DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug
Administration
Rockville MD 20857

DEC 10 1997

WARNING LETTER

Liu Guilian, Factory Director
Guangdong Pharmaceutical Factory
91 Fungcun Dadao
Guangzhou China 510380

Dear Mr. Liu Guilian:

This letter is regarding a United States Food and Drug Administration (FDA) inspection of your human and veterinary Active Pharmaceutical Ingredient (API) manufacturing facility in Guangzhou, China by Investigator Robert Sharpnack and Research Chemist John Tomlinson beginning on September 23 through September 27, 1997. The inspection revealed significant deviations from Current Good Manufacturing Practices (CGMP) in the manufacture of active pharmaceutical ingredients. The deviations were presented to Lin Yin Chang, Vice Director on an FDA-483, Inspectional Observations form, at the close of the inspection. These CGMP deviations cause your API's to be adulterated within the meaning of section 501(a)(2)(B) of the U.S. Federal Food, Drug, and Cosmetic Act. Section 501(a)(2)(B) of the Act requires that all drugs, both for human and veterinary use, be manufactured, processed, packed and held according to current good manufacturing practice. No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals. Failure to comply with CGMP constitutes a failure to comply with requirements of the Act.

We note that the two previous FDA inspections of your manufacturing site also revealed numerous deficiencies. A Warning Letter dated April 23, 1997 was issued to your firm, following the January 27 - 29,1997 inspection. A Warning Letter was also issued on March 10, 1995, following the September 5 - 7, 1994 inspection.

Some of the deficiencies found during the recent inspection, such as validation and incomplete/inaccurate records, were similar to those seen in the two previous FDA inspections.

We acknowledge the considerable effort and expense your firm has expended in order to improve the physical facility. However, our review of the last three inspections of your firm indicates that individual CGMP deficiencies are often corrected without a more global approach to achieving comprehensive CGMP compliance.

We have reviewed your October 24, 1997 written response to the FD-483. While several deficiencies appear to have been corrected, the response lacks the necessary commitments, documentation, and detail to satisfactorily address many of the deviations observed during the September 1997 inspection. Our concerns include, but are not limited to, the following:

QUALITY CONTROL UNIT

1. Failure of the quality control unit to establish a system to review analytical data to assure accuracy and completeness, and to establish that the tests were actually performed, and that all discrepancies have been fully investigated. (FDA-483 items VI & VIII) For example:

   a. The investigators observed 20 pages containing undated acceptable water test results which were not supported by test data.

   b. In-process test results are not traceable to raw data.

   c. Various calculation errors were not detected by authorized reviewers.

   d. Impurity chromatograms were cut and new chromatograms were pasted in their place, and the originals were not retained.

Your response fails to address your practice of entering test data on water test logbooks prior to conducting tests, inadequate checks by authorized reviewers which fail to identify errors in calculations, and the absence of original test data to support transposed data. Corrections regarding the training of new personnel in the Workshop Laboratory are not adequate without retraining of other analysts, management, and authorized reviewers to identify and eliminate weaknesses.

Your response that cutting and pasting of chromatograms was due to deficiencies with the instrument and the chromatograms does not address the problem. It is unacceptable to cut and paste chromatograms or to discard originals. Any inadequate original raw data should be retained and the failure must be investigated and documented. The investigation should be reviewed and approved by the person authorized by your firm for that responsibility. When problems such as this arise, there is an underlying reason which requires evaluation and prompt resolution. Your firm's failure to have a procedure to identify and correct these problems indicates a serious lack of quality control.

The USP Method used to establish the data submitted in the DMF requires the use of a capillary column with direct injection. Your firm '
your laboratory, but used an older GC with a packed column. A capillary column would allow detection of lower levels of analyte compared to a packed column. The older unit was

reportedly used because the however, no maintenance records or service repair orders were provided. Furthermore, there was no data available to show that the results from the older instrument and method are equivalent to that of the method specified in the DMF.

2. Failure of the quality control unit to have formalized procedures for initiating and revising manufacturing and laboratory procedures. For example, on various occasions, posted standard operating procedures were observed with no documented history of the procedure including, date (or date of change) and approving official's signature. (FDA-483 item IV.A)

Your response is inadequate because it fails to address how you intend to provide a documented history of the procedure including, date and approving official's signature. Such information could not be found for any test or procedure where revisions had occurred. This issue goes well beyond the simple failure to have each posted procedure dated and signed. It requires a formal documented review and dated approval by an authorized qualified official prior to using the new procedure. The approving official should be someone which your firm designates to perform this duty.

From a CGMP standpoint, a quality control unit is responsible for ensuring that controls which assure drug product quality are implemented during the manufacturing operation. This includes assurances that out-of specification results are investigated. The inspection has revealed that your quality control unit is not adequately performing this function.

VALIDATION

3. Inadequate validation of production and process controls for Active Pharmaceutical Ingredients. For example, the retrospective validations failed to include evaluation of: critical process parameters, process water quality, particle size, impurity profiles data and microbiological quality attributes. (FDA-483 item III)

Your response states that you will supplement the retrospective validation with evaluations of the process control areas mentioned above. This is unacceptable because the historical data is incomplete, not supported by raw data, and was not always collected by validated analytical methods. We recommend that you develop and implement appropriate production controls and analytical methods, then conduct prospective process validation studies.

