

Our Reference: BLA 125611/0

Novo Nordisk Inc.
Attention: Ms. Patricia D. Wilson
November 22, 2016
Sent by email

Dear Ms. Wilson:

We are reviewing your May 16, 2016 biologics license application for Coagulation Factor IX (Recombinant), GlycoPEGylated. We are providing the following comments and request for additional information to continue our review based on your amendment received on September 30, 2016 (eCTD sequence 0011):

1. Potency by One Stage Clotting Assay

- a. The modified (b) (4) analyses may address intermediate precision but not repeatability. Please provide repeatability data as previously requested.
- b. It is our understanding that linearity may be determined by ANOVA analysis, but not by F-test, however, this may be a semantic issue. Please describe your method of analysis and provide representative calculations for your F-test.
- c. Your parallelism criterion of (b) (4) is too relaxed as is obvious from the Response to Information Requests, Amendment 11, Fig. 3. Please provide the actual p-values you obtained to date for the lot-release testing and stability studies of your drug. Please let us know how many of the analyses would have been invalid if the p value is set at (b) (4)
- d. Please provide a comparison of the upper and lower asymptotes and the slope ratio between the test sample and standard to demonstrate method linearity.

2. (b) (4) Content by (b) (4) Assay

- a. You have shown results in the Response to Information Request, Amendment 11, to indicate that your LOQ is (b) (4) . Please explain with data why you adapted (b) (4) as the LOQ. Please provide precision and accuracy data at your adapted LOQ, (b) (4) . Alternatively, revise your validation report to reflect (b) (4) as the LOQ. Also, please revise your SOP to express any results above (b) (4) as the true value, and any values (b) (4) as <LOQ.
- b. The modified (b) (4) analyses may address intermediate precision but not repeatability. Please provide repeatability data as previously requested.

- c. For your robustness study on selected operational parameters you only provide system suitability data. This does not show evaluation of the method robustness. For robustness demonstration, you need to provide data for the drug product. Please provide adequate robustness data with your drug product with small deliberate variation of the experimental parameters.

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 and your notification of the shipment for this request as an amendment to this file by December 13, 2016 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.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is June 3, 2017.

Please send an acknowledgement message for receipt of this request.

If you have any questions, please contact me at (240) 402-8443.

Sincerely,
Edward Thompson
Regulatory Project Manager
FDA/CBER/OTAT/DRPM