DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Chicago District
550 West Jackson Blvd., 15th Floor
Chicago, Illinois 60661
Telephone: 312-353-5863

December 18, 2006

WARNING LETTER
CHI-3-07

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Patrick Soon-Shiong, M.D.
Chairman of the Board and Chief Executive Officer
Abraxis Bioscience, Inc.
11777 San Vincente Blvd, Suite 550
Los Angeles, CA 90049

Dear Dr. Soon-Shiong:

An inspection of Abraxis Pharmaceutical Products (APP), 2020 Ruby Street, Melrose Park, IL, was conducted from May 16 through June 29, 2006. FDA investigators documented significant deviations from current Good Manufacturing Practice (cGMP) Regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211, with regard to the production of pharmaceutical products by this facility. These cGMP deviations were listed on an Inspectional Observations (Form FDA-483) form issued to and discussed with John F. Harmon, Executive Vice President, Global Operations. A copy of the Form FDA 483 is enclosed. These cGMP 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) [21 U.S.C. § 351(a)(2)(B)]

We also have completed review of your August 2, 2006 response to the Form FDA-483 observations. As noted in the individual citations below, the cGMP deficiencies need more timely and comprehensive corrections than the actions you have proposed or taken.

cGMP Charges

1) Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and failure to validate sterilization processes as required by 21 CFR 211.113 (b).

a) You have not conducted bacterial filtration retention validation for all of your aseptically filled products. We note in your response that you have established a [redacted] plan to complete such validation for all products by the fourth quarter of 2008. Please indicate if you intend to ship any product that has been manufactured without a validated sterilization process. If so, then please identify the product and provide your justification for releasing such product.

b) During the inspection, the investigators observed that not all items brought into the Class 100 areas of the aseptic processing lines during filling of a batch are sanitized prior to entry into the area. The investigators observed employees take stainless steel trays containing stoppers from the Class 10,000 areas of fill rooms into the Class 100 areas of the fill line. The surfaces of the trays, which may be wet during storage in the Class 10,000 area, were not sanitized before being brought into the Class 100 areas. The operators were observed placing the trays directly over the open hoppers containing sterile stoppers. Also, the stopper hopper is not a site selected for environmental monitoring.

2) Failure to thoroughly investigate or maintain a written record of the investigation of any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has been distributed, and the failure to extend the investigation to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy as required by 21 CFR 211.192.

Examples of your failure to conduct adequate investigations, and notably, to properly extend failure investigations to all associated batches or product are discussed below:

a) Investigations of two positive sterility tests did not determine conclusive or probable root causes for the contamination. Although root causes were not determined, both investigations conclude that "the impact of the sterility test positive was isolated to the affected batch" and all other batches placed on hold when the test failures were found were released for distribution. However, significant errors that impact directly on the determination of the potential scope of the sterility assurance problem were noted with each investigation as follows:

i) Chorionic Gonadotropin for Injection, USP, Lot [redacted] (This lot was aseptically filled on December 17, 2005, on line #2, only 12 days after production of commercial lots began following a 4 month shutdown as a result of a number of media fill failures.) The contaminating organism was identified as *Propionibacterium acnes*, which is described as part of the indigenous human epidermal and dermal flora which was tested and found to be an obligate anaerobic microorganism. The "Product Impact Reassessment" report dated January 16, 2006, which was prepared as a result of the investigation, stated that no microbial growth was recovered from personnel monitoring performed during manufacture of the lot. However, the inspection disclosed that only aerobic testing was performed on personnel at that time and our investigators were told that anaerobic monitoring of personnel has never been performed by APP. In addition,

another statement in the Product Impact Reassessment incorrectly states, "Fill Line 2 does not process oxygen sensitive products, thus all lots manufactured on Line 2 do not have an anaerobic environment present in the filled and sealed vial." This lot was produced with a nitrogen bleed in the lyophilization chamber, thereby creating an anaerobic environment in the sealed vial. These errors, which significantly affect the potential scope of lots impacted by the sterility failure, were not detected by those reviewing and approving the final report, which included a quality control unit representative.

ii) Progesterone Injection, USP, Lot [redacted] The lot was aseptically filled on Line 4 on April 26, 2006. The contaminating organism was identified as *Bacillus pumilus,* which is one of the primary microbiological contaminants identified in the multiple media fill failures investigated under [redacted] The investigation of this sterility failure fails to mention this correlation and does not discuss the impact of a new adverse trend with regard to the detection of this problematic organism. The organism was detected nine times in 2006, and seven of the nine samples were in the same month of manufacture as the failed lot, including a viable air sample in the aseptic core of an adjacent filling line the day after the manufacture of this batch. The investigation also incorrectly associates this sample result with the detection of the same organism in a media preparation hood for a different sample. These deficiencies in the investigation, which also have a bearing on the scope of lots potentially implicated by the sterility failure, were not detected by those reviewing and approving the final report.

