U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

APP Pharmaceuticals, LLC 2/22/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New York District
Food & Drug Administration
158-15 Liberty Avenue
Jamaica, NY 11433

February 22, 2012

WARNING LETTER NYK-2012-14

Via United Parcel Service

John Ducker, CEO & President
APP Pharmaceuticals, LLC
1501 East Woodfield Road, Suite 300E
Schaumberg, Illinois 60173

Dear Mr. Ducker:

During our June 13-July 8, 2011 inspection of your pharmaceutical manufacturing facility, APP Pharmaceuticals, LLC ("APP"), located at 3159 Staley Road, Grand Island, New York, 14072-2028, investigator(s) from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product 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)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with CGMP.

In addition, you manufacture prescription drugs without an approved application. As described below, these drugs are unapproved new drugs and, by introducing them into interstate commerce, you are in violation of sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)]. Our inspection also revealed that you failed to submit NDA Field Alert Reports (FARs) to FDA in compliance with 21 C.F.R. § 314.81 (b)(1)(ii), as required by section 505(k) of the Act [21 U.S.C. § 355(k)].

We have reviewed your firm's response of July 29, 2011, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

CGMP

1) Your firm has not thoroughly investigated any unexplained discrepancy whether or not the batch has already been distributed [21 C.F.R. § 211.192]. For example:

a. In January 2010, your firm identified an insect floating in a waste container in aseptic filling room **(b)(4)**. During your root cause analysis, you stated that the most likely cause was the stopper supplier; however, you did not conduct an audit of the supplier until April 2011. In addition, you stated that there was a pest control program in place, therefore, no corrective action was needed. You continued to find insects in your manufacturing area, in finished product (two vials), and you received a complaint for an insect in a distributed vial. You also stated a potential root cause was the gowning supplier; however, your audit of this supplier was not scheduled to be conducted until December 2011. You did not adequately investigate the original deviation for an insect in the sterile manufacturing area and did not implement appropriate corrective actions to prevent recurrence.

In your response, you state that you have enhanced your pest control program and scheduled audits of the suppliers potentially involved. Although the last occurrence of the presence of an insect was March 2011, the effectiveness of these corrective actions will need to be monitored to ensure that this issue does not recur.

b. Your firm has received seven complaints for vials with missing labels between January 2010 and July 2011. Four of these complaints involve Packaging Line **(b)(4)**; however, in your complaint investigation# **(b)(4)**, you state that this is the only complaint of this type for this lot and no further action is required.

In your response, you describe enhancements to your reserve room procedures and your complaint management procedure; however, you failed to identify a trend in missing labels because your investigation focused on this lot only. Your response is inadequate because you failed to develop and implement a process that describes how to identify and handle trends.

c. Your firm failed to identify an assignable cause for a failing assay result for Heparin Lock Flush (OOS# **(b)(4)**) and failed to extend your investigation into other batches of Heparin Lock Flush.

In your response, you state investigation **(b)(4)** was completed to identify the root cause of the out of specification (OOS) results. We cannot evaluate your response since investigation **(b)(4)** was not included in your response. We are also concerned about a potentially related trend of OOS assay results for other batches of heparin active pharmaceutical ingredient (API) and Lock Flush. Please provide the following information or data: 1) A copy of investigation **(b)(4)** including root cause analysis and corrective actions implemented for this batch; 2) Whether other associated lots may be affected by this issue; 3) Whether you have implemented, for commercial production and release, the new filter and tubing that was being used when you produced the failing exhibit batch; and 4) A three-year history of heparin API and Heparin Lock Flush batches that have had OOS results, the testing results obtained, the root cause, and the investigation conclusion.

d. Your firm has failed to thoroughly investigate several customer complaints. For example, you received complaint #**(b)(4)** on March 1, 2010, citing dark particulate matter in a vial of Heparin. You investigated and determined that the particle was most likely due to a vendor issue; however, you did not perform an assessment of the vial supplier.

