Inspections, Compliance, Enforcement, and Criminal Investigations

Abbey Color, Inc. 2/19/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
PHILADELPHIA DISTRICT
900 U.S. Customhouse
2nd end Chestnut Streets
Philadelphia, PA 19106
Telephone: 215-597-4390

WARNING LETTER
13-PHI-11

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

February 19, 2013

Mr. Richard S. Nielsen
Abbey Color, Inc.
400 E. Tioga Street
Philadelphia, PA 19134

Dear Mr. Nielsen:

During our March 13, 2012 through March 23, 2012, inspection of your active pharmaceutical ingredient (API) manufacturing facility, Abbey Color, Inc., located at 400 E. Tioga St, Philadelphia, PA, an investigator from the U.S. Food and Drug Administration (FDA) identified deviations from current good manufacturing practice (CGMP) for the manufacture of APIs. These deviations cause your APIs 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.

We have conducted a detailed review of your firm's response, dated April 12, 2012, and note that it lacks sufficient corrective actions.

Our investigator observed specific violations during the inspection, including, but not limited to, the following:

1. Failure to validate and monitor the water purification system to ensure that water is of appropriate quality.

Your firm uses water in the final purification step of Fluorescein USP, an API intended for use in sterile drug products. However, your firm failed to demonstrate that your purified water system

can consistently produce water that is suitable for use in the manufacture of this API.

This is a repeat observation from the July 21-August 8, 2010 inspection. In your response to observations made at the 2010 inspection, your firm promised actions it would take to assure reliable water quality. However, those changes were inadequate, as you continued to get periodic out-of-specification (OOS) endotoxin and total organic carbon (TOC) test results.

In your response to the observations noted during the 2012 inspection, you indicated your firm's intention to conduct a comprehensive gap analysis of the purified water system. However, you have failed to indicate when you will initiate this gap analysis and when it will be completed. Your firm also failed to detail how you will determine the source(s) of high endotoxin and TOC in your purified water and how your firm will remedy identified problem (s). We note that, for example, your firm installed an endotoxin removal unit on your purified water system in January 2011 in response to the OOS results for endotoxin in the water used for API. However, your firm has not demonstrated that the water produced by the purified water system is now suitable for use in production. The operational parameters and effectiveness of the new endotoxin removal unit have not been qualified. Your firm does not monitor the microbial and chemical attributes of the feed water, and have no assurances that the purified water system is capable of consistently producing water that meets specifications for a given quality of feed water. Your gap analysis should also include evaluation of factors such as feed water quality, whether each component of the purified water system is meeting its performance specifications, and whether the system's output is reproducible. Your firm has not determined the source of the endotoxin failures in the past, and it is essential that you demonstrate that changes in design and operational procedures have resulted in a reliable water system.

2. Failure to adequately investigate and document OOS test results.

For example, your rinse water from cleaning equipment used to manufacture **(b)(4)** lots of Fluorescein, USP from October 2010, to December 2011, had **(b)(4)** results that were OOS for endotoxin and/or total organic carbon (TOC). Your firm failed to document that these were OOS results, conduct an investigation to determine the root cause of these recurring failures, or implement corrective actions.

Executive management of your firm is responsible for assuring quality system effectiveness. A basic part of this responsibility is prompt identification and remediation of problems that indicate manufacturing control problems, including an evaluation of the impact of these deviations on the quality of your APIs.

We acknowledge that you indicate in your response the intention to conduct a comprehensive gap analysis of your firm's investigation and remediation processes pertaining to non-conformances, deviations, OOS events, and quality-related complaints. However, you did not indicate when you will initiate this gap analysis or any timeline for its completion. Your response also does not indicate what specific interim steps (e.g., initial procedural revisions, train employees) you intend to take to ensure that thorough investigations are conducted in a timely manner.

3. Failure to establish an adequate stability program to monitor the stability characteristics of APIs and to use the results to confirm appropriate storage conditions and retest or expiry dates.

For example, your firm has only put one Fluorescein USP API lot on stability, lot #**(b)(4)**, distributed December 15, 2010. Your firm has limited data to demonstrate that the API is stable for the recommended retest date of **(b)(4)** years. Your firm also failed to test stability samples for identification at the end of **(b)(4)** of the four storage quarters **(b)(4)** as required by your firm's procedure.

This is also a repeat observation from the 2010 inspection. As part of your firm's corrective actions following that inspection, you implemented a standard operating procedure, **(b)(4)**,

entitled "**(b)(4)**." However, your procedure require only monitoring, not control, of temperature and humidity storage conditions for stability samples, and it does not define what testing is to be performed on stability samples or reference documents that do define such testing. At the 2012 inspection, our investigator found that temperatures in the USP cage in which you store stability samples can reach **(b)(4)** in the winter and **(b)(4)** in the summer.

Your current response is inadequate in that you have not defined the stability testing you will perform. You state that your firm will "…subject each sample to our standard battery of tests..." and "…will coordinate a microbe study on all sample lots." However, you did not describe what testing will be conducted, other than the identity and endotoxin tests that will be performed by a third party. Please provide documentation of this correction in your response, and specify how your firm's stability program will monitor the characteristics of the API. Your response should also detail how you will confirm or establish your retest date and storage conditions. In addition, you should describe how this information will be provided to customers and if your finished Fluorescein USP API labeling will be changed to include this information.

The violations cited in this letter are not intended to be an all-inclusive list 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 and the occurrence of other violations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the amount of 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 so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

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 corrective actions have been completed.

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 provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute Fluorescein USP, provide the date and reason you ceased production.

Your reply should be sent to the following address: U.S. Food and Drug Administration, U.S. Customhouse, Room 900, 2nd and Chestnut Sts., Philadelphia, PA 19106, Attn: Kristina Donohue, Compliance Officer. If you have questions regarding any issues in this letter, please contact Kristina Donohue at (215) 717-3078 or Kristina.Donohue@fda.hhs.gov.

Sincerely,
/S/
Kirk D. Sooter
District Director
Philadelphia District

(b)(4)

Page Last Updated: 02/25/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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