Inspections, Compliance, Enforcement, and Criminal Investigations

Novo Nordisk A/S 12/12/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-13-03

December 12, 2012

Mr. Lars Rebien Sorensen
Chief Executive Officer and President
Novo Nordisk A/S
Krogshoejvej 55
DK-2880 Bagsvaerd, Denmark

Dear Mr. Rebien Sorensen:

During ourMarch 12-20, 2012 inspection of your pharmaceutical manufacturing facility, Novo Nordisk A/S located at Novo Alle, Bagsvaerd Denmark, investigator(s) from the U.S. 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(s) 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 and note that it lacks sufficient corrective actions.

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

CGMP VIOLATIONS

1. Your firm has not established or followed the 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. Approximately 846 environmental monitoring (EM) samples were not collected in the Class 100 (Grade A) and the Class 10,000 (Grade C) areas from March 2010 to February 2012 during the manufacture of sterile **(b)(4)** products.

This substantial number of missed samples suggests a pattern that raises concerns regarding your environmental program. Collecting scheduled EM samples is a critical aspect of any environmental control program at an aseptic manufacturing facility. Since 2010, your

Manufacturing and Quality Units were unable to implement effective corrective actions to ensure all of the environmental monitoring (EM) samples are consistently collected.

Your response mentions that some of the "missed" samples were actually samples for which the exposure time for the plate had been exceeded or delayed, which suggests that you may have rejected or invalidated some results. Your response did not address why the ongoing actions implemented as early as December 2010 have not been effective at eliminating missed environmental monitoring samples.

In response to this letter, provide your updated corrective action and preventive action (CAPA) plan to ensure that all environmental monitoring samples are collected and tested. Also explain how release of products during this period was justified by your firm when there was a lack of required data available to evaluate suitability of the environment of batch manufacture.

b. Operators working inside the aseptic core during the manufacture of **(b)(4)** batches were observed wearing goggles that had not been adequately sterilized and had two openings on the top.

The goggles currently worn in the Class 100 area are not sterilized but rather sanitized. Your disinfectant qualification document "*Validation of in-use efficacy of* **(b)(4)** *on production surfaces*" does not describe specific studies to demonstrate effective recovery of organisms from the goggles. The qualification study's acceptance criteria following disinfection are < **(b)(4)** cfu/contact plate of *Aspergillus brasiliensis* and < **(b)(4)** cfu/contact plate for all other organisms. Our expectation is that gowning components, including goggles, be sterilized before use in an aseptic processing area. However, disinfection may be appropriate if your firm demonstrates full decontamination. Provide data to support the effectiveness of the disinfection of the goggles.

Additionally, the investigator noticed that the goggles used in the aseptic core were observed with two openings of approximately **(b)(4)** cm x **(b)(4)** cm. Your firm's response indicated that you are evaluating a redesign of the goggles. However, your redesign does not appear to consider the use of goggles with more protective venting mechanism for operators working in the aseptic core. Please clarify whether you plan to use the goggles suggested in your firm's response or you will explore implementation of more suitable goggles for use in the aseptic areas. Regardless of the design you ultimately select, it is your responsibility to demonstrate that it is an appropriate design and the goggles used are not a contamination source.

c. The environmental monitoring for non-viable particulates is performed a substantial distance away from the filling station on the aseptic fill line **(b)(4)**.

Your response indicates that the **(b)(4)** location is more critical than the filling needles for the non-viable particles monitoring. However, your response fails to provide scientific data and justification to support your conclusion.

In your response to this letter, provide a diagram describing the positioning of each non-viable particle monitoring probe on the filling line and a justification for each position. Please explain if the **(b)(4)**, which you have deemed a critical position, will continue to be monitored in lieu of a position sufficiently closer to the point of fill.

2. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192]. For example,

Your Quality Unit failed to investigate and quantify the impurity peak seen at an approximate retention time of **(b)(4)** minutes during the high-performance liquid chromatography (HPLC) analysis of **(b)(4)** (**(b)(4)**/mL and **(b)(4)**/mL) and **(b)(4)** (**(b)(4)**/mL) products. This impurity peak was also observed in other batches at 1, 2, and 3 month stability time points on both your long-term and accelerated stability programs. Your firm's response indicates that the peak has been identified as **(b)(4)**, a component of other drug products manufactured on the same equipment as **(b)(4)** drug products, and that the **(b)(4)** compound tends to adhere to

surfaces in the HPLC injection system. However, your response did not provide data to support this conclusion or a description of the impact of **(b)(4)** residues remaining in the HPLC injection system and how this may impact analysis of other products.

We are concerned with your proposed CAPA in which samples containing **(b)(4)** are to be analyzed at the **(b)(4)** of the chromatographic run while samples not containing **(b)(4)** (processed on the same HPLC system) are to be analyzed **(b)(4)**. Your response did not address the need to eliminate carry-over between chromatographic runs, nor did you commit to integrate and report the assumed **(b)(4)** peak in all sample types.

Additionally, we are concerned that no investigation was conducted until this situation was brought to your attention by our investigator. Your Quality Control laboratory has been approving HPLC analyses without initiating a formal investigation into this "unknown" peak. Your response also lacked an evaluation of other analytical methods for the same problem.

In response to this letter, describe how the HPLC is cleaned to avoid residues from adhering to the system or to remove any carry over when the drug product containing **(b)(4)** is assayed. Additionally, describe your procedures for integrating and reporting the assumed **(b)(4)** peak, and state the acceptance criterion for this impurity peak for each sample type tested using these methods.

In your April 11, 2012 response, you stated that **(b)(4)** is a **(b)(4)** compound that "tends to adhere to surfaces in the HPLC." In your response to this letter, please discuss whether there are similar cleaning difficulties associated with **(b)(4)** manufacturing equipment. Include cleaning validation and verification data for the manufacturing process addressing whether the cleaning procedures used for shared, **(b)(4)**-contacting equipment are adequate to prevent cross-contamination of other drugs with **(b)(4)**.

In your response, please also provide an update on your current manufacturing and US supply plans for **(b)(4)** injection, **(b)(4)**mg/ml strength.

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.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at Novo Nordisk A/S Bagsvaerd, Denmark into the United States. 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 CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the 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 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.

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 violations. Include an explanation of each step being taken to prevent the recurrence of violations 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.

Please send your reply to the following address:

Rafael Arroyo, Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51 Room 4237
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-4839
Fax: (301) 847-8741

Sincerely,
/S/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Page Last Updated: 02/04/2013
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