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) 594-2202

WARNING LETTER

FEDERAL EXPRESS
SEP 7 1999

WL No. 320-99-06

Mr. Dejung Meng
Chairman of the Board
Long March Pharmaceuticals
120 Baiyung Rd.
Leshan, Sichuan, 614006
Peoples Republic of China

Dear Mr. Meng:

The Food & Drug Administration has completed its review of the inspection of your pharmaceutical manufacturing facility in Sichuan, China, by FDA investigator Robert Sharpnack, Microbiologist Raymond T. Oji, and Chemist Liang-Lii Huang, Ph.D., during the period of August 3-9, 1999. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of active pharmaceutical ingredients. The deviations were presented to your attention on an FDA-483 List of Observations at the close of the inspection. These CGMP deviations cause your active pharmaceutical ingredients (APIs) to be unacceptable for use in the United States, since, under United States law, the CGMP deviations render your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Significant deviations observed during the inspection include but are not limited to:

DATA INTEGRITY

1. Multiple records presented during the inspection lacked integrity. Your firm failed to provide original batch records.

Our inspection found that many records were rewritten and the original records were not retained. For example, the batch production record for lot [ ] was rewritten without any explanation. All original records associated with the manufacture and control of each batch must be retained. This serious deviation from US law was confirmed by your firm's management.

PROCESS CONSISTENCY

2. Failure to institute proper processing controls and quality systems for the production of [ ] drug substance intended for parenteral use.

Active ingredient to be used in the manufacture of dosage forms for parenteral administration should be produced in a manner which ensures minimal contribution of endotoxin (or other pyrogens). Your firm's manufacturing procedures should include provisions to prevent endotoxin contamination at steps in the process which present such a risk. Rather than minimizing the contribution of endotoxin, our inspection found that operating conditions at your firm allowed for an unpredictable and often high contribution of endotoxin to the parenteral-grade drug substance.

We also note that your firm has received complaints from US parenteral manufacturers regarding high endotoxin content in your APIs dating to 1997, but failed to implement corrective measures. This is a continued deficiency. Our inspection of January, 1998 found that in-process impurity problems were inadequately investigated. Your firm should have adequate systems in place to detect such quality issues and require implementation of corrective measures to prevent their recurrence. A written record should adequately document the investigation of the problem (e.g., failure to meet established specifications or standards; discrepancies), conclusions, and followup.

3. Failure to validate processes and major process changes, or to demonstrate batch uniformity with regard to quality, and purity.

Our inspection found that your firm lacked an adequate qualification and validation program. While [ ] has been manufactured for several years, no studies have been performed to evaluate critical process steps for reproducibility. The reliability of the process, including such key aspects as quality and purity at these process stages was not adequately evaluated.

Sampling for chemical and microbiological testing is based upon composite sampling. Variability in endotoxin has not been evaluated via testing discrete parts of a batch. Data from validation and routine batches should evaluate the uniformity of a given batch and any deviation from standards that are established based on the intended use of the API should be investigated. If data indicates variability in character or quality of the batch, appropriate process improvements should be implemented.

A scaled-up process requiring equipment changes has been used since September, 1995. [ ] new [ ] steps, which use [ ] were added to the manufacturing process in 1999. These changes were not validated. Your firm should institute change control systems to evaluate if a change alters the identity, strength, quality, or purity of the APIs manufactured by your firm.

MANUFACTURING PRACTICES AND DOCUMENTATION

4. Failure to maintain adequate and complete batch records. For instance, we observed many instances in which the same person signed as the operator and checker. FDA expects the execution of written production and process control procedures to be properly documented at the time of performance. The completion of each major process step by one person should be accompanied by verification by a second person.

Our inspection team also observed inadequate equipment usage documentation for the [ ] used for multiple products.

WATER SYSTEM MONITORING AND CONTROL

5. Unsuitable water systems were used to supply water for processing and equipment cleaning. Specifically:

a) Water of inappropriate quality was used for processing of active ingredients and cleaning associated equipment.

Lots manufactured up to and including June, 1999, used deionized or tap water for processing, including [ ] and final processing steps. Your firm had performed no endotoxin testing of this water prior to June of this year. Moreover, initial testing [ ] has consistently revealed significant endotoxin content.

