



9/19/01

October 12, 2001

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

WARNING LETTER
CHI-2-02

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

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

Dear Dr. Soon-Shiong:

An inspection of your pharmaceutical manufacturing facility located at 2020 Ruby Street, Melrose Park, IL, was conducted from July 12 through August 16, 2001, by investigators David Perkins and Yvonne Lozanno. During the inspection, the investigators documented significant deviations from Current Good Manufacturing Practice (cGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (21 CFR), Parts 210 and 211. These deviations cause your firm's pharmaceutical products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) in that the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding are not in conformance with cGMP regulations. We acknowledge receipt of Dr. Rajesh Kapoor's written response to the FDA 483, Inspectional Observations, dated September 7, 2001, that was issued to Dr. Kapoor at the conclusion of the inspection.

These deviations include, but are not limited to the following:

Failure to thoroughly investigate unexplained discrepancies [21 CFR 211.192 and 211.165]. For example:

- a. Investigation Report 01-060 for testing on 6/9/01 records that Doxorubicin Hydrochloride Injection, USP, lot 0199014B, was out of specification and lots 190866 and 190879 were out of trend. However, an improper correction in determining the results lowered the actual reported values. Without the improper correction, all lots would have been out of specification. Without the improper correction, the results for lots 0199014B upright, 0199014B inverted, 190886, and 190879 should have been [REDACTED] [REDACTED] [REDACTED] and [REDACTED] respectively, thus making them all out of specification.

In the response to the FDA 483, Dr. Kapoor acknowledges that the correction was improper but claims that the correction was inadvertent. However, the investigators reported that the laboratory notebooks and chromatograms they reviewed show that when the analyst first calculated the test results, there were no peaks observed in the placebo injection and no correction was made. The initial results reviewed by our investigators showed that the results were out of specification. The investigators report that the documentation clearly shows that the analyst manually integrated the valley of the solvent from the placebo injection.

Dr. Kapoor also indicated that the root cause of the OOS results was precipitation of the active pharmaceutical ingredient in the sample solution. He indicated that the problem is with the test method and not with the product. Should the problem indeed be with the test method, please discuss how APP can rely on any of the test results using this test method.

- b. Out of specification and reported out of trend results for impurities obtained in stability testing three lots of Doxorubicin Hydrochloride Injection, USP, were voided based on the investigations concluding that the approved sample preparation resulted in precipitation of the sample. Lot 0199014B was tested at the 24-month station three separate times with data being rejected each time: first as documented in investigation 01-029, then due to system suitability failure, and then again as documented in investigation 01-060. Lots 190879 and 190866 were tested at the 18-month station with the data being rejected as documented in investigation 01-060.
- c. Folic Acid Injection, USP, lot 110383, was tested a total of five times for benzyl alcohol determination prior to acceptable results being obtained. The lot was out of trend from the target specification of [REDACTED] three times and was out of specification from the finished product specification of [REDACTED] once. Data from two of the test runs were voided due to HPLC system problems, however a review of the chromatograms showed that system suitability was maintained throughout the run.
- d. Out of specification results for finished product and stability testing of impurities obtained in testing four lots of Fluorouracil Injection, USP, were voided based on investigations concluding that the HPLC columns used in testing were contaminated due to improper storage. Lots 100710, 100676, and 100724 were OOS on 10/6/00, at finished product testing with data being rejected as documented in investigation 00-356. Lot 190297 was tested at the 18-month station on 10/21/00, with data being rejected as documented in investigation 00-362. Lot 100970 was OOS on 12/4/00, at finished product testing with data being rejected as documented in investigation 00-372. All out of specifications were overcome with retesting using new sample and standard preparations.

- e. An investigation was not initiated for voiding a finished product and stability test run for five lots of Fluorouracil Injection, USP. Fluorouracil finished product lots 110544, 110572, and 110557, and stability lots 110243 and 101082 were tested on 6/19/01. However, this run was voided due to system problems with odd peak shapes. A review of the chromatograms showed that system suitability was met and maintained throughout the run. Sample results were not quantitated and there was no investigation initiated. New standards and samples were prepared for testing.

In his response, Dr. Kapoor states that the data was voided due to “split peaks” caused due to some kind of HPLC system error. Investigator Perkins reviewed the chromatograms of the high concentration samples and he observed that the “split peaks” was an unresolved, unknown peak coeluting with the active pharmaceutical ingredient. Investigator Perkin’s observation is supported in that no injections of the primary reference standards exhibited any sort of peak splitting.

- f. Out of specification investigations do not always extend to other lots associated with the specific failure or discrepancy. For example:

Investigation report 01-030 for an out of specification in-process assay of Folic Acid, lot 110383, concluded that the original and second analysts failed to correct for standard potency as listed on the folic acid, USP, reference standard. The investigation failed to evaluate if any other lots were tested using standards that were not corrected for potency.

The above identification of violations and the Form FDA 483 issued at the conclusion of the inspection are 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 cGMPs. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. This includes seizure and/or injunction. A copy of the Form FDA 483 is enclosed.

You should notify this office in writing within 15 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 working days, state

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the reason for the delay and the timeframe within which corrections will be completed. Your reply should be sent to the attention of George F. Bailey, Compliance Officer, at the above listed address.

\s\
Sincerely,

Raymond V. Mlecko
District Director

Enclosure: Form FDA 483 dated 7/12-8/16/01

cc: Rajesh Kapoor, Ph.D, Vice President
Quality Assurance/Quality Control
American Pharmaceutical Partners, Inc.,
2020 Ruby Street
Melrose Park, IL 60160