reprocessed, but it is not

practical to destroy the batch as it is associated with a substantial dollar value, and the bulk may be used for manufacturing new batches.

5. **Master production and control records lack complete manufacturing and control instructions such as sampling and testing procedures, specifications, special notations and precautions to be followed. [21 CFR 211.186 and 211.188] Additionally, there is a lack of procedures for production and process control to assure that drug products have the identity, strength, quality, and purity they purport or are represented to possess, and failure to have procedures that require that any deviation from written production and process control procedures are recorded and justified. [21 CFR 211.100]**

Your master and batch production records do not contain all significant manufacturing steps. For example, the batch record for Tri-Vitamin infant drops with fluoride lot #D308 states to “dissolve methyl and propyl paraben in polysorbate 80” and to “dissolve ascorbic acid caramel and EDTA in purified water.” The occasional use of a heating belt to help dissolve in-process materials, as explained to our investigator, was observed around your transfer tank, but is not listed in batch records. The time and temperature to which in-process materials are heated is not described in the batch record. Moreover, because specific time and temperature requirements have not been established and validated, there is no assurance that use of the heating belt does not adversely impact the quality and strength of the in-process material and the drug product. We acknowledge your written commitment to complete master production and control records for each batch size of each different product.

Your firm must ensure that all significant manufacturing steps for each product are specified in master and batch production records and reviewed and approved by qualified individuals in your firm’s quality unit. Any deviations from approved procedures in master production records must be fully documented with the rationale, as well as reviewed and approved by qualified individuals in the quality unit. Additionally, your firm should have written procedures for change control to ensure that any significant changes from approved manufacturing procedures are documented, appropriately validated and approved.

6. **Failure to establish written procedures for the cleaning and maintenance of manufacturing equipment, including utensils, used in the processing, packing or holding of a drug product. [21 CFR 211.67(b)]**

Your firm has still not performed cleaning validation for several pieces of manufacturing equipment used to manufacture a variety of different prescription drug products. For example, cleaning validation studies for the semi-automatic filling machine, 35 liter stainless steel mixing pot and hand mixing utensils have not been performed. Therefore, there is a lack of assurance that cross contamination does not occur between drug products manufactured sequentially with the same equipment. Additionally, a microbiological assessment of the effectiveness of your cleaning

agent was not determined, and chemical residue limits were not established for your cleaning agent.

The lack of cleaning validation was previously brought to your attention during the January 22, 1997 inspection of your firm. In your March 12, 1997, correspondence you committed to "evaluate whether or not previous cleaning validation studies remain valid" and if found to be not validated, "we will redo all cleaning validation studies. Estimated time of completion 9/30/97." As mentioned, we remain concerned about your failure to fulfill past commitments made to the agency.

We acknowledge your renewed commitment, as stated in your November 26, 2003 response, to include cleaning procedures for all pieces of manufacturing equipment used by your firm, and to incorporate microbiological limits in all cleaning validation studies. During our next inspection, we intend to verify the corrections that you have promised to make.

- 7. Failure to assure that equipment, including laboratory equipment, used in the manufacture, processing, testing, packing or holding of a drug product is of an appropriate design to facilitate operations for its intended use [21 CFR 211.63], and calibrate instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written procedure. [211 CFR 160(b)(4)].**

Your firm has not qualified your manufacturing equipment and there is no assurance that the equipment can consistently operate within the limits and tolerances you desire. Additionally, your firm has no written procedure for the calibration of laboratory equipment, and there is no assurance that your laboratory equipment is yielding accurate and reliable results. We acknowledge your commitment to qualify all manufacturing equipment, and to establish a written calibration procedure, and maintenance program for all laboratory equipment. We will verify your implementation of new procedures during our next inspection.

We have the following comments concerning PSE Carbinoxamine DM Syrup and Dynatuss Syrup:

Carbinoxamine containing drug products were reviewed under the agency's Drug Efficacy Study Implementation (DESI) program. All drug products evaluated under the DESI program are new drugs and, pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act, require an approved application before marketing. All drug products that are identical, similar, or related to products evaluated under the DESI program are also new drugs and require an approved application before marketing.

The drug products PSE Carbinoxamine DM Syrup and Dynatuss Syrup, (both containing Carbinoxamine Maleate, Pseudophedrine HCl, and Dextromethorphan Hydrobromide) are similar or related to the carbinoxamine products reviewed under the DESI program and are, therefore, new drugs subject to the provisions of Section

505 of the Act. No approval of an application filed pursuant to Section 505 is in effect for these drugs. The marketing of these products without approved new drug applications violates section 505 of the Act.

The above violations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that all drug products manufactured by your firm are in compliance with federal laws and regulations. We are extremely concerned by your failure to fulfill past commitments, and we intend to verify your progress toward the timely completion of all corrections that you have again promised.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice. These actions include, but are not limited to, seizure of your products or injunction. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter of the additional specific steps you will take to correct these violations, including an explanation of each step being taken to prevent the recurrence of the violations, as well as how you plan to assure that each of the systems at your firm are in an overall state of control. If corrective actions cannot be completed within 15 working days, please state the reason for the delay and the time frame within which corrective actions will be completed.

In addition, we note that your firm markets Rx cough/cold combination products (e.g., Carbodex DM Syrup and Rondamine DM Syrup) that contain combinations of ingredients covered under the final regulations on OTC cough/cold drugs at 21 CFR 341.40. These regulations become effective on December 23, 2004. At that time, all cough/cold combination products covered by those regulations are to be marketed as OTC drugs that must be formulated and labeled in compliance with the requirements of that section.

We also note that your firm reformulated Carbodex DM Syrup without changing the product's name. Because Carbodex DM Syrup is a trade name associated with a previously marketed formulation, the continued use of the same trade name may cause confusion to drug prescribers and dispensers, who may be unaware that the product has been reformulated. Such confusion may result in the product being prescribed erroneously, thereby risking dangerous drug interactions and overdoses. In reply to this letter, please advise us of the steps that you have taken or will take to notify both prescribers and dispensers of the changes to your product.

Tri-Med Laboratories, Inc.
Somerset, NJ 07607

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You should address your reply to this letter to the U.S. Food and Drug Administration, 10 Waterview Blvd., Parsippany, New Jersey 07054, Attn: Joseph F. McGinnis R.Ph, Compliance Officer.

Sincerely,



Douglas I. Ellsworth
District Director
New Jersey District