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

TELEPHONE: (301) 594-0093
FAX: (301) 827-2202

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-01-05

DEC 14 2000

Mr. Jia Zhao Xu
General Manager
Tianjin Xin Xin Pharmaceutical Corporation
Chenglin Zhuang Industrial District
Tianjin, People's Republic of China

Dear Mr. Zhao Xu:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Tianjin, China by the United States Food and Drug Administration during September 4 - 7, 2000. The inspection revealed significant deviations from U.S. good manufacturing practice in the manufacture of bulk [ ] and [ ] that resulted in the issuance of a twenty-item FDA Form 483 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 (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 8, 2000 response to the FD-483 observations submitted to FDA's Central Document Room and resubmitted to CDER's Office of Compliance on October 27 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. In addition, we noted that some deviations are similar to deviations noted during our March 28, 1996, January 12 - 14, 1998, and October 25 - 27, 1999 inspections. Our comments regarding the most significant observations are shown below:

1. Validation of the [ ] analytical method for detecting residual solvents in [ ] remains inadequate.

Our October 1999 inspection revealed that validation of the [ ] method for determining residual solvents in [ ] did not include [ ] studies in the range of expected values. In your written response to this inspection, you committed to revalidate the [ ] procedure for determining residual organic solvents in [ ] by the end of 1999 and indicated that this would include [ ] actual test results, etc.

During the September 4 - 7, 2000 inspection, our investigators reviewed the revalidation study and again uncovered many inadequacies. For example, the [ ] included in the study show that [ ] In addition, the [ ] system suitability test did not incorporate a [ ] Thus, accurate [ ] could not be achieved.

Furthermore, the [ ] was not distinguished from the noise level of the system. In addition, the [ ] study of [ ] was done at the [ ] than the specification. Therefore, we conclude that the revalidation study fails to show that the [ ] analytical method can accurately quantify residual solvents in [ ] at the limit of the test.

Your October 8, 2000 response indicates that you will discuss these concerns with [ ] to resolve the problems with [ ] are equivalent to the specific limits. This work would be completed by the end of December 2000. Please forward additional documentation to show that you have resolved these long outstanding deficiencies in the [ ] analytical method for determining residual solvents in

2. Validation of the [ ] analytical method for detecting residual solvents in [ ] is also inadequate in that an unknown [ ] was determined above the limit of the test.

Our October 1999 inspection disclosed that the [ ] method used to detect residual solvents in [ ] was not suitable. A new [ ] method was developed and validated. However, when our investigators reviewed this new method during the September 2000 inspection, they noticed a [ ] They were informed that this [ ] was found in all lots of [ ] and is unknown. Furthermore, they observed that the accuracy of the test for [ ] and [ ] was determined at a higher concentration than the limit, and linearity and limits of detection for [ ] were determined above the limit of the test.

Your October 8, 2000 response indicates that you will also discuss these concerns with [ ] Please forward additional documentation to show that you have resolved these outstanding deficiencies in the [ ] analytical method for determining residual solvents in [ ]

3. Assay methods for fresh and recovered [ ] and recovered [ ] are not purity indicating. In addition, you have not validated the [ ] assay method for fresh and recovered [ ]

Your October 8, 2000 response reports that the analytical test methods for [ ] used as a solvent in [ ] production, and [ ] used in the production of [ ] will be completed by the end of December 2000. Please submit an analytical methods validation report to us for review.

4. Facilities and equipment used in the production of APIs are not designed or maintained in a clean and sanitary manner to prevent extraneous contamination of APIs with dust, rust, paint chips, metal, and insects.

During the inspection of Buildings [ ] and [ ] where [ ] and [ ] are manufactured, our investigators observed that rooms where reactions take place are open to the outside in that there are fans in the walls near the ceiling that are not screened. They also observed open windows and doors in the processing areas allowing the ingress of insects.

In addition, the rooms where crude [ ] is transferred from the cart to the [ ] and from the [ ] into intermediate drums for transport to the [ ] were observed with pealing and flaking paint on the walls and ceilings. Flying insects were also observed in these rooms.

Furthermore, some equipment was observed in a state of disrepair. The inside of the [ ] was corroded toward the bottom of the chute and was missing several knives. The interior of the [ ] for crude [ ] was rusted.

Other conditions that could result in extraneous contamination of APIs were observed during the inspection. These included transfer of crude [ ] from the [ ] to the [ ] using an uncovered metal chute placed underneath a metal platform in a building open to the outside, and (2) transfer of [ ] into the [ ] during final processing of [ ] using flailed rubber tubing with rough, uneven edges.

Your response reports that you have taken corrective actions to address these facility and equipment deficiencies, and that this work would be finished in one month (November 2000). However, no documentation of these corrective actions (i.e., completed work orders, photos, etc.) was submitted with your response, Please submit appropriate documentation of these corrective actions for our review.

5. The process validation study for [ ] failed to define all significant processing steps/parameters and was based only on the review of laboratory data.

