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. 320-00-04

JUN 19 2000

Sun Piao-Yang
General Manager
Jiangsu Hengrui Medicine Co., LTD.
No 145 Renmin Rd.. (E)
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 March 6-7, 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.

We have reviewed the April 18, 2000, written response to the FDA-483 observations submitted to FDA by[ ] 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. Master production records were not approved by appropriate personnel and failed to include complete manufacturing and control procedures.

2. Batch production records did not adequately document the steps taken or the individuals performing and checking each step in the production of each batch.

The response includes new and revised standard operating procedures (SOPs), master production records, and batch records intended to correct these deficiencies. While the documents submitted appear satisfactory, the implementation of the written procedures, the employee's adherence to the master production records, and the completion and review of batch production records will have to be evaluated during an on-site reinspection of this facility. It is also important that the appropriate Drug Master Files (DMFs) are accurate and are amended to reflect any major changes in production procedures

3. Manufacturing facilities were not maintained in a good state of repair.

Some of these observations pertain to the [ ] production facility where no production was occurring during the inspection, but others appear to apply to all APIs. The response addresses these deficiencies by establishing new SOPs. Effective corrections depend on management and quality control oversight of the entire facility which will be evaluated during a re-inspection of the facility.

4. Equipment cleaning records are incomplete and equipment cleaning procedures have not been validated. The previous inspection in November 1994 also reported a similar deficiency regarding validation of the [ ] cleaning procedure.

The response provides cleaning verification data which appears to represent a one time examination of the cleaning of the [ ] used for [ ] production. Additional cleaning validation studies for any other multiple use equipment should also be conducted.

5. Laboratory equipment, methods, and procedures were deficient. [ ] and [ ] equipment were not calibrated, there was no SOP for calibrating the [ ] apparatus, analytical methods were different than what is described in the subject DMFs, system suitability tests were not performed, degradation studies were not performed, the analytical method for residual solvents was not validated, and there were no written procedures for cleaning reused pipets.

6. Laboratory records were incomplete. Laboratory raw data was not properly recorded or reviewed, changes in raw data were not initialed or dated, in-house analytical methods were not properly reviewed or approved, and the humidity in stability chambers was not recorded.

The response indicates that new or revised SOPs and employee training have been developed to correct these deficiencies. New recording and alarm equipment has also been installed and validation studies have been performed. These initial efforts appear satisfactory, but sustained compliance requires continued oversight by management and quality control personnel which will be evaluated during the next inspection of this facility.

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. If you wish to continue manufacturing 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. We recommend that you evaluate your facility and quality control systems for CGMP compliance on an overall basis.

Until the FDA reinspects your facility and confirms that these deficiencies have been corrected and the facility is compliance with CGMP, this office will recommend disapproval of any applications listing your firm as a manufacturer of APIs. If corrections are not initiated promptly, any API manufactured by your firm may be denied entry into the United States.

Please direct your written response to the issues discussed in this letter 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:

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