**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| Director, Division of Inspections and Surveillance; FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue (WO71-5128)<br>TEL: 240-402-9159<br>Silver Spring, MD 20993-0002<br>Email: CBER483responses@fda.hhs.gov<br>Industry Information: www.fda.gov/oc/industry | 04/27/2023-05/04/2023<br>FEI NUMBER<br>3002807751 |

| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED | |
|---|---|
| Mr. Preben Haaning, Senior Vice President | |
| TO:<br>FIRM NAME<br>Novo Nordisk A/S | STREET ADDRESS<br>Hallas Alle |
| CITY, STATE, ZIP CODE, COUNTRY<br>DK-4400 Kalundborg, Denmark | TYPE ESTABLISHMENT INSPECTED<br>Licensed Biological Manufacturer |

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:**

## OBSERVATION 1

Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to (b) (4) processing of (b) (4) Specifically,

Multiple mold recoveries were reported in Grade (b) (4) areas where (b) (4) (b) (4) are manufactured. Your written procedure, (b) (4) for handling of results from environmental samples from classified areas of Building (b) (4) did not require monitoring of bacterial and mold spore formers until September 2022.

For example,

| Occurrence date | Room/Sample type | Grade/ISO | Identification | Batch | Status |
|---|---|---|---|---|---|
| 9/7/2020 | Hallway, (b) (4) Air Sample, active | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | N/A | N/A |
| 9/7/2020 | Personnel/Glove | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | N/A | N/A |
| 10/28/2020 | Equipment storage, (b) (4) Surface | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | (b) (4) | Released (non-US) |

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (*Print or Type*) | DATE ISSUED |
|---|---|---|---|
| | /S/ | Prabhu P. Raju, Investigator<br>Unnee Ranjan, Investigator<br>Mikhail Ovanesov, Research Biologist<br>Sergey Akimov, Biologist | 05/04/2023 |

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| Director, Division of Inspections and Surveillance; FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue (W071-5128)<br>TEL: 240-402-9159<br>Silver Spring, MD 20993-0002<br>Email: CBER483responses@fda.hhs.gov<br>Industry Information: www.fda.gov/oc/industry | 04/27/2023-05/04/2023<br>FEI NUMBER<br>3002807751 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
Mr. Preben Haaning, Senior Vice President

| TO: FIRM NAME | STREET ADDRESS |
|---|---|
| Novo Nordisk A/S | Hallas Alle |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| DK-4400 Kalundborg, Denmark | Licensed Biological Manufacturer |

| | | | | | |
|---|---|---|---|---|---|
| 10/30/2020 | Hallway, (b) (4) Air Sample, active | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | | |
| 10/30/2020 | Hallway, (b) (4) Air Sample, active | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | | |
| 11/30/2020 | Hallway, (b) (4) Air Sample, active | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor/Penicillium chrysogenum | (b) (4) | Released (US) |
| 11/30/2020 | Personnel/Gown/mouth cover | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | | |
| 12/01/2020 | Personnel airlock, (b) (4) /Surface | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | (b) (4) | Released (non-US) |
| 12/10/2020 | Hallway, (b) (4) Air Sample, active | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor/Penicillium chrysogenum | (b) (4) | Released (non-US) |
| 12/12/2020 | Hallway, (b) (4) Air Sample, active | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor/Penicillium chrysogenum | N/A | N/A |
| 12/22/2020 | Personnel/Gown/mouth cover | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | N/A | N/A |
| 2/14/2021 | Hallway, (b) (4) Air Sample, active | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | N/A | N/A |
| 4/11/2021 | Hallway, (b) (4) Air Sample, active | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | N/A | N/A |
| 4/16/2021 | Personnel/Glove | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | N/A | N/A |

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (*Print or Type*) | DATE ISSUED |
|---|---|---|---|
| | /S/ | Prabhu P. Raju, Investigator<br>Unnee Ranjan, Investigator<br>Mikhail Ovanesov, Research Biologist<br>Sergey Akimov, Biologist | 05/04/2023 |

