DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Warning Letter

Via Certified and Registered Mail

WL: 320-04-03

FEB 10 2004

Ding You Xin
Factory Director
Shanghai Medical Ltd.,
No. 15 Pharmaceutical Factory
1440 Bei Di Road
Shanghai, China

Dear Mr. Ding:

We have completed our review of the inspection of your pharmaceutical manufacturing facility in Shanghai, China, by Investigator Robert C. Horan, Ph.D. and Chemist Susan W. Ting, during the period of 27-31 October 2003. The inspection revealed significant deviations from U.S. current Good Manufacturing Practice (cGMP) in the manufacture of active pharmaceutical ingredients (APIs). The deviations were presented to you on an Inspectional Observations (FDA-483) Form, 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.

We have reviewed your November 7, 20 and December 22, 2003, responses to the FDA 483 Inspectional Observations sent through [ ]Group Vice President, of [ ]These responses do not sufficiently address the deviations observed during the aforementioned inspection.

Specific areas of concern include, but are not limited to:

1. Qualifications of those working in the Quality Assurance (QA) and Quality Control (QC) units have not been demonstrated to be adequate.

In your response dated November 20, 2003, you state that, "Our parent company has transferred two qualified QC supervisors" and that, "The interim head of QC has been replaced with a qualified individual." In the organization chart that you provided as Appendix 3, two of these individuals are identified as having Bachelor of Science degrees in engineering and one as being a Licensed Pharmacist having graduated from a Secondary Technical School. Further, no one on the organizational chart, including supervisors in QA and QC, are identified as having academic or other suitable training in

chemistry or microbiology. This is of particular concern because all of the items listed on the FDA 483 related to the chemistry and microbiology deviations in the quality control unit. The investigative team also stated that analysts could not always answer their questions about testing. For example, a supervisor and QC manager could not explain how the calculation was done for the[ ] assay determination for [ ]and[ ]In addition, the analyst performing this assay was unaware that it is necessary to enter the[ ]in order for the result to be calculated properly. Lastly, the two microbiologists interviewed were unable to accurately answer questions about growth promotion and the identification of microorganisms.

In your recent correspondence you offered to provide our office a copy of the internal audit that resulted from this inspection. We would like to see your audit findings.

2. One of the discussion points with management concerned missing data for the analysis of[ ]and[ ]by[ ]There were six entries in the[ ]logbook that could not be found in the correlating computer files.

In your response, you state that these were samples tested for training purposes and their [ ]were subsequently discarded. We fail to see how this could be accurate since the analyst conducting the test on 2/13/03 conducted 24 other acceptable tests before this. In addition, the analyst conducting the tests on 2/21/03, 2/23/03, 2/25/03, 2/27/03, and 3/01/03 conducted analyses on 2/20/03, 2/24/03, 2/26/03, and 2/28/03. These test results were entered as acceptable prior to completion of what you are telling us is training. We are concerned about this discrepancy.

3. The microbiological test records all appear to be recently written in spite of the fact that some date back as far as two years.

You state that the documents may appear new because they are kept in plastic folders away from heat and light. The investigative team says they never observed any of the documents they requested from the microbiological laboratory being removed from plastic folders, nor did they observe this practice anywhere else in the firm. In addition, the investigative team expressed concerns that the records having one entry per day appeared to have multiple entries in the same handwriting written at a single time. Also, entries identified as being performed by a single person appeared to be written in more than one person's handwriting. They observed this with virtually all of the documents they reviewed in the microbiological laboratory, including such documents as equipment usage logs, logs for record receipt of materials, and for transfer of cultures. You failed to address this in your responses.