Review of the process validation study for [ ] conducted in November 1999, revealed that the latter consisted of a retrospective review of [ ] batches. The validation was conducted without identifying all critical process steps and critical operating parameters. Only the [ ] were identified as critical operating parameters. Furthermore, the retrospective validation involved only a review of laboratory data. Production records were not reviewed to assure that API batches meet appropriate in-process acceptance criteria.

Your October 8, 2000 response includes a revised SOP for [ ] production validation and reports that you will implement this new validation procedure to confirm the production parameters of the key reaction steps and evaluate the un-reacted material. However, you fail to say when this revalidation will be completed.

Furthermore, our review of the revised validation procedure indicates that you propose to conduct a retrospective revalidation of the [ ] process once a year by reviewing data on [ ] continuous batches of a given month (See Page 1 of SOP [ ] Effective as of October 4, 2000). This show a lack of understanding of the principals of process validation.

Retrospective validation may be conducted for a well-established process used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities or the production process. This validation approach may be used where:

(1) Critical quality attributes and critical process parameters have been identified;

(2) Appropriate in-process acceptance criteria and controls have been established;

(3) There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and

(4) Impurity profiles have been established for the existing API

Once an existing process has been validated retrospectively, and the process needs to be revalidated due to changes that may affect the quality of an intermediate or API, the validation should be done prospectively, or in certain limited cases, concurrently. Most important, these changes should be controlled by a formal change control system that evaluates the potential impact of proposed changes on the quality of the intermediate or API. Scientific judgement should determine what additional testing and validation studies should be conducted to justify a change in a validated process.

Please address these issues in your response to this Warning Letter.

6. Laboratory standards used for analysis were not identified in the analyst notebooks.

During our inspection of the laboratory operations, our investigators noted that analyst notebooks did not document the lot number of the secondary (working) reference standard nor the analytical balance used for the analysis.

Your response reports that the batch of the reference standard used is now recorded in analyst notebooks, but does not address recording of the analytical balance used during the analysis. Furthermore, it indicates that a copy of the original record was enclosed to show correction, but this was not included in our copy of the response. Please submit copies of pages from several analyst notebooks to document these corrections.

Apart from the above observations, we remain concerned about the continuing noncompliance of your API manufacturing facility as demonstrated by FDA inspections in the last five years. Our inspection of March 28, 1996 prompted the issuance of a Warning Letter on June 18, 1996 due to many significant CGMP deficiencies in the

manufacture and control of[ ]and[ ] These included: failure to have a formal change control system in place; failure to determine actual and expected yields at appropriate phases of manufacturing; inadequate stability data to justify a five-year expiration date for both APIs; incomplete forced degradation studies; inadequate process validation data; and lack of impurity profiles.

The inspection of January 12 - 14, 1998 again uncovered many significant CGMP deficiencies, including some repeat observations from the March 1996 inspection reiterated in the Warning Letter. An Untitled Letter was issued citing: failure to validate second crop[ ]batches produced from recovered mother liquors; inadequate controls of in-process materials; failure to maintain raw data supporting validation of critical process steps; use of unvalidated and non-stability indicating analytical methods for stability studies; and failure to calculate actual and theoretical yields.

Our inspection of October 25 - 27, 1999 resulted in the issuance of a second Warning Letter due to significant CGMP deviations noted in the production of both APIs. These include: inadequate control of analytical sheets used to record lab analysis data; incomplete forced degradation studies for[ ]; inadequate control and monitoring of temperature and humidity in the stability sample storage room; failure to perform linearity and quantitation limit studies during validation of the[ ]test for determining residual solvents in[ ]; failure to identify [ ]with sample identity adequately, date and time of analysis, and test parameters; incomplete[ ]calibration records; lack of specifications and tests of mother liquors used to produce second crops of[ ] and others.

This comprehensive five-year history shows an unwillingness or inability of your firm to carry out appropriate corrections and bring your API facility into CGMP compliance. Thus, the FDA will not reinspect your API manufacturing facility until a GMP expert conducts an extensive evaluation of your API operations and certifies to this office that your facility is in substantial compliance with U.S. standards of good manufacturing practice for active pharmaceutical ingredient manufacturers. This expert should be qualified by education, training, and experience, and should not have personal or financial interest in your organization or its officers.

Until this certification is submitted, found acceptable, and FDA reinspection confirms compliance with CGMPs, this office will continue to recommend disapproval of all applications listing your firm as a supplier of bulk[ ]and[ ] Since the September 2000 inspection again revealed systemic CGMP deviations, many of which are repeated or similar to deviations noted during previous inspections, we will continue to deny entry of all active pharmaceutical ingredients manufactured by your firm for clients 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).

In your response please submit English translations of supporting documents, procedures or other information detailing corrective actions that you plan to take or have taken to bring your API facility into compliance. If you have questions or concerns regarding this letter, please contact 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

Please reference Central File Number 9611047 in all correspondence.

We have informed the Director of FDA's Division of Emergency and Investigational Operations (HFC-134), not to schedule a reinspection of your API facility until advised by this office.

Sincerely,

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

cc: [ ]