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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

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

Telephone (973) 331.4910

April 16, 2007

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Venkat E. Kakani
President and COO
Medico Labs, Inc.
1000 Nottingham Way
Hamilton, New Jersey 08609

07-NWJ-10

Dear Mr. Kakani:

An inspection of your manufacturing facility located at 1000 Nottingham Way, Hamilton, NJ was conducted from November 2 through November 16, 2006. During the inspection, our investigator documented deviations from the Current Good Manufacturing Practice (CGMP) Regulations, Title 21 Code of Federal Regulations, Parts 210 and 211 (21 CFR 210 and 211) for drug products manufactured and tested at this site. These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Food, Drug and Cosmetic Act (the Act) (21 U.S.C. section 351(a)(2)(B)), and are as follows:

1. Failure to establish and follow procedures prescribing a system for reprocessing batches to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics [21 CFR 211.115(a)]. Specifically, the following batches were reprocessed without a scientific basis for the reprocessing method or the quantities of additional excipients or active drug substance charged in during reprocessing. There is no assurance that the reprocessed batches, which represent new formulations, are assigned the appropriate expiration dating. The original failing or low assay values were not investigated and no root cause was determined.
   a) [redacted] (Guaifenesin, Dextromethorphan Hydrobromide, Pseudoephedrine HCl) Batch #[redacted] was reprocessed by adding additional raw materials (Propylene Glycol, USP, Glycerine,USP and Purified Water,

USP) to decrease the concentrations of Guaifenesin and Dextromethorphan Hydrobromide which exceeded specification at release testing. Original Guaifenesin assay values ranged between 110.07% and 111.44%. Original Dextromethorphan assay values ranged between 111.94% and 114.52%. This reprocessed lot was released to the market and expires 10/07.

b) [redacted] Children's Allergy Medicine (Diphenhydramine HCl, USP 12.5mg per 5mL) Batch #[redacted] was reprocessed by adding additional active pharmaceutical ingredient to the batch after low bulk assay values were obtained from the top of tank sample (90.88%) and the bottom of the tank sample (90.19%). This lot was released to the market and expires 12/07.

2. Written records were not always made of investigations into unexplained discrepancies, nor did investigations of unexplained discrepancies extend to other batches of the same drug product or other drug products that may have been associated with the specific failure or discrepancy [21 CFR 211.192]. Specifically, out-of-specification assay results for several of your drug products including [redacted], [redacted] and [redacted] had no written investigations or documentation of corrective actions. Although you informed our investigator that these batches were validation or stability batches and not released to the market, investigations must be conducted to determine if batches of the same product on the market have been impacted. Failure to determine the root cause of out-of-specification results and take appropriate corrective action undermines any assurance that your manufacturing process is in a state of control and consistently produces drug products that meet their specifications and quality attributes.

3. Failure to establish a written testing program designed to assess the stability characteristics of your drug products [21 CFR 211.166(a)]. There were no written stability protocols for any of the drug products that your firm manufactures. Such stability study parameters as sample sizes and test intervals, storage conditions, test methods and specifications, container-closure system, and number of lots to be placed on stability to determine appropriate expiration dating were not established in written stability testing protocols approved by your firm's quality control unit. In addition,

   a) There is no data demonstrating that the methods used for stability testing of any drug products manufactured by your firm are stability indicating [211.166(a)(3)]. Consequently, there is no assurance that stability data generated for each of your firm's drug products is reliable and that marketed drug products are assigned appropriate expiration dating.
   b) Drug products manufactured by your firm have not been evaluated for the presence of impurities and degradation products [211.160(b)].
   c) Review of stability data for [redacted] Children's Allergy Medicine, Batch [redacted], shows that assay and microbial test data are missing from the one month accelerated test station, there is no data reported for the two month

accelerated test station and product description, pH and specific gravity data are missing from the three month accelerated test station [211.166 (a)].

4. The master production and control records are deficient in that they lack a justification for the variation in the amount of components used in the preparation of a dosage form [21 CFR 211.186(b)(4)]. Specifically, several of your products, including [redacted], [redacted] and [redacted] are formulated with overages of the active pharmaceutical ingredient ranging from [redacted], however, there is no documented scientific justification to explain why the overages are necessary.

5. Evaluations were not conducted at least annually to review records associated with a representative number of batches, whether approved or rejected [21 CFR 211.180(e)(1)]. Specifically, your firm failed to conduct annual product reviews for all drug products to evaluate batches manufactured, rejected, and reprocessed, as well as other issues, including trends in complaints, investigations, or manufacturing that warrant corrective actions.