4. Individuals responsible for overseeing testing, other management, [ ] technical managers, and the individual hired by [ ] as a cGMP consultant were not forthcoming with testing documents for [ ] testing by [ ]

The investigative team was together during the interaction with the above mentioned individuals regarding the test records for [ ] testing. Both give the same account of what happened. They have documented a detailed description of who they spoke with and what responses they received. None of the responses from the above mentioned individuals was accurate until the investigative team found the test results on the [ ] computer. All of the above mentioned individuals initially denied that the firm has ever tested [ ] for [ ] by [ ] Then, the QC manager said that they had done the test once a long time ago, but did not have record of the test. Later, when the investigative team looked at the [ ] computer files, they found that [ ] testing for [ ] was routinely performed. In addition, the QC Manager denied having a written test method for [ ] testing for [ ] by [ ] but the written test method was later found locked in her office desk. Lastly, when asked why the testing was performed, both the QC Manager and the Assistant Plant Manager both stated that the test was done for no reason. When the investigative team spoke with you and your management team the following day (10/30/2003) they say that you told them the testing was done at a customer's request. The investigative team also said that you admitted that your firm had been untruthful about the testing. As the investigative team expressed to you that they did not have confidence in the integrity of your test data as a result of this incident, so we also express our concern that your test records may be unreliable.

Another related observation stated that one [ ] test result represented as many as five and eight lots of finished [ ] and [ ] API, respectively. Although you have responded to this observation, it nonetheless adds to our concerns about the reliability of the records at your firm.

5. Compendial and secondary reference standards were not properly stored.

The investigative team found the compendial and secondary reference standards stored in the controlled room temperature stability room. We do not have assurance that these reference standards used to test the finished APIs have not degraded as a result of being subjected to the temperature and humidity conditions in the stability room. In your response, before installing a ceiling fan, you state that the temperature was [ ] at the outlet of the heater. The observation indicates that this air was blowing directly on the reference standards. Reference standards that are not stored under appropriate conditions could result in false test values. Product that is out of specification could test within specification. This draws into question your test results for product shipped to the United States.

6. Microbiological testing was inadequate in that the[ ] samples was not neutralized prior to performing the[ ]testing.

In your response you expressed concern that if the[ ]in the sample was neutralized, you would not be testing the[ ]"as is". It is necessary to neutralize the[ ] because it interferes with microbiological testing. Without the neutralization step, the [ ]test will likely show a lower number of bacteria than is actually present in the sample.

The procedure you submitted with your response indicates that you will add a neutralizing agent, [ ]to the sampling container prior to[ ] Please submit to data or scientific rational that the[ ]does not alter the effectiveness of the neutralizing agent. In addition, the procedure should require swabbing the sample port and running[ ]for five minutes if this is how you draw the[ ]before adding it in the manufacturing process.

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. It is the responsibility of your firm to assure compliance with all U.S. standards for current Good Manufacturing Practice.

Due to the significance of these deficiencies the FDA will deny entry of drugs manufactured by your firm into the United States. The articles will be subject to refusal of admission pursuant to Section 801(a)(3) of the Act 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.

Until FDA can confirm compliance with cGMP and correction to the most recent inspection deficiencies, this office will recommend disapproval of any new applications listing your firm as the manufacturer of active pharmaceutical ingredients.

Please contact Karen K. Moksnes, Compliance Officer, at the address and telephone number shown below if you have any questions related to human drugs.

U.S. Food & Drug Administration
Center for Drug Evaluation and Research
Foreign Inspection Team, HFD-325
11919 Rockville Pike, 4th Floor
Rockville, MD 20852
Tel: (301) 827-9008; FAX (301) 827-8909

Or, contact Jorge F. Christian, Compliance Officer at the address and telephone number shown below if you have any questions related to veterinary drugs.

U.S. Food & Drug Administration
Center for Veterinary Medicine
Division of Compliance, HFV-232
7500 Standish Place
Rockville, MD 20855
Tel: (301) 827-0152; FAX (301) 827-1498

Sincerely,

Joseph C. Famulare
Director
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research

Gloria Dunnavan
Director
Division of Compliance
Office of Surveillance and Compliance
Center for Veterinary Medicine

cc: [redacted]
Group Vice President
[redacted]