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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Food and Drug Administration
Detroit District
300 River Place
Suite 5900
Detroit, MI 48207
Telephone: 313-393-8100
FAX: 313-393-8139

WARNING LETTER
2008-DT-05

October 31, 2008

Daniel H. Movens
Chief Executive Officer
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Dr.
Detroit, Michigan 48202

Dear Mr. Movens:

From May 1 to June 11, 2008, the Food and Drug Administration (FDA) conducted an inspection of your manufacturing facility in Detroit, Michigan. The inspection revealed significant deviations from current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals (Title 21, *Code of Federal Regulations*, Parts 210 and 211). These CGMP deviations were listed on a List of Inspectional Observations (FDA-483) form issued to you at the close of the inspection. These CGMP deviations cause the drug products being manufactured at your facility to be adulterated within the meaning of Section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)] of the Federal Food, Drug, and Cosmetic Act (the Act) in that the manufacture, processing, and holding of drugs does not conform with CGMP to assure that such drugs meet the requirements of the Act as to safety, and have the identity and strength and meet the quality and purity characteristics that they purport or are represented to possess.

The CGMP deviations observed during the inspection include, but are not limited to the following:

1. Failure of the Quality Control Unit (QCU) a) to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed and b) to thoroughly investigate a batch or any of its components not meeting any of its specifications and extend investigations to other batches of the same drug product and other drug products that may have been associated with the specific failure [21 CFR § 211.192].

   a) Your QCU failed to fully investigate the contamination of Tramadol HCl, 50 mg tablets, lot (b)(4) and Metoprolol Tartrate USP, 50 mg tablets, lot (b)(4). On February 19, 2008, Tramadol HCl, lot (b)(4) was found contaminated with Metoprolol Tartrate. On February 25, 2008, Metoprolol Tartrate USP, lot (b)(4) was found contaminated with Metformin HCl. More than two months after the contamination issues were discovered, the Director of Quality provided only a draft investigation for the Tramadol HCl tablets and no information for the Metoprolol

Tartrate tablets investigation. Rather than extending the investigation of two, closely-related, confirmed incidents of contamination of lots that were not released, to other potentially impacted drug products, the QCU placed these investigations into a low priority status, without isolating the source of the contamination, and continued releasing drug products from the same time period in which the two cross-contaminated lots were processed.

Your July 10, 2008 response regarding the failure to thoroughly investigate discrepancies and out-of-specification (OOS) results, states in part that products under investigation were "placed on QA Hold or the entire batch was rejected upon discovery." We note significant inadequacies in your response, including inconsistencies with other explanations you provided previously during the inspection. First, none of the other drug products that may have been associated with the same failure during the cross-contamination incidents (i.e., Jan 2008) were placed on QA Hold or rejected (e.g. Carbamazepine, Citalopram HBr, Baclofen, (b)(4) . Second, your response to observation 1A (from the FDA-483) states in part that the two cross-contamination investigations "were initiated at the time of [*sic*] the incidents first occurred" and "extensions were granted to facilitate a complete report." Our investigators were provided with a draft incident report for the Tramadol HCl investigation, which had not been reviewed by your Director of Quality (until approximately four months after the cross-contamination incident), and your firm had not started an incident report for the Metoprolol Tartrate investigation. Approved extensions to the investigations were not granted by your QCU.

In addition, your response regarding the failure to extend the investigation to other drug products is troublesome. When discussing the issue of extending the investigation to other drug products, your response states in part "any potential cross-contamination would be identified during release testing of other batches...." Your release test methods are not validated for the detection of every potential contaminant and have not been demonstrated to be suitable under actual conditions of use (e.g. detection of any low level contaminant); therefore, we do not agree with your statement and advise you to fully investigate discrepancies and OOS results with reliable test methods that are validated for their intended purpose. The response also states in part "probable cause of the contamination was due to an operator error.... When this conclusion was made, the scope of lots potentially impacted became more definitive." The scope of the products potentially impacted did not become known until approximately four months after the incident began and three months after confirming the OOS results. Failure to conduct investigations in a timely manner and to extend the investigations to other drug products that may have been impacted by the same failures while investigations of confirmed cross-contamination (without a probable root cause identified) were ongoing demonstrate the failure of your QCU to provide adequate oversight and ensure procedures are followed. Please note that as significant time elapses, investigations become more challenging. We note that your firm documented such

a concern in another incident report: "An interview with the operators involved in the operation of these lots was not possible at this time, as substantial time has passed, and the accuracy of the information obtained through interviews at this point could not be verified as reliable."

