

Information Request Letter, June 24, 2013 - Novoeight

Our Reference: BL125466/0

Novo Nordisk Inc.
Attention: Lewis Pollack, PhD
June 24, 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:

1. Regarding the acceptance criteria for -----(b)(4)----- in the Drug Substance Specification, the results of batch analyses (section 3.2.S.4.4) indicate that the (b)(4) levels are consistently lower than the proposed acceptance limit of ---(b)(4)--- (equivalent to -----(b)(4)----- of FVIII). Please tighten the acceptance limit for (b)(4) based on the manufacturing capability, or provide a risk assessment based on data to justify the proposed (b)(4) level of --(b)(4)--.
2. -----(b)(4)----- impurities in Drug Substance and Drug Product are assessed by -----(b)(4)----- determined by ---(b)(4)---. To better represent all (b)(4) impurities, please use the -----(b)(4)----- to calculate the percentage, and revise the acceptance criteria for (b)(4) impurities in the Drug Substance and Drug Product Specifications accordingly.
3. Specific Activity is not included in Drug Product Specification based on the reasoning that it can be calculated from the Specification parameters *Content* and *Potency*. Please include *Specific Activity*, as a parameter to define product purity, in the Drug Product Specification.
4. Acceptance limit for *Endotoxin* is calculated based on requirements of -----(b)(4)-----" which results in increasing acceptance limits for higher dosage strengths (e.g., from -----(b)(4)-----). The release and 18-month long-term stability data indicate that the Endotoxin levels in the Drug Product, even at the highest dosage strength (3000 IU), are -----(b)(4)----- . To better ensure product safety and represent manufacturing capability, please tighten

the limit of *Bacterial Endotoxin* and use one limit for all dosage strengths in the Release and Stability Specifications based on your manufacturing experience.

5. Please correct the dilution factor of samples from ----(b)(4)---- in the Endotoxin Validation Report and revise the Report accordingly (Sequence #0010 dated 15 March 2013).
6. Analyses of Excipients are not included in Drug Product Specification based on the reasoning that --(b)(4)--- is an adequate indicator of excipient concentrations and (b)(4) is an indicator for Histidine content in the reconstituted product. However, ---(b)(4)--- does not provide information on the relative contents of the excipients, and (b)(4) does not measure the exact amount of Histidine in a solution. Therefore, please include quantitative measurements of excipients (calcium chloride, sodium chloride, L-Histidine and Sucrose) in the Drug Product Specification.
7. Recommendations regarding the Labeling (Prescribing Information and vial/carton labels) will be provided as part of the labeling review. In particular, please:
 - a. Use the proper name *Antihemophilic Factor (Recombinant)* in the labeling and remove definition Plasma/Albumin-Free.
 - b. Provide respective details of the manufacturing process in section 11
Description: "No additives of human or animal origin are used in the production (the cell culture and purification processes) or in the formulation of NovoEight."
 - c. Indicate the *actual* potency of the NovoEight lot in International Units on the vial and carton labels.
8. With reference to Table 3 in the file named novoDOCS:001161268, Novo is planning to keep sterility testing but remove the parameter bacterial endotoxin from the proposed on-going stability protocol. Considering that sterility testing has its scientific and practical limitations, please also keep the parameter bacterial endotoxin in this protocol through its shelf-life.
9. The acceptance criterion of Purity is set to be --(b)(4)-- in all stability protocols, whereas all stability data provided in the submission indicated that the test results for purity were (b)(4). To better control product quality and represent manufacturing capability, please revise the acceptance criterion of Purity.
10. Regarding batch ---(b)(4)--- in the in-use stability study (novoDOCS:001118426), the test result of -----(b)(4)----- was out of the specification of (b)(4) at the 4-hour time-point during storage at 30°C after reconstitution. Please provide data to support the proposed in-use stability of the reconstituted final product for 4 hours at 30°C.
11. Please confirm the following Post Marketing Commitment (PMC):

Novo Nordisk commits to include at least one commercial batch each of 500 IU, 1000 IU, and 1500 IU strengths in their stability study, and these batches should be

monitored under the referenced storage conditions as described on page 4 of 11 of the document novoDOCS: 001161237. The interim stability data from these batches should be submitted as annual updates (PMC Submission – Status Update) through the dating period, and a final report should be submitted within 3 months of completion (PMC Submission – Final Study Report).

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 July 29, 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 Pracht
Regulatory Project Manager
FDA/CBER/OBRR/DBA/RPMB

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