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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Mid-Atlantic Region

Telephone (201) 331-2906

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

October 1, 1997

WARNING LETTER

Dr. David P. Jacobus
President
Jacobus Pharmaceutical Co., Inc.
37 Cleveland Lane, PO Box 5290
Princeton, New Jersey 08540

RELEASE
REVIEWED BY GM 10/9/97
DATE

File No.: 97-NWJ-52

Dear Dr. Jacobus:

During an inspection of your Manufacturing facility located at Schalks Crossing Road, Plainsboro, New Jersey 08536, between June 11-July 3, 1997, one of our investigators documented significant deviations from current Good Manufacturing Practices (cGMPs) in the manufacture of Active Pharmaceutical Ingredients (APIs) and finished pharmaceuticals.

The aforementioned inspection revealed that API products and finished pharmaceuticals manufactured and released at this facility are considered adulterated within the meaning of section 501(a) (2) (B) of the Federal Food, Drug & Cosmetic Act (the Act).

Although the GMP regulations under Title 21 Code of Federal Regulations, Parts 210 and 211, are used as guidelines in the API industry, Section 501 (a) (2) (B) of the Act requires that all drugs be manufactured, processed, packed, and held in accordance with cGMPs. No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals. Failure to comply with cGMPs constitutes a failure to comply with requirements of the Act.

Examples of deviations from cGMPs were outlined on the FDA-483, List of Inspectional Observations, issued to you at the Plainsboro facility at the close of the inspection. Deficiencies regarding Active Pharmaceutical Ingredients include, but are not limited to the following:

There was no validation plan in place for the Dapsone API or the Aminosalicyclic Acid API that identified or evaluated purification steps, processing equipment, critical processing parameters and operating ranges, drug substance characteristics, sampling and testing data to be collected, the number of processing runs needed to demonstrate consistency of the process, and what would constitute acceptable results.

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There were no written cleaning procedures along with the lack of cleaning validation for the precipitation kettle, used in the Dapsone bulk purification process.

A written stability program, which employed stability indicating and purity indicating test methods, had not been established to evaluate the chemical stability of the Dapsone API over its expiration or re-test period.

The specification for the crude Dapsone starting material allowed for up to [REDACTED] impurities. There was no data to show that the Dapsone purification process was capable of removing impurities at or near the [REDACTED] level. The [REDACTED] method used to evaluate impurities in the crude Dapsone starting material did not allow the actual impurity levels to be quantified.

Examples of deviations from cGMPs for finished pharmaceutical products are listed below. These include, but are not limited to:

No formal system existed to assure that changes in manufacturing processes were drafted, reviewed and approved by appropriate organizational units and reviewed and approved by the Quality unit. Examples of changes which were made without review and approval of the Quality unit include the following:

- 1) The addition of a [REDACTED] step in the manufacture of Paser granules was made after dissolution failures were exhibited by three consecutive batches of Paser granules. This manufacturing change was not evaluated to determine how it affected product quality or whether re-validation of the manufacturing process was required.
- 2) The batch size of Paser granules lot 10224 was reduced from [REDACTED] kg to [REDACTED] kg due to a shortage of active ingredient. This smaller batch size was not evaluated with respect to whether the change would affect critical processing steps and parameters and whether product quality would be acceptable throughout the shelf life.

Samples taken to demonstrate blend uniformity during the manufacture of Dapsone 25 mg Tablets were not of an appropriate size. The total tablet weight as shown on the batch record is 91.7 mg. Samples taken to demonstrate blend uniformity were 30 grams. Generally, an appropriate sample size would be 1 to 3 times the dosage weight.

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There was insufficient data to demonstrate that the purified water system was capable of providing water which consistently met chemical and microbiological specifications. Critical attributes of the system and sampling and testing schedules were not outlined; daily sampling after each phase of the system was never conducted; and there were no written sampling procedures. In addition, grooved, flexible piping was used to transfer purified water from the DI beds to the holding tank. There was no data to show that this piping could be adequately sanitized.

This Purified Water is used [REDACTED] and [REDACTED] step for Aminosaliclyic Acid. Since you lack validation of this purified water system, you have not demonstrated that this water is suitable for its intended use and this may adversely alter the quality of the Aminosaliclyic Acid.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practices. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

During the aforementioned inspection, our investigator noted that you limited corrective actions to specific observations outlined in a previous Warning Letter dated February 20, 1996. As evidenced by the observations listed on the July 3, 1997 FDA-483, deviations at your facility extend beyond those listed on the Warning Letter of February 20, 1996.

We are in receipt of your response dated July 10, 1997 and your proposed corrective actions will be confirmed during the next establishment inspection of your firm. However, we would like to schedule a meeting with you to be held at our district office to discuss how you plan to evaluate your entire facility and systems in order to prevent serious cGMP deficiencies from occurring in the future.

Please contact our office within three days of receipt of this letter to schedule a meeting. You should direct your call to Joseph F. McGinnis, Compliance Officer at (201) 331-2906. You should be prepared to bring documentation to the meeting which

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outlines the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations, and the time needed to complete the corrections.

Sincerely,



DOUGLAS I. ELLSWORTH
District Director
New Jersey District

CERTIFIED MAIL-
RETURN RECEIPT REQUESTED

JFM:np