b) Rather than following SOP (b)(4), which requires the approval of any incident report (IR) before the batch can be released, your QCU:

   i. released 408 bottles of Methimazole Tablets, USP, 10 mg, lot (b)(4), which at the time had an open investigation for equipment failure, and

   ii. released two products, Tramadol HCl tablets (lots (b)(4) and (b)(4) and Tramadol/Acetaminophen tablets (lot (b)(4)), which at the time had an open investigation for a shortage of (b)(4) (3%) of Tramadol drug substance (the raw material reconciliation limit is (b)(4)

   Your July 10, 2008 response regarding the lack of adequate investigation into instances of raw material reconciliation is inadequate and inconsistent. You state the intent of the investigation was "to provide a comprehensive investigative document for the file." You also state that "Quality issued the proper extensions to meet this objective." Your firm did not follow your written procedure to grant an extension to the investigation. While the procedure states that the investigation will be forwarded to your QCU within (b)(4) unless an extension is granted, your incident report is dated April 1, 2008 and the extension you refer to occurred on July 9, 2008. Your firm does not provide adequate rationale to justify the decision of your QCU to disregard these procedures to ensure discrepancies are thoroughly investigated and investigations are completed before product release.

c) Your QCU failed to fully investigate and close incident reports from March 2007, concerning content uniformity failures for Metoprolol Tartrate tablets (lots (b)(4), (b)(4), and (b)(4) listed as rejected), and from August 2007, concerning dissolution failures for Carbamazepine tablets USP (lots (b)(4), (b)(4) and (b)(4)). As of May 2008, the reports were incomplete with no information for the manufacturing investigations.

d) Your QCU failed to fully investigate (b)(4) (dated September 12, 2007) concerning a shortage of (b)(4) (3.7%) of Citalopram HBr raw material, lot (b)(4) (b)(4) thus failing to meet the raw material reconciliation limit (b)(4). Your investigation did not expand to other products dispensed on the same day, speculated without justification that "it could be due to short weight sent by supplier," and concluded that there was no impact on product quality.

e) Your QCU failed to fully investigate metal scrapings and foreign matter in compressed Metformin HCl tablets, 1000 mg (lot (b)(4), (b)(4) (dated February 27, 2008). As of June 11, 2008, there had been no written investigation.

   Your July 10, 2008 response regarding the metal contamination in Metformin HCl tablets, states in part "Operator failed to properly tighten the (b)(4) .. during

machine set-up." Your investigation was not adequate since the scope of the investigation did not evaluate whether the operator was involved in similar occurrences.

This is a repeat violation of the 2005, 2006, and March 2008 inspections.

2. Failure of the QCU to follow written procedures [21CFR § 211.22(d)].
   a. Your QCU did not follow SOP (b)(4) Approval for Product Finishing, Packaging and Disposition," as drug product subject to an open investigation was released (e.g. Methimazole tablets, lot 80012A; Tramadol HCl tablets, lots (b)(4) and (b)(4)
   b. Your QCU did not follow SOP (b)(4) "QA HOLD," (b)(4) Rather than placing a QA Hold on several Methimazole lots (e.g. (b)(4) (b)(4) (b)(4) because of an equipment failure (i.e., air handling unit associated with the fluid bed dryer (FBD) failed its HEPA recertification), your QCU released the lots without the required QA Hold which is intended to quarantine material from further processing or from being released.
   c. Your QCU did not follow SOP (b)(4) "Incident/Event Reporting and Documentation," by failing to track incident reports to ensure that required actions are completed and implemented as per internal procedures and to grant extensions when investigations cannot be completed within (b)(4) calendar days.

This is a repeat violation of the 2006 and March 2008 inspections.

3. Failure of the QCU to approve or reject all procedures or specifications impacting the identity, strength, quality, and purity of the drug product [21CFR § 211.22(c)].
   a. Your QCU has not established procedures to evaluate changes which may impact the validation status of your manufacturing processes and parameters (e.g. Tramadol granulation, Tramadol/Acetaminophen tablets).
   b. Your QCU has not established procedures to assure that components are not contaminated during the dispensing procedure. For example, SOP (b)(4) "Raw Material Dispensing Procedure," (b)(4) does not include provisions to prevent contamination from opened component containers.

      Your July 10, 2008 response to the failure of the QCU to follow procedures on preventing cross-contamination when multiple materials are in the same room is inadequate. The associated SOP (b)(4) lacks adequate controls to prevent cross-contamination of materials during the dispensing procedure.

4. Failure to maintain component records that include reconciliation of the use of each component with sufficient information to allow determination of any batch or lot of drug product associated with the use of each component [21CFR § 211.184(c)]. The control of materials is not adequate. For example,

a. Material inventories are adjusted to achieve a zero balance without determining the source or final disposition of the extra material (e.g. Metformin HCl, lot RM(b)(4) 12.044 kg; Tramadol HCl, lot (b)(4), 1.776 kg).

b. Upon receipt from your component suppliers, starting quantities of raw materials are not verified, resulting in unreliable and inaccurate inventory records.

