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
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# WARNING LETTER

**FEDEX**
DEC 6 2000

WL No. 320-01-04

Fabrizio Nidiaci, PhD.
Technical Director
Societa Italiana Medicinali Scandicci
Loc. Filarone, Incisa Valderno
50064 Firenze
Italy

Dear Dr. Nidiaci:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Florence, Italy by the United States Food and Drug Administration from October 17-20, 2000. The inspection revealed significant deviations from U.S. good manufacturing practices in the manufacture of APIs, and resulted in the issuance of an FDA Form 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 and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

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

1. Investigations and follow-up of out of specification results and complaints are inadequate or incomplete.

2. Equipment cleaning procedures used for cleaning multiple use equipment have not been validated.

3. The computer systems used to control and/or monitor production, reconcile raw materials, assign batch numbers, and control solvents, have not been validated.

The validation of the computer system used to control the [ ] process is incomplete.

4. Qualification of processing equipment has not been completed.

We have also reviewed your November 3, 2000 written response to the FDA-483. Your response to deficiency 1 regarding investigations is satisfactory regarding the specific investigations listed on the FDA-483, and regarding a new standard operating procedure to prevent recurrence, but fails to address all the other investigations not specifically listed. Your proposed corrective actions for deficiencies 2, 3, and 4 regarding validations appear satisfactory except that the validations will not be completed until the end of March, 2001 and imply that you would continue to use the unvalidated computer systems and equipment cleaning methods until then.

Although not listed on the FDA-483, the inspection team also discussed two other deficiencies regarding incomplete process validation and the lack of Quality Assurance review of batch production records with you at the conclusion of the inspection. Your written response also addressed these deficiencies but indicate that they will not be corrected until the end of March, 2001.

The above deficiencies are not to be considered as an all-inclusive list of the deficiencies at your facility. FDA inspections are audits which are not intended to determine all deviations that exist at a firm. If you wish to continue manufacturing 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 on an overall basis tor CGMP compliance.

Until these deficiencies have been corrected, this office will recommend disapproval of any applications listing your firm as a manufacturer of APIs. When the corrective actions described in your response have been completed, please submit documentation of the corrections to this office. Specifically, please submit the final validation reports regarding computer system, equipment cleaning, and process validation. Documentation that all out of specification investigations have been completed and documented, and that all batch production records are reviewed by Quality Assurance, should also be submitted.

Please direct your written response to Compliance Officer John M. Dietrick at the address shown above. Please reference CFN# 9610238 within your written response and provide English translation for the documents submitted.

To schedule a reinspection of your facility after corrections have been completed, send your request to: Director, International Drug Section, HFC-133, 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

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