In your response, you state that you have not identified any other defects of this nature. Your response is inadequate since you have not addressed the potential root cause of a vial defect as identified in your investigation.

2) Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)]. For example:

a) Your Process Simulation Policy requires incubation of all integral vials. However, the investigator observed integral vials placed in a white pail labeled "to be destroyed," yet your firm did not document the rationale for their destruction.

In your firm's attempts to reconstruct the events of this process simulation, you indicated that the operators dropped the vials. This information was not documented on the process simulation records. Inaccurate documentation of, or failure to document the events occurring during the process simulation qualification studies is not acceptable. Although you committed to revise your procedure, based on the inspectional findings, it appears that further improvements are needed to ensure proper documentation and oversight of your process simulation. For example, please note that it is typical for firms to videotape and have quality staff observe process simulations.

b) During the inspection our investigators noted operators rapidly walking from a class 10,000 area to a class 100 area and opening the plastic curtains that separate these areas. In addition, the investigators noted an operator excessively shaking the stopper bag while loading the stopper bowl and knocking on the conveyor belt to fix a stuck vial.

You have had at least **(b)(4)** media fill failures, and identified that the root cause for **(b)(4)** of those failures was related directly to aseptic technique.

In your response, you state that you are implementing engineering solutions, reducing the number of required aseptic connections, dedicating Fill Line **(b)(4)** to liquid product and enhancing your aseptic technique training. Please explain your plan to ensure that these corrective actions will be effective, include how you intend to monitor the effectiveness of the corrective actions and what metrics you will use to indicate when additional changes are necessary.

3) Your firm failed to follow procedures for the handling of all written and oral complaints regarding a drug product, including specific complaint information or a reason that an investigation was found not to be necessary [21 C.F.R. § 211.198]. For example:

Your procedure, Complaint Management Procedure, requires you to perform an initial impact assessment of all customer complaints; however, your firm failed to perform this assessment on approximately **(b)(4)** customer complaints received since January 2010 (e.g., particulate matter, leaking vials, and discoloration).

In your response, you state that you have initiated a deviation investigation to determine the root cause for failure to follow the complaint procedure. In addition, you state that the facility will be in full compliance with the procedural requirements by September 30, 2011. Please provide a summary of the root cause analysis and any corrective actions you have implemented in your quality system to address the root cause.

4) Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and/or purity they purport or are represented to possess [21 C.F.R. § 211.100(a)].

For example, on June 15, 2011, during the semi-automatic, **(b)(4)** visual inspection, investigators observed that the visual inspection was performed at a rate of **(b)(4)** vials per minute (vpm); however, your qualification records do not indicate the rate of inspection during the qualification of your visual inspection operators. Upon review of the qualification data, the investigators calculated that employees can inspect approximately **(b)(4)** vials per minute. In addition, an investigator noticed the visual inspection operator looking away from the vials several times without stopping the inspection machine.

In your response, you state that you are enhancing the qualification program and retraining visual inspection personnel. Please explain your plan to ensure that these corrective actions will be effective, including how you intend to monitor the effectiveness of the corrective actions and what ongoing oversight and metrics you will use to indicate when additional improvements are needed.

5) Your firm has failed to follow written responsibilities and procedures applicable to the quality control unit [21 C.F.R. § 211.22(d)]. For example, your firm has completed approximately **(b)(4)** media fill simulations since December 2010; however, you have not completed the reports, and the quality unit has not approved them as per your procedure which requires you to complete all final reports within **(b)(4)** days of reviewing all of the data.

In your response, you state that you have reviewed open items and have closed **(b)(4)** action items and all media fill reports. In addition, you state that you will begin ensuring appropriate resources for newly created activities in your Management Review Meeting, per SOP 10-01-02-0043. We cannot assess the adequacy of this corrective action because you did not provide a copy of the SOP or other written plan for ensuring the inclusion of the items in this meeting. Please provide a copy of the SOP, explain your plan to ensure that these corrective actions will be effective, include how you intend to monitor the effectiveness of the corrective actions and what quality management oversight, including metrics, you will use to indicate when other corrections or improvements are necessary

Unapproved New Drug
In regard to your unapproved drugs, on September 19, 2011, FDA published a revision to its June 8, 2006 guidance entitled "Marketed Unapproved Drugs-Compliance Policy Guide (CPG)," which explains FDA's 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 FDA's webpage at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf[1]. Other related information can be found on http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActiohsonUnapprovedDrugs/default.htm[2].