5. Failure of the appropriate organizational unit and the QCU to review and approve any changes to established written procedures [21 CFR § 211.100(a)].

a. Your manufacturing process has not been validated for repeated changes to the drying time parameter of the oven dryers in the (b)(4) granulation. The changes were implemented in an attempt to ensure granulation is not too dry without establishing a minimum specification and without an assessment of product quality.

Your July 10, 2008 response regarding the failure to establish acceptable range for the LOD (loss on drying) states in part that "The LOD specification for (b)(4) (b)(4) has always been NMT (b)(4)" However, your response does not address statements made by the Vice President of Manufacturing and Director of Quality regarding concerns of granulation becoming too dry which prompted the change in drying times to obtain acceptable product. Please clarify the conditions and specifications which may produce a granulation too dry for compression with supporting documentation and your firm's plan to prevent this from recurring.

b. For: (b)(4) tablets, lot (b)(4) nine process change requests were implemented without evaluating the impact of the changes to product quality.

6. Failure to establish valid in-process specifications derived from previous acceptable process average and process variability estimates where possible [21 CFR § 211.110(b)]. Your firm does not have information to support in-process hardness specifications for (b)(4) tablets, USP, (b)(4)

7. Failure to maintain equipment at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements [21 CFR § 211.67(a)]. Your firm did not perform any maintenance on the air supply unit (including the HEPA filter) associated with the FBD equipment (#(b)(4) prior to its use in manufacturing operations. After use in production, the HEPA filter housed inside the unit failed the maintenance recertification.

This is a repeat observation of the 2005 inspection.

We have additional comments to your July 10, 2008 response as follows:

Your July 10, 2008 response to observation 7 of the FDA-483, regarding the failure to maintain complete batch records by excluding product discrepancies found during the inspection, is inadequate. Rather than allowing your operators to continue the in-process

inspections of tablets (which appeared to be effectively detecting product defects), your response indicates that QCU will no longer allow the operators to perform these inspections in an effort to eliminate redundancies (inspections are performed by the QCU) and inspection discrepancies concerning the inadequate documentation of batch records. Please provide information to demonstrate that the inspections performed by your QCU are producing the same or better results than the ones performed by the manufacturing operators. You should not eliminate a process that improves the quality of your products without sound justification.

You state in your July 10, 2008 response that your firm continues to undergo annual external audits with the most recent audit conducted (b)(4). Our last inspection conducted in June 2008 and your firm's compliance history raise concerns about the effectiveness of the audits. Most of the corrections to the inspectional observations were initiated after the FDA investigators discovered the failures in your CGMP systems. Please comment on how future audits will ensure that the Quality Management System will identify and correct deficiencies and prevent reoccurrences.

We received your written responses dated June 19, July 10, July 25, August 8, August 22, September 05, September 19, October 3, and October 24, 2008. We acknowledge your commitment to take specific steps to both correct the noted deficiencies, and to make comprehensive systematic corrections to assure that similar violations will not recur. We also acknowledge the corrective actions promised by your firm including, but not limited to the following: organizational changes; commitment to complete and close all delinquent incident reports; training; hiring of consultants; revision to standard operating procedures, process parameters, and quality attribute specifications; and revision to the material system. However, we have serious concerns regarding: a) your firm's compliance history including several past inspections that documented significant CGMP deficiencies, b) the serious nature of the observed violations, c) your plans for expansion under these violative conditions, and d) the risk to consumers associated with the CGMP deviations involving potential product contamination.

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 assure that your firm complies with all requirements of the CGMP regulations and with the Act.

You should take prompt action to correct deficiencies at your facility. 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.

Please respond to this office in writing within fifteen working days of receiving this letter. Your response should describe any specific actions, other than those already submitted, you will take, or have taken, to correct the violations described above including the dates the corrective actions were completed, and proposed timeframes for completion of each remaining corrective action. Include an explanation of how each action being taken will prevent recurrence of similar violations, as well as copies of related documentation. Please state the reason for any delays in implementing the corrective actions along with the time frames within which corrective actions will be completed. If you no longer manufacture or market any of your products, your response should so indicate, including the reasons for, and the date on which, you ceased production. We will review and evaluate the implementation and adequacy of your corrective actions during our follow-up inspection of your firm.

Please direct your response to Judith A. Putz, Compliance Officer at U.S. Food and Drug Administration, 300 Rive Place, Suite 5900, Detroit, Michigan 48207.

Sincerely,

Joann M. Givens
District Director
Detroit District