HFD-322 WL 00008

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

DEC 30 1997

Tianjin Pharmaceutical Corp.
91 Cheng Lin Zhuang Road
Hedong District
Tianjin 300161
People's Republic of China

Dear

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Tianjin, China by the United States Food and Drug Administration on September 15 - 18, 1997. The inspection revealed significant deviations from U.S. good manufacturing practice in the manufacture of bulk that resulted in the issuance of a fifteen-item FDA Form 483 at the completion of the inspection. These deviations cause this API to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice (CGMP). No distinction is made between APIs and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have reviewed the one page October 14, 1997 response to the FD-483 observations submitted by at Tianjin Pharmaceuticals Corp., and conclude that the response is inadequate in that it lacks sufficient details, explanations, or documentation to address the deviations observed during the September 1997 inspection. Our comments regarding the most significant observations are shown below:

1. Stability studies of bulk are inadequate in that the U.S.P. HPLC assay method is used for stability testing without any modifications. This method has not been shown to be stability indicating. In addition, testing for impurities is limited to the detection of

Our inspection disclosed that your firm uses the U.S.P. HPLC assay method, which has not been shown to be stability indicating, for stability testing of Your response fails to state how you will address this issue.

In addition, our investigators noted that your firm's impurity testing is limited to the detection of Your firm does not test for other impurities that may arise from the breakdown of such as and

Please submit an SOP in English describing your stability testing program. The program should be based on the use of stability-indicating assay methods that can detect degradants, process impurities, and residual solvents.

2. The reprocessing procedure for does not specify what type of testing or evaluation is conducted on returned batches prior to reprocessing, nor does it specify the number of reprocessed batches that are placed on stability.

Our inspection revealed that batches of returned in June 1996 were reprocessed without any qualitative testing beforehand to determine their suitability for reprocessing. In addition, none of these reprocessed batches were placed on your firm's ongoing stability test program.

Your "SOP of Returned Batches of " submitted with the October 14, 1997 response does not adequately address our concerns. First, the latter was not reviewed and approved by the quality control unit. Secondly, the SOP does not specify the conditions and limitations for reprocessing by physical manipulations nor does it require a formal evaluation of each non-conforming batch to determine its suitability for reprocessing.

Furthermore, the SOP does not specify what analytical tests are conducted on reprocessed batches to ensure that reprocessing does not adversely affect the quality or purity of the API. These tests should include, as appropriate, purity, physical attributes, and impurity profiles. In all cases, the significance of the non-conformance and its impact on the critical

quality attributes of the API or intermediate should determine how much analytical data is sufficient to justify the reprocessing.

Please provide us with an English copy of the protocol covering the handling and subsequent reprocessing/reworking of non-conforming batches. The protocol should also describe the tests conducted on reprocessed batches to ensure that the reprocessing did not adversely affect the quality or purity of the active pharmaceutical ingredient.

In addition, please submit complete stability data for all U.S.P. batches placed on your ongoing stability testing program in the last three years. Identify all lots placed on stability, to include reprocessed lots.

3. is used in the manufacturing process for , but is not included in the organic volatile impurity (OVI) testing. In addition, a complete impurity profile has not been established for this API manufacturing processes.

Our inspection disclosed that is used in the manufacturing process, but your OVI testing is limited to tests for Your management indicated that since is not used in the final step, testing for it was not necessary. In most cases, it is reasonable to control levels of solvents used in the last two synthetic steps in addition to the final purification step (s). Unless you have data showing that does not carryover to the API, you should test for the presence of residues.

In addition, no data was presented during the inspection to show that a complete impurity profile has been established for U.S.P. XXIII (Chapter 1086, Page 1923) defines an impurity profile as "A description of the impurities present in a typical lot of a drug substance produced by a given manufacturing process." The impurity profile includes "the identity or some qualitative analytical designation (if unidentified), the range of each impurity observed, and the classification of each identified impurity."