In your response to the Form FDA 483 you do not acknowledge any deficiencies in the investigation of these sterility test failures, and you provide no additional information to support the conclusion, which was based on inaccurate and/or insufficient data, that the contamination which led to the product failures was isolated to the two lots. In rare instances, especially without an identified root cause, it is acceptable to deem sterility failures of aseptically filled product an "isolated event." However, in light of the significant problems you encountered with the control of the Melrose Park facility in 2005 as well as the significant CGMP deviations documented during the current inspection, our confidence in your investigative conclusion for the sterility failures noted above is further weakened. These deviations, individually, decrease the level of sterility assurance for aseptically-filled product, and collectively, raise significant concern with sterility assurance level of products that were produced under these conditions.

While we acknowledge that you are taking steps to address many of these deficiencies, please provide your rationale for the distribution of products potentially implicated by the lack of control, the sterility failures, and the significant cGMP deficiencies.

b) The corrective actions implemented after contaminated vials were found in two media fills performed in October 2005 did not extend to similar high risk manipulations involving the handling of partially stoppered vials. The investigation report "[redacted] dated November 16, 2005, indicates that partially-stoppered vials may have been contaminated during interventions. As a result, some SOPs that describe the handling of partially-stoppered vials were revised; however, additional SOPs were not also updated to address the handling of these at-risk vials during other interventions and routine operations that require the manual movement of partially stoppered vials.

Your response recognizes the need to control interventions and commits to evaluating all interventions that affect partially stoppered vials; however, this was not going to be completed until November 2006 and any changes in SOPs will not be implemented until February 2007. These actions should have been taken by your firm in 2005 as a result of the investigation into the positive media fill vials. Please provide your rationale regarding why the SOPs will not be implemented until 2007.

c) On June 1, 2006 the investigators identified a vial with an improperly seated stopper traversing an uncontrolled environment prior to capping, where the stopper was then fully seated. This sequence of events presents a potential product contamination issue. When this unit was identified on-line by the investigators, an operator removed the suspect vial from the line. However, an investigation into this deviation was not initiated and no immediate action was taken to assure that additional vials produced on this line were not exposed to this unacceptable condition. Our investigators observed this problem again with multiple vials in a brief period of time on line 5 on June 26, 2006. Your response to the Form FDA 483 acknowledges the need to assure proper stopper placement and environmental protection throughout the manufacturing process, yet you do not address why you failed to take appropriate action at the time of this incident to assess the scope of the problem and implement appropriate corrective action to prevent recurrence of this potential contamination issue.

3) Failure to establish an adequate air supply that is filtered through high-efficiency particulate air filter filters under positive pressure, regardless of whether flow is laminar or non-laminar as required by 21 CFR 211.42(c)(10)(iii).

For example,

a) The testing of HEPA filters in the Aseptic Core during the Winter 2006 (January 2006) shutdown, found widespread HEPA filters failures in the Class 100 areas. Leaks requiring patching or replacement were found in 75% to 100% of the HEPA filters in Fill Rooms 1, 2, 4 and 5.

The HEPA filters used in these areas are rated for an efficacy of 99.99% for particles greater than 0.3 microns at a face velocity of 90 FPM, but much higher face velocities (from [redacted] to [redacted] FPM) are used in some of the aseptic filling rooms. A study conducted for you by [redacted], as part of the investigation concluded that excessive non site specific penetration (ENSSP) of HEPA filters can result when filters are used at velocities for which they are not designed. The study documents a direct correlation between air flow rate and unacceptable ENSSP. Please provide your rationale for continuing to operate the aseptic filling lines at these excessive velocities until replacing them with proper filters during your planned shut down in August 2006.

b) Air flow pattern testing done to demonstrate unidirectional airflow in the critical areas of the five aseptic fill lines are not done under simulated operating conditions with operators present performing routine and non-routine aseptic manipulations, such as: adding vials to the line; adding stoppers to the hopper while in the Class 100 area; removing vials from the line for weight checks while in the Class 100 area; removing fallen or defective vials while in the Class 100 area; or moving HEPA transfer carts fully into the Class 100 areas (Lines 2 and 6 only).

Your response to the FDA 483 indicates that you intended to conduct some additional air flow testing in August 2006; however, you did not commit to conducting enhanced air flow pattern studies (to include the activities identified above) in the Class 100 area until December 2006. Please provide the results for the testing that occurred in August, and any corrective actions resulting from the testing. Please provide the timeframe for the review and assessment of the studies occurring in December.

4) Equipment for adequate control over micro-organisms is not provided when appropriate for the manufacture, processing, packing or holding of a drug product as required by 21 CFR 211.46 (b).

