



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

EMAIL & UPS EXPRESS MAIL

Helle Skov
Executive Vice President
ALK-Abello A/S
Boge Alle 6-8
DK – 2970 Horsholm, Denmark

Dear Ms. Skov:

The Food and Drug Administration (FDA) conducted an inspection of ALK-Abello A/S, located at Boge Alle 6-8, DK-2970 Horsholm, Denmark, between March 3-14, 2016. During the inspection, FDA investigators documented deviations from current good manufacturing practice (CGMP) requirements in the manufacture of your licensed biological drug products and intermediates. Deviations from CGMP include the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act), the requirements of your biologics license application (BLA) approved under Section 351(a) of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Parts 210 and 211. At the close of the inspection, FDA issued a Form FDA 483, List of Inspectional Observations, which described a number of significant objectionable conditions relating to your firm's compliance with CGMP. Significant deviations observed during the inspections include, but were not limited to, the following:

1. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including validation of all aseptic and sterilization processes [21 CFR 211.113(b)] as follows:

- a. The (b) (4) WFI use points for Pharmedgen aseptic manufacturing are only monitored (b) (4) every (b) (4) for endotoxin and TOC.
- b. There is no procedure in place that specifically addresses the requirements and actions to be taken for use points with consecutive action level bioburden excursions.
- c. Environmental isolates are not used for growth promotion studies of media used in media fill simulations. This is a repeat observation from the 2014 inspection.
- d. There have been approximately 80 action level bioburden excursions in the Aseptic Production Facility since the 2014 inspection. No corrective or

preventive actions were initiated until January 2016.

- e. Expired agar plates were used for environmental monitoring in the Aseptic Production Facility.

2. Failure to routinely calibrate, inspect, or check automatic, mechanical, or electronic equipment according to a written program designed to assure proper performance [21 CFR 211.68(a)]. For example:

- a. Lyophilizer (b) (4) has not been re-qualified since March 2000.
- b. There is no documentation demonstrating that Lyophilizer (b) (4) has been adequately re-qualified after temperature mapping failures.
- c. There have been a number of aborted lots due to problems with the lyophilizers. For example:
 - i. Pharmalgen batch (b) (4) was aborted due to the bulk exceeding the (b) (4) as a result of a malfunction of the Lyophilizer (b) (4) sequence.
 - ii. Pharmalgen batch (b) (4) was aborted due to the leaking of Lyophilizer (b) (4).
 - iii. Pharmalgen batch (b) (4) was aborted due to Lyophilizer (b) (4) lacking a connection to the (b) (4) program on the Lyophilizer memory card.
- d. The filling machine on line (b) (4) is not adequately maintained to prevent malfunctions during the fill process such as overfilling, empty vials and the removal of stoppers by a (b) (4).

3. Failure to establish and follow a written testing program designed to assess the stability characteristics of drug products [21 CFR 211.166(a)]. For example:

- a. There is no procedure which specifies where or when Pharmalgen stability samples are selected for testing.
- b. Since 2014, approximately 125 Pharmalgen, Grass and Ragweed drug product and drug substance samples were not tested at the required stability time points.

4. Failure to withhold from use each lot of components, drug product containers, and closures until the lot has been sampled, tested, or examined,

as appropriate, and released for use by the quality control unit [21 CFR 211.84(a)]. Specifically, there is no documentation that (b) (4) used during the Grass and Ragweed (b) (4) process is sampled, tested, or examined, and released for use by the quality control unit.

REVIEW OF YOUR INSPECTIONAL RESPONSES

We acknowledge receipt of your written response dated April 7, 2016, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection of ALK-Abello A/S, Horsholm, Denmark. Additionally, we acknowledge your commitments of corrective and preventive actions you have planned to address the above deficiencies. However, you have provided insufficient detail in your response. In many of your responses you simply indicate that the written procedures will be updated and training will be improved. Further information and discussion with ALK-Abello A/S will be necessary to adequately review and assess your planned actions. We also note the use of expired components in the manufacturing of Pharmalgen, including (b) (4). Please provide additional information on your actions to correct this issue and prevent recurrence.

Neither this letter, nor the observations listed on the Form FDA 483 presented at the conclusion of the inspection, is intended to be an all-inclusive list of deviations that may exist at your facility. We remind you that it is the responsibility of ALK-Abello A/S to ensure that your establishment is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, all applicable federal laws and regulations, and the standards in your license.

Your reply should be sent to me at the following address: US Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave. WO71 - G112, Silver Spring, MD 20993-0002. If you have any questions regarding this matter, you may contact Lisa Andersen, Consumer Safety Officer, in the Division of Case Management at (240) 402-6207.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Steven Haynes
US Agent for ALK-Abello, Inc.
Senior Manager of Regulatory Compliance