DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

APR 2 1 2008

Warning Letter

Via FedEx and facsimile

WL: 320-08-01

Dr. Yan Wang, Ph.D.
General Manager
Changzhou SPL Company, Ltd (a/k/a "Kaipu")
3 Changhong West Road
Hutang Township, Wujin City
Changzhou
China

Dear Dr. Wang:

We have completed our review of the Establishment Inspection Report (EIR) for the inspection conducted at your active pharmaceutical ingredient manufacturing facility in Wujin City, Changzhou, China by U.S. Food and Drug Administration ("FDA") Investigator Regina T. Brown and Chemist Zi Qiang Gu on 20-26 February 2008. The inspection 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 inspection.

These CGMP deviations cause your API 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, as defined in the Act, are adulterated when the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drugs meet the requirements of this Act as to safety and have the identity and strength and meet the quality and purity characteristics, which they purport or are represented to possess.

Our review included your March 17, 2008 and April 15, 2008 written responses to the FDA-483 observations. We note that some corrections appear to have been implemented and that you have promised that others 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. **There is no assurance that processing steps used to manufacture heparin sodium, USP are capable of effectively removing impurities.**

Our inspection disclosed that your firm lacked an adequate evaluation of the effectiveness of critical processing steps designed to remove impurities, and critical process parameters were not well defined or controlled (observation #1 of the FDA-483). The inspection also found that an impurity profile has not been established for the heparin sodium API (observation #2 of the FDA-483).

In your March 17, 2008, response to observation #1, you state that the firm has conducted two successful process validation studies, one in 2002 and one in 2004. However, the validation studies failed to determine whether the process was capable of adequately removing identified and unidentified impurities. Your response does not include data to demonstrate that your process will consistently remove impurities, and your firm continues to lack established impurity limits for the API. It is essential that your firm establish that controls are in place for assuring the consistent performance of the processing steps to remove impurities in order to ensure the identity, quality and purity of the drugs your firm produces.

In your response, your firm acknowledges certain deficiencies in providing evaluations of critical processing steps. Please provide data from validation studies that assess whether the process is capable of consistently removing impurities, and your evaluation of the reliability of the controls used to establish and monitor performance of the processing steps.

In your March 17, 2008, response to observation #2, you state that the current testing regimen for heparin sodium is consistent with industry practice reflected in the ICH Q7A Guidance (Laboratory Controls, Testing of Intermediates and APIs) which states that "Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin." Although a full impurity profile may not be necessary as part of the batch-to-batch testing of certain APIs, it is necessary that specifications for impurities be established for the production of all API and that each API batch be tested for conformance to these specifications. The ICH Q7A Guidance (Laboratory Controls, General Controls) states that appropriate specifications should be established for APIs, including for control of impurities. Your firm failed to establish appropriate specifications for identified and unidentified impurities for the heparin sodium API. Your firm also failed to perform adequate tests to detect impurities in this API.

In your March 17, 2008, response to observation #2 your firm also states that the complexity of the investigation into the recent heparin product recalls demonstrates the

difficulty of isolating and identifying impurities in heparin due to the nature of the [ ] mixture of [ ] However, the mere fact that it is difficult to isolate and identify impurities is insufficient rationale for not establishing appropriate specifications for, and routinely monitoring, impurities during production. In fact, we note that you committed in your response to include an "impurity profile update" in each DMF annual report.

Please note that it is essential for your firm to establish appropriate specifications and adequate testing to ensure the consistent removal of undesirable impurities, including those that are potentially harmful to human health.

It is your responsibility to ensure that your API meets the identity, quality and purity characteristics that it is represented to possess.

2. **You fail to have adequate systems for evaluating the suppliers of heparin crude materials, and the crude materials themselves, to ensure that these materials are acceptable for use.**

Our inspection found (Observation #6 of the FDA-483) that you received lots of material from an unacceptable workshop vendor that were used in your API. In your March 17, 2008, response to observation #6, your firm acknowledges inadequacies in the firm's supplier qualification efforts. For example, you state that the firm received and used heparin crude materials from a workshop that had been designated by your firm in a "pre-audit" as "unacceptable" and that was ultimately not approved by your firm. Your firm used this crude material in the production of API lots that were shipped to the United States.

Your system for evaluating suppliers of crude heparin material is ineffective to ensure that materials are acceptable for use. As described above, your firm accepted and used heparin crude material from a supplier that you had preliminarily determined was unacceptable. Your system failed to verify that the supplier was acceptable prior to the use of the crude material. Furthermore, after your firm determined that the supplier was not acceptable, your firm failed to take any corrective action with respect to the processed raw material.

All raw materials that are received and used in producing heparin sodium API should be qualified using a system to ensure that raw materials are of acceptable identity, quality and purity before use. It is important to establish appropriate specifications for these materials and to assure your suppliers provide materials meeting these specifications. These specifications should be approved by the quality unit. Your firm has failed to establish appropriate specifications for your incoming crude materials.