Impurity profiles are an important part of process validation and FDA expects manufactures to establish appropriate impurity profiles for each API as part of the process validation effort. This includes collecting data on (1) actual and potential organic impurities that may arise during synthesis, purification, and storage of the API; (2) inorganic impurities that may arise from the manufacturing process; and (3) organic and inorganic solvents used during the manufacturing process that are known to carry over to the API.

Please submit a SOP detailing your firm's impurity profile testing program and data showing the actual impurities in this API with acceptance controls and specifications.

4. Failure to perform system suitability tests on chromatographic instruments as described by the United States Pharmacopeia XXIII.

Our September 1997 inspection disclosed that system suitability tests for HPLC assays do not contain calculations for peak resolution and relative standard deviations (*RSD*) as described on Pages 1776 and 1777 of the United States Pharmacopeia XXIII. Management stated that resolution is checked daily, but none of the HPLC chromatograms reviewed and collected contained peak resolution or RSD calculations.

Your response failed to include a copy of your protocol specifying the frequency or conditions for conducting system suitability tests. FDA expects that chromatographic systems be subjected to a suitability test before use and during testing, or whenever there is a significant change in equipment, in a critical agent, or when a malfunction is suspected. Please submit an English copy of your protocol for our review.

5. Many assay system suitability tests showed instability in the HPLC system and peak integration calculation errors. In addition, no solvent blanks were noted in any HPLC chromatographic runs for assay, impurities or organic volatile impurity testing.

During the inspection, our investigators documented numerous instances of drift in the retention time for the standard and sample during chromatographic runs, denoting instability in the system. On other occasions, the retention time of became shorter as the analysis progressed, again denoting chromatographic system instability.

In addition, many of the assay system suitability tests showed peak integration calculation errors, in that an "E" next to the peak area, automatically entered on the chromatogram by the integrator, indicated that the input voltage was out of range. Analysts failed to understand the significance of this error message and did not invalidate the system suitability and assay test results, nor did they repeat the system suitability tests and assays.

Furthermore, our investigators noted that all chromatographic runs lacked solvent blanks, to show that the solvent used to dilute the samples did not contribute to the assay and to assure that there was no carryover of product to other chromatographic runs.

Please address these deficiencies in your written response.

6. There are no training records nor formal GMP training program for laboratory personnel.

Our investigators noted that your firm lacked training records and a formal GMP training program for laboratory personnel. The lack of proper training was evident by the analyst's failure to detect error notations and retention time drifts on HPLC chromatographic runs, failure to run solvent blanks during HPLC assays, and using a non-stability indicating method for stability testing of

Please submit a procedure for on-the-job and GMP training of laboratory personnel for our review.

The above deficiencies are not to be considered as an all-inclusive list of the deficiencies at your plant. FDA inspections are not intended to uncover all CGMP deviations that exist at a firm. We recommend that you conduct a complete evaluation of your facility for CGMP compliance. If you wish to continue shipping products to the United States, your firm is responsible for assuring compliance with U.S. standards of good manufacturing practice for active pharmaceutical ingredients.

Until the FDA reinspects your facility and confirms that these deficiencies have been corrected, this office will recommend disapproval of all applications listing your firm as a supplier of bulk Since the September 1997 inspection revealed systemic CGMP deviations in your production and control of APIs, we may also recommend that all APIs you manufacture for U.S. clients be denied entry into the United States. These articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act because 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).

Please contact Edwin Rivera Martínez, Consumer Safety Officer, at the address and telephone numbers shown below, if you have any questions or wish to submit additional information detailing corrective actions that you plan to take or have taken to bring your operations into compliance.

Foreign Inspection Team, HFD-322
Food and Drug Administration
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855-2737

Telephone: (301) 594-0095
FAX: (301) 827-0145

Please reference in all correspondence.

To schedule a reinspection of your facility after corrections have been completed, contact Deborah Browning, Consumer Safety Officer, Drug Group at FDA's Division of Emergency and Investigational Operations (HFD-133), 5600 Fishers Lane, Rockville, Maryland, 20857. You can also contact this office at (301) 827-5648 or by FAX at (301) 443-6919.

Sincerely,

John M. Dietrick
Acting Director
Division of Manufacturing and
Product Quality, HFD-320

cc: