DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Warning Letter

Via Fed Ex

WL: 320-07-02

SEP 6 2007

Mr. Su Weng Xing, General Manager
Kunshan Chemical and Pharmaceutical Co., Ltd.
No. 60, 339 Provinicial Highway
Kunshan City, Jiangsu
China

Dear Mr. Su,

We have completed our review of the Establishment Inspection Report (EIR) for the inspections conducted at your active pharmaceutical ingredient facilities on Kun Tai Road and Provincial Highway in Kunshan City, China, by FDA Investigator Robert C. Horan, Ph.D, in April 2007. These inspections revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) in the manufacture of Active Pharmaceutical Ingredients (API). These deviations were listed on an Inspectional Observations form (FDA-483), issued to you at the close of the inspections.

These CGMP deviations cause your APIs to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act(the Act) [21 U.S.C. 351(a)(2)(B)]. This section of the Act states that drugs are adulterated when they are not manufactured, processed, packed, and held according to current good manufacturing practice. Failure to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have also reviewed your written response to the FDA-483 observations, dated 5/29/2007. We note that many corrections have been, or will soon be implemented. However, your response does not adequately address some of the deficiencies, as further discussed below. Specific areas of concern include, but are not limited to:

1. Batch production records do not include complete information relating to the production and control of each API batch.

Both the Kun Tai Road (Old Site) and Provincial Highway (New Site) facilities show a pattern of non-compliance with CGMP documentation and records requirements. Refer to **Observation #1** for the Kun Tail Road site (Old Site) and **Observations #5 and #6** for the Provincial Highway site (New Site). Deficiencies included the lack of

contemporaneous documentation of production steps in batch records, inadequate instructions in batch records, and improper completion of production steps. These same types of deficiencies were also observed during the inspection at the Kun Tai Road site (Old Site) in May 2002. Your response to the FDA 483 related to that inspection, dated June 2002, promised corrections and retraining. Observations from the current inspections indicate that unacceptable practices continued at the Kun Tai Road site (Old Site). We also noted that these poor practices were adopted during your initial validation operations at the Provincial Highway site (New Site). Therefore, it does not appear that the corrections and retraining were effective.

Your current response again indicates that deficiencies will be corrected with revised SOPs and retraining of employees. Ensuring that each production step is completed and documented according to the instructions in the batch record is critical to the quality of the API. Without this assurance, there is insufficient confidence in the identity, quality, and purity characteristics of the APIs manufactured by your firm. A re-inspection will be necessary to evaluate these corrective actions.

2. Method validation documentation did not include appropriate data to verify that the analytical method produced accurate and reliable results.

Your response to **Observation #2** for the Provincial Highway (New Site), regarding the [ ] method for related substances, does not include method validation documentation to support that the proposed specification for [ ] can be achieved as part of the extended system suitability requirement. You should also consider [ ] of the "proven sample" throughout the [ ] to ensure that the system suitability is consistent throughout the run.

3. Production equipment was not adequately cleaned and was not maintained in a good state of repair.

Regarding **Observation #2,** we note that you recognized this deficiency and plan to cease production at the Kun Tai Road site (Old Site). However, we also note that you have continued to export [ ] to the U.S. from this site.

4. Laboratory equipment calibration was not adequately documented.

Regarding **Observation #7,** we noted that calibration documentation for [ ] equipment lacked sufficient detail identifying the individual components of the system or specific parameters that were evaluated. The corrections described in your response appear satisfactory, and the adequacy of calibration documentation for [ ] and other equipment will be evaluated during the next inspection.

Based on the previous and current inspectional observations, FDA has concluded that production of APIs at the Kun Tai Road site (Old Site) was not conducted under current Good Manufacturing Practice. In addition, your written response to the FDA-483 observations admits that "the focus on quality systems was somewhat laxed [*sic*] at the old site after the last [ ] US product production run was completed in August 2006."

It has come to our attention that products from the Kun Tai Road site (Old Site) are still being shipped to the U.S. During the inspection of the Kun Tai Road site (Old Site), it was reported to Investigator Horan that production of [ ] API was intended for non-U.S. markets. Furthermore, your written response to the FDA-483 observations states that, "the old site is now used for the production of [ ] intended for non-US markets." However, our databases indicate that your firm has made several shipments of [ ] to U.S. firms, as recently as March 2007. Please provide us with a complete list of all products (including date, quantity, and consignee) that were manufactured at the Kun Tai Road site (Old Site) and shipped to the U.S., by you or any third party, since 2005.

Please respond to this letter within 30 days of receipt and identify your response with FEI# 3006255265. Any future shipments of APIs manufactured at the Kun Tai Road site (Old Site) will be 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 [21 U.S.C. 381(a)(3)] in that 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) of the Act [21 U.S.C. 351(a)(2)(B)]. Until all corrections have been completed and FDA can confirm compliance with CGMPs, this office will continue to recommend disapproval of any new applications or supplements listing your firm as the manufacturer of active pharmaceutical ingredients.

Please note that a guidance document entitled "Q7A Good Manufacturing Practice Guidance of Active Pharmaceutical Ingredients" (ICH CGMP Guidance), prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), describes current good manufacturing practice (CGMP) for manufacturing of APIs. The guidance is intended to help ensure that all APIs meet the standards for quality and purity they purport or are represented to possess. Although the ICH CGMP Guidance does not impose requirements, FDA considers its recommendations, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under Section 501(a)(2)(B) of the Act. To obtain the ICH CGMP Guidance for your reference, refer to the following website: http://www.fda.gov/cder/guidance/4286fnl.htm

Please contact Douglas A. Campbell, Compliance Officer, at the address and telephone numbers shown below, if you have any questions, further information, or further proposals regarding this letter.

U.S. Food & Drug Administration
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Rockville, MD 20852
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To schedule a re-inspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Field Investigations HFC 130, 5600 Fisher's Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,

Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research