Your vendor qualification program should provide adequate evidence that the manufacturer can consistently provide reliable and safe materials. Suppliers should be monitored and regularly scrutinized to assure ongoing reliability. It is your responsibility to ensure that raw materials received are suitable and approved by the quality unit prior to use.

3. **The test methods performed for heparin sodium USP have not been verified to ensure suitability under actual conditions of use.**

Our inspection found (Observation #4 of the FDA-483) that you have not ensured that certain USP compendial test methods were verified under actual conditions of use. Specifically, you have failed to conduct adequate verification of USP compendial test methods as applied to the production of your firm's API. The data you provided in your March 17, 2008, response did not include information about the suitability, accuracy, and detection limits of certain test methods for API, such as the protein test method, used by your firm. There was no indication from these data that your firm's test methods could reliably detect and quantify the presence of proteins in the finished API. In addition, your firm had not conducted suitability testing of the method to determine the limit of detection for the method. The suitability for use of the protein method for in-process testing was also not established.

In your March 17, 2008, response to the FDA-483, you state that the firm has conducted suitability tests. In addition, you state that the test method was not verified because it was a basic compendial test. You assert that USP <1226>, Verification of Compendial Procedures, states that verification is not required for basic compendial test procedures that are routinely performed unless there is an indication that the compendial procedure is not appropriate for the article under test. In your response, you also state that the laboratory performed basic suitability testing on the heparin sodium API analytical method in accordance with your standard operating procedures (SOPs).

We disagree with your assertions that verification is not required for those USP test methods used by your firm. In accordance with cGMP, analytical methods should be validated unless the methods used are included in a relevant pharmacopoeia or other recognized standard reference. If the method is a compendial method, verification of the methods should be conducted to determine that the method is suitable for its intended use under actual conditions. We acknowledge that the USP informational chapter <1226> suggests that there is a lesser need for verification for the simplest tests such as loss on drying, residue on ignition, and pH measurements. However, these do not include the test methods at issue, including the protein test method.

Further, the ICH Q7A guidance (Good Manufacturing Practices for Active Pharmaceutical Ingredients) at section 12.8 "Validation of Analytical Methods" states clearly that "the suitability of all testing methods used should nonetheless be verified

under actual conditions of use and documented." Thus, although it is not necessary to validate USP test methods, it is necessary to verify that these USP methods are suitable for the specific conditions of use. Furthermore, the suitability tests you describe in your response do not verify that the USP tests are suitable for the specific conditions of use.

Please provide data that demonstrate that the compendial test method has been verified and determined to be suitable under actual conditions of use.

4. **Equipment used to manufacture heparin sodium USP is unsuitable for its intended use.**

Our inspection team observed (Observation #7 of the FDA-483) that equipment tanks used in the final[ ]step were constructed of[ ] These tanks were identified as clean. However, unidentified material was observed adhering to the inside surfaces of tanks. It was also observed that surfaces of the tank were scratched, not smooth. We also note that volume markings on the outside of the [ ]tanks had tape adhered to it with markings. In addition, the cleaning method used for cleaning these tanks was not qualified.

There should be written procedures for cleaning of equipment. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. Acceptance criteria should be established and cleaning procedures should be defined and evaluated.

In your response to observation #7, you stated that the[ ]tanks used in the final[ ]step will be replaced with[ ] This[ ]will be equipped with clean-in-place system and an automated level reader. Until the new tanks arrive, you state that you will replace the existing[ ]tanks with new[ ]tanks and conduct cleaning validation on the new tanks using the manual cleaning methods after each cleaning.

Please provide data that show how the[ ]tanks are qualified and the cleaning procedures are validated.

Your corrective action to replace[ ]tanks with[ ]is noted. However, it is your responsibility to ensure that equipment used to process heparin sodium does not meaningfully alter quality of the API by being additive, reactive or absorptive.

Once you have installed and qualified the[ ] please provide information on equipment qualification and cleaning validation for these tanks.

The inspectional observations listed on the FDA-483 and the concerns described above indicate significant deficiencies in your overall quality system. An effective quality system must assure that a firm's manufacturing operations are adequate and that the API meets its established specifications for identity, quality and purity. There should be a quality unit that is independent of production and capably discharges quality assurance and quality control responsibilities. Please respond to the FDA with your corrective action plan to address the above concerns with respect to your quality system.

The CGMP deviations identified above or on the FDA-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMP that exist at a firm. If you wish to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practice.

Shipments of articles manufactured by your firm 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 CGMP, this office will continue to recommend disapproval of any new applications or supplements listing your firm as the manufacturer of active pharmaceutical ingredients.

Please respond to this letter in English (including attachments) within 30 days of receipt and identify your response with FEI# 3003335664. Any future shipments of API manufactured at your 3 Changhong West Road site will be refused admission into the United States.

Please contact Anthony A. Charity, Compliance Officer, at the address and telephone numbers shown below, if you have any questions or concerns regarding this letter.

U.S. Food & Drug Administration
Center for Drug Evaluation and Research
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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 Investigation, HFC-134, 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