U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Akzo Nobel Chemicals, S.A. de C.V. 11/16/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL **WL: 320-12-004**

November 16, 2011

Mr. Ricardo Castanedo Saintmartin
Gerente General
Akzo Nobel Chemicals, S.A. de C.V.
Ave. Morelos 49, Col. Tecamachalco
Los Reyes La Paz, Edo. México 56500

Dear Mr. Castanedo:

During our June 2011 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Akzo Nobel Chemicals, S.A. de C.V., located at Ave. Morelos 49, Col. Tecamachalco Los Reyes La Paz, Edo. Mexico, Mexico 56500, investigators from the Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture of APIs. These deviations caused your API 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 reviewed your firm's response of July 11, 2011, and note that it lacks sufficient corrective actions.

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

1. Failure to review and investigate all production deviations.

The inspection documented that your firm failed to investigate and document contamination of your **(b)(4)** API (**(b)(4)**). For example, between April 4, 2011 and June 6, 2011, thirteen (13) batches of **(b)(4)** API (batch/lot numbers **(b)(4)**) were observed by production personnel to contain black particles. During the manufacture of these batches, production personnel also reported hydraulic oil leaking from the **(b)(4)** and **(b)(4)**. However, you performed no investigation to identify the contaminant or to determine its root cause.

Your response states that you repaired the leaking equipment (**(b)(4)** and **(b)(4)**) each time the leaking oil was detected and that you will revise your procedure for process deviations investigations to address documentation of the investigations, root cause analyses, and corrective & preventive actions.

Your response is inadequate because it does not describe the specific changes you will make to your procedures or the timeframes for their completion and implementation, nor did you describe any additional process controls to prevent contamination of the API. In addition, your firm has assumed that the black particles are hydraulic oil contamination, without an investigation or any identification of the contaminant. Furthermore, you did not describe what steps you will be taking with regard to the API manufactured using defective production equipment. In your response, please include your proposed action plan regarding the final disposition of the thirteen (13) lots identified above as well as your proposed action plan for any other lots that may be contaminated, including a review of production, maintenance, complaints, analytical data, and retain samples associated with these lots.

Please include in your response a copy of the revised process deviation investigation procedure.

2. Failure to have appropriate procedures (or practices) in place to prevent the use of quarantined API.

A contaminated lot (lot **(b)(4)**) of **(b)(4)** USP, manufactured on May 12, 2011, was released and shipped to your distribution center in the United States (U.S.) on **(b)(4)**. Once you had discovered that you shipped this lot in error, you arranged for the material to be returned to your site in Mexico. However, the API was improperly identified as released while in transit, both to and from your distribution center.

In your response you stated that your current materials management system does not allow the appropriate identification of quarantined materials. You also stated that your materials management system requires approval at the corporate level. It is FDA's expectation that materials are properly identified as to their status to prevent their unintentional or unauthorized use. In response to this letter, please provide detailed corrective actions showing that you have amended your materials management system to ensure that accurate classification of a material's status is maintained throughout your custody, including during its transport between company units. Please provide evidence that the correction has been implemented for all relevant company units.

In addition, in your response you did not address the failure of your quality unit to prevent the shipment of contaminated material in the first place. Your firm should implement adequate controls to ensure that only API of the quality intended is distributed in the U. S. In response to this letter please include the controls that your QC unit will implement to prevent recurrence.

3. Failure to have an adequate maintenance procedure to prevent contamination or carry-over of a material that would alter the quality of the API.

For example, the inspection revealed that between August 2010 and August 2011, at least ten (10) maintenance requests were submitted as a result of oil leaks detected during manufacturing. This trend of contamination of API with hydraulic oil indicates an inadequate equipment maintenance program.

Your response acknowledges continued repairs to equipment for leaking hydraulic oil and states that you repaired the equipment each time a leak was detected. However, your response is inadequate because it fails to explain why your firm continually authorized the use of manufacturing equipment known to be defective. In addition, your response did not provide a prevention strategy to minimize the possibility of future contamination.

In response to this letter you should provide an evaluation of your entire preventive maintenance program. Your response should also include an evaluation of all major pieces of manufacturing equipment to determine if they are suitable for the manufacture of drugs. Note that if a piece of equipment requires constant repairs, the maintenance program may not be enough to offset its inadequacy.

In your response to this letter, please provide a target date by which all corrective actions will be implemented. Once you determine that your facility is ready for inspection, please send a letter indicating this.

The deviations detailed in this letter are not intended to be an all-inclusive statement of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations. If you wish to continue to ship APIs to the U.S., it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the deviations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, until such time as your manufacturing practices are verified to comply with CGMPs, your firm will remain under FDA Import Alert and FDA will continue to refuse admission of all articles manufactured at Akzo Nobel Chemicals, S.A. de C.V. into the U.S. The articles are subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S.C. § 381(a)(3)] in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351 (a)(2)(B)].

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 deviations. Include an explanation of each step being taken to prevent the recurrence of deviations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute active pharmaceutical ingredients, and provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3003882630.

If you have questions or concerns regarding this letter, contact Cesar E. Matto, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
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10903 New Hampshire Ave
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Sincerely,
/S/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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