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| Director, Division of Inspections and Surveillance; FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue (W071-5128)<br>TEL: 240-402-9159<br>Silver Spring, MD 20993-0002<br>Email: CBER483responses@fda.hhs.gov<br>Industry Information: www.fda.gov/oc/industry | 04/27/2023-05/04/2023<br>FEI NUMBER<br>3002807751 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
Mr. Preben Haaning, Senior Vice President

| TO: FIRM NAME | STREET ADDRESS |
|---|---|
| Novo Nordisk A/S | Hallas Alle |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| DK-4400 Kalundborg, Denmark | Licensed Biological Manufacturer |

| | | | | | |
|---|---|---|---|---|---|
| 4/24/2021 | Personnel/Gown/mouth cover | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | N/A | N/A |
| 5/26/2021 | Personnel/Glove | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | (b) (4) | Released (non-US) |
| 9/26/2022 | Equipment storage, (b) (4) Surface | Grade (b) (4) ISO (b) (4) | Aspergillus terreus | (b) (4) | Released (US) |
| 9/27/2022 | (b) (4) room, (b) (4) Air Sample, active | Grade (b) (4) ISO (b) (4) | Byssochlamys spectabilis | | Four batches were rejected |
| 9/27/2022 | Personnel/Glove | Grade (b) (4) ISO (b) (4) | Byssochlamys spectabilis | | |
| 9/27/2022 | (b) (4) room, (b) (4) Settle plate | Grade (b) (4) ISO (b) (4) | Byssochlamys spectabilis | | |
| 9/28/2022 | (b) (4) room, (b) (4) Settle plate | Grade (b) (4) ISO (b) (4) | Byssochlamys spectabilis | | |
| 9/28/2022 | Cleaning room, (b) (4) Surface | Grade (b) (4) ISO (b) (4) | Chaetomium globosum | | |
| 9/28/2022 | (b) (4) room, (b) (4) Settle plate | Grade (b) (4) ISO (b) (4) | Byssochlamys spectabilis | | |
| 2/13/2023 | Personnel/Glove | Grade (b) (4) ISO (b) (4) | Aspergillus versicolor | (b) (4) | Quarantine |

## OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already (b) (4). Specifically,

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (*Print or Type*) | DATE ISSUED |
|---|---|---|---|
| | /S/ | Prabhu P. Raju, Investigator<br>Unnee Ranjan, Investigator<br>Mikhail Ovanesov, Research Biologist<br>Sergey Akimov, Biologist | 05/04/2023 |

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| Director, Division of Inspections and Surveillance; FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue (W071-5128)<br>TEL: 240-402-9159<br>Silver Spring, MD 20993-0002<br>Email: CBER483responses@fda.hhs.gov<br>Industry Information: www.fda.gov/oc/industry | 04/27/2023-05/04/2023<br>FEI NUMBER<br>3002807751 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
Mr. Preben Haaning, Senior Vice President

| TO: FIRM NAME | STREET ADDRESS |
|---|---|
| Novo Nordisk A/S | Hallas Alle |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| DK-4400 Kalundborg, Denmark | Licensed Biological Manufacturer |

a) Multiple mold recoveries were reported in the manufacturing areas of (b) (4) (b) (4) between September 2020 to May 2021 from ISO (b) (4) Grade (b) (4) area including hallway, personnel samples and equipment storage rooms. Materials including (b) (4) assembly parts that have been treated with (b) (4) are generally not wrapped, unloaded to hallway and transferred to equipment storage rooms. These parts are transferred as unwrapped to the (b) (4) rooms.

The firm's investigations (DV (b) (4) and INV (b) (4) ) concluded that the (b) (4) manufactured during this period were not affected as the disinfection step using (b) (4) for (b) (4) contact time, prior to the setup of (b) (4) unit, is efficient on molds/conidia. However, the disinfectant study ( (b) (4) test of (b) (4) on molds, dated 5/19/2021) did not include surface challenge tests to ensure that the disinfection is effective on all types of material transferred to Grade (b) (4) unit as unwrapped. Your firm released (b) (4) batches of (b) (4) manufactured during this period, including batch (b) (4) and (b) (4) to US market.

b) DV (b) (4) dated 1/17/2022, reported three consecutive bacterial infections in Building (b) (4) (b) (4) On 1/17/2022, a bacterial infection (*Ralstonia picketti)* occurred in the (b) (4) the batch was discarded, and an investigation was initiated. The bacterial infection was believed to be caused by a defective (b) (4) (b) (4) (b) (4) was cleared for production, and a new bacterial infection (*Ralstonia picketti*) occurred on 2/19/2022. A new root cause was found to be a (b) (4) . Inside this (b) (4) , there was stale water which was thought to be the origin of the infection. This was deemed to be the right root cause and (b) (4) was cleared for production. A new bacterial infection (*Ralstonia picketti)* occurred on 4/30/2022. A new investigation revealed a new root cause which was improper temperature of the (b) (4) which resulted in a wet (b) (4) Three total (b) (4) batches, (b) (4) were discarded, as a result of the three consecutive bacterial infections.

