



## WARNING LETTER

FEDEX

WL No. 320-01-12

JUL 27 2001

Mr. Nobuo Nunomura  
Executive Director  
Kaken Pharmaceutical Co., Ltd..  
301 Gensuke, Fujieda-shi  
Shizuoka 426-8646  
Japan

Dear Mr. Nunomura:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Shizuoka, Japan by the United States Food and Drug Administration on May 15-18, 2001. The inspection revealed significant deviations from U.S. good manufacturing practices in the manufacture of APIs, and resulted in the issuance of a 29-item form FDA- 483 to you at the completion of the inspection. These deviations cause these APIs 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. No distinction is made between active pharmaceutical ingredients or finished pharmaceuticals, and failure of any to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have also reviewed your June 27, 2001 written response to the FDA-483. We acknowledge the commitments to correct the deficiencies but the response does not provide documentation that any of the corrections have been successfully implemented. Specific areas of concern include, but are not limited to:

1. There were inadequate written procedures for production, process control, and laboratory operations to assure that APIs have the appropriate quality and purity. The inspection reported the lack of adequate written procedures for the following:
  - Annual reviews
  - Change control
  - Raw material sampling
  - RO water sampling & testing

2. Written procedures for production, process control, and laboratory operations were not always followed to assure that APIs have the appropriate quality and purity. The inspection reported numerous instances regarding the following operations which present a general practice of not following written procedures:
  - Stability testing
  - Storage of quarantined and released materials
  - Making software changes
  - Drying of finished API
  
3. There were inadequate laboratory procedures and records to assure that APIs have the appropriate quality and purity. The inspection reported deficiencies regarding the following laboratory procedures and records:
  - Analytical methods validation
  - Systems suitability testing
  - Incomplete laboratory records
  - Inaccurate laboratory calculations
  - Inadequate calibration of laboratory equipment

Your response states that written procedures have been or will be developed or revised, but as indicated in number two above, written procedures are not always followed. No documentation that the written procedures have been implemented and are being followed, or that employees have been trained regarding these procedures was submitted. The response also states that the quality control unit has corrected the laboratory deficiencies described in number 3 above, but no documentation of such corrections was submitted.

The CGMP deviations identified above or on the FDA-483 issued to you are not to be considered as an all-inclusive list of deficiencies at this 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 APIs to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for current good manufacturing practices. We recommend you evaluate all written procedures and your employee's adherence to written procedures.

Please respond to this letter and provide a status report on the corrective actions within 30 days, with documentation that the corrections have been applied to all operations and have been successfully implemented. Please submit English translations of all documentation. Until FDA has reinspected this facility and confirms compliance with CGMPs and correction of these deficiencies, this office will recommend withholding approval of any new drug applications listing this facility as the manufacturer of APIs. Failure to promptly correct these deficiencies may result in the refusal to permit entry of these APIs or finished products made from these APIs into the United States.

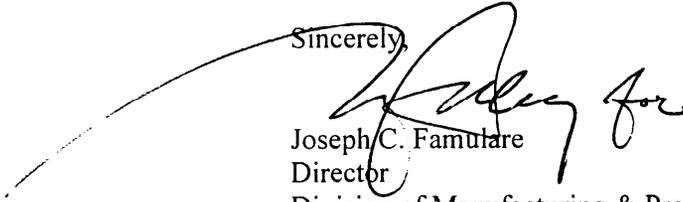
Please direct your written response to Compliance Officer John M. Dietrick at the address shown below. Please reference CFN# 9612799 within your response.

Kaken Pharmaceutical Co.,Ltd.  
Shizuoka, Japan  
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U.S. Food & Drug Administration  
CDER HFD-322  
7520 Standish Place  
Rockville, MD 20855-2737  
Tel: (301) 594-0095  
FAX (301) 594-1033

To schedule a reinspection of this facility after corrections have been completed and it is in compliance with CGMPs, contact: Director, International Drug Section, HFC-133, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, MD 20857, Tel. (301) 827-5655 or FAX (301) 443-6919.

Sincerely,



Joseph C. Famulare  
Director

Division of Manufacturing & Product Quality  
Center for Drug Evaluation & Research