Inspections, Compliance, Enforcement, and Criminal Investigations

K.C. Pharmaceuticals Inc. 6/21/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Los Angeles District
Pacific Region
19701 Fairchild
Irvine, CA 92612-2506
Telephone: 949-608-2900
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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

W/L 23-10

May 21, 2010

Mr. Joseph Sutedjo, President
K.C. Pharmaceuticals Inc.
3201 Producer Way
Pomona, CA 91768

Dear Mr. Sutedjo,

During our December 14 - 30, 2009 inspection of your medical device and pharmaceutical manufacturing facility, KC Pharmaceuticals, Inc., located at 3201 Producer Way, Pamona, California, investigators from the United States Food and Drug Administration (FDA) identified significant violations of Quality System Regulations for Medical Devices, Title 21, Code of Federal Regulations, Part 820, and 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 medical device(s) and drug product(s) to be adulterated within the meaning of section 501(h) and section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act) [21 U.S.C. §§ 351(h) and 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, holding, or installation do not conform to, or are not operated or administered in conformity with the Quality System Regulation or CGMP.

On February 3, 2010, your firm attended a meeting in the Los Angeles District Office to address serious concerns regarding the results of the December 14 to December 30, 2009 inspection. Subsequently, a teleconference was held on March 1, 2010, to discuss your proposed corrective actions.

We reviewed your written response dated January 18 and have considered this information in our evaluation and have included our comments as they pertain to each item below.

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

1. Failure to adequately ensure that when the results of a process cannot be fully verified by subsequent inspection and test that the process shall be validated with a high degree of assurance and approved according to established procedure [21 C.F.R. § 820.75(a)].

Specifically, the procedure "Validation of the Aseptic Filling Process Utilizing the Media Fill Method," **(b)(4)**, states that initial validations should be conducted consecutively and prior to routine production fills and subsequent re-qualifications should be performed **(b)(4)** as appropriate. In addition, the procedure states that routine production may not resume until acceptable qualification or validation runs are achieved or until all appropriate investigations and/or repeat media fills have been performed with acceptable results. However, validation of the aseptic filling process in filling suite **(b)(4)** for **(b)(4)** bottles was inadequate in that the **(b)(4)** re-qualification of the **(b)(4)** Aseptic Filling Process utilizing the Media Fill Method **(b)(4)** performed on March 23, 2009 failed. The failure produced **(b)(4)** contaminated units out of approximately **(b)(4)** units inspected. In addition, the subsequent validation of **(b)(4)** for filling **(b)(4)** and **(b)(4)** bottle **(b)(4)** performed on May 20, 2009 also failed. This failure produced **(b)(4)** contaminated units out of approximately **(b)(4)** units inspected. **(b)(4)** lots of Sterile Saline Solution preserved in **(b)(4)** bottles were filled on March 31, 2009 and April 2, 2009 in **(b)(4)** filling suite. The **(b)(4)** lots were filled in between the two failed media fills.

We have reviewed your response and have concluded that it is inadequate. Your firm indicated that the **(b)(4)** lots **(b)(4)** were aseptically filled, met all their respective release criteria (i.e., **(b)(4)** and therefore were deemed safe to release for marketing. Your firm did not provide a reason why they manufactured and released the **(b)(4)** lots of products before the **(b)(4)** filling suite was re-qualified as indicated in the procedure. In addition, you did not provide evidence of implementation of the correction and corrective action.

2. Your firm has not extended investigations of an unexplained discrepancy to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy [21 C.F.R. § 211.192].

For example, your investigation regarding the media fill failures for eye wash aseptic filling suite **(b)(4)** is inadequate because it was attributed solely to improper aseptic techniques during the filling operation without scientific justification to support this conclusion. Further, your film's investigation did not include re-validation of the **(b)(4)** filling operations prior to resuming aseptic filling operations.

Your firm has not conducted a thorough investigation regarding the media fill failures in your **(b)(4)** filling suite. The Non-Conformance Report **(b)(4)** dated July 2, 2009), indicated that the microorganisms identified in your investigation are considered waterborne and are prevalent within the water system. Your firm did not conduct an adequate investigation to ensure that microbiological contamination sources were eliminated from the **(b)(4)** water system and the manufacturing process before it was returned to operation.

