

Information Request, May 1, 2013 - Novoeight

From: Pracht, Leigh
Sent: Wednesday, May 01, 2013 11:54 AM
To: LEWP (Lewis Pollack)
Subject: STN 125466 Information Request
Our Reference: BL 125466/0
Novo Nordisk Inc.
Attention: Lewis Pollack, PhD
May 1, 2013
Sent by email

Dear Dr. Pollack:

We are reviewing your October 15, 2012 biologics license application (BLA) for Antihemophilic Factor (Recombinant), Plasma/Albumin Free [NovoEight]. We determined that the following information is necessary to continue our review:

The following comments are to get clarification and additional information about the manufacturing of the 0.9% NaCl diluent at -----(b)(4)----- facility in ---(b)(4)---.

1. You stated that visual inspection of the final product is performed per -(b)(4)- SOPs. Please describe the visual inspection procedure, what defects are being evaluated, what are the acceptance criteria, and the criteria for accepting or rejecting a lot. Please clarify if the inspection is manual, semi automated or automated.
2. You stated that container closure integrity ---(b)(4)--- test was performed on 0.9% NaCl PFS containing (b)(4) that had been subjected to -----(b)(4)----- cycles to cover a worst case scenario, and that no -----(b)(4)----- was detected by visual inspection. Please provide the studies performed to demonstrate the validation of this method – conditions under which ---(b)(4)--- was performed as well as positive and negative controls.
3. Please clarify if any part of the container closure system that is product contact contains latex. Aside from the depyrogenation of the syringe, do you evaluate and mitigate the endotoxin level of other product contact parts of the container closure? Please explain.
4. Please clarify if the filling equipment (or which part) is dedicated for the manufacture of 0.9% NaCl diluent. Please provide a summary of the validation studies performed to demonstrate cleaning and sterilization of the filling equipment.
5. You provided a summary report of the sterilization of the final product. Please describe the ---(b)(4)--- and the sterilization method. You stated that the -----(b)(4)-----

----- showed no -----(b)(4)----, please provide a schematic diagram showing the -----(b)(4)----- and the justification why they represent coverage

of the -----(b)(4)----- (and worst case ----(b)(4)----). Please also provide the -----
----- (b)(4)-----, and why these ---(b)(4)--- are
considered representative (or worst case) ---(b)(4)---.

6. Please list the number of --(b)(4)-- that support the production of 0.9% NaCl diluent and their uses.

7. You stated that equipment and primary packaging materials are sterilized using ----
---(b)(4)---. Please describe the ---(b)(4)-- and the sterilization method. Please provide
the sterilization validation studies, including the different (b)(4) qualified.

8. In section 3.2.A.1 Facilities and Equipment Report for Sodium Chloride manufacturing facility, you stated that Sodium Chloride is currently classified as a worst case substance for cleaning. Please provide results of studies performed to demonstrate that NaCl is the worst case soil, and provide summary reports of studies performed to validate the cleaning procedures.

9. You stated that CIP/SIP is used for cleaning and sterilization of equipment. Please describe the parameters used, and provide the results of studies performed to validate the CIP/SIP process. Please list the equipment cleaned/sterilized by CIP/SIP.

10. In the submission, there is a brief description of the facility water. As (b)(4) is used as an ingredient in the manufacture of the diluent, please describe your procedures for monitoring the quality of the (b)(4).

11. Please describe your procedures for packaging and shipping the 0.9% NaCl to Novo Nordisk facilities.

The following letter ready comments pertain to the manufacturing of Turoctocog alfa drug substance and drug product at Novo Nordisk facilities in Denmark.

12. Please submit the container closure testing performed to demonstrate the integrity of the container closure of the final drug product.

13. During the PLI, you stated that you implemented changes to the areas used for formulation and filtration of the drug product; and that (b)(4) Batches of Turoctocog alfa for clinical trials were manufactured -----(b)(4)----- (after implementing the changes) . Please submit the qualification of the area as an amendment to BLA 125466/0.

14. Please provide the EMPQ for the Grade (b)(4) areas in the (b)(4) facility, and include the frequency and acceptance criteria (alert and action limits) for routine monitoring.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response to this information request as an amendment to this file by May 17, 2013 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

The action due date for this file is October 15, 2013.

If you have any questions, please contact me at (301) 827-6116.

Sincerely,

Leigh A. Pracht

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