DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue WO71 - 5118 Silver Spring, MD 20993-0002 TEL: (240) 402-8914	October 19-28 and November 6, 2015
	FEI NUMBER 3002807751

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Lars G. Karlsen, Senior Vice President Product Supply Quality

FIRM NAME	STREET ADDRESS
Novo Nordisk A/S	Hallas Alle 1
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
4400 Kalundborg Denmark	Drug Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. There is inadequate microbial control during the (b)(4) steps for factor VII drug substance. For example:

   a. There is no bacterial endotoxin testing of the (b)(4) harvest, or the (b)(4) eluate (b)(4) (b)(4)

   b. (b)(4) factor VII (b)(4) (b)(4) (b)(4) (b)(4) The exterior of the bottles are not cleaned or disinfected prior to this step.

   c. There is no bioburden or bacterial endotoxin testing of the (b)(4) tank prior to (b)(4)

2. There is inadequate control over unlabeled and labeled drug products. For example:

   a. Factor VII (b)(4) (b)(4) There is approximately (b)(4) staff that have access to this cooler for picking of material and approximately (b)(4) of the warehouse staff can scrap (discard) an unlabeled vial(s) if applicable.

   b. Rejected labeled and unlabeled drug product syringes such as Histidine solvent, Sodium Chloride syringes, and (b)(4) syringes have been sent to (b)(4) on several occasions. This facility is a warehouse and a contracted facility for cleaning of trays which are used to hold filled syringes prior to labeling & packaging operations.

3. There are no written procedures describing the practices of the warehouse personnel with respect to issuing and receiving labels from personnel on the packaging line. Specifically, two non-conformance reports were initiated where pre-printed labels containing lot numbers were received back into the warehouse and were subsequently issued to a packaging line to label the lot. Written procedures governing warehouse procedures are deficient in describing the responsibility with warehouse personnel to ensure printed labels are not returned to the warehouse and subsequently issued to another lot for labeling.

4. Excess labeling from packaging operations having the lot or control numbers is not destroyed. Specifically, while viewing the packaging of NovoSeven RT lot (b)(4) used cartons, package inserts and labels were not defaced before being discarded into waste bins.

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	Debra M. Emerson	Debra M. Emerson, CSO Simone E. Pitts, CSO	November 6, 2015

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5. A strict controlled environment is not maintained over labeling issued for use in drug product labeling operations. Specifically, there are approximately (b)(4) persons who have access to printed and un-printed labels stored in the labeling section of the warehouse. During a walkthrough of the facility on October 19, 2015, labels were found on shelves in clear plastic bags, clear hard boxes, cardboard boxes and opened on the shelving.

6. The following corrective and preventative actions were found inadequate:

a. Non-conformance investigation 3005673 describing a water breach from the cooling system surrounding Tank (b)(4) holding (b)(4) leaked into the holding tank due to an improper weld on the filter house. The length of time for the leak cannot be determined. The cooling liquid is made of (b)(4) (b)(4) and is circulated as a system to cool other tanks and subsequent filter housing. As part of the investigation, cooling liquid was analyzed and the microorganism *Bacillus thurengiensis* was recovered. No corrective actions have been initiated at the time of the inspection to clean, disinfect, sanitize or sterilize the cooling system.

b. Non-conformance 3007593 was opened for a contact sample which had 96 CFU's which included *Methylobacterium sp.* and spore-forming rods. This was a surface sample from the top of vessel (b)(4) in fermentation which has a limit of (b)(4) On 10/15/15, operators in fermentation were trained to wipe the top of the tank with (b)(4) after entering the tank and performing their cleaning operations.

c. Non-conformance 199148 was opened after tubes of microbial test organisms (such as *Pseudomonas aeruginosa, Exigobacterium multivorum, Sphingomonas multivarum, and Klebsiella pneumonia*) were placed into the (b)(4) containing Factor VII API. After later moving the microbial test organisms to a different (b)(4), the FACTOR VII bottles were wiped with (b)(4) and moved to a different (b)(4) while the first (b)(4) was cleaned. The firm did not provide data that wiping the bottles could remove the microbial organisms which had been stored in the (b)(4)

d. A scale was installed in the warehouse cooler which is to be used by warehouse personnel as a corrective action to multiple internal complaints for missing or too many drug product vials sent to packaging for labeling & packaging operations. The intent was to use the scale to count the vials. There was no training provided to warehouse personnel on how to use the scale or to tare a container.

