DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
White Oak, Bldg. 51
Rockville, MD 20857

February 5, 2009

WARNING LETTER

VIA Federal Express WL No. 320-08-04

Barrie Levitt, M. D.
Chairman and CEO
Taro Pharmaceuticals U.S.A., Inc.
3 Skyline Drive
Hawthorne, NY 10532

Dear Dr. Levitt:

This letter is regarding an inspection of your pharmaceutical manufacturing facility in Brampton, Ontario, Canada, by FDA Investigator Daryl A. DeWoskin and Chemist Marianela Aponte Cruz during the period of July 28-31, 2008. The inspection revealed significant deviations from Current Good Manufacturing Practices (CGMP) Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211) in the manufacture of non-sterile cream and ointment finished drug products.

These CGMP deviations were listed on an Inspectional Observations (FDA-483) form issued to Mr. (b) (6), General Manager, at the close of inspection. These deviations 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 Act) [21 U.S.C. 351(a)(2)(B)] in that they were not manufactured, processed, packed, and held in compliance with current good manufacturing practice.

We have reviewed the Establishment Inspection Report (EIR) and your September 26, 2008 response to the FDA-483 observations. We acknowledge that some corrections appear to have been completed, or will soon be completed. However, your response fails to adequately address multiple serious deficiencies. Specific areas of concern include but are not limited to the following aspects of your firm's quality system:

1. The written stability testing program is inadequate to assess the stability characteristics of drug products and for determining appropriate storage conditions and expiration dates [21 CFR 211.166(a)]. In addition, expiration dates on drug product labeling have not been determined by appropriate stability testing [21 CFR 211.137(a)]. For example:

   A. Three out of twenty four lots of Fluocinonide cream USP, 0.05% (36-month shelf-life), failed the ANDA limit of 6.0% for the relative standard deviation (RSD) of

the top, middle and bottom assays for tube uniformity stability at 18-month (lot (b) (4)) and 36-month (lots (b) (4)) time stations.

B. Five lots of Betamethasone Valerate cream USP, 0.05% (48 months shelf-life), (b) (4), failed to meet established purity specifications at the 36- and 48-month stability time point. Additionally, lot (b) (4) also failed the 24-month time point for purity testing.

C. Two of the three validation lots of Ciclopirox Olamine cream USP, 0.77%, (b) (4), failed relative standard deviation (RSD) specification limits for tube content uniformity at 24-month and 12-, 18- & 24-month stability time points, respectively. Following the stability failures, the shelf-life of Ciclopirox Olamine cream was reduced on May 12, 2006 to 18 months and six lots were marketed with this reduced shelf-life. Furthermore, on October 10, 2006, the shelf-life was increased to 24 months without adequate justification. The product was reformulated and marketed in January 2008 without any supporting stability data.

   Your response to the Form 483 stated that the validation lot (b) (4) failed the product RSD limit for the 12-month stability time point, but your response did not acknowledge the stability failures of the 18- and 24- month time points. We are concerned that your response did not consider the above failures as significant enough to take corrective measures, such as reduction of the expiration date commensurate with the stability data.

D. Eleven lots of Mupirocin Ointment USP 2% in 2007 and 2008 (b) (4), which were projected to fail the established 18-month shelf life, were assigned reduced expiration dates (either 15 or 16 months) without adequate justification. The adjustment of expiration dates was based on (b) (4) of three validation batches (b) (4) This is not a valid method for determining expiration dates.

   Your response to the Form FDA-483 asserted that stability failure of a few batches of a drug product is a minor deficiency and that the expiration date for the product is still valid. The frequency of stability failures outlined above is significant, and there is no evidence that your drug products meet the standards of strength, quality and purity at the time of their use within the expiration period. Your response did not specify the corrective measures that you will take in the event of these and any future stability failures. In addition you have provided no rationale for these failures and no corrective actions.

   Field alert reports for stability failures were not always reported to the FDA within three working days of becoming aware of information concerning significant chemical, physical, or other change or deterioration in the distributed

drug product, or any failure of one or more distributed batches of the drug product to meet the specifications established for it in the application, as required under 21 CFR 314.81(b)(1)(ii). For example, field alert reports were not submitted for the stability failures of Fluocinonide cream USP 0.05%, lot (b) (4) and Ciclopirox Olamine cream 0.77%, lot (b) (4), for tube uniformity, and for Nystatin Triamcinolone Acetonide cream USP lot (b) (4) for assay.

When an applicant becomes aware of any information stated in 314.81(b)(1), the applicant is required to report it to the jurisdictional district office within 3 working days. An applicant is required to submit information concerning any failure of one or more distributed batches of a drug product related to final stability point testing even if the testing is conducted after the expiry date.

Your September 26, 2008 response did not address the written statement made during the inspection by Mr. (b) (6), General Counsel of your firm, that it is your firm's policy not to report to the FDA stability failures at the last stability time point of your products.

2. Out-of-specification (OOS) results or unexplained discrepancies were neither thoroughly investigated nor performed in a timely manner by your firm's quality control unit, as required per 21 CFR 211.192. For example,

   A. QA Summary Reports (QAS), generated after the first two stability failures of Fluocinonide cream USP 0.05% in December 2007 and April 2008 (lots (b) (4)) only reiterated the contents of the lab investigation reports (LIR) without extending the investigation to address the trend analysis of all stability data, process, and R&D related issues. A broader QA investigation following the failure of a third lot, (b) (4), in May 2008 was not reported until July 17, 2008, and it did not include a review of batch records or the adequacy of process controls.

