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February 7, 2000

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

WARNING LETTER  
CHI-12-00

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

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

Dear Dr. Soon-Shiong:

During an inspection of your pharmaceutical manufacturing facility, located at 2020 Ruby Street, Melrose Park, Illinois, conducted from November 16 through January 11, 2000, Investigators Susan Bruederle and Alicia Mozzachio documented significant deviations from Current Good Manufacturing Practice (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). The 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:

The procedures used to make Adenoscan (Adenosine Injection) do not assure the final product is consistently free of critical defects. The process validation final report identifies the source of glass chips in filled vials as the vial washing process. This washing process was not changed to prevent the chipping of vials. The process validation study was approved on 6/14/99, and additional lots of Adenoscan have been made using the same processing step. In fact, Adenoscan, Lot 190677, was released for distribution on 11/4/99, although it exceeded the action limit for total defects. The defects were identified as glass chips and were, again, attributed to the washing process. We note that your firm classifies glass chips in vials as critical defects, which are defined as defects "likely to result in hazardous or unsafe conditions for the individual using the product."

Reddish-brown particulate matter has been a recurring problem with Calcium Gluconate since March 1998. The cause of this particulate matter problem has not been determined. However, 14 lots of Calcium Gluconate, exhibiting this defect at a level exceeding the established action limit for defects, have been released since that time.

None of the autoclave cycles used to terminally sterilize the 11 lots of Adenoscan (Adenosine Injection) made in 1999, met all "Critical Release Criteria" specified in the master production and control record for Adenoscan or in NDA 20-059.

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:

The shortened terminal sterilization warm-up times used for the 11 lots of Adenoscan were found acceptable based on investigations detailed in Incident Reports. However, five of the Incident Reports refer to and use data from the wrong qualification study to justify the acceptance of the cycles. These discrepancies were not noted or investigated by the quality control unit.

The written investigation [#032-99I] of the OAL (over-action-limit) non-viable particle counts in Fill Room 1 does not include justification for releasing lots 190365, 190362, 190374, 190383 and 190389. These lots were aseptically filled on the ■ Filler, which the investigation report identifies as the source of the high particle counts. Four other lots made on the same equipment during the same time period were rejected. In addition, four of the lots were released for distribution before the investigation was completed on 7/12/99. For example, Lot 190389 was released for distribution on 6/4/99; Lot 19383 was released on 6/2/99; Lot 190374 was released on 6/1/99; and Lot 190365 was released on 5/25/99.

Adenoscan, Lot 190677, was released for distribution on 11/4/99, although this lot exceeded the action limit for total defective units. The report of the investigation of this failure, Incident Report 99-306, concludes there is no impact on the lot because the GII level AQL (acceptable quality level) sample was within specifications. However, the raw data shows that the first GII Level AQL inspection failed because glass chips were found in the sample. This first failure is not discussed in the report of the investigation.

Some investigations of incidents and out-of-specification test results are not completed and reported in a timely manner. For example: Incident Report 99-186 was written on 11/24/99, although it describes an HVAC equipment failure that occurred on 7/6/99; Incident Report 99-107 was written and reviewed on 11/24/99, although it describes a pressure reversal in the aseptic area that occurred on 4/5/99; and the investigation into the green dye test failure of Haloperidol Decanoate stability lot 180056 was initiated on 6/18/98, but not completed until 9/28/98.

Laboratory investigations of out-of-specification test results do not consistently include detailed information regarding the conduct of the investigation. Additionally, conclusions of investigations are not always justified.

There is no documentation of the source of additional samples tested as a result of out-of-specification investigations.

Failure of the quality control unit to assure that the procedures and specifications assure the identity, strength, quality, and purity of the drug products [21 CFR 211.22]. For example:

There is no quality system in place to assure that corrective actions recommended as the result of investigations or validation studies are accomplished in a timely manner.

A Document Change Request submitted for SOP (01) 05-03-0004 entitled *Cleaning of Tanks, Carboys and Equipment Used in Preparation and Filling Department*, was reviewed and approved by senior management on 9/15/99, without scientific justification for all changes.

Discrepancies between raw data and statements in reports are not always noted or investigated by the quality control unit during their review of the documents.

