



Our Reference: BLA 125611/0

Novo Nordisk Inc.
Attention: Ms. Patricia D. Wilson
October 21, 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:

1. For analytical procedure (b) (4) "Protein Content and (b) (4) (novODOCS ID 001357555):
 - a. A (b) (4) containing (b) (4) is used. Please provide data to demonstrate that (b) (4) of the protein is not affected by such high level of (b) (4). In particular, we are concerned about the change in (b) (4) content of the sample. Please provide data that show that (b) (4) contents in (b) (4) DP are not altered by your assay method.
 - b. Please describe in detail how the peak area integration is done using necessary extended chromatograms to (b) (4)
2. For "Validation of Analytical Procedure (b) (4) Protein Content and (b) (4) (novODOCS ID 001713052):
 - a. You have not provided sufficient data to demonstrate the accuracy of the (b) (4) determination. We do not agree that accuracy can be inferred automatically from the results of the specificity, linearity and precision. Please provide details of your data analysis to show how you inferred accuracy of your method from the results of the specificity, linearity and precision. Alternatively, you may demonstrate the accuracy of the (b) (4) determination from (b) (4) studies or by comparing results obtained using an (b) (4) method.
 - b. In section 6.6 "Detection and quantitation limit (DL/QL)", you determined the QL to be (b) (4) which apparently has (b) (4) peak area equivalent to (b) (4)

- (b) (4) sample which has (b) (4). We do not agree with your approach to determine QL/DL. Please provide data supporting QL by either using a sample containing (b) (4) percent with (b) (4) from the (b) (4) peak plus adequate precision and accuracy of the measurement, if such sample is available, or by plotting (b) (4) peak area versus (b) (4) percent with at least (b) (4) levels close to anticipated QL and using the equation (b) (4), where σ stands for the standard deviation of the peak area and S for the slope of the linear regression.
- c. Please provide the actual test results and the statistical evaluation of your results to support your conclusion for the robustness study in section 6.7.
3. For the analytical procedure (b) (4) (novoDOCS ID 001742468) "Identity, PEG Profile and Product Related Impurities by (b) (4)", the peak which represents the rFIX (b) (4) (pages 14-15). Please describe in detail, including figures, how the (b) (4) between rFIX (b) (4) and rFIX is determined for the integration of these peaks in order to calculate the rFIX (b) (4) and rFIX percentages consistently.

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 November 3, 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