6. Appropriate controls are not exercised over computers or related systems to assure that changes in analytical methods or other control records are instituted only by authorized personnel [21 CFR 211.68(b)]. Specifically,

   a) There was a failure to validate the [redacted] software to assure that all data generated by the system was secure. This software runs the laboratory HPLC equipment, generates and stores data, and performs calculations during testing of raw materials, in-process materials, finished products, and stability samples.

   b) User access levels for the [redacted] software were not established and documented. Currently, laboratory personnel use a common password to gain access to the system and there are no user access level restrictions for deleting or modifying data. Furthermore, your system does not have an audit trail to document changes.

7. Cleaning validation studies for all products manufactured at this site have not been completed. Your firm has not established specifications for acceptable levels of active pharmaceutical ingredient residues or detergent residues in rinse samples [21 CFR 211.67 (b)]. Additionally, method validation studies for the determination of these residues have not been completed [21 CFR 211.194].

8. Failure to qualify manufacturing equipment such as the liquid filler, homogenizer and colloidal mill, which were used to manufacture all liquid finished products at your facility [21 CFR 211.68(a)].

Neither the list above nor the examples on the FDA-483, List of Inspectional Observations, which was issued to you firm on November 16, 2006 is intended to be an

all-inclusive list of deficiencies at your firm. It is your responsibility to ensure adherence to each requirement of the Act and its regulations.

Also, some of the OTC drug products manufactured by your firm fail to bear required labeling information, as described below. These deviations cause your drug products to be misbranded within the meaning of sections 502(a) and (c) of the Act (21 U.S.C. §§ 352 (a) and (c)) as follows:
The [redacted] Children's Pain Reliever and [redacted] Children's Allergy drug products are misbranded under section 502(a) of the Act (21 U.S.C. § 352(a)) because the tamper-evident packaging (TEP) labeling statements, "Do not use if tamper evident seal under cap is broken or missing" and "Packed with tamper evident seal below bottle cap" each fail to reference the required identifying characteristic in the feature.
(21 C.F.R. § 211.132(c))

The [redacted] Tussin DM, [redacted] Tussin, and [redacted] Tussin DM Syrup drug products are misbranded under section 502(a) of the Act (21 U.S.C. § 352(a)) because the tamper-evident packaging (TEP) labeling statements, "Do not use if induction seal is tampered or destroyed," on each product fail to clearly describe the placement of the TEP feature so that the consumer will be able to locate the specific feature. (21 C.F.R. § 211.132(c))

The [redacted] Tussin DM, [redacted] Children's Pain Reliever, [redacted] Tussin DM, [redacted] Tussin DM, [redacted] Tussin, [redacted] Tussin-DM Syrup, and [redacted] Children's Allergy product are also misbranded under section 502(c) of the Act (21 U.S.C. § 352(c)) because the labeling fails to fully comply with the Drug Facts Format regulations in 21 C.F.R. § 201.66. Specifically, the "directions for use" on each of the products is placed on the principal display panel of the label instead of in the Drug Facts Format box as required by 21 C.F.R. § 201.66(c)(6).

We have received your written response to the FDA-483 observations dated January 5, 2007; it will be made part of our official files. Our specific comments are detailed below. In general, however, considering the nature of the deficiencies, your response is inadequate.

While we acknowledge your commitment to improve your CGMP compliance, inadequacies in several significant CGMP areas found during the inspection cause the Agency to question the quality of the drug products released from your facility. In order to ensure the quality of marketed product, your firm should promptly initiate a full review of all lots within expiration in the market to assure that the released drug products have their appropriate identity, strength, quality, and purity. Appropriate action regarding compromised or questionable product must be taken.

We have reviewed your proposed corrective actions and have the following comments and questions. These follow the FDA-483 numbering for ease of review.

1. We do not find your response to be satisfactory. Please explain and justify what you intend to do about the two product lots cited in the observation. These product lots are both within expiry and were released to the market. You have not provided any assurance that these reprocessed batches will remain stable throughout their respective expiry periods. Furthermore, your Reprocessing SOP QA-067-00, dated November 3, 2006, does not require an assessment to determine
    a. the need to validate the reprocessing procedure and the extent of the validation
    b. the possible impact on long term stability of the reprocessed lot.

2. Your response was incomplete in that it did not address change control. The Complaint SOP does not include a time frame for the completion of the investigation and corrective and preventive action as necessary. Additionally, your Reprocessing SOP is inadequate as stated above (1a &1b).

   Regarding computer validation and security issues, you did not provide a time frame for writing and implementation of a computer security SOP. Your response regarding data back-up indicated that a separate server was being considered and would be implemented by "[redacted]" We believe this date was to have read [redacted]. Please explain why this correction cannot be completed in a more timely fashion.

