



January 11, 2001

Chicago District
300 S. Riverside Plaza, Suite 550 South
Chicago, Illinois 60606
Telephone: 312-353-5863

WARNING LETTER
CHI-10-01

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Patrick Soon-Shiong, Ph.D.
Chairman and Chief Executive Officer
American Pharmaceutical Partners, Inc.
10866 Wilshire Blvd, Suite 1270
Los Angeles, CA 90024

Dear Dr. Soon-Shiong,

During an inspection of your pharmaceutical manufacturing facility, located at 2020 Ruby Street, Melrose Park, Illinois, conducted from November 1 through December 14, 2000, FDA Investigators Bruce McCullough, Alicia Mozzachio, and Jason Chancey documented significant deviations from Current Good Manufacturing Practices (cGMPs) for Finished Pharmaceutical Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211). These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). These deviations include, but are not limited to, the following:

Failure to have or to follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100]. For example:

- Vancomycin lot 100310, Vancomycin lot 100420, and Cisplatin lot 100501 were released for distribution even though they failed your firm's initial finished product release criteria for critical glass defects (e.g. loss of integrity).
- Procedure (01)05-07-112, "In-Process AQL Sampling for Filled and Capped Product," allows for visual inspection for critical defects of a lot to be conducted up to three times to obtain results which meet your firm's specifications for release.

FDA reminds you that similar deviations regarding release of product with the possibility of critical glass defects were noted in Warning Letter CHI-12-00, dated February 7, 2000, issued by Chicago District to your firm following the previous inspection of this facility.

- Heparin Sodium Injection USP, lot 100838, was released for distribution prior to identifying and conducting a safety evaluation of the unknown impurity detected in the benzyl alcohol raw material lot used in this formulation.

Failure to establish and follow procedures designed to prevent objectionable microorganisms in drug products purporting to be sterile [21 CFR 211.113]. For example:

- Growth promotion testing performed on media fill vials does not include evidence the media is capable of detecting environmental isolates found in class 100 filling areas. For example, mold organisms are not used to challenge media, even though mold isolates have been identified in filling room 1.
- There is no assurance media fills represent the worse case filling conditions. For example, the lyophilization step for media fills does not include pulling and releasing a partial vacuum to simulate production steps.
- Airborne bioburden sampling of class 100 filling areas does not assure that results obtained reflect environmental conditions present during routine manufacture. For example, our investigators cited several examples of months where approximately [REDACTED] of the airborne bioburden samples collected were taken with no operators in the class 100 filling area. Also, only [REDACTED] cubic meters of air are taken for each airborne bioburden sample in class 100 filling areas and adjacent class 10,000 areas.
- FDA Investigators observed several leaks in the WFI system, including the following locations:
 - pipes leading into the main WFI storage tank
 - clean steam return line
 - formulation water return line
 - main storage tank recirculation line leading to the tank's sprayballs
 - mix loop return line
 - rinse loop #1 return line
- No microbiological testing was conducted of the clean steam points of use supplying lyophilizers [REDACTED] and [REDACTED] for extended periods in several quarters of [REDACTED] ([REDACTED] weeks/[REDACTED] weeks for lyophilizer [REDACTED] and [REDACTED] weeks/[REDACTED] weeks for lyophilizer [REDACTED]). In addition, your SOP (01)10-01-0004 is deficient in that it allows clean steam samples at the lyophilizer to be sampled "as the production schedule allows."
- On 11/27/00, FDA investigators observed an operator extend his arm over open, empty vials on the accumulating table under HEPA filters in the class 100 area during filling of Protamine Sulfate, lot 101010.

Failure of the quality control unit to assure that all unexplained discrepancies or failures of batches to meet specifications are thoroughly investigated and that the records of the investigations are complete, including conclusions and follow-ups [21 CFR 211.192]. For example:

- There is no assurance that all lots of released finished product manufactured with the suspect lots of 100 mL [REDACTED] vials [including control #91788 [REDACTED], 00594 [REDACTED], and 00497W] are free from critical glass defects, including loss of integrity. [REDACTED] investigation determined the cracked vials in these lots to be due to defective vial mold cavities specific to each lot. During the inspection, FDA investigators determined that your firm released approximately [REDACTED] other lots of finished products that were manufactured with the suspect lots of 100 mL vials. Your investigation reports only state that inspection results were reviewed for these [REDACTED] lots and none reached the action limit for glass defects. FDA has concerns regarding the vial integrity of products released to market that used the suspect lots of [REDACTED] vials, since the vial defects were related to specific mold numbers. We are concerned your inspection process is not capable of detecting this mold-specific defect. Please address this concern in your written response.

The above list of violations, as well as the Form FDA-483, issued to Dr. Rajesh Kapoor, Vice President, Quality Assurance/Quality Control, is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure that all of your firm's products are in compliance with the requirements of the Act and its implementing regulations. Federal agencies are advised of the issuance of all Warning Letters so that they may take this information into consideration when considering the award of contracts. A copy of the Form FDA-483, List of Observations, is attached.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action without further notice, such as seizure and/or injunction.

Please notify this office, in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations and prevent the recurrence of similar violations. If corrective action cannot be completed within 15 days, state the

reason for the delay and the time within which the corrections will be completed. Your response should be directed to the attention of Richard Harrison, Compliance Director, Chicago District Office.

Sincerely,

\s\
Raymond V. Mlecko
District Director

Enclosure

cc: Rajesh Kapoor, Ph.D.
Vice-President, QA/QC
American Pharmaceutical Partners, Inc.
2020 Ruby Street
Melrose Park, IL 60160