DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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

March 29, 2007

WARNING LETTER
CHI-4-07

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Arthur S. Przybyl
President and CEO
Akorn, Incorporated
2500 Millbrook Drive
Buffalo Grove, IL 60089

Dear Mr. Przybyl:

An inspection of Akorn, Inc., 1222 West Grand Avenue, Decatur, IL, was conducted from September 12 through September 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) issued to and discussed with Mark M. Silverberg, Senior Vice-President, Global Quality Assurance/Regulatory Compliance. 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 have completed review of Mr. Silverberg's October 13, 2006 response to the Form FDA-483 observations. Our comments on the deviations revealed during the inspection and Mr. Silverberg's response letter are discussed below.

I. Failure to establish and follow adequate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211.113(b)]. For example:

a. Smoke studies conducted by your firm in filling rooms "P," "D," "C" and "K" do not fully demonstrate air flow movement away from work surfaces during representative personnel activities and manual simulations of the aseptic processes as is required by your SOP [redacted]' Your FDA-483 response does not address this issue and does not offer any corrective action.

b. Your firm's Protocol # [redacted] is intended to generate information that, "..[redacted]" through monitoring of the grid system. The summary report from this protocol documents that non-viable particle measurements within the ISO 5 (Class 100) aseptic fill areas under static conditions (i.e., at rest conditions) are within the established [redacted] for particles [redacted] in size specification.

However, the report fails to include data to document the non-viable particle measurements under real-time dynamic conditions demonstrate that the grid system identifies critical zones / areas within the ISO 5 area. We acknowledge your firm's commitment in the FDA-483 response to conduct studies to evaluate all class 100 grid locations for criticality by the end of 2006. However, we have not received any documentation to confirm completion of this corrective action.

II. Failure to conduct and document a thorough investigation of any unexplained discrepancy or failure of a drug product batch to meet its specifications or to extend the investigation to other batches that may been associated with the specific failure or discrepancy [21 CFR 211.192]. For example:

a. The investigations conducted by your firm since 2004 into the origin and nature of visible precipitate, which you now have identified as [redacted] in the firm's AK-Flour (Fluorescein Injection) products and into numerous illness/injury complaints for the products are inadequate since no attempt has been made to determine whether there is any correlation between the lots displaying this product defect and the complaints. Although your firm documented that adverse reactions to the drug substance itself are not unusual in this product, the question of a possible connection between the illnesses and injuries reported and the precipitate still needs to be addressed, either to confirm such a connection or to rule it out. Although the corrective action outlined in your firm's October 13, 2006 response to the FDA-483 and in other correspondence to the district office, the addition of instructions that the products be administered through a sterile syringe filter, is a positive step, this is not an acceptable permanent solution to the [redacted] problem and does not address the root causes of the defect.

b. Your firm failed to follow its own SOP [redacted] dated January 9, 2006, which requires that complaints similar in nature should be globally investigated to determine the root cause and that after completion of the global investigation subsequent investigations of similar complaints should reference the global investigation. None of the [redacted] AK-flour complaints received since the last FDA inspection in 2005, including [redacted] that have occurred since the effective date of the SOP, referenced the 2004 Global investigation of AK-Flour. The assertion made in your FDA-483 response that the subsequent complaints were not subject to the SOP because they were not similar in nature lacks credibility. [redacted] of the [redacted] complaints were for the same product codes that were the subject of the complaints leading to the 2004 Global Investigation and most of these involved illness and injury, as did the 2004 complaints.

c. Timeframes for investigations are not met and investigation extension requests are not approved as required by your firm's written procedures. For example:

(1) SOP [redacted] requires that OOS investigations are completed within 30 days or an Investigation Extension Request approval be obtained. [redacted] of the [redacted] OOS investigations which have been initiated since August 1, 2005 were not completed within 30 days and did not obtain Investigation Extension Request approval.

(2) SOP [redacted] requires that deviation from a standard procedure be documented. [redacted] of the [redacted] OOS investigations that did not meet the timeframes established in [redacted] did not have a deviation report initiated and completed per the timeframes established in [redacted]

We note that failure to follow written procedures pertaining to investigation follow-up and completion of corrective actions within specified timeframes is a repeat observation from our November 8-19, 2004 inspection of your firm.

III. There is a failure of the equipment used in the manufacture, processing, packing or holding of drug products to be of appropriate design, of adequate size, and suitably located to facilitate operations for its intended use [21 CFR 211.63]. For example:

The aseptic filling lines have multiple non-viable particulate monitoring devices located within the ISO 5 aseptic filling area. The inspection revealed that not all of the non-viable particulate monitoring probes are positioned or located within the ISO 5 area to obtain a measurement within close proximity to the filling zone and exposed product. For example, the non-viable measurement probes are located approximately:

(1) [redacted] from the ophthalmic filling area for fill line "P";
(2) [redacted] from the vial filling area for fill line "K"; and,
(3) [redacted] rom the Cozzoli vial filling area for fill line "D."

In the FDA-483 response addressing this observation, Mr. Silverberg states that Akorn feels that while some of the subject probes are not physically within [redacted] of the open containers, there is greater potential for these probe locations to experience higher counts in their current locations due to their proximity to areas of greater movement. During the inspection, our investigator asked why the laser particle counter (LPC) units were placed from [redacted] away from the critical aseptic fill zone. He was told that the general shape and size of the LPC units and the position of the attached monitoring tubing present some limitations with regard to the placement of the LPC units. While the optimal positions for monitoring may not necessarily be within [redacted] of the aseptic fill zone, the size and shape of the monitoring equipment should not be the deciding factor in selecting these locations.