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (*Print or Type*) | DATE ISSUED |
|---|---|---|---|
| | /S/ | Prabhu P. Raju, Investigator<br>Unnee Ranjan, Investigator<br>Mikhail Ovanesov, Research Biologist<br>Sergey Akimov, Biologist | 05/04/2023 |

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| Director, Division of Inspections and Surveillance; FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue (W071-5128)<br>TEL: 240-402-9159<br>Silver Spring, MD 20993-0002<br>Email: CBER483responses@fda.hhs.gov<br>Industry Information: www.fda.gov/oc/industry | 04/27/2023-05/04/2023<br>FEI NUMBER<br>3002807751 |

| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED | |
|---|---|
| Mr. Preben Haaning, Senior Vice President | |
| TO:<br>FIRM NAME<br>Novo Nordisk A/S | STREET ADDRESS<br>Hallas Alle |
| CITY, STATE, ZIP CODE, COUNTRY<br>DK-4400 Kalundborg, Denmark | TYPE ESTABLISHMENT INSPECTED<br>Licensed Biological Manufacturer |

c) DV (b) (4) dated 12/22/2022, reported bacterial infection in (b) (4) Lot (b) (4) and the (b) (4) ( (b) (4) Lot (b) (4) ). The QA conclusion for this deviation determined the root cause to be similar to DV (b) (4) dated 8/24/2022, where loose (b) (4) on the (b) (4) created an entry point for microorganisms. The DV (b) (4) QA Conclusion also noted that that corrective actions from DV (b) (4) had not been implemented. DV (b) (4) documented that the bacterial infection of (b) (4) (b) (4) Batch (b) (4) was due to leakage from the (b) (4) and the root cause was missing procedures for examination of (b) (4) for leaks during (b) (4) and before starting a production batch. The equipment, (b) (4) were released for use, but there was no requirement to ensure that containment was in place if the corrective action could not be implemented immediately (ensuring that the (b) (4) is still tight when production starts, and didn't become loose during (b) (4)). (b) (4) Lot (b) (4) and (b) (4) Batch (b) (4) were rejected.

d) Major Deviations DV (b) (4) (occurred), DV (b) (4) (occurred 01-Apr-2021), and DV (b) (4) (occurred 10-Jun-2022) for exceeding internal (alert) release limits and/or external (approved) release limits for (b) (4) in (b) (4) (b) (4) and rFVIIa drug substance batches concluded that elevated (b) (4) was caused by a single batch of raw material (b) (4) (b) (4) batch (b) (4) which was found to contain atypical levels of (b) (4) and was removed from production. The (b) (4) (b) (4) batches affected by (b) (4) batch (b) (4) that were in compliance with external release limits, were released for (b) (4) (b) (4) The (b) (4) batches and associated drug substance (b) (4) batches, affected by (b) (4) batch (b) (4) were evaluated for compliance with external release limits but were not placed on stability program to confirm that (b) (4) rate is not increasedduring storage.

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (*Print or Type*) | DATE ISSUED |
|---|---|---|---|
| | /S/ | Prabhu P. Raju, Investigator<br>Unnee Ranjan, Investigator<br>Mikhail Ovanesov, Research Biologist<br>Sergey Akimov, Biologist | 05/04/2023 |

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| Director, Division of Inspections and Surveillance; FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue (W071-5128)<br>TEL: 240-402-9159<br>Silver Spring, MD 20993-0002<br>Email: CBER483responses@fda.hhs.gov<br>Industry Information: www.fda.gov/oc/industry | 04/27/2023-05/04/2023<br>FEI NUMBER<br>3002807751 |

| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED | |
|---|---|
| Mr. Preben Haaning, Senior Vice President | |
| TO:<br>FIRM NAME<br>Novo Nordisk A/S | STREET ADDRESS<br>Hallas Alle |
| CITY, STATE, ZIP CODE, COUNTRY<br>DK-4400 Kalundborg, Denmark | TYPE ESTABLISHMENT INSPECTED<br>Licensed Biological Manufacturer |

e) Major deviation DV-(b) (4) opened on 12-Sept-2022 for unapproved (b) (4) (b) (4) drug substance batch (b) (4) allowed for its use for (b) (4) production under condition that release specifications for drug substance (b) (4) are met. (b) (4) drug substance batch (b) (4) were not placed on stability program to confirm that unapproved (b) (4) procedure did not affect (b) (4) stability.