The following written procedures were approved by the quality control unit although they contain several errors: 10-11-00-0006, *Field Alert Report*; (01)10-01-0004, *Microbiological Testing of Water*; 10-08-00-0003, *Treatment and Handling of Analytical Test Results*.

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

On 11/24/99, the investigators observed standing water on the covers of trays containing sterile stoppers during the filling of Vancomycin, Lot 190931, on Line 2. A tray with drops of water still on the cover was moved into the Class 100 area and held directly above the hopper containing sterile stoppers.

There is no established procedure or written test method for conducting smoke pattern testing of the HVAC systems. There is no written document that defines terms, establishes acceptance criteria, or describes how the tests should be done, recorded and reviewed. The smoke pattern tests reviewed during this inspection were not completely described and/or documented. Employees have not received training on how to do airflow pattern tests.

As of 12/15/99, there was no written procedure that described the specifications for and the replacement of the plastic curtains that separate Class 100 areas in Class 10,000 rooms. In addition, the replacement of the curtains is not documented in any log or work order.

Tests are not routinely done to determine if rooms/areas in the aseptic core meet air classification requirements of Fed. Std 209E. For example, the last time the Class 100 area in Fill Room 1 was tested to assure the area complied with Fed. Std. 209E was in 1994.

Failure to assure that the components used in the production of drug products are withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit [21 CFR 211.84].

For example, the following components were used in finished product before testing was completed: Doxorubicin Hydrochloride, USP, Receiving Lots 91620 and 180315; Edetate Disodium, USP, Receiving Lot 91255; and Chlorobutanol NF (anhydrous), Receiving Lot 81732.

The investigators also reported that samples of Water For Injection (WFI) are not taken from the same tubing that is used to feed the water from the WFI loop to the compounding tanks. According to SOP (01)10-01-0004, *Microbiological Testing of Water*, dated 6/30/99, some drops in the WFI distribution system are sampled and tested for microbial content and endotoxin levels quarterly (■ times a year).

The above list of violations, as well as the Form FDA 483, List of Observations, issued at the conclusion of the inspection to Mr. Mitchell Clark, Vice President, Regulatory Affairs, is not intended to be an all-inclusive list of deficiencies at your facility. It is your

responsibility to assure adherence with the requirements of current Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters so that they may take this information into account 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 and to establish procedures to prevent their recurrence. Failure to promptly correct these violations may result in regulatory action without further notice, such as seizure and/or injunction.

We acknowledge that since the completion of the inspection, your firm has indicated that it will recall all lots of Adenoscan. We commend you for that action. With regards to the status of those lots of Calcium Gluconate discussed in Item #5 of the FDA- 483, please comment on the fact that your firm released several lots even though these lots contain particulates in excess of your firm's █% action level. An investigation revealed these particulates to include acrylate and silicone oil. As of the conclusion of the inspection, APP had not determined the cause of this problem, nor had your firm identified the size of the particulates or the hazard status of the silicone particulates found. Please submit any additional information you have on this issue.

Your firm had two true sterility test positives in 1999, that is, two lots aseptically processed in your facility were found to be non-sterile. Lots R199-005 and 190902 were not distributed, but the investigations into the processing failures did not identify causes of the contamination. According to the investigation reports, no corrective actions were taken. Please comment on what has been done to assure there is no recurrence and what was done to determine that other drug products made under the same conditions are acceptable.

The final approved copy of Incident Report 99-107, which is referred to by FDA-483 Observation #7, was provided to the investigators on 12/13/99. The Report describes a reversal of air pressure between the storage area in the aseptic core and Fill Room 1 that occurred on 4/5/99. A statement added to the final version of the report says there was no product impact because nothing was filled in Room 1 on 4/5/99. However, other records collected by the investigators during the inspection show that Calcium Gluconate Injection, Lot 190263, was filled in Room 1 on 4/5/99 from 6:18 am until 5:40 pm. Please explain this discrepancy and comment on the status of Lot 190263.

Please notify this office, in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

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Your reply should be directed to the attention of George F. Bailey, Compliance Officer.

Sincerely,

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Raymond V. Mlecko  
District Director