IV. Failure to establish written procedures for the cleaning and maintenance of equipment used in the manufacturing, processing, packing or holding of drug product [21 CFR 211.67(b)]. For example:

Until September 15, 2006, there had been no preventive maintenance schedules established for approximately [redacted] of [redacted] stability chambers/incubators/cabinets [redacted] of the [redacted] coolers, or [redacted] of the [redacted] freezers used.

This deviation was also reported to Akorn on the FDA-483 issued after the inspection that was conducted from August 15 through September 8, 2005. In the written response to the September 8, 2005 FDA-483, Akorn stated that "***a global check of all calibration and preventive maintenance schedules has been performed to assure that such documentation contains the Quality approval required by procedure***." The deviations discussed above indicate that the promised corrective action had not been completed.

V. Failure to establish separate or defined areas or other control systems as are necessary to prevent contamination or mix-ups during the course of aseptic processing [21 CFR § 211.42(c)(10)]. For example:

a. The personnel with the factory scrubs and dedicated shoes are allowed access to common personnel hallways, corridors, and stairways that are also used by personnel with street clothes and non-factory dedicated shoes.

b. There is insufficient space available in the locker rooms for personnel to adequately change into the requisite factory attire and reduce the ingress of viable and non-viable contamination from the outdoor environment. Inside the locker rooms the dedicated factory shoes come into contact with the same floor area as the street shoes that potentially contain microbial contaminants from outside. There are no measures in the locker rooms to prevent this kind of cross-contamination.

Your FDA-483 response states that the above arrangements will be addressed as part of a general renovation of your facility that may occur after transfer of production from filling room "D." Allowing this cGMP deficiency to remain unaddressed in the meantime is not acceptable. The building areas in question are not in proximity to filling room 'D' and there is no reason for corrective actions to be dependent on the status of this filling room.

VI. Failure to establish and follow adequate written procedures applicable to the quality control unit [21 CFR 211.22]. For example, [redacted] requires that QA verify implementation of corrective actions. Corrective action was not implemented in response to CAPA 05-00044, which was initiated in response to OOS investigation 05-1-2-0025. The OOS investigation, dated October 14, 2005 identified [redacted] The CAPA was issued on October 18, 2005 and QA verified corrective action on March 1, 2006. However, the proposed corrective action, [redacted] had not yet been implemented at that time. Effective corrective action, replacement of the scale, was not implemented until March 31, 2006, after three additional out of specification pre-fill assays were assigned the same root cause.

We note that your response discusses management review and global investigations. For example, your firm has written procedures that mandate performance of a "global investigation" in response to multiple complaints or discrepancies of a similar nature. However, your response and our inspection indicate an incomplete commitment to identify global issues. Please note that management review of product quality issues and adverse trends is integral to identifying and promptly correcting problems. Review and appropriate global response to adverse trends ensures ongoing control of manufacturing by promptly correcting root causes. Such activities are a fundamental part of the Quality Control Unit oversight role and are underpinned by a vigilant management review system. Ongoing assurance of quality and trends help identify appropriate management action to ensure sustainable quality and prevent deviations, failures, and defects. Please explain how you intend to address our concerns.

The issues and violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A reinspection may be necessary.

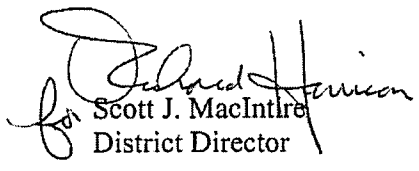
The inspection also revealed that your firm markets several injectable and topically applied sterile drugs which include: Fluorescein Injection, USP (PC# 5009, 5010, 5011 and 5012); Ephedrine Sulfate Injection (PC# 501); Phenylephrine Hydrochloride Ophthalmic Solution, USP (PC#5023. 5030, 5031); and Fluorescein Sodium/Benoxinate Ophthalmic Solution (PC# 5145). Based on our information, you do not have any FDA-approved applications on file for these, and possibly other, drug products.

We note that on June 8, 2006, FDA issued a guidance entitled "Marketed Unapproved Drugs--Compliance Policy Guide," which explains Agency policies aimed at ensuring that all drugs marketed in the U.S., prescription and over-the-counter, have been shown to be safe and effective. This guidance can be found on the internet via http://www.fda.gov/cder/guidance/6911fnl.pdf. Other, related information can be found on http://www.fda.gov/cder/drug/unapproved_drugs/default.htm. The guidance clearly articulates FDA's expectation that manufacturers of products requiring approval submit applications to FDA to show that their products are safe and effective, and describes the very strict criteria under which the Act permits drugs to be marketed without approval. The guidance also outlines the Agency's enforcement policies aimed at efficiently and rationally bringing all drugs requiring approved applications into the approval process. As described in the CPG, all drugs marketed without required applications are subject to enforcement action at any time, without additional notice.

Within 15 working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within 15 working days, state the reason for the delay and the time within which you will complete the correction. If you no longer manufacture or market any products, your response should so indicate, including the reasons for, and the date on which, you ceased production.

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,



for Scott J. MacIntire
District Director

Enclosure: cy of FDA-483