It is important to note that drug substances intended for use in the manufacture of parenteral drug products should be manufactured using water of high purity. The final steps [ ] of parenteral-grade API production should include the use of WFI quality water.

b) Deionized and tap water was used for equipment cleaning. Your firm had performed no testing of this water for endotoxin purity. Cleaning procedures should not contaminate equipment. WFI quality water should be used for appropriate rinses of direct product contact surfaces of all equipment which may introduce contaminants which can be carried through intermediate or final stages of API synthesis.

c) Water systems were not validated.

Large quantities of water are used extensively throughout the manufacture of [ ] API. These water systems, in both present and past configurations, have not been validated. Your firm began use of an [ ] component in June, but no microbiological count tests had been performed and the system had not been validated.

d) Lack of any piping or instrument drawings of the deionized water or the recently modified water system for the purposes of system maintenance, monitoring and operation.

e) Lack of a monitoring program for water systems supplying water for API processing and equipment cleaning. There is no routine testing or monitoring of the quality of water used.

In your written response, please explain your firm's rationale for continuing any use of either tap and deionized water for pharmaceutical processing or equipment preparation. We note that the tap water in the region in which your firm resides is considered to be unfit for drinking. Please provide evidence that any tap water used by your firm will consistently meet standards for potable water.

Please provide a chart or equivalent schematic detailing uses of water for all aspects of [ ] equipment preparation/cleaning and API manufacture. For both, state the relevant process step and the quality (i.e., the formal specifications used by your firm) of the water used at that point, and provide evidence that such changes have been instituted.

LABORATORY CONTROLS

6. Inadequate laboratory controls:

a) Microbiology laboratory controls were inadequate.

Our inspection found that Bacterial Endotoxin Testing of water and finished product did not conform to USP XXIII. Specifically, routine finished product testing did not include the positive product control containing two Lambda endotoxin, as required by USP. LAL reagent sensitivity tests are performed only once, and not at the time of each analysis as required by USP. The [ ] Control Standard Endotoxin lots were not standardized against the USP Endotoxin Reference Standard.

b) Chemistry laboratory controls were deficient, including failure to adequately validate test methods.

Our inspection found significant failures to meet minimum CGMP with regard to chemistry laboratory operations. For instance [ ] system suitability was only conducted monthly. The current USP testing procedure for analysis of [ ] content was not used. Impurity test methods for [ ] had not been validated.

working standards were not adequately qualified against the USP Reference Standard, and certificates of analysis were not available for either the USP reference standard or secondary reference standard. The stability sample storage room was not adequately monitored.

The CGMP deviations identified above 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 CGMPs that exist at a firm. We recommend that you evaluate your facility on an overall basis for CGMP compliance. If you wish to ship your products to the United States, it is the responsibility of your firm to assure compliance with U.S. standards for current good manufacturing practices for pharmaceutical manufacturers.

Until FDA has confirmed that your firm is in CGMP compliance, we will not recommend approval of any applications listing the facility as a supplier of active pharmaceutical ingredients intended for use in parenteral products. We have recommended that your firm's products be placed on import alert and 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 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.

Please contact Compliance Officer Richard L. Friedman of this division at the above address or telephone number if you have any questions. Please respond in writing to the above CGMP issues within thirty days. Within your response, detail corrective actions you plan to take or have taken to bring your operations into compliance. Include a timetable of when each of the corrections will be completed and attach supporting documents, as well as a complete list of FDA-regulated products shipped to the US. Please reference **CFN# 9611046** within your written response.

Upon receipt of this letter, we request immediate feedback on your firm's intentions regarding active pharmaceutical ingredient lots marketed in the United States. Based upon our findings at your facility, FDA is extremely concerned about the quality of these lots. Finally, because of the urgency of this matter, we have sent a copy of this letter, on the date of its issuance, to your attention by facsimile.

To schedule a reinspection of your facility, after corrections have been completed and your firm has comprehensively evaluated overall compliance with CGMP requirements, send your request to: Director, International Drug Section, HFC-134, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,

Joseph C. Famulare

Joseph C. Famulare
Director
Division of Manufacturing & Product Quality