   Stability failure investigations of Fluocinonide cream identified the assignable cause as separation of components in the finished product during its shelf life and recommended reformulation of the product. However, your OOS investigations did not include a corrective action plan.

   Your response to the Form 483 stated that there is no need for reformulation of Fluocinonide cream USP 0.05%. You contend that stability failure of 3 out of 24 batches was a minor deficiency and that the 36-month expiration date for the product is still valid. We are concerned that you have not taken any action to reformulate, reduce the shelf-life, or withdraw this product, which is not supported by stability data.

   B. Multiple OOS investigations failed to identify the root cause of the failure of five Betamethasone Valerate lots (b) (4) with respect to

batch-to-batch variability of the Betamethasone (b) (4) impurity and total impurities in the stability samples. The investigations did not address the need for corrective actions such as withdrawing the product from the market, quarantine of the product in stock or reduction of the expiration date commensurate with the stability data.

Your response to the Form 483 stated that the production of Betamethasone Valerate at your US plant was discontinued in 2006, and hence, process-related investigations could not be performed. However, your response did not include corrective measures to assure that the drug product meets the standards of strength, quality and purity at the time of its use. We are concerned that the product was not withdrawn from the market and the expiration date for the product was not reduced.

C. The investigation by your Research and Development department into the change in the texture of Clobetasol Propionate cream, USP 0.5%, which was initiated in 2005 due to consumer complaints, was not reviewed and signed by the R&D Director until July 2008. The report concluded that the product needs to be reformulated.

Your response to the Form 483 stated that the viscosity associated with scale-up of the Clobetasol Propionate cream to (b) (4) was at a lower value than batches manufactured at either the (b) (4) or (b) (4) batch sizes. You also state that you received only one complaint regarding (b) (4) lots manufactured in 2007. The data you provided are inadequate to reach a conclusion regarding the stability of the product, as they did not include consumer complaint data for all three lot sizes, including lot numbers, manufacturing data and complaint receipt dates, for the last three years. Additionally, your response did not address whether the corrective and preventive actions regarding root causes identified in the July 2008 R&D report were implemented, or whether such actions were effective in resolving the problem.

D. Lots (b) (4) of Hydrocortisone 1% cream with oatmeal were found to be contaminated with Candida Parapsilosis (Yeast) over a period of six months. Additionally, mold contamination was found in lots (b) (4) in July 2008. Multiple OOS investigations were not timely and failed to identify the root cause of the microbiological contamination.

E. Multiple OOS investigations of Mupirocin ointment USP 2% conducted in 2007 and 2008 failed to identify the root cause of the decrease in potency over the shelf-life of the product.

4. The quality control unit failed its responsibility to reject drug products that did not meet specifications impacting identity, strength, quality and purity of drug products.

21 CFR 211.22. It also failed to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated as per 21 CFR 211.22(a).

For example, the quality control unit did not adequately ensure that the drug products released to the market were supported by appropriate stability data. It also did not ensure that investigations of laboratory results for drug products were completed, and corrective actions were implemented, in a timely manner. Several products failed stability testing for potency, purity and tube uniformity, and your firm did not conduct thorough investigations in a timely manner. We refer to examples 1, 2, and 3 of this letter.

The deviations identified above or on the FDA-483 issued to you are not to be considered as an all-inclusive list of deficiencies at this facility. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for current good manufacturing practice. 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 ensure that your firm complies with all FDA regulations.

You should take prompt action to correct the violations cited in this letter. This office will recommend disapproval of any new applications or supplements listing your firm as a manufacturing location of finished dosage forms and active pharmaceutical ingredients until all corrections have been completed and FDA can confirm your firm's compliance with CGMPs. In addition, shipments of articles manufactured by your firm may be subject to refusal of admission pursuant to Section 801(a)(3) of the act [21 U.S.C. 381(a)(3)] in that the methods and controls used in their manufacture do not appear to conform to good manufacturing practice within the meaning of Section 501(a)(2)(B) of the Act [21 U.S.C. 351(a)(2)(B).

Please respond to this letter within 30 days of receipt. Identify your response with FEI #3002808384. Please contact Dr. Muralidhara (Mike) Gavini, Compliance Officer, at the address and telephone numbers shown below if you have any questions, further information or proposals regarding this letter.

U.S. Food & Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing Product Quality
International Compliance Team
White Oak Building 51, Room 4228
10903 New Hampshire Avenue
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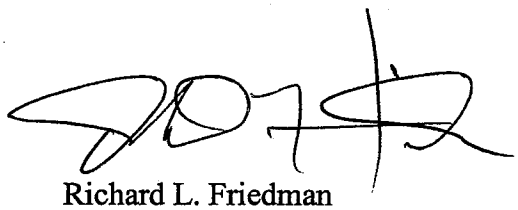
To schedule a reinspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Field Investigations, HFC 130, Room 13-74, 5600 Fishers Lane, Rockville, MD 20857. You may also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,



Richard L. Friedman
Director
Division of Manufacturing & Product
Quality, Office of Compliance
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