DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

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SEP 5 1997

WARNING LETTER

Erik Bogsch, Managing Director
Gedeon Richter, Ltd.
Budapest, P.O.B. 27
Hungary, H-1475

Dear Mr. Bogsch:

This is regarding an inspection of your Active Pharmaceutical Ingredient (API) manufacturing facility in Budapest, Hungary by Investigator Terri L. Dodds of the United States Food and Drug Administration (FDA) conducted April 14 - 17, 1997. The inspection revealed significant deviations from Current Good Manufacturing Practices (CGMPs) in the manufacturing of active pharmaceutical ingredients. The deviations were presented to you on an FDA-483, Inspectional Observations form, at the close of the inspection. These CGMP deviations cause active pharmaceutical ingredients manufactured by your facility to be unacceptable for use in the United States, since under United States law, the CGMP deviations make these products adulterated within the meaning of Section 501(a) (2) (B) of the Federal Food, Drug and Cosmetic Act (the Act).

The written response submitted by your company dated, April 28, 1997, signed by Laszlo Godo, M.Sc., Director, Production, was also reviewed but was considered inadequate. The response to the FDA-483 Observations did not provide any documentation to demonstrate corrections and lacked sufficient detail to adequately address all the deviations noted during the inspection. The most significant observations and our comments, are shown below:

1. Failure to have written failure investigation procedures and to conduct investigations of batches that fail to meet specifications, for example:

   There was no written procedure for conducting failure investigations, nor failure investigation reports assessing the cause for failure and the corrective actions for three (3) batches which failed release specifications for; impurities, morphology and sulphated ash.

   The response to item 8 of the FDA-483 failed to provide the new failure investigation procedures and the results of the investigation of the

destination was the United States. Also, when a batch of material is rejected, an evaluation as to whether other batches could have been similarly affected, should be carried out. Please indicate whether other lots destined for the U.S. were affected.

2. Failure to demonstrate that intermediates (crude material) and recovered solvents met validated process control specifications prior to further processing. There was no written evidence that further processing of intermediates and the subsequent usage of recovered solvents resulted in products meeting specifications established through validation studies, for example:

   The acceptance criteria (purity levels) for the

   The individual impurity results for crude material tested in the final processing stage was not recorded to demonstrate the material met impurity specifications.

   The response for items 4, 7, and 9 on the FDA-483 failed to provide the protocols for establishing purity requirements, analytical methods for the recovered solvents, and records demonstrating recording of the intermediate impurity results. Also, please indicate in your response whether the in-process requirements for recovered solvents and intermediates were derived from process validation studies.

3. Inadequate validation of production procedures and process controls of Active Pharmaceutical Ingredients, for example:

   The retrospective validation manufactured in the year 1996 was based on finished product testing results, but failed to identify and establish limits for critical processing parameters such as, but not limited to,

   The response to item 5 on the FDA-483 promised corrections but failed to provide documentation such as the validation protocol indicating inclusion of the operating characteristics of the process, e.g., time, temperature, humidity, and equipment settings. Please provide the validation protocols for our review.

4. Failure to adequately validate the cleaning procedures used for multi-use equipment that is used to package API products, for example:

   The equipment used to repackage (packaging cabin) active pharmaceutical ingredients lacked a validated cleaning procedure.

   The response to item 13 of the FDA-483, failed to provide a protocol and procedures for our evaluation. The response indicated that the cleaning procedures for the

packaging area will be revised and assessed by the end of 1997, and a protocol and the validation report completed during 1998. In the meantime, please indicate how your firm will assure that products destined for the U.S. have no traces of other products which use the same equipment.

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.

Failure to promptly correct these deficiencies may result in FDA denying entry of these products 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.

You may contact Edwin Melendez, Compliance Officer, at the address and telephone numbers shown above if you have any questions, written response or concerns regarding these decisions. Please include your Central File Number "9610154" in any correspondence with this office.

Sincerely,

Mark A. Lynch, Acting Director
Division of Manufacturing and
Product Quality, HFD-320