3. The response is incomplete. You stated that Annual Product Reviews would be completed for all batches manufactured in 2004 and 2005, but you did not address batches manufactured in 2006. In addition, you did not provide any written procedures for conducting periodic product reviews.

4. Based upon your response, it appears that investigations of the Out-of-Specification results cited on the FDA-483 have still not been conducted and documented, nor have you assessed whether any of the failures cited may also affect marketed product lots, for instance, in terms of the ability of the marketed lots to meet all specifications throughout the labeled expiry period.

   In addition, your response states that your investigation procedures were "strictly followed" even though the response also states "no formal documentation were finalized." We do not understand your conclusion that procedures were followed if investigations were not documented.

   Furthermore, after reviewing your SOP QC-029-00, Out of Specification, it appears that your use of the term "retesting" is different than FDA's meaning of the word. Retesting, as defined by FDA, is a complete repeat of the entire analysis to include the sample preparation step. During the first phase of an OOS

investigation, i.e., the laboratory investigation, the original test preparations may be re-analyzed as a means to explore if something went wrong during the original analysis, but this is not considered retesting.

Retesting occurs at a later stage of the investigation and involves an entirely new preparation from the original sample. We are concerned that your procedure as written will not assure that decisions regarding retesting and possible release of batches will be appropriate. You did not specify the maximum number of retests to be performed. This should be specified in advance in a written standard operating procedure. The number may vary depending upon the variability of the particular test method employed, but should be based on scientifically sound principles. The number of retests should not be adjusted depending on the results obtained. Your procedure should identify the point at which the additional testing ends and the batch is evaluated.

Also, the issue of averaging results, which is discussed in section VIII, Reporting, is not clear. FDA does not recommend averaging results unless the averaging of individual results within a single analysis is called for as part of the analytical method. Unless the OOS result is due to a confirmed laboratory error, all results, original OOS and retesting results should be reported.

Please refer to FDA's "Guidance for Industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production" published in October 2006 to assist you in revising your SOP. This Guidance can be found at http://www.fda.gov/cder/guidance/3634fnl.htm

5. The response is not satisfactory. You have produced no evidence, either in the response or during the inspection, to show that the analytical methods are stability indicating. You referred to the USP; however, not all USP methods are stability indicating. You must evaluate your specific products for potential impurities or degradation products and determine if specifications for them need to be established.

   Regardless of whether your products are equivalents of national brands, the stability of your specific products, including impurities and degradation products, must be demonstrated by validated methods. Stability studies are incomplete and insufficient if the methods used therein are not stability indicating.

6. Your response discusses future stability studies, but there has been no commitment to review completed or on-going studies to determine if they were adequate, especially since your SOP RD-003-00, Protocol for Stability Testing, does not appear to have been followed.

Your response states that you have taken action to maintain a consistent temperature throughout the stability chamber, but you did not provide a description of the specific actions taken. Please elaborate on these corrective actions.

We note that you have committed to monitoring the humidity in the stability room; however, the time frame for implementing this action was given as [redacted]. Please explain why this correction cannot be completed in a more timely fashion.

7. See the comments under #2 above.

8. Although you state that the "error in judgment" regarding lot [redacted] will not be repeated, you have provided no details on any changes in procedures that are designed to preclude this type of error in the future.

9. The response to this observation is not satisfactory. You have provided no scientific justification for the overages in existing products. Your response suggests that you will determine overages based on patterns of degradation. Overages for stability purposes are not recommended. If an overage of active is needed so that the product remains within specification at the end of the expiry period, it raises a potential clinical concern. With a [redacted] or [redacted] overage in a product, there is potentially 15% or 20% degradant(s) in the product at the end of the expiry period. Your firm has not evaluated the possible degradants or impurities in your drug products.

10. The response is not satisfactory. Please provide us with details on the actions you are taking to address all of the specific issues in the FDA-483 observation as well as a specific time frame for the completion of those specific actions.

11. Your cleaning program and procedures will be evaluated at the next inspection.

12. You did not include a time frame for completing equipment qualification studies. Your qualification studies will be evaluated during the next inspection.

We remain concerned that the underlying system problems resulting in the violations have not been fully addressed. Given the serious nature of the violations, more information about your actions is necessary before we can consider your response adequate.

The issues and violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their

recurrence or the occurrence of other violations. It is your responsibility to conduct a comprehensive audit of your facility and operations and assure compliance with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A reinspection may be necessary.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the time within which you will complete the correction. If you no longer manufacture or market any products, your response should so indicate, including the reasons for, and the date on which, you ceased production.

Your response should be addressed to: U.S. Food & Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054, Attn: Sarah A. Della Fave, Compliance Officer.

Sincerely yours,

Douglas I. Ellsworth
District Director
New Jersey District Office