



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

WL No. 320-01-03

NOV 29 2000

Piaoyang Sun
President
Jiangsu Hengrui Medicine Co., LTD.
No 145 Renmin Rd. (E), Xinpu
Lianyungang, Jiangsu Province
China

Dear Mr. Sun:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Lianyungang, China, by the United States Food and Drug Administration on September 11-13, 2000. The inspection revealed significant deviations from U.S. good manufacturing practices in the manufacture of APIs, and resulted in the issuance of an FDA Form 483 to you at the completion of the inspection. These deviations cause these APIs 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. No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

The previous FDA inspection of this facility also revealed significant CGMP deviations which were described to you in a Warning Letter dated June 19, 2000. Your response was that all deficiencies had been corrected and the facility was in compliance with CGMP, and you requested an immediate re-inspection of the facility.

We have reviewed the November 6, 2000, written response to the FDA-483 observations submitted to FDA by [redacted]. We have concluded that this response lacks sufficient details, explanations, or documentation to adequately address all of the

significant deviations observed during the inspection. Our concerns regarding the most significant observations are discussed below:

1. No written procedures for notifying the Quality Control Unit (QCU) of process deviations, for the investigation of deviations, or for annual review of production and control records.

Your firm's written response states that this deficiency has been corrected by the issuance of a new SOP and training of the employees. The response does not address notifying the QCU of process deviations or conducting and documenting investigations as discussed during the inspection. It does not indicate that any annual reviews have actually been completed and does not include the results of any annual reviews.

2. Laboratory tests for assay, impurities, heavy metals, and residual solvents were not performed according to the established procedures described in the individual Drug Master Files (DMF) which specify USP methods.

Similar deviations were observed during the previous inspection. Your firm's response at that time was that the DMFs were incorrect, but have been corrected. The response to the current observations is also that the DMFs were not correct and that they have been corrected, the laboratory SOPs have been corrected to comply with the DMF, or that the analysts have now been trained to follow the correct or corrected procedures. We recommend that you evaluate all laboratory methods and procedures to assure that they are appropriate, that SOPs are accurate and specific, that analysts have been properly trained in the procedures, and that the correct procedures are described in your firm's DMF.

3. Laboratory procedures are inadequate in that raw data was not always recorded, impurity standards were not properly identified, one internal standard was four months old with no data on its stability over that period, [] were not properly identified, and equipment system suitability was not always determined. In-process [] testing was also inadequately performed.

The previous inspection revealed similar observations regarding laboratory procedures and records. Your written response to those observations stated that the specific deficiencies were corrected by the issuance of new SOPs or that the deficiencies were the results of mistakes by the analysts, which was corrected by training. Your response to the current observations also states that the specific deficiencies have been corrected by the issuance of new SOPs and employee training. The response does not document that all other laboratory procedures have been reviewed for similar deficiencies, that the new SOPs are now followed, or that management or the QCU assures that they are followed. In addition, our review of both the Chinese version and the English translation of the new SOP on in-process [] tests finds they are not clear regarding what samples are []

4. Analytical methods validation was inadequate in that they did not always include accuracy, and for validation of the residual solvents tests, the range for the accuracy and linearity tests were outside the limits for these solvents.

Your response indicated that the specific deficiencies listed were corrected by revalidation studies but does not address a review of all laboratory methods to assure they have been adequately validated as appropriate for their intended uses.

5. Process validation for one API was inadequate in that it was not performed following a written protocol, critical processing parameters were not identified, and the scaled-up [] step was not included in the validation study.

The response states that retrospective validation studies have been completed for all APIs and that the protocols and final validation reports are attached. Only the Chinese versions were attached and we assume that you have not had sufficient time for translation of these documents into English. We are unable to evaluate these studies at this time.

6. The [] system was not appropriately designed to minimize microbiological contamination, in that it was a non-recirculating system and used valves which may harbor and cause proliferation of microorganisms.

7. Testing of [] used in production was inadequate in that it has not been tested for [] and samples used for testing of microbiological and other specifications are not collected in a manner indicative of actual use, points of use were not identified, and the amount of [] collected was not specified. [] used in the [] for processing an API intended for the manufacture of injectable drug products was not evaluated for, nor routinely tested for []

8. Validation of the [] systems was inadequate in that the initial bioburden of the source [] was not evaluated, total aerobic count of the [] was not evaluated, sanitization was not evaluated, microorganisms were not identified, and growth promotion testing of the media used in microbiological testing of the [] was inadequate.

Your responses to these observations state that the specific design problems and, testing deficiencies have been corrected, and that based on [] testing of [] since the inspection, you are changing to use [] rather than [] in the production of APIs intended for use in injectable drug products. You also provided a protocol for validation of the [] system after the design changes, and an SOP for routine monitoring of the [] system.

Review of the records submitted to document these corrections however, indicate that the new [] testing of [] is based on only 7 days of testing. The microbiological testing of the [] was for 8 days for total microorganisms and the presence of 4 pathogenic organisms, but did not include identification of the microorganisms found. The protocol for validation of the [] system after the design changes covers only an initial phase of 21 days. No validation or routine monitoring results were provided.

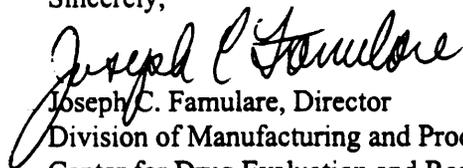
The above deficiencies are not to be considered as an all-inclusive list of the deficiencies at your facility. FDA inspections are audits which are not intended to determine all deviations that exist at a firm. We recommend that you evaluate your facility and quality control systems for CGMP

compliance on an overall basis and initiate universal procedures to correct all deficiencies and prevent their recurrence. If you wish to manufacture APIs for use in the U.S., it is the responsibility of your firm to assure 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 and the facility is in compliance with CGMP, this office will continue to recommend disapproval of any applications listing your firm as a supplier of APIs. We have also recommended that your firm's APIs be placed on import alert and denied entry into the United States. These articles are subject to refusal of admission 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 practices within the meaning of Section 501(a)(2)(B) of the Act.

Please direct your written response to the issues discussed in this letter within 30 days to Compliance Officer John M. Dietrick at the address shown above. To schedule a reinspection of your facility after corrections have been completed, send your request to: Director, International Drug Section, HFC-133, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, Maryland, 20857. You can also contact that office at (301) 827-5655 or by FAX at (301) 443-6919.

Sincerely,


Joseph C. Famulare, Director
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research

cc: