DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

# Warning Letter

**Via FedEx** **WL: 320-04-02**

January 5, 2004

Mr. Y.C. Chen
President
Delta Synthetic Co., Ltd
15 Min-Shen Street
Tu Chen City, Taipei Hsien 23607
Taiwan, Republic of China

Dear Mr. Chen:

We have completed our review of the inspection of your Active Pharmaceutical Ingredient (API) manufacturing facility in Taiwan, Republic of China, by Investigator George J. Flynn and Chemist Richard Needham, during the period of October 27-29, 2003. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practices (CGMP) in the manufacture of Active Pharmaceutical Ingredients (API's). The deviations were presented to you on an Inspectional Observations (FDA-483) 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 Federal Food, Drug, and Cosmetic Act, 21 USC section 351(a)(2)(B).

Our review also included your company's response letter dated November 26, 2003 to the FDA-483 observations. We note that many corrections have been completed, or will soon be implemented. There are however, issues which need more comprehensive corrections. We have concluded that this response lacks sufficient details, explanations or documentation to adequately address all of the significant deviations observed during the inspection. Specific areas of concern include, but are not limited to:

LABORATORY CONTROLS SYSTEMS:

1) Appropriate laboratory tests to determine conformance to specifications have not been performed on each batch of [ ]

- The laboratory did not have an adequate impurity profile for [ ] that identifies organic, inorganic and solvent impurities to monitor unidentified and apparent impurities in the API to ensure that they are appropriately controlled. For example: an unidentified [ ] which has not been characterized was

seen at about the[ ]level in all[ ]of[ ] reviewed during the inspection.

Your response indicates that you have started to monitor this unidentified[ ]and will attempt to identify its structure. You also indicate that you have established an impurity profile for[ ]except for the unidentified impurity. However your response fails to adequately address the unidentified impurity within the impurity profile. Please provide documentary evidence that a complete impurity profile has been compared to the impurity profile in the regulatory submission and to historical data, so that your firm can detect changes to the API manufacturing process.

An impurity profile describing the identified and unidentified impurities present in a typical batch produced by the specific controlled production process should be established for each API. The impurity profile should include the identity or some qualitative analytical designation, the range of each impurity observed, and classification of each identified impurity. The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data to detect changes to the API resulting from modifications in raw materials, equipment, operating parameters, or the production process.

- Stability-indicating methods were not used in the stability testing program for [ ]

Your response indicates that you will use stability indicating methods in the future stability testing of[ ] However, it fails to indicate whether you are currently using stability indicating methods in your stability program and did not provide a timeframe for beginning the use of stability indicating methods.

The test procedures used in stability testing should be validated and be stability indicating. Please provide documentary evidence that you are currently using stability indicating methods for all stability testing of[ ] and any other API manufactured for the US market.

- The inspection of the microbiological laboratory fails to document the lot number and expiry date of the[ ] used to prepare the media;[ ]of the media in the[ ]such as[ ] Additionally, the[ ]was not calibrated.

Your response did not address the[ ]

It should be noted that laboratory controls such as testing should be documented at the time of performance and records should include complete data derived from all tests

conducted to ensure compliance with established specifications and standards including examinations and assays.

MATERIALS SYSTEM:

2) Sampling and Testing of incoming [ ] used in the manufacture of [ ] were inadequate.

- At least one test to verify the identity of the incoming material was not conducted.
- The reliability of the suppliers' certificate of analysis (COA) was not established in that a complete analysis was not performed and compared with the COA at the appropriate intervals.

Your response indicates that you have initiated a testing procedure for incoming [ ] However, your response did not provide any documentary evidence of corrective actions.

At least one test to verify the identity of each batch of materials should be conducted. Furthermore, supplier approval should include an evaluation that provides adequate evidence that the manufacturer can consistently provide material meeting specifications. At a minimum a complete analysis should be performed at appropriate intervals and compared with the COA. Reliability of the COA should be checked at regular intervals. Please provide documentary evidence that corrective actions have been completed.

3) Procedures for the recovery of solvents were inadequate.

- Procedures for solvent recovery had not been established to ensure that solvents are controlled and monitored to assure that they meet appropriate standards before reuse or commingling with other approved materials.
- There were no specifications established or testing performed for the reuse of redistilled [ ]
- There were no procedures established for determining the number of [ ] cycles required for the [ ] recovery process.

Your response indicates that you have initiated a testing procedure for recovered [ ] and established specifications and testing methods for controlling [ ] used in the manufacture of [ ] However, your response did not provide any documentary evidence of these corrective actions.

Solvents can be recovered and reused in the same processes or in different processes, provided that recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or commingling with other approved materials. Fresh and recovered solvents can be combined if adequate testing has shown their

suitability for all manufacturing processes in which they may be used. The use of recovered solvents should be adequately documented. Please provide documentary evidence that corrective actions have been completed.

PACKAGING AND LABELING SYSTEM

4) Failure to have written procedures describing the receipt, identification, quarantine, sampling, release, and handling of labeling materials. Furthermore, incoming labels received from the vendor are not proofed against the master label.

Your response indicates that you have created a new procedure [redacted] to incorporate all of the corrective actions. However, you did not provide a copy of this SOP or evidence that these corrective actions have been completed.

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. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure that all APIs manufactured by your firm are in compliance with all U.S. standards for Current Good Manufacturing Practices.

Failure to correct these deficiencies may result in FDA denying entry of articles manufactured by your firm into the United States. The articles could 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 Practices within the meaning of Section 501(a)(2)(B) of the Act.

Please respond to this letter within 30 days of receipt. Your response should include data collected in your correction of the deficiencies cited as well as copies of procedures not already submitted. Please identify your response with FEI: 1545. Until FDA can confirm compliance with CGMP's 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 Marybet Lopez, Compliance Officer, at the address and telephone numbers shown below, if you have any questions, written response or concerns regarding these decisions.

U.S. Food & Drug Administration
CDER/DMPQ/HFD-325
11919 Rockville Pike, Montrose Metro II
Rockville, MD 20852
Tel: (301) 827-9055; FAX (301) 827-8909

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) 827-3777 or by fax at (301) 443-6919.

Sincerely,

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