The inspection disclosed that for Filling Lines 1, 4 and 5, stoppered vials exit the aseptic processing rooms and enter the capping lines, which are located in unclassified rooms. Improperly stoppered vials are exposed to the uncontrolled environment prior to capping and crimping, since the clear plastic tunnels over the line only extend from the exit of the filling room to about 6 inches before the capping and crimping machine. In addition, the investigators observed that the tunnels are opened by operators multiple times during the capping process.

a) On June 1, 2006, while watching the aseptic filling and capping of Lot [redacted] of Protamine Sulfate Injection on Line 5, they observed a vial with a stopper that was not fully seated into the neck of the vial leave the aseptic filling environment and enter the capping line. The sides of the stopper were exposed to the room environment as it entered the capping machine. They mentioned this to the operator who stopped the line and rejected the vial before it could be capped.

b) On June 27, 2006, the investigators observed 3 vials of Haloperidol Injection, Lot [redacted] with improperly seated stoppers enter the capping area on Line 5 in 10 minutes. The stopper on one of the vials was blown entirely off the vial as it entered the capping area and this vial was rejected by the on-line vision system. Another vial with an improperly seated stopper successfully passed through the on-line vision system and was capped. A third vial with an improperly seated stopper successfully passed through the on-line vision system toward the capping machine. The investigators mentioned this to the operator who stopped the line and rejected this vial before it could be capped.

Your response to the Form FDA 483 acknowledges the need to assure proper stopper placement and environmental protection throughout the manufacturing process; however, it states that a corrective action (raised stopper detector) will not be implemented until November 2006. Please provide details on any interim measure that was implemented to assure that stoppers were properly placed and that appropriate environmental conditions were maintained prior to this corrective action and confirm that the promised corrective action was, in fact, implemented and effective.

5) Failure to have an adequate system for monitoring environmental conditions in an aseptic processing area as required by 21 CFR 211.42(c)(10)(iv).

There is no documented explanation or justification for the selection of the surfaces defined in SOP [redacted] Monitoring of Surfaces," dated May 23, 2006, as "Class 100 Critical Sites." The four sites described as critical are surfaces on the in-feed turntable, two equipment platforms and the conveyor motor cover. The critical sites listed in the SOP do not include any surfaces that come in direct contact with the sterile product or sterile components.

Your response indicates that you will continue to monitor the same sites until at least February 2007, and makes no commitment to monitor equipment surfaces that come in direct contact with the sterile product or sterile components.

New Drug and Misbranding Charges

Based on the information your firm submitted to FDA's Drug Registration and Listing System (DRLS) as required by Section 510 of the FDCA [21 U.S.C. § 310], as well as a list of currently marketed drug products that your firm provided to FDA, you market calcium chloride, levothyroxine sodium, and vasopressin. These injectable products are drugs within the meaning of Section 201(g) of the Federal Food, Drug and Cosmetic Act (FDCA) [21 U.S.C. § 321(g)], because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. Further they are new drugs within the meaning of Section 201(p) of the FDCA [21 U.S.C. § 321(p)], because they are not generally recognized as safe and effective for their labeled uses. Under Section 301(d) and Section 505(a) of the FDCA [21 U.S.C. § § 331(d) and 355(a)], a new drug may not be introduced into or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for the drug. Based on our information, you do not have any FDA-approved applications on file for these drug products.

In addition, these drugs are misbranded. Adequate directions cannot be written for these prescription drugs so that a layman can use them safely for their intended uses. Consequently, their labeling fails to bear adequate directions as required under Section 502 (f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] and, lacking required approved applications, they are not exempt from this requirement under 21 CFR 201.115.

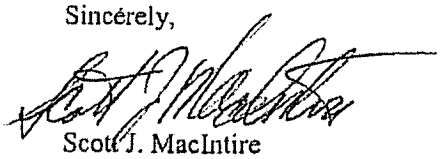
Neither this letter nor the observations noted on the Form FDA 483 are intended to be an all-inclusive list of the deficiencies that may exist at your facilities or your firm's drugs that are marketed in violation of the drug approval requirements. It is your responsibility to ensure that your operations and each of the drug products that you manufacture are in full compliance with all applicable requirements of the Act and the implementing regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations, and you should establish procedures whereby such violations do not recur. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction. Until FDA can confirm correction of the deficiencies observed during the most recent inspection, this office can recommend disapproval of any new applications listing this site as a manufacturer of drugs.

We request that you reply in writing within 15 working days of receipt of this letter, stating the action that you will take to correct the noted violations and ensure that corrections will be put in place. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed.

Your response should be directed to the attention of Compliance Officer George F. Bailey at the address listed above. If you have any questions regarding any issue in this letter, please contact Mr. Bailey at (312) 353-5863.

Sincerely,



Scott J. MacIntire
District Director

Enclosure: Form FDA 483 copy

cc: John Francis Harmon
Executive Vice President Global Operations
Abraxis Pharmaceutical Partners, Inc.
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