## OBSERVATION 3

(b) (4) processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce (b) (4) conditions. Specifically,

a) The procedure, (b) (4) version (b) (4) used for cleaning and disinfection of (b) (4) gloves, at Grade (b) (4) side of (b) (4) allows cleaning/disinfection from dirty to clean direction, for example, shoulder to fingertips. In addition, hold time is not established for the (b) (4) water for injection used for cleaning of (b) (4) gloves. Your procedure, (b) (4) version (b) (4) allows cleaning and reuse of (b) (4) gloves and they are replaced at a frequency of (b) (4) batches.

b) (b) (4) equipment ID (b) (4) used for drying of (b) (4) ( (b) (4) containing (b) (4) prior to July 2021, and (b) (4) after July 2021) are not monitored for microbial contamination. Multiple mold recoveries were reported in the manufacturing areas of (b) (4) between September 2020 to May 2021 from ISO (b) (4) Grade (b) (4) area and concluded that one of these (b) (4) was the source of contamination.

## OBSERVATION 4

| | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (*Print or Type*) | DATE ISSUED |
|---|---|---|---|
| SEE REVERSE OF THIS PAGE | /S/ | Prabhu P. Raju, Investigator<br>Unnee Ranjan, Investigator<br>Mikhail Ovanesov, Research Biologist<br>Sergey Akimov, Biologist | 05/04/2023 |

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| Director, Division of Inspections and Surveillance; FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue (W071-5128)<br>TEL: 240-402-9159<br>Silver Spring, MD 20993-0002<br>Email: CBER483responses@fda.hhs.gov<br>Industry Information: www.fda.gov/oc/industry | 04/27/2023-05/04/2023<br>FEI NUMBER<br>3002807751 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
Mr. Preben Haaning, Senior Vice President

| TO: FIRM NAME | STREET ADDRESS |
|---|---|
| Novo Nordisk A/S | Hallas Alle |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| DK-4400 Kalundborg, Denmark | Licensed Biological Manufacturer |

Complaint records are deficient in that they do not always include the findings of the investigation, the reason an investigation was not considered necessary, and appropriate follow-up. Specifically,

a) Complaint No: (b) (4) dated 7/16/2021, (b) (4) Batch (b) (4) reported (b) (4) cracked after it was prepared to be administered, and was not able to be administered to the patient. The Investigation Results conclusion section stated the (b) (4) was not returned for examination. This section did not include an assessment on whether there were other cracked (b) (4) complaints associated with this batch, if an abnormal trend was detected, and the rate of cracked (b) (4) complaints for previous batches manufactured.

b) Five (b) (4) complaints: (b) (4) (Batch (b) (4) ), dated 5/10/2021, (b) (4) (Batch (b) (4) ), dated 7/13/2021, (b) (4) (Batch (b) (4) ), dated 7/21/21, (b) (4) dated 10/8/2021, and (b) (4) dated 11/28/2022, reported the (b) (4) carton box was open, and there was no documentation of why assessing packaging box retains was not considered necessary. The individual complaint (b) (4) Complaint Reply Report conclusion sections state that cartons that are not completely closed will be rejected automatically during packaging.

***DATES OF INSPECTION**
4/27/23 (Thu), 4/28/23 (Fri), 5/1/23 (Mon), 5/2/23 (Tue), 5/3/23 (Wed), 5/4/23 (Thu)

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (*Print or Type*) | DATE ISSUED |
|---|---|---|---|
| | /S/ | Prabhu P. Raju, Investigator<br>Unnee Ranjan, Investigator<br>Mikhail Ovanesov, Research Biologist<br>Sergey Akimov, Biologist | 05/04/2023 |