DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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MAY 9 1997

WARNING LETTER

Mr. Ekkehard Wienhofer
Huls AkG Werk Witten Plant
D-58453 Witten, Germany

Dear Mr. Wienhofer:

FDA has completed its review of the inspection of your active pharmaceutical ingredient manufacturing facility in Witten, Germany by Investigator Nancy Rolli on February 17-20, 1997. 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 by pharmaceutical dosage form manufacturers in the United States, since, under United States law, those CGMP deviations make your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Specific areas of concern include, but are not limited to:

1. Failure of your Quality Control Unit to:

   a. Properly exercise the authority and responsibility for rejecting non-conforming/out-of-specification batches.

   b. Failure to conduct an investigation as to the cause for the failing batch.

   c. Failure to review and approve the use of a reprocessing procedure for a finished active pharmaceutical ingredient.

d. Failure to assure that a reprocessing step is validated and will produce the same quality product conforming with all established standards, specifications and characteristics.

2. Failure to include critical manufacturing parameter results (temperature) within the manufacturing master production and control record.

Our review has determined that there are some repetitive violations found during the February 1997 inspection which were also cited during the February 1993 inspection of a different grade of the same material inspected in February 1997. Some of our concerns include the following:

a. Although production employees may and should reject a batch of product failing to meet any of its in-process or finished product release criteria, your quality control unit has the responsibility to oversee this operation. This function should be documented in some manner to demonstrate that their responsibility has been carried out and the documentation should be made part of the batch record. Similarly, any failed batch should be fully investigated as to the cause of the failure. This investigation should, at a minimum, evaluate the impact of the failure on the lot itself and on other lots of the same product or similar products. The investigation should also address procedures to prevent future failures. If the investigation is carried out by production employees, the written record of the investigation should be approved or rejected in a documented review by the quality control unit.

Additionally, no failed batch or portion of any failed batch should be used in subsequent production until a full investigation of the failure has been completed and reviewed by the quality control unit. If the failed batch is to be reprocessed this should be done only under a validated system with the approval of the quality control unit.

b. As in the previous 1993 FDA inspection, your firm has continued its failure to document important manufacturing control results such as temperatures involved in production operations. Without documentation that your firm adequately controls critical process parameters as identified in validation studies, you can not assure unifromity of any future production.

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 assurance that out-of-specification results are investigated. The February 1997 inspection has revealed that your Quality Control Unit is not adequately performing this function.

Please respond in writing as to what actions your firm will take to correct these deficiencies.

The issues disclosed during the February 1997 inspection indicate cGMP concerns with the quality systems within your organization. As was stated in the Warning Letter dated November 3, 1995 for the Witten facility, we strongly recommend that you evaluate your firm on an overall basis for cGMP compliance. If such an action is planned to be part of your corrective actions, please include it in your response to this letter.

In addition to the items discussed with your management at the conclusion of the inspection, we have the following concern for the product covered during the inspection:

1. The active pharmaceutical ingredient (API) product covered during the February 1997 inspection is intended for use in an intravenous finished drug product. The inspection disclosed that your firm does not perform any microbial or endotoxin analysis for this product, which is shipped to the United States.

FDA recommends that your firm consult with your customers who purchase active pharmaceutical ingredients for use in intravenous products to develop microbiological and endotoxin specifications, and appropriate testing procedures for the active pharmaceutical ingredient.

2. We are also concerned with your current microbiological analysis which is performed at another Huls firm, located in Marl, Germany. During the February 1997 inspection, your personnel explained to the FDA investigator that microbiological testing is performed between the first and tenth of the month and that your products are tested only on a rotating basis. Additionally, your personnel also stated that products are released prior to results being received or reviewed by quality control. Releasing batches before test results are known is an unacceptable practice. Please provide a list of products which are subject to microbiological testing and are shipped to the United States, and assurance that such products will not be released prior to receipt and review of all test results.

The cGMP deviations identified above are not to be considered an all-inclusive list of the deficiencies at your firm. 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 firm on an overall basis for CGMP compliance. If you wish to continue 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 your firm as a supplier of the active pharmaceutical ingredients.

Failure to promptly correct these deficiencies may result in FDA denying entry of drug products 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 controls used in the manufacture do not appear to conform to Current Good Manufacturing Practices within the meaning of Section 501 (a)(2)(B) of the Act.

In any response to this agency, you should include copies of SOPs generated or records amended, as well as data collected in your correction of deficiencies brought forward during the inspection. Specific time frames for correction and commitments with follow up documentation should also be supplied or reported as forthcoming. Please include translations in English with your supporting documents and reference **Central File Number # 9612624** on all correspondence sent to this office.

You may contact Patricia L. Alcock, Consumer Safety Officer, at the address and telephone numbers shown above if you have any questions, written response or concerns regarding these decisions.

To schedule a reinspection of your facility, after corrections have been completed and your firm is in compliance with cGMP requirements, send your request to: Deborah Browning, Consumer Safety Officer, Drug Group, Division of Emergency and Investigational Operations (HFC-134), 5600 Fishers Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 827-5653 or by fax at (301) 443-6919.

Sincerely,

Douglas I. Ellsworth
Director
Division of Manufacturing and
Product Quality, HFD-320