7. After a viral contamination event occurs in the (b)(4) of Factor VII, the (b)(4) (b)(4) however as this process is a (b)(4) the site will go back and test a sample (b)(4) which takes about (b)(4) to complete. If this test is negative (b)(4) (b)(4) (b)(4) The firm has not been

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able to detect where the virus is entering the process. They believe that the (b)(4) is the source of the contamination but when they have tested the (b)(4) they have never gotten a positive result. Additional samples are not tested from the previous harvests in an effort to verify that virus is not present in low concentrations or non-uniformly throughout the fermenter.

8. After performing the initial cleaning validation on a piece of equipment or system, there is no procedure or requirement to repeat the cleaning validation or re-evaluate it. There have been two non-conformances generated because the original cleaning validation was insufficient or had been changed:

a. Non-conformance 216859 was opened 5/30/14 after two valves had been observed to have visible residue. The valves are associated with tank (b)(4) which holds sterile (b)(4). One valve is located above the tank and the second valve is located below the tank. The valves were opened as part of a cleaning verification after changing to (b)(4) No samples were taken of the residue observed on the valves for identification or microbiological testing. It was thought to be aggregated protein residue from previous batches which occurred because the flushing of one piping had been removed and the wash of the second valve and piping was insufficient. This event applied to (b)(4) tanks (b)(4) and a total of (b)(4) valves. The investigation states that this event affects product manufactured (b)(4) Quality approved the investigation 7/11/14 with no product impact.

b. Non-conformance 219603 was opened because residual water was detected inside piping for tanks (b)(4) and rouge was observed inside tank (b)(4) on 7/21/14. This equipment is used during (b)(4) for (b)(4) and was last cleaned on 6/26/14. There were no swabs taken inside the tanks or piping for microbiological testing. There was no bioburden or bacterial endotoxin testing of the remaining liquid inside the pipes/tanks. The investigation determined that not all piping was included/evaluated as part of the cleaning validation that had been performed between 2009 and 2010. Quality approved the investigation on 8/28/14.

9. Equipment which had been previously cleaned and verified cleaned by an operator was observed to contain residue on 10/20/15. For example:

a. Dried white residue was observed inside on the bottom of column (b)(4) which is used in the (b)(4) step. The column had been cleaned and verified cleaned on 9/6/15.

b. Dried white residue was observed inside the top of the column and spots on the bottom of column (b)(4) which is used in the (b)(4) step. The column had been cleaned and verified cleaned on 9/4/15.

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10. There has been no microbial evaluation for holding equipment wet after it has been cleaned. For example:

a. On 10/20/15, Tank (b)(4) used for (b)(4) was observed to contain a significant amount of residual liquid which covered more than 80% of the bottom of the vessel. This tank had been last sterilized on 10/16/15. The maximum hold time for this tank after SIP is (b)(4)

b. On 10/20/15, some residual liquid was observed on the bottom of tank (b)(4) This tank had been cleaned and sterilized on 9/4/15.

c. On 10/20/15, residual moisture of varying degrees was observed inside (b)(4) columns (b)(4) Column (b)(4) is used in the (b)(4) step and Column (b)(4) is used in the (b)(4) step, both columns were last cleaned on 9/3/15.

11. There is inadequate cleaning of the fermentation and purification areas. The following was observed on 10/20/15:

a. The bottom half of tank (b)(4) contained brown stains down the outside of the tank which were raised and had areas with white and black centers.

b. The trench next to the steam condenser in fermentation contained growth-like blobbed material as well as black mold-like material.

c. One leg for tank (b)(4) was observed to have black mold-like material on it.

12. Stability Acceptance criteria for the Master Cell Bank has not been established in that during the review of stability data for analytical testing; the results for total cell count and viability is only compared to the historical values from previous lots and not against an established acceptance criteria.

13. There is inadequate control over the access to stored (b)(4) There are (b)(4) staff who have access to the room, there are (b)(4) (b)(4) of these people need access to the (b)(4) as part of their job. Non-conformance 205533 was opened when an analyst placed 10 terminated culture samples from fermentation in this (b)(4), which is against the firm's operating procedures.

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