HFD-030
FOI

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0093
FAX: (301) 594-2202

MAY 16 1997

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Helmut Schickaneder
Managing Director
Irotec Laboratories, Ltd.
90 South Mall
Little Island
Cork, Ireland

Dear Dr. Schickaneder:

This is regarding an inspection of your Active Pharmaceutical Ingredient (API) manufacturing facility in Cork, Ireland, by the United States Food and Drug Administration on January 20 - 23, 1997. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) in the manufacture of APIs that resulted in the issuance of an FDA Form 483 List of Observations. The deviations cause the APIs to be unacceptable for use by pharmaceutical dosage form manufacturers in the United States, because under U.S. law CGMP deviations make the products adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). 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 and finished pharmaceuticals, and failure of either to comply constitutes a failure to comply with the requirements of the Act.

We have also reviewed your response to the FD-483 observations, dated March 14, 1997, submitted to the FDA's Division of Emergency and Investigational Operations by Ms. Meg McCarthy, Quality Assurance & Regulatory Affairs Section Head. We conclude that it presently lacks sufficient detail, commitment, or documentation to adequately address the deviations observed during the January 1997 inspection. Specific areas of concern include, but are not limited to the following:

PRODUCT SPECIFICATIONS:

The inspection revealed that you failed to establish in-process or finished product release specifications for residual levels of processing solvents and particle sizes.

1. In-process or finished product release specifications

   not been established, and there was no validation data to show that processing
   ... are reduced to acceptable levels during the manufacturing process.

Your response indicated that you intend to show that
The response also indicated you intend to conduct a

, we urge you to conduct a similar study

. Your response also indicated that you have performed some development work to show processing removes Please forward the data for evaluation when these studies are complete.

2. Lack of appropriate written specifications for in that particle size has not been established. Your response indicates you intend to establish particle size specifications in the updated DMF. Please forward the data for evaluation when these studies are complete.

VALIDATION:

1. Adequate cleaning procedures have not been established in that you have not conducted cleaning validation studies for non dedicated manufacturing equipment. Your response indicated that you intend to perform cleaning validation studies by the end of June 1997. Please forward the results of these studies for evaluation.

2. batches are reworked without data to demonstrate that the procedures used will consistently yield product that conforms to specifications. For example, failed to meet solubility and sulphate ash specifications, due to excessive inorganic salt levels. The lot was reworked times but still failed solubility and sulphate ash specifications.

Your response indicated that you do not analyze failed batches for specific inorganic content prior You also indicate that levels acetone are not out of specification result, but an analytical adjustment in the gas chromatography method for solvent recovery and that you may raise the specification. FDA expects to see conclusive results of detailed investigations to justify reworking or corrective actions,

to demonstrate that you understand and control the various variables involved to assure that all specifications are consistently met. Please provide copies of your completed investigations into these matters.

LABORATORY RECORDS AND CONTROLS:

1. The inspection found numerous deviations from CGMPs in the manner in which you maintain raw data, evaluate samples, maintain equipment and report data. There is a lack of adequate raw data to support analytical method validation data contained in the Drug Master Files. The inspection disclosed: that the only raw data available was chromatograms; there was no raw data for standard weights, samples, volumes, dilutions and calculations. For example, there was a lack of adequate raw data to support residual solvents test method validation data contained in the Drug Master File.

2. There is no assurance that all chromatographic data is reported and reviewed. For example, the consecutive chromatograms were missing for precision and accuracy tests for the residual solvent test method validation

Your response indicated that you would compile an injection sequence table for the future and that "all valid results" would be included. There was no explanation for the routine discarding of data which deviates significantly from the average. This selective retention and reporting of data can raise doubts about the overall quality and reliability of the data reported. While some data may be invalidated with scientific justification and therefore not used in the batch evaluation, all analytical data must be retained.

3. There is no assurance that current HPLC related substance methods would be able to identify potential degradants. The potential degradants have not been identified by exposing the drug substances to extreme conditions
.. Please submit the results of stress testing you perform.

4. Written standard operating procedures (I.S.O.P. - 003) are not always followed, in that you did not perform weekly calibration checks for the
. The inspection revealed failure to document corrective action regarding instrument calibration checks which did not meet specifications. Please submit documentation to verify calibration is being done.

5. Laboratory records are not adequate, for example: (1) The analyst who performed a TLC impurity test on
record the weights and dilutions used for the reference standard solution. (2) No permanent record was kept of the appearance (3) Raw data (weights/volumes) were not recorded for the preparation of limit reference standard solutions, such as heavy metals and chloride.

Your response indicates that new procedures will correct these deficiencies. Please submit copies of these procedures which describe training programs to prevent similar laboratory records deficiencies.

6. There were no written procedures determining how TLC and HPLC "related compounds" test results are to be reported for release lots and stability lots. The response indicates that this has been corrected with new SOP and data sheets, please submit these for review.

The above deficiencies are not to be considered all-inclusive. 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.

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 practice within the meaning of Section 501(a)(2)(B).

To schedule a reinspection of your facility after corrections have been completed, contact International Technical Operations Branch (HFC-133) Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, Maryland 20857. Phone: (301) 827-5648 Facsimile: (301) 443-6919.

Please contact Clyde D. (Russ) Rutledge, Compliance Officer, at the address and telephone numbers given on the first page if you have any questions or concerns regarding these decisions.

Sincerely,

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