STABILITY

4. Failure to have an appropriate stability testing program designed to assess the stability characteristics of API's. For example, there was no evidence that stability indicating methodology was employed, and there were no degradation studies performed on any of the API's. (FDA-483 item IX)

Your response is incomplete in that laboratory personnel have not performed degradation studies. Therefore, any identification of components in any stability HPLC chromatograms would be extremely difficult.

LABORATORY CONTROLS

5. Failure to establish and follow appropriate laboratory controls to assure that API's conform to appropriate standards of identity, strength, quality, and purity. (FDA-483 items VII & X) For example:

   a. There were no tables or charts used to plot the potential difference versus the values of titration.

   b. Neither the analyst nor the reviewer detected errors in the

   c. The analyst used commingled class A and non-class accounting for which pipettes were used.

Your response to the potential difference plot fails to recognize the lack of reliability in test results obtained using this technique. You may refer to the USP <541> in this matter. For manual titrimetric assay, it is poor laboratory practice to fail to plot the potential difference versus the volume of titrant. Not recording this information fails to assure that the end point has been reached creating possible errors in the results of analysis using potentiometric titration. Results from such test procedures are not considered reliable.

Your response regarding defective instruments indicated both the polystyrene film and the infra-red spectrophotometer will be replaced. This responds to only a portion of the problem at issue. FDA is very concerned that the responsible personnel in the laboratory had not identified and corrected these problems. The practice of calibrating this instrument with a damaged polystyrene film only twice yearly is unacceptable. This deviation identified a basic lack of training and calls into question the reliability of the results of tests performed with this instrument.

Your response regarding commingled pipettes does not clearly explain accountability used for pipettes. Usually are used for quantitative analyses. However, since you use for analyses, they should be identified, and used for each analysis should be documented.

PROCESS CONTROLS

6. Failure to demonstrate that the compressed air used for product transfer between equipment does not add objectionable contaminants to the drug product. For example there was no documentation available to demonstrate that the compressed air met in-

house specifications for pressure, oil, humidity, temperature, water, rust, and that the particulate filter was installed as required (FDA-483 item VI.B)

Your response stated that appropriate methods would be developed, and filters installed to retain foreign impurities. However, your response failed to specify the foreign impurities for which these methods will be developed. Further, you should provide specifications for the filter types, change frequency and test methods employed to assure the compressed air does not contaminate the product. Compressed air coming in contact with API's should be produced by an oil free compressor, to prevent the ingress of oil, and the system should be equipped with a dehumidifier to minimize moisture in the air distribution lines.

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 CGMPs that exist at a firm. We recommend that you continually evaluate your facility on an overall basis for CGMP compliance.

Until FDA has confirmed compliance with CGMPs and correction to the deficiencies noted during the most recent inspection, we will recommend disapproval of any applications listing your firm as the supplier of any human or veterinary active pharmaceutical ingredients. We have also recommended your firm's APIs be placed on import alert and be denied entry into the United States. The articles are 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.

Please notify this office in writing of the specific steps you have taken to correct these violations, including documentation of each step you have taken to prevent their recurrence. Such documentation should include evidence of adequate change control procedures and a Quality Control System which utilizes validated production and analytical methods required by the New Drug Applications, New Animal Drug Applications referenced to your DMFs and VMFs, and documentation that trained personnel are certified as competent to perform the analysis or production functions they are assigned and reviewing officers are trained in their Quality Control responsibility and possess the qualifications to perform their assigned function. You should also provide documentation that your system has been totally evaluated and that it is in full compliance with current good manufacturing practice.

Please contact Edwin Meléndez, Compliance Officer, at the address and telephone numbers shown below if you have any questions or concerns regarding theses decisions. Please include your Central File Number "9611833" in any correspondence with this office.

Foreign Inspection Team, HFD-322
Food and Drug Administration
Center for Drug Evaluation and Research

7520 Standish Place
Rockville, Maryland, 20855-2737

Telephone: 301-594-0095
Telefax: 301-594-2202

For issues regarding veterinary drug products you may contact Compliance Officer José R. Laureano, Division of Compliance (HFV-232), Center for Veterinary Medicine at telephone number 301-594-0151, or by FAX number 301-594-1812. His mailing address is:

U.S. Food & Drug Administration
Center for Veterinary Medicine - Division of Compliance (HFV-232)
7500 Standish Place
Rockville, MD 20855

To schedule a reinspection of your facility after corrections have been completed and a response has been submitted, contact Deborah S. Browning, Consumer Safety Officer, Drug Group, of FDA's Division of Emergency and Investigational Operations (HFC-133), Division of Field Investigations, 5600 Fishers Lane, Rockville, Maryland 20857. You may wish to contact her office at 301-827-5648 or by FAX at 301-443-6919.

Sincerely,

Mark A. Lynch, Acting Director
Division of Drug Manufacturing and Product Quality (HFD-320)
Center of Drug Research and Evaluation

Gloria Dunnavan

Gloria Dunnavan, Director
Division of Compliance (HFV-230)
Office of Surveillance and Compliance
Center for Veterinary Medicine