DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Warning Letter

Via Fed Ex

WL: 320-07-03

OCT 3 1 2007

Mr. Liu Zhen
President and General Manager
Northeast General Pharmaceutical Factory
No. 37 Zhonggong Bei Street
Tiexi District
Shenyang, Liaoning
1234 China

Dear Mr. Liu,

We have completed our review of the Establishment Inspection Report (EIR) for the inspections conducted at your active pharmaceutical ingredient manufacturing facility at No. 37 Zhonggong Bei Street in Shenyang, China, by FDA Investigators Sharon K Thoma and Robert D Tollefsen, on 27-30 August 2007. This 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 Mr.[ ]Vice President of Management Quality, at the close of the inspection.

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 as defined in the Act, are adulterated when they are not manufactured, processed, packed, and held in conformity with current good manufacturing practice.

We have also reviewed your written response to the FDA-483 observations, dated 1 October 2007 sent through one of your U.S. Agents[ ]of[ ] 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. **Manufacturing facilities and equipment were not maintained to prevent API contamination.**

The[ ]production area, which was not operational during the inspection, has rust and flaking paint on the inside of[ ] Above these ports was an unclean and damaged ceiling. Over one of the ports there was also an open window. Inside the[ ] of another vessel were numerous dried white paint drips running down the inside of the vessel. In the bottom of this vessel were white flakes that appear to be chipping paint. Above this port, the ceiling was damaged and white flaking paint was observed. There was a brown residue on the inside of the[ ]used to feed[ ]into one of the vessels. Inside the[ ]used following the final[ ]step was an unknown soft, yet flaking, black residue. The inside was also rusted. During the last step of your manufacturing process, the API passes through a[ ] and is [ ]into open transfer baskets. The bolts were rusting and the paint was flaking on the[ ]above where the open transfer baskets would be positioned. These conditions pose a potential for product contamination.

Your response states that you have not manufactured[ ]since 30 May 2006, have not sold product since 29 December 2005, will not sell the API after the end of October 2007, and are building a new[ ]facility. The inspection report states that you maintain[ ]batches of rejected[ ]manufactured in 2002 in quarantine, and approximately[ ]passing batches that were manufactured in 2004 and 2006. We are concerned that the dark residue on your processing equipment is process related residue. If that is correct, it likely accumulated over time and was present on the equipment when batches of API were manufactured. If it is some other contaminant, we would like to know what it is and if it was present during API production. We are also uncertain when the rust and flaking paint were first observed during API production. Please respond with an assessment of the product impact and corresponding corrective action. This assessment should address the disposition of finished APIs still being held at your facility and especially any that have been shipped to the United States.

The[ ]production area has damaged ceilings, including holes open to the sky, rust, and flaking paint over[ ]on vessels. The inspection team also observed dripping oil, unclean ceiling lights, and a one meter by two meter uncovered opening to the outside. Under some of the vessels near the[ ] was an unknown black flaking material, rust, and flaking paint. The exhaust vent above the open[ ]in the final[ ]area was unclean, having flaking tape, flaking paint, and what appeared to be flaking metal. These conditions pose a potential for product contamination.

Although your proposed corrective actions for the[ ]production area appear to adequately address the deficiencies, we request that you provide us an assessment of the time period for which these conditions persisted, the product impact, and corresponding corrective action.

2. Stability samples were not tested at the scheduled intervals.

Three batches of [ ] API were not tested at the [ ] month interval. The previous FDA-483 issued to your firm on 7 November 2003 cited the same observation where 12 batches of API were not tested at 15 scheduled intervals. The termination of stability studies at 6 months was also an observation on the Warning Letter issued to your firm on 2 October 2001. These repeat observations lead us to question the acceptability of, and your commitment to, your proposed corrective action. Please explain why your previous corrective action failed and why your proposed corrective action will adequately address the deviation.

3. Failure of the Quality Control Unit to oversee and evaluate manufacturing and laboratory controls.

This is a repeat observation from the FDA-483 issued to your firm on 7 October 2003. The CGMP deviations for potential contamination and stability testing explained above in this Warning Letter, as well as many other CGMP deviations listed on the FDA-483 issued 30 August 2007, indicate inadequate oversight by the Quality Control Unit. We recommend you consider a knowledgeable and independent third party to help you identify the controls necessary for you to implement in order to maintain CGMP compliance.

General Comments

The inspection report states that your sample room may also be used to take samples of raw materials used in other facilities. Raw materials for [ ] were specifically identified. This sampling of sensitizing raw materials may indicate a potential for cross-contamination in the sampling room. Please identify to us which raw materials you sample for these finished APIs and any other sensitizing APIs you manufacture at your other sites. Include an assessment of whether or not you consider these raw materials sensitizing. Please also include an assessment of the potential for cross-contamination from any sensitizing raw materials that are sampled at your facility.

Please respond to this letter within 30 days of receipt and identify your response with FEI# 3002807700. Any future shipments of APIs manufactured at your firm 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 Karen Takahashi, 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,

Edwin Rivera Martinez
Acting Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research