DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NOV 18 1998

Proviron Fine Chemicals, NV
Stationsstraat 123 bus 2
B-8400 Oostende
Belgium

Dear Mr.

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Oostende, Belgium by the United States Food and Drug Administration from August 18 to 21, 1998. The inspection revealed significant deviations from U.S. good manufacturing practice in the manufacture of bulk that resulted in the issuance of a form FDA-483 to you at the completion of the inspection. These deviations cause this API 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 and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have reviewed your October 21, 1998 response to the FD-483 observations. We also acknowledge receipt of your October 28, 1998 letter requesting confidentiality and confirm that all documents will be treated in accordance with Freedom of Information Act (FOIA) regulations and procedures. We conclude that this response lacks sufficient details and documentation to adequately address the deviations noted during the August 1998 inspection. Our comments regarding the most significant observations are shown below:

POTENTIAL FOR CROSS-CONTAMINATION

1. The cleaning procedures used on multi use equipment have not been shown to be effective in removing For example, the effectiveness of equipment cleaning was not demonstrated prior to the manufacture of batches of in 1997. Evaluation of the effectiveness of the cleaning procedure prior to the manufacture of batches in 1998 was inadequate because analytical methods and laboratory procedures were not sufficient to assure accurate determination of residual levels, and depended on a approach. The cleaning procedure is not consistent and has not been validated.

2. The equipment used to manufacture bulk was also used for the production of a pesticide chemical. We recommend that pharmaceutical products not be manufactured in the same facilities or the same equipment as that used for production of many non-pharmaceutical chemicals, including pesticides, because of the risks of product mix up and toxic material carryover.

LABORATORY PROCEDURES

1. Laboratory procedures are inadequate to assure that each batch of conforms to appropriate standards of identity, strength, quality, and purity. For example, the U.S.P. identification tests and the U.S.P. limit of test were not performed on batches of The assay method has not been adequately validated, and the laboratory did not have a copy of U.S.P. 23 or any U.S.P. standard.

2. Written laboratory procedures allowed product with initial out-of-specification results to be released based on a single retest.

3. The laboratory staff has not received any documented CGMP training.

Your written response states your firm will develop, validate, and document an effective cleaning procedure within months or before the start of the next campaign. Your response also commits to correcting the deficiencies in the laboratory procedures used to determine if equipment has been adequately cleaned, and to validating the analytical methods which will be used during validation of the cleaning procedure.

The response also states that you plan to continue campaigning these products in the same facility and using the same equipment. If you wish to further pursue this approach, you should provide to this office a complete description of the facility and the

controls employed to prevent cross contamination and product mix-ups, including air handling systems and control of personnel and materials. To further evaluate any plan to continue to use the same equipment, we would need a description of any multi use equipment, identification of any non-pharmaceutical chemicals processed on that equipment, and a description of any campaigning and equipment cleaning procedures, including any disassembly and reassembly procedures. Your response should state what residue acceptance levels have been established for the non-pharmaceutical chemicals and cleaning agents, and provide the justification for these levels. This justification should be based on complete toxicity information on the non-pharmaceutical chemical and the chemical properties and intended use of the You should include a complete description of sampling methods, recovery studies, and analytical methods validation, and provide a copy of the protocol which will be used for equipment cleaning validation prior to the next campaign.

Your written response also states that the deficiencies regarding laboratory methods used to analyze finished product will also be corrected and that all analytical methods will be validated prior to the next campaign. Please provide documentation of the analytical methods validation, documentation that the appropriate U.S.P. method and standards have been obtained, and copies of the results of additional tests performed on the 1997 batches by your U.S. Supplier, and on retesting of the 1998 batches after analytical methods validation is completed.

The above deficiencies are not to be considered as an all-inclusive list of the deficiencies at your plant. FDA inspections are audits which are not intended to determine all deviations that exist at a firm. If you wish to continue processing APIs for use in the U.S., it is the responsibility of your firm to assure compliance with U.S. standards of good manufacturing practice for active pharmaceutical ingredients. We recommend that you evaluate your facility for CGMP compliance on an overall basis.

Until the FDA reinspects your facility and confirms that these deficiencies have been corrected, this office will recommend disapproval of any applications listing your firm as a manufacturer of APIs. If corrections are not initiated promptly, any API processed by your firm may be denied entry into the United States.

Please direct your written response to the issues discussed in this letter to Compliance Officer John M. Dietrick at the address shown above. Please provide English translation for any significant information in documents submitted to FDA, and reference CFN# 9613194 within your written response.

To schedule a reinspection of your facility after corrections have ~~been~~ completed, send your request to: Director, International Drug Section, HFC-134, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, Maryland, 20857. You can also contact that office at (301) 827-5655 or by FAX at (301) 443-6919.

Sincerely,

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