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

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

AUG 24 1998

Poli Industria Chimica S.p.A.
Via Volturno 48
20089 Quinto De'Stampi
Rozzano MI - Italy

Dear Dr.

This letter is in reference to the recent inspection of your active pharmaceutical ingredient and finished dosage form manufacturing facility in Rozzano, Milan, Italy. The inspection was conducted by Investigator Alicia Mozzachio and Chemist Nicholas Falcone on June 15 - 24, 1998. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of active pharmaceutical ingredients and in the manufacture of The deviations were presented on an FDA-483 List of Observations at the close of the inspection. These CGMP deviations cause your products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Our review included your firm's response to the FDA-483, dated July 24, 1998. We have found the response unacceptable because the response lacks sufficient details, explanations, and documentation to address the deviations observed during the June 1998 inspection. We are also concerned about your firm's quality systems, since many of the FDA-483 Observations demonstrate a lack of proper quality control over the manufacture of your drug products.

Training

Your firm was cited for not having a formalized training program for employees regarding SOPS (FDA-483 Item # 4). We understand a new, revised SOP entitled Training, will be written to include training documentation. Please provide a copy of the SOP, and explain, how the personnel will be trained.

In addition, we are quite concerned with the number of times your personnel had to be retrained in your written procedures and proper good manufacturing practices. Examples include:

1. Improper cleaning procedures of the floor and walls in the area as observed during the inspection (FDA-483 Item # 5)
2. Incomplete documentation of sanitization of the system (FDA-483 Item # 12)
3. Failure to follow an established calibration schedule (FDA-483 Item # 14)
4. From March 1998 through June 1998, a broken recorder was not replaced for the , making it impossible to document readings during this time frame (FDA-483 Item # 15)
5. Lack of quality review of active pharmaceutical ingredient batch records to detect incomplete documentation (FDA-483 Item # 19)
6. Failure to perform testing of used to test the (FDA-483 Item # 20)
7. Hand written corrections made to batch records were not dated (FDA-483 Item #21)

In each of the examples noted above, your firm committed to retraining the necessary personnel. While this is part of the corrective action needed, the frequency that personnel had to be retrained on GMPs may represent inadequate attention to quality on the part of your managers and a failure of the Quality Control Unit to assure products are manufactured in accordance with CGMPs.

Computer Validation

The inspection found that the [ ] Computer System, used to add bulk quantities of solvents to the manufacturing processes (from a for drug substances has not been validated (FDA-483 Item # 16).

The response to FDA-483 Item # 16 is inadequate. Your firm's commitment is to revalidate the system "to add bulk quantities of solvent to the manufacturing processes for drug substances." The response fails to address how your firm intends to demonstrate that the [ ] Computer System will not allow the operator to add the "wrong" solvent to a particular batch. FDA expects validation data to support such issues.

The response to FDA-483 Item # 16 also states, "Until validation is complete an operator will check and record the quantity of bulk solvent that has been added to the manufacturing process". Please describe in detail, how the operator will be verifying the appropriate amount of solvent. In addition, will the operator be able to identify which solvent was added?

Please provide a copy, of the validation protocol for the [ ] Computer System. Upon completion of the validation, we would like a copy of the final validation report.

We recommend that you evaluate your facility on an overall basis for CGMP compliance. If you wish to continue to ship 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.

Supporting Documentation and Request for More Information

Please provide the following supporting documentation to your July 24, 1998 response. In any response to this Agency, copies of supporting documentation, such as SOPS, validation protocols etc., with translations in English, should be included with your response.

1. Please provide a copy of SOP , Pharmaceutical Dosage Form Stability, which was revised in response to FDA-483 Item # 3.

2. Please provide a copy of the validation protocol for the revalidation of the manufacturing process. The revalidation was part of your firm's corrective action in response to FDA-483 Item #6 & 7.

3. Please provide a copy of the validation protocol for the new [redacted] The revalidation, as part of your corrective action, will include the necessary samples, in response to FDA-483 Item # 9.

4. Please explain the reason for the delay in completion of the analytical method validation on residues detection. During the inspection, your personnel explained that a contract laboratory was working on the method. Your July 24, 1998 response, to FDA-483 Item # 10, indicates the validation will not be completed until October 31, 1998.

5. Please provide a copy of SOP # Laboratory Out-of Specification Results, which was revised in response to FDA-483 Item # 11.

6. Please explain what actions are being taken to assure that a failure in your quality systems personnel will detect errors in the Master Batch Record, as cited on FDA-483 Item # 18. Please describe what actions and improvements your firm has taken or plans to take to meet your commitment to evaluate the quality systems.

7. Please provide a copy of the revised Master Batch Record for which was revised, in response to FDA-483 Item # 19.

8. Please provide a copy of the method validation, which was being validated for in response to FDA-483 Item # 21.

Status of Company

During the inspection, your firm's management explained to Investigator Alicia Mozzachio that had taken over the pharmaceutical (Finished dosage form) operations. Please advise this office as to the status of that change and any effect

the change will have on pending or approved applications. Please include a list of pending or approved applications Poli Industria intends to maintain and any applications which were sold or transferred to In addition, please note that DMFs may also have to be updated to reflect these changes.

Please include any changes in management, and corporate structure diagrams.

The CGMP deviations identified above 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.

Please contact Compliance Officer Patricia L. Alcock at the numbers or address listed above, if you have any questions. Within your written response to this letter, detail corrective actions you plan to take or have taken to bring your operations into compliance. Please include a timetable of when each of the corrections will be completed and attach English translations of supporting documents.

Please reference **CFN# 9611868** within your written response.

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 ingredient or immediate release tablets.

Sincerely,

Joseph C Famulare

Joseph C. Famulare
Director
Division of Manufacturing and
Product Quality, HFD-320