

Information Request Letter, April 9 2013 - Novoeight

Our Reference: BL125466/0

Novo Nordisk, Inc.

Attention: Cindy Cao, PhD

Sent by email

April 9, 2013

Dear Dr. Cao:

We are reviewing your October 15th, 2012 biologics license application (BLA) for Antihemophilic Factor (Recombinant), Plasma/Albumin Free [NovoEight]. We are providing the following comments and request for additional information to continue our review:

CHEMISTRY, MANUFACTURING AND CONTROLS

1. Regarding CHO-derived Anti-FVIII monoclonal antibody (mAb), please provide:

- a) Information on the specificity of the antibody, the analytical method used to establish its epitope recognition within the FVIII molecule, and the supporting experimental data.
- b) Information on the affinity of CHO-derived Anti-FVIII mAb for FVIII and the analytical method used to determine the binding constant. Please include this parameter (K_d) in the Release Specifications and in Stability Program for the end-of-study time point.
- c) Please add process-related impurities, -----(b)(4)-----, as Specification parameters, with established acceptance limits, or justify your decision not to include these parameters in Specification.
- d) Please submit up-to-date stability data for Anti-FVIII mAb and Anti-FVIII affinity matrix.

2. Regarding the purification process for turoctocog alfa Drug Substance, please submit the validation report for the claimed hold times for the intermediates for Steps -----(b)(4)-----.

3. Please re-submit results of Batch analyses for the PPQ batches (Drug Substance and Drug product) compared to the *final* specifications. For Drug Product PPQ batches please include Potency values determined by both the chromogenic substrate and one-stage clotting assays.

4. Please provide updated data from stability studies No. 717-S507, NovoDOCS: 001288236 and 001118375, and trend analyses of stability-indicating parameters.

5. Please provide updated data from stability study NovoDOCS: 001230802 for 0.9% sodium chloride solution.

6. Please note that viral clearance studies should include at least two enveloped viruses to represent a wide range of physico-chemical properties. Please add pseudorabies virus (PRV) as a model virus for large DNA enveloped viruses with medium resistance in your validation studies for the manufacturing processes of

turoctocog alfa and Anti-Factor VIII monoclonal antibody used in the affinity chromatography resin.

7. With reference to 3.2.A.2 Adventitious Agents Safety Evaluation,

a) In Table 4, please provide the actual clearance data for -----(b)(4)----- by the 20 nm nanofiltration step.

b) In Table 5, please provide the clearance data for -----(b)(4)----- by step (b)(4) (Anti-FVIII matrix affinity chromatography) after the resins were used (b)(4). Also, please provide Cumulative Reduction Factors (Total clearance) for all viruses with the used resins. If the steps were not evaluated, please provide justification.

Analytical Procedures and Assays

8. Please provide qualification reports for (b)(4), Particulate Matter and --(b)(4)-- that verify their suitability under actual conditions of use.

9. The provided verification data for Sterility of the final drug product (FDP) only support the system's capability to detect microorganisms. To verify its capability to assess sterility in the FDP, the test organisms should be spiked into the reconstituted FDP prior to the filtration and ---(b)(4)---. Please comment.

10. With reference to the validation of assays for Bacterial Endotoxin for -----(b)(4)- ----- final drug product, please clarify if an Endotoxin standard was spiked into the matrix as a positive control, and used to measure recovery. In addition, please submit the validation protocols for these studies.

11. With reference to your Response to Request 1 in the amendment dated 4 April 2013, you stated that the -----(b)(4)---- is -----(b)(4)----- -----(b)(4)----- is.

12. Please provide the following documents (or indicate where they may be located in the original application):

a) Validation of the FVIII Bethesda Assay (----- (b)(4) -----) for the Detection and Quantification of FVIII inhibitors in human plasma, Mar 2009

b) LKF WP 0096 (FVIII-Inhibitor (----- (b)(4) -----), Version 1.00, May 2009; Version 2.00, Nov 2009; Version 3.00, Sep 2010, Version 4.00, Nov 2011.

CLINICAL

13. We are unable to verify the trial results using the datasets and pdf files that you submitted in the original BLA submission. To evaluate the inhibitor rate, annualized bleeding rate and hemostatic efficacy we will need the relevant data files in SAS format, the corresponding readme files that explains each data file, and the program codes used to generate the study results. Please provide the following data in SAS format for each trial and for pooled trials separately:

a) Inhibitor test dates and titer results for each of the pre-specified testing dates

b) All bleeding episodes, including cause of bleed, site of bleed, number of infusions required, hemostatic rating

c) Relevant baseline characteristics, including subject age, region (country and site), prophylaxis regimen, exposure days, and type of surgical procedure.

14. In Appendix I, Table 23 of the Summary of Clinical Safety, you provide anti-CHO test results for subjects with at least one positive test. However, you have not submitted the titers for each test. Please submit in tabular format a list of all subjects with positive anti-CHO antibodies, their FVIII regimen prior to enrollment, and the titer results at each

pre-specified testing dates. FDA needs this information to assess changes in titers after repeated exposure to the product.

Human Factors

15. You reported one count of a hemophilia HCP drawing the full amount of mixed drug instead of the calculated dose, which could lead to dosing errors (underdosing/overdosing). You also reported one count of an ER nurse while preparing a 3mL calculated dose, they first emptied 1 mL of solvent from 4 mL prefilled syringe prior to reconstitution, which we were not clear of potential clinical consequence. Both of these counts were observed while the participants were performing the calculated dose scenario. Review of your Instructions for Use revealed that the critical task of drawing draw out a specified volume of the reconstituted drug into the syringe (less than the full contents of the reconstituted solution) does not appear to adequately draw the reader's attention to that task. Please revise your Instructions for Use to address this concern.
16. You reported several counts of performance that could lead to contamination (two counts of an adult participant touching the top of the syringe while removing air bubbles; and four counts of 1 child/adolescent, 2 haemophilia HCPs, and 1 ER nurse of not cleaning the rubber stopper with an alcohol swab). Six counts of ER nurses removing the vial adapter with fingers from protective cap, but did not touch fluid path. We suspect that these actions might also lead to contamination. Review of your Instructions for Use revealed that it does not communicate the negative consequence of contaminating the product while assembling the components, and the importance of cleaning the rubber stopper, not touching the syringe while removing air bubbles, and not using fingers to remove the vial adapter. Please revise your Instructions for Use to address this concern.
17. You reported four counts of ER nurses did not remove the protective cap correctly leading to removal and then remounting of the adapter. The success criteria specified that the participant would not be able to continue if this task fails. Unclear if participants did not remove the protective cap correctly would be considered as task failures. Please provide a clarification.
18. You reported multiple counts of assembling the components not according the sequence specified in the Instructions for Use. However, you did not discuss whether any of the techniques applied by these test participants had any potential negative consequences to the patient or the user. Please note that if any of the techniques applied could result in patient harm, the Instructions for Use/labeling should be modified to warn users of those potential consequences. Please provide a clarification.

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 the clinical data in SAS format (comment #13) at your earliest convenience, and your response to other comments of this information request as an amendment to the BLA file by May 13th, 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 16th, 2013.

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

Sincerely,
Leigh Pracht
Regulatory Project Manager
FDA/CBER/OBRR/DBA/RPMB

Page Last Updated: 03/12/2015

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