



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-01-11

JUN 28 2001

Mr. Fang Yu Lee
President
Yung Shin Pharm. Inc. Col, Ltd.
1191, Sec. 1, Chung Shan Road
Tachia, Taichung
Taiwan, R.O.C.

Dear Mr. Yu Lee:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Tachia, Taiwan by the United States Food and Drug Administration during May 4 - 8, 2001. The inspection revealed significant deviations from U.S. good manufacturing practice in the manufacture of bulk [] that resulted in the issuance of a twelve-item FDA Form 483 at the completion of the inspection.

These deviations cause this API to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice (CGMP). No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have reviewed the May 31, 2001 response to the FD-483 observations submitted by your US Agent [] on June 1, 2001. We conclude that this response lacks sufficient details, explanations, or documentation to adequately address all of the deviations observed during the May 2001 inspection. Our comments regarding the most significant observations are shown below:

1. Well water and city water used in the manufacture of APIs has not been demonstrated to be suitable for its intended use. In addition, your firm lacked a written procedure for the routine monitoring of both sources of

water and the actual monitoring of both waters for chemical and microbial attributes is very limited.

Our inspection disclosed that well water is used for the initial rinsing of manufacturing equipment and as a component for preparing []

[] The well water is processed through []

[] In addition, city water taken directly from the spigot without further treatment, is used for the final rinsing of equipment. Both water sources have not been qualified to demonstrate suitability for use in manufacturing of APIs.

Furthermore, your firm lacked a written procedure for routine monitoring of water for chemical and microbial attributes and monitoring of the water was very limited. Well water is tested [] a month from only one of three points of use on a rotating basis and after the [] filter [] months. City water is tested [] a month from only one of three points of use on a rotating basis.

Your written response reports that a new validation protocol for the water systems was approved on May 25, 2001, equipment installation and operational qualification was completed on May 31, and you have initiated performance qualification on June 4. The latter will be completed by July 5, 2002.

Our review of the Document No. [] Performance Qualification Protocol of the [] "Water and Tap Water" (Attachment 3), disclosed that the latter refers to a microbial alert limit of [] and an action limit of [] for [] filtered water and city tap water. These alert and action limits are excessive. The United States Pharmacopeia (USP 24) recommends a microbial action limit of 500 CFU/ml for potable (drinking) water.

Furthermore, our review disclosed that you plan to continue to use city water directly from the spigot without further treatment or chlorination. Since the quality of municipal water often varies significantly from day to day and throughout the seasons, we recommend that tap water be collected in a storage tank and subjected to further treatment (i.e., filtration and/or chlorination) and testing for chemical and microbial attributes before its use in the manufacture of APIs.

Please address these concerns in your written response and provide results of chemical and microbial testing of [] filtered and tap water obtained to date to show that the water is suitable for use in manufacturing APIs.

2. The sterilization cycle of the [] and the [] have not been validated.

Your response reports that protocols for validating the sterilization cycles for both were approved on May 15, 2001. These protocols provide for []

[] You indicate that the validation process for [] was initiated on May 15, 2001 and will not be completed until September 30, 2001.

Your time frame for completing validation of the sterilization cycles seems excessive. Please explain why it will take 4 ½ months to complete this validation. Also your response does not indicate whether production of [] will continue during this validation phase. Please address these issues in your response to this letter.

3. The laminar flow hood in the micro lab and [] filters in the Class 100,000 production area had not been certified.

Your response acknowledges that you have inadequately certified the [] filters in the Class 100,000 production areas and laminar flow hood in the microbiology laboratory. You report that the validation protocol for the HVAC system of the [] plant and laminar flow hood were revised to include tests for air flow and air changes, [] filter [] integrity testing, and sampling of the air for viable particulates. This qualification was initiated on June 5 and will be completed by June 20, 2001.

However, our review of the protocol for integrity testing of [] filters disclosed two deficiencies. First, the SOP does not address sampling of the [] filters to calibrate the []

[] Second, it does not provide for [] Please address these issues in your response.

The above deficiencies are not to be considered as an all-inclusive list of the deficiencies at your plant. FDA inspections are not intended to uncover all CGMP deviations that exist at a firm. We recommend that you conduct a complete evaluation of your facility for CGMP compliance. If you wish to ship APIs to the United States, your firm is responsible for assuring compliance with U.S. standards of good manufacturing practice for active pharmaceutical ingredients manufacturers.

Until the FDA reinspects your facility and confirms that these deficiencies have been corrected, this office will recommend disapproval of all applications listing your firm as a supplier of bulk [] We may also recommend that all APIs you manufacture

for U.S. clients be denied entry into the United States. These articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act because 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).

In your response please submit English translations of supporting documents, procedures or other information detailing corrective actions that you plan to take or have taken to bring your API facility into compliance. If you have questions or concerns regarding this letter, please contact Edwin Rivera Martínez, Compliance Officer, at the address and telephone numbers shown below:

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
FAX: (301) 594-1033

Please reference Central File Number 9612854 in all correspondence to this office.

To schedule a reinspection of your facility after corrections have been completed, contact the Director of FDA's International Programs and Technical Support Branch (HFD-134), Division of Field Investigations, 5600 Fishers Lane, Rockville, Maryland, 20857. You can also contact this office at (301) 443-1855 or by FAX at (301) 443-6919.

Sincerely,



Joseph C. Famulare
Director, Division of Manufacturing and
Product Quality, HFD-320

cc:

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