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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Warning Letter

Via FedEx

WL: 320-07-04

JAN 1 4 2008

Mr. Yoshihiro Tomita
Chief Executive Officer and Chairman
Tomita Pharmaceutical Co., Ltd
85-1 Aza-maruyama, Akinokami, Seto-cho
Naruto-City, Tokushima 7771-0360
Japan

Dear Mr. Tomita:

We have completed our review of the inspection of your pharmaceutical manufacturing facility in Tokushima, Japan, by Investigator Katherine E. Jacobitz and Analyst Luis M. Burgos Medero, during the period of July 31 – August 2, 2007. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) in the manufacture of active pharmaceutical ingredients (APIs).

The deviations were presented on an Inspectional Observations (FDA-483) form at the close of the inspection to Mr.[ ] Quality Assurance Division Manager and Product Security Pharmacist. These CGMP deviations cause your APIs to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). In addition, your firm failed to provide copies of documents requested throughout the inspection.

During the close-out meeting, Mr.[ ] indicated that the firm would respond in writing to the FDA-483 observations within 30 days. We have not yet received a written response. Based on the review of the EIR, specific areas of concern include, but are not limited to:

Laboratory system

1. The analyst worksheets were deficient in that the following was observed:

    a) There was no reference to the analytical test methods used
    b) There was no reference to the[ ] or instruments used
    c) There was no reference to the manufacturer's standards and/or the lot number used

d) There were unidentified post-it notes with the sample and standard weights and no reconcilability of the batches being tested
e) There were weights reported without indicating the gross, tare, or net weight

This is a repeated deviation from the August 1-3, 2005, inspection of your site. After that inspection, in your response dated 8/29/05, your firm stated that "We begin to apply the record details of analyst work, calculations and pertinent information in any of analyses such as [ ] and so on by the end of this year."

Please note that laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards. This includes the signature of the person who performed each test and the date(s) the tests were performed, as well as the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

2. Failure of your investigations of out-of-specification (OOS) results to determine if corrections or preventive actions are needed.

During the inspection, it was noted that at least 7 OOS results were found and confirmed by your firm. Your firm failed to continue its investigation of the OOS results outside of the laboratory in order to determine the cause of the results. Your firm promised corrective action, however, no documentation and/or written commitment was provided.

Any OOS result obtained should be investigated and documented according to a procedure. This procedure should include analysis of the data, assessment of the extent and cause of the problem, allocation of the tasks for corrective actions, and conclusions. Any resampling or retesting after OOS results should be performed according to a documented procedure.

Written procedures should be established and followed for investigating deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

3. Failure to have a validated and secure computerized system. Additionally, there were no written protocols to assign levels of responsibilities for the system.

It was noted that the [ ] instrument model [ ] used for the analysis of [ ] failed to have password control for the analysts and the supervisor. It

was observed that the data stored on the computer can be deleted, removed, transferred, renamed or altered.

While your firm's management stated that they would like to implement certain improvements in order to establish a security system, no documentation or commitment has been provided.

Please note that computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent data omissions and assure back-up. There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

The CGMP deviations identified above or on the FDA-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practices.

During the inspection, your firm refused to provide copies of production records, laboratory records, and written procedures requested by the FDA Investigator and Analyst for their later review. Your refusal to provide documents hinders FDA's ability to perform an inspection and determine your firm's compliance with CGMP requirements. Thus, FDA considers your refusal to provide documents as a refusal to allow inspection. APIs manufactured by your firm may be refused entry into the U.S. pursuant to Section 801(a)(3) of the FD&C Act in that the methods and controls used in their manufacture do not appear to conform to current good manufacturing practice within the meaning of Section 501(a)(2)(B) of the FD&C Act, if documents necessary for an inspection and CGMP assessment are not provided.

We recommend that you conduct a complete and extensive evaluation of your facility to help ensure that APIs meet the quality and purity characteristics that they purport, or are represented, to possess. Please note that a guidance document entitled "Q7A Good Manufacturing Practice Guidance of Active Pharmaceutical Ingredients" (ICH CGMP Guidance), prepared under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), describes CGMP for manufacturing of APIs. The guidance, adopted by the FDA on September 25, 2001, is intended to help ensure that all APIs meet the standards for quality and purity that they purport or are represented to possess. Although the ICH CGMP Guidance does not impose requirements, FDA considers its recommendations, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's APIs have been manufactured, processed, packed, and held according to CGMP under Section 501(a)(2)(B) of the Act. To obtain the ICH CGMP Guidance for your reference, refer to the following website: http://www.fda.gov/cder/guidance/4286fnl.htm

Please respond to this letter within 30 days of receipt. Your response should include documentation with translation in English to address the deficiencies cited as well as copies of procedures. Please identify your response with FEI #3002808375. Until all corrections have been completed and FDA can confirm your firm's compliance with CGMPs, this office will recommend disapproval of any new applications or supplements listing your firm as a manufacturer of APIs.

Please contact Marybet Lopez, Compliance Officer, at the address and telephone numbers shown below, if you have any questions, further information, or further proposals regarding this letter.

U.S. Food & Drug Administration
Center for Drug Evaluation and Research, HFD-325
11919 Rockville Pike
Rockville, MD 20852
Tel: (301) 827-9004
FAX (301) 827-8909

To schedule a re-inspection 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, 5600 Fisher's Lane, Rockville, MD 20857. You can 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 and Product Quality
Office of Compliance
Center for Drug Evaluation and Research