FDA does not believe your water system has been adequately designed and qualified to ensure the prevention of microbial contamination. It is unclear if your firm has determined the root cause of the problem or has attempted to resolve it. Due to the microbial contamination identified in your water system, please explain the appropriate interim measures your film plans to take including but not limited to passivation, routine sanitization, and additional representative sampling. The water system used to produce your sterile drug products should be properly designed, controlled, monitored, tested, sampled and maintained to ensure a continuous state of control. It is essential that pharmaceutical water routinely and reproducibly meet appropriate specifications. Please provide your firm's short and longer term (e.g., design modifications) corrective actions, and timeframe for completion.

3. 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 C.F.R. § 211.63].

For example, your firm's **(b)(4)** water system is deficient in that unused portions of piping (dead-legs) were observed in the **(b)(4)** piping of the **(b)(4)** water system. Biofilm may form in the unused portions of piping.

Dead-legs are not acceptable in water systems used for the manufacture of sterile drug products. Please provide appropriate corrective actions to address the dead-legs in your water system, including an explanation of design modifications that would address the issue. In addition, please provide the following: 1) additional cleaning/sanitization data to support that bacteria are effectively removed from the water system; 2) documentation for qualification of the water system that demonstrates the water system is capable of consistently producing the desired water quality; and 3) the timeframe for completion.

4. Your firm does not have an adequate system for monitoring environmental conditions in aseptic processing areas [21 C.F.R. § 211.42 (c)(10)(iv)].

For example, environmental monitoring is inadequate in the **(b)(4)** eye wash aseptic filling suite **(b)(4)**. Your procedure **(b)(4)** "Environmental Monitoring Program" (February 08, 2008) is inadequate because **(b)(4)** air monitoring is limited to **(b)(4)**

We disagree with your analysis that a **(b)(4)** cannot be used for **(b)(4)** monitoring: It can be integrated into a **(b)(4)** process monitoring system using related software. Please provide a corrective action(s) which will ensure that **(b)(4)** monitoring of non-viable particulates is conducted at your firm and that appropriate environmental conditions are maintained.

5. Failure to establish and maintain an adequate procedure for implementing corrective and preventive action to include requirements for investigating the cause of nonconformities relating to product, processes, and the quality system [21 C.F.R. § 820. 100(a)(2)].

Specifically, your firm's procedure **(b)(4)** "Corrective Action/Preventive Action (CAPA) Management System" was not adequately implemented. Your film's CAPA #CP-09-001 (dated July 1, 2009) was created for media failures on **(b)(4)** filling suite and the Quality Risk Assessment part states that "a review of all batch records using the **(b)(4)** filling suite reveals no suspect results, all sterility passed." However, on January 14, 2009, Non-conformance Report **(b)(4)** was initiated for a sterility failure on Sterile Saline Solution Preserved (SALP) Lot **(b)(4)** filled in **(b)(4)** filling suite on December 29, 2008. The entire lot was rejected and removed from inventory on March 3, 2009 because it was considered potentially contaminated.

We have reviewed your response and have concluded that it is inadequate. Your firm stated that a specific section to address any potentially affected lot will be added to **(b)(4)** Quality Risk Assessment section. In addition, the firm stated that it will update the **(b)(4)** procedure to include a requirement to review all potentially affected lots. However, your firm did not provide the revised procedure **(b)(4)** and the updated **(b)(4)** for review and therefore its adequacy could not be determined at this time. In addition, your firm did not provide any discussion or evidence of a systemic corrective action, such as a retrospective review of CAPAs to ensure there are no other CAPA discrepancies with regard to product potentially impacted.

We acknowledge your commitment to cease manufacturing until additional testing is conducted on your water system and in your clean rooms as verbally stated in the February 19, 2010 teleconference with FDA. However, you should evaluate the design of your water system to ensure that it meets its intended use and is designed to prevent microbial contamination. It is essential that you demonstrate that your manufacturing facility and your **(b)(4)** water system are operating in an appropriate state of control before resumption of operations and commercial distribution.

You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Also, federal agencies are advised of the issuance of all Warning Letters about drugs and medical devices so that they may take this information into account when considering the award of contracts. Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

This letter is not intended to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious problems in your manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. 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. Additionally, your response should state if you no longer manufacture or distribute medical device or drug products, and provide the date(s) and reason(s) you ceased production.

Your response should be sent to:

Daniel Cline
Acting Director, Compliance Branch
Food and Drug Administration

19701 Fairchild
Irvine, CA 92612-2506

If you have any questions about the content of this letter please contact Marco S. Esteves, Compliance Officer at 949-608-4439.

Sincerely,
/S/

Alonza E. Cruse
District Director
Los Angeles District
Sacramento, CA 95899-7413

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