U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Teva Pharmaceutical Industries 1/31/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-008

January 31, 2011

Mr. Shlomo Yanai
President and C.E.O.
Teva Pharmaceutical Industries, Ltd.
Petach-Tikva 5 Basel Street
P.O. Box 3190
Petach Tikva 49131 - Israel

Dear Mr. Yanai:

During our September 12-16, 2010 inspection of your pharmaceutical manufacturing facility, Teva Pharmaceutical Industries, Ltd., located at 24 Professor Hartum Street, Har Hozvim, Jerusalem, Israel, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations 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 the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response of October 7, 2010, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already bee distributed, and you failed to extend the investigation to other batches of the same drug product that may have been associated with the specific failure or discrepancy [21 C.F.R. § 211.192]. For example,

   a. Your firm did not thoroughly investigate **(b)(4)**mg **(b)(4)** mg lot #**(b)(4)**, when it failed to meet the established specification for both the single largest impurity and for total impurities amount.

   Specifically, the laboratory test results for lot #**(b)(4)** had a single impurity at RRT-**(b)(4)** minutes of **(b)(4)** (specification limit NMT **(b)(4)** %) and total impurity result of **(b)(4)**% (specification limit **(b)(4)**%). Your firm subsequently invalidated these results although your investigation was unable to confirm a root cause of the failure. Your firm selectively used passing results from a different analysis to approve the lot.

   We reviewed your written response dated October 7, 2010. You do not provide adequate justification for invalidating the original results and utilizing retest results to release the batch. In your response you state the investigation results concluded that the original sample was contaminated during the processing of the test sample in the laboratory. However, you fail to describe how that conclusion was determined, or identify the root cause of the sample contamination, other than relying on the retest results being within specification. In addition, you fail to provide corrective actions to prevent a recurrence.

   We recommend you review the FDA guidance for industry entitled, "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production," for some basic principles regarding conduct of OOS investigations. The guidance states that when laboratory errors are not convincingly identified in the initial tesl there is a lack of scientific basis for invalidating initial OOS results in favor of passing retest results. In addition, the guidance notes that all test results should be reported and considered in batch release decisions.

   b. Your firm did not thoroughly investigate **(b)(4)** mg/**(b)(4)**mg lot #**(b)(4)** when black particles were found in the sample powder during laboratory analysis.

   Specifically, the investigation no. PRI-030 concludes that the original powder was probably contaminated by a weighing instrument in the laboratory. However, the black particles were not identified and source was not determined. In addition, there was no attempt to determine if the black particles originated from the manufacturing process, or if additional lots were affected.

   Your response lacks an explanation and documentation to support your conclusion that the powder was contaminated in the laboratory. Provide in your response to this letter the corrective and preventive actions implemented to address this deficiency.

   c. Your firm did not thoroughly investigate **(b)(4)** tablets **(b)(4)** mg lot #**(b)(4)** when it failed to meet the finished product assay specification.

   Specifically, the finished product assay specification result was **(b)(4)**% (specification of **(b)(4)**%). A reinjection of the sample obtained a value of **(b)(4)**%, confirming the original OOS results. Your firm decided to prepare a new working solution. This sample resulted in **(b)(4)**%, which is on the lower limit of the specification.

   Your firm retested six new samples from the same original laboratory sample tested and obtained the following values: **(b)(4)**% (four of the six results were also close to the lower limit of the specification).

   Your investigation lacks data to support its conclusion that the OOS results were probably related to samples not being properly extracted during the standard solution preparation stage. It also lacks a thorough evaluation of the manufacturing process and other lots that may have been affected prior to invalidating th OOS results.

   In your response to this letter, please include your stability data for **(b)(4)** lot #**(b)(4)** to demonstrate that it remains within specification throughout its shell life. In addition, include data to support that a laboratory error occurred, and provide corrective actions to prevent a recurrence. We also recommend that your firm evaluate trends for results that may indicate a lack of control over the manufacturing process, or may affect the safety and efficacy of the products that marginally meet the established specifications for release.

We are concerned that your firm has released and distributed finished drug batches to the U.S. market in which the OOS investigations were not scientifically sound. Specifically, we are concerned that laboratory results were invalidated without supporting data and the investigations did not extend to other batches that may have been associated with the failure.

Include in your response to this letter a complete list of all finished drug batches shipped to the United States within expiry (include lot number, date of shipment, customer name and address), in which there was an OOS investigation conducted. We request that you conduct a retrospective review of all opened and closed OOS investigations associated with these U.S. lots. Please supply supporting documentation for your evaluation and conclusions for each OOS investigation, as well as your corrective actions to prevent a recurrence, where appropriate. Inform this office of any additional action you plan to take to correct this violation and ensure that adulterated drug product have not been released to the U.S. market.

2. Your firm has not established separate or defined areas or such other control systems as necessary to prevent contamination or mix-ups during drug manufacturing [21 C.F.R. § 211.42(c)].

For example, your firm lacked an adequate assessment of the cross-contamination risks posed by the manufacture of several potentially hazardous compounds (e.g., **(b)(4)**) at your facility. Your facility contains shared manufacturing areas where you produce potentially hazardous compounds in multi-product equipment that are high powder generating operations, including **(b)(4)** drug products intended for the U.S. market. Your firm should ensure that a documented justification and well-designed contamination prevention strategy is in place to minimize the possibility of contamination. To achieve proper product protection, sound design and control approaches must be used. Without proper separation, your firm lacks assurance that one drug does not contaminate another drug.

We recognize that your October 7, 2010 response states that you are in the process of developing a risk management program for control of cross-contamination of the products produced at the Jerusalem Oral Solid Dosage (OSD) plant. However, you did not submit that plan, or data to support the effectiveness of the plan, with your response. We also recognize your commitment to finish the risk assessment within four months. Please provide us with any update on your timeline, and the identification of resources allocated to address this issue. Please also include in your risk analysis, procedures and data addressing the following potential routes for cross-contamination: mix-up, retention, mechanical transfer, and airborne transfer.

The 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 and the occurrence of other violations. 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 CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, failure to correct these violations may result in FDA refusing admission of articles manufactured at Teva Pharmaceutical Industries, Ltd. located at 24 Professor Hartum Street, Har Hozvim, Jerusalem, Israel into the United States. The articles are 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 Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

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 and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Please identify your response with FEI #3005202697.

If you have questions or concerns regarding this letter, contact Denise M. DiGiulio, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
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Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
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Sincerely,

/s/

Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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