DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-01-06

December 18, 2000

Mr. Liu Jin Jiang
Factory Director & Senior Engineer
Xinjiang Pharmaceutical Factory
8 Liyushan Road
Urumqi City
Xinjiang, People's Republic of China

Dear Mr. Jin Jiang:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Xinjiang, China by the United States Food and Drug Administration during September 18 - 19, 2000. The inspection revealed significant deviations from U.S. good manufacturing practice in the manufacture of bulk [ ] that resulted in the issuance of an eleven-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 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 October 20, 2000 response to the FD-483 observations submitted by your U.S. Agent, [ ] We conclude that this response lacks sufficient details, explanations, or documentation to address all of the deviations observed during the September 2000 inspection adequately. Our comments regarding the most significant observations are shown below:

1. The [ ] manufacturing process has not been validated.

During the September 2000 inspection, our investigator requested to review validation studies of the [ ] manufacturing process and was told that the process had not been validated. She was shown a draft validation protocol that had not been approved or signed by production or Q.C. management. The protocol did not identify critical process steps, critical process parameters, in-process tests or specifications. In addition, the protocol did not specify that validation should extend to those operations determined to be critical to the quality and purity of the API.

Your October 20, 2000 response reports that key production equipment will be qualified by April 2001, the validation protocol will be completed by March and the process validated by June 2001. You explain that these time frames are a consequence of the seasonal production schedule, and that production of [ ] will cease in December 2000 and resume in April 2001. Please submit a copy of the equipment qualification and process validation reports when these are completed.

2. The analytical method used for stability testing is not stability indicating. In addition, an impurity profile has not been established for [ ]

Our inspection revealed that your firm is using the U.S.P. titration method for testing of [ ] which is not a stability indicating method. In addition, your firm has not established an impurity profile for this API.

In your response, you commit to developing and validation a stability indicating [ ] analytical methods, which will include forced degradation studies. Please submit a copy of the analytical methods validation and results of your forced degradation study in your response to this Warning Letter.

We note, however, that your response does not address the establishment of an impurity profile for [ ] FDA expects manufacturers to establish an impurity profile for each API that describes the identified and unidentified impurities present in a typical batch produced by a controlled production process. The impurity profile includes the identity or some qualitative analytical designation (e.g., retention time), the range of each observed impurity observed, and classification of each identified impurity (e.g., inorganic, organic, or solvent). This impurity profile should be compared at appropriate intervals against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process. Please address this issue in your response to this Warning Letter.

3. There are no documented investigations of process deviations or out of specification (OOS) laboratory results.

During the inspection, our investigator requested to see investigations of process deviations and out of specification laboratory test results. She was informed that these investigations are conducted but not documented.

Your response maintains that all out of specification results or manufacturing deviations are investigated by the Quality Assurance Department of the Xinjiang Pharmaceutical Factory, but acknowledges that neither of these investigations were documented. You also report that the Quality Assurance Department is preparing SOPs to address these issues and that these will be completed at the end of November 2000. Please submit English translations of these new procedures for our review.

4. Recovered[ ]solvent used in the[ ]step is not tested to determine its quality. In addition, production records do not identify whether[ ]or [ ]is used during the[ ]step.

Our inspection revealed that[ ]solvent used in the[ ]step is[ ] However, the solvent is not tested or monitored to ensure that it meets appropriate quality standards before[ ]

Your response reports that Xinjiang Pharmaceutical Factory has discontinued the practice of reusing[ ]solvent effective immediately and that only[ ]is used in the production of[ ] However, no documents (i.e., memo of action, revised batch production records or revised SOPs) were submitted to verify this corrective action. Please submit appropriate documentation of this corrective action for our review.

5. Production records do not include complete information relating to the production and control of each batch.

Our inspection revealed that batch production records for[ ]do not include manufacturing directions, nor do they include documentation that each significant step was completed and observed by a second person. In addition, the batch records are issued by the production department and are not checked by the quality unit for accuracy and completeness before issuance.

Your response reports that these deficiencies will be rectified by the creation of Master Batch Records for each phase of the manufacturing process. The latter will contain the process details in a descriptive format and will completed by the end of March 2001. Please submit copies of these Master Batch Records when completed.

6. Prior to September 2000, there was no documentation that production and control records were reviewed and approved to determine compliance of each batch of[ ]with established specifications before release and distribution.

Your response reports that a record of this review will be included with the revised batch production record formats. Please submit this record along with the revised BPR formats.

7. Change control procedures are inadequate in that they did not provide for documenting changes to production or analytical procedures.

During the inspection, our investigator reviewed a recently issued analytical procedure for testing of the final API that was revised to add more detail. The previous analytical method was not dated nor signed as approved, nor was there a documented history of changes to the analytical procedure.

Your response acknowledges that at the time of the inspection, there was a procedure for handling changes in either the manufacturing or analytical procedures, but this procedure did not contain a provision for documenting the history of changes. You report that the change control procedure will be revised to include the history of changes, and that this revision will be completed by the end of November 2000. Please submit copies of the revised procedures for our review.

8. The quantity of[ ]used for[ ]during the [ ]step is not recorded.

During the inspection, our investigator noted that[ ]is added for[ ]during the[ ]step to[ ] However, operators do not record the quantity of[ ]required or actually added during this step in the batch production or in-process control records.

Your October 2000 response reports that batch production records will be reviewed and revised accordingly by the end of November 2000, to include ranges for the amounts of reagents used during production. Please submit copies of these revised batch production records for our review.

We recommend that you conduct a complete and extensive evaluation of your facility for CGMP compliance. If you wish to continue shipping APIs to the United States, your firm is responsible for assuring compliance with U.S. standards of good manufacturing practice for active pharmaceutical ingredient manufacturers.

Until FDA reinspects your API facility and confirms compliance with CGMPs, this office will recommend disapproval of applications listing your firm as a supplier of bulk[ ] Based on your responses, we may also recommend that all active pharmaceutical ingredients manufactured by your firm 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 notify this office, within 30 working days of receipt of this letter, of the specific steps you plan to take to have taken to correct the noted violations. Direct you response to Edwin Rivera Martínez, Compliance Officer, at the address and telephone numbers shown below:

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

Include English translations of supporting documents, procedures or other information detailing your corrective actions. Please reference Central File Number 9613779 in all correspondence to this office.

To schedule a reinspection of your API facility after corrections have been completed, contact the Director of FDA's Division of Emergency and Investigational Operations

(HFC-134), 5600 Fishers Lane, Rockville, Maryland 20857. You can also contact that office by telephone at (301) 827-5653 or by FAX at (301) 443-6919.

Sincerely,

Joseph C. Famulare
Director, Division of Manufacturing and
Product Quality, HFD-320

cc: [redacted]