

Information Request, June 18, 2013 - Novoeight

From: Pracht, Leigh
Sent: Tuesday, June 18, 2013 12:44 PM
To: LEWP (Lewis Pollack)
Subject: Information Request STN 125466/0 June 18, 2013

Our Reference: BL 125466/0

Novo Nordisk Inc.
Attention: Lewis Pollack, PhD
June 18, 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:

Turoctocog alfa drug product

1. For the (b)(4)- sterilization (-(b)(4)-, Denmark), please provide the ----- (b)(4)-----, and justify why they are representative (worst case) of the ----- (b)(4)-----.

For (b)(4) sterilization (-(b)(4)-),

2. You stated that the sterilization (b)(4) are defined in the SOPs and validated. Please describe the sterilization (b)(4), and justify the -----(b)(4)----- in each validation (b)(4).

3. You reported in the BLA the sterilizing filters are sterilized -----(b)(4)-----, please describe the ----(b)(4)---- used for the sterilization of the filters.

4. The initial validation studies for the closures included separate validations for the stoppers and the caps. Please describe the validated (b)(4), and provide additional information to demonstrate that the validations are applicable to the stoppers and caps of turoctocog alfa drug product. Please justify the -----(b)(4)----- in each validation (b)(4).

5. For the re-validation studies of the closure -----(b)(4)-----, you stated maximum and minimum (b)(4) for closures – however you did not specify whether it was stopper or closure (b)(4). Please explain.

6. Please explain why the initial validation of the closures for ----(b)(4)--- was performed in 2011, and clarify whether this is the first validation of the closure (b)(4) in this -(b)(4)-.

7. For -----(b)(4)-----, please clarify what you mean by “the latest initial validation” performed for (b)(4) in 2012, and explain what prompted this validation. Please clarify if you performed -----(b)(4)----- to identify the worst case -----
----(b)(4)----- . Please justify your response.

Media Fills

8. You have submitted the media fill using the (b)(4) vials. Since the submission of the BLA you must have performed a media fill using (b)(4) vials. Please provide the most recent media fill using the (b)(4) vials. Also provide the environmental monitoring data collected during the media fill. Alternatively, please provide data from medial filled vials that bracket the (b)(4) size, provided that such vials use the same stopper/vial neck dimensions.

9. You state in the Process Performance Qualification Summary for Drug Product report (3.2.P.3.5 Process Validation for turoctocog alfa) that “the aseptic process is qualified by media fill, see 3.2.R Procedure and Specifications for Media fills”; however, this section is not included in the submission. Please provide the information.

Sterile Filtration

10. During validation of sterile filtration, two studies were performed for the bacterial retention evaluations: one using the 250 IU product and the other using the 3000 IU product. Please clarify why the two processes are run at different durations and flow rates.

Container Closure for turoctocog alfa

11. Please clarify if the stoppers are latex free and provide documentation to support that. Are the stoppers endotoxin free and has that been validated by the vendor and verified by Novo Nordisk (sampling of lots)?

12. You state that vials (used for filling) are cleaned by rinsing with (b)(4). Please provide the tests performed to ensure that the vials are free of particles prior to depyrogenation.

Lyophilization process

13. Please clarify if the current validated cycle for the lyophilization of turoctocog alfa is variable for the following parameters: time, temperature and pressure, and clarify how these three parameters (and their combined effect) are monitored and controlled throughout the lyophilization cycle.

14. In the Justification validation report you stated that during qualification you have placed (b)(4) on every shelf, yet during the justification validation, the sensors were placed in the -----(b)(4)----- . Please explain the rationale for using the -----(b)(4)----- - only, and why do you consider these points representative of the whole lyophilizer.

15. In the Justification process validation studies you reported that the lyophilization process was validated for the lowest, middle and highest concentration to cover the range (shelves -(b)(4)-). Yet you loaded shelves -----(b)(4)----- . So you did not provide data to support that the products lyophilized on those shelves meet the acceptance criteria. Please provide explanation/data to demonstrate that all products lyophilized on all shelves met the acceptance criteria.

16. You stated that sampling in duplicates was performed in a -----
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----- (b)(4) ----- for each of the justification studies. You also stated that samples for turoctocog alfa drug product were taken from shelf ----- (b)(4) ----- . Samples were also taken from ----- (b)(4) ----- for documentation of the lyophilization process. Please explain your rationale for not collecting samples from the other ----- (b)(4) ----- . In addition you sampled the challenged (---(b)(4)---) lyophilized turoctocog alfa drug product for water content, (b)(4), content, purity, (b)(4), anti-oxidant and ----- (b)(4) ----- . Please explain why you only tested these parameters, and not all the parameters tested during release of the product.

17. In the justification studies, you have reported that a number of vials were discovered broken following lyophilization. Please provide the investigation for the broken vials during the lyophilization justification studies, and describe the corrective methods that were implemented.

18. In Table 14 of eCTD 3.2.P.3.5 Process Validation – PPQ Summary for Drug Product, you did not describe all the defects as was the case in the justification studies. Please describe what you mean by the critical and non critical errors for stoppers, vials, capsules and lyophilized cake, and justify your characterization. Please provide the number of lyo cakes that are collapsed or melted.

19. In Table 22 of eCTD 3.2.P3.5, Process Validation: Process Verification for Lyophilization. Some defects (visual inspection) that were listed in the justification studies were not included in the verification study. Please provide the data for those defects. There are some defects described in the justification studies that were not included. Please provide the number of defective lyo cakes.

20. All the PPQ batches and the verification batches used (b)(4) for lyophilization. In addition you stated that “the latest initial validation” performed for ---(b)(4)--- was in 2012. Please describe the modifications to (b)(4) and whether they have been submitted to the agency. Please clarify whether you have revalidated (b)(4) for the manufacture of turoctocog alfa, and submit the relevant data.

Placement of scale on the Prefilled Syringe

21. The lab studies to verify that the attachment of the label to the syringe is accurate and durable are not sufficient to validate the process. During the PLI, Novo Nordisk stated that they completed the validation studies in 2013. Please provide the validation studies for the placement of the scale on the syringe.

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 provide shipping information, as a written amendment to this file, by July 2, 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

Regulatory Project Manager

FDA/CBER/OBRR/DBA

WOC1; RM562N; HFM-380

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