The guidance clearly articulates FDA's expectation that illegally marketed products, products marketed without required FDA approval, be removed from the market. The guidance also outlines FDA'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.

During the June 13-July 8, 2011 inspection, we found that your firm is manufacturing the following prescription drugs:

(b)(4)

Based on our information, there are no FDA-approved applications on file for these drug products. You should contact FDA's unapproved drugs coordinator, Dr. Sally Loewke, at 301-796-0710 for assistance in communicating with the FDA on the application process for your unapproved drugs. Also, please note that if you are no longer marketing these products, you must update the Drug Listing files in accordance with 21 C.F.R. 207.30(a)(2).

NDA- Field Alert Report
Your firm failed to submit NDA-Field Alert Reports (FARs) within three (3) working days of receipt of information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug products as required by 21 C.F.R. § 314.81 (b)(1)(ii). For example:

a. Your April 2009 to March 2010 reserve sample inspection report for lyophilized products, dated August 8, 2010, identified three lots in which major defects were observed. You did not submit a FAR within 3 days of identification of the defect. According to your records these defects may include vials with defects such as foreign matter, particulate matter, and vials with defective glass.

b. Your firm did not submit a FAR for Heparin Sodium Injection, lot #408196, when you confirmed the presence of particulate matter in reserve samples after receiving a complaint of particulate matter in a distributed vial.

In your response letter dated of July 29, 2011, you state that based on the type and quantity of the defects identified during the inspection process, the conditions to issue a Field Alert per SOP 10-11-00-0006, NDA/ANDA- Field Alert Report, Version 10.0, effective March 26, 2010, were not reached. Note that when you become aware of significant problems (e.g., particulates or foreign material in reserve samples, defective glass, or complainant samples containing particulates) you are required to submit a FAR to the Agency within three working days. You should revise your procedure to meet the requirements of the regulation and conduct appropriate training to ensure timely reporting of any of the situations indicated in the relevant regulations. We will verify the implementation and effectiveness of this corrective action during our next routine inspection of your facility.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. In addition, this letter is not intended to contain an all-inclusive list of your firm's unapproved drugs. You are responsible for investigating and determining the causes of the violations identified above, preventing their recurrence and the occurrence of other violations, and determining the complete status of all of the drugs manufactured by your firm. It is your responsibility to assure compliance 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 drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify conective actions have been completed.

Based upon the nature of the CGMP violations identified at your firm and previous inspectional findings, it is apparent that APP Pharmaceuticals, LLC's has failed to implement global corrective actions. Be advised that corporate management is responsible for ensuring the quality, safety, and integrity of its drug products. FDA expects your corporate management to undertake a comprehensive and global assessment of your manufacturing operations immediately, including procedures, processes, and systems, and, in particular, your aseptic processing capabilities, to ensure that drug products conform to FDA requirements.

If, as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov in order to ensure that your action(s) does not adversely affect the public health.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations and copies of supporting documentation. If you cannot complete a corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, state in your response if you no longer manufacture or distribute the drug product(s) manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Send your reply to Dean Rugnetta at the following address: U.S. Food and Drug Administration, 300 Pearl Street, Suite 100, Buffalo, NY 14202.

If you have any questions concerning this letter, you can contact Mr. Rugnetta at 716-541-0324.

Sincerely,
/S/
Ronald M. Pace
District Director
New York District

cc via Email:

J. Frank Harmon, COO - Frank.Harmon@fresenius-kabi.com
Mitchell L. Ehrlich, Vice-President, Quality- Mitchell.Ehrlich@fresenius-kabi.com

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