



Our Reference: BLA 125611/0

Novo Nordisk Inc.  
Attention: Ms. Patricia D. Wilson  
October 24, 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. Regarding 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 (b) (4)
2. Regarding "Validation of Analytical Procedure (b) (4) Protein Content and (b) (4) (novoDOCS ID 001713052)
  - a. We do not agree that accuracy can be inferred automatically from the results of the specificity, linearity and precision. You have not provided any data to demonstrate the accuracy of the (b) (4) determination. 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 limit and quantitation limit (DL and QL)", you determined the QL to be (b) (4)

- (b) (4). We do not agree with your approach to determine QL/DL. Please provide data supporting QL by either using a drug product sample containing (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  $\sigma$  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. Regarding "Validation of Analytical Procedure (b) (4) Identity, PEG Profile and Product Related Impurities by (b) (4) (novoDOCS ID 001745960):
- a. Please provide peak percentages of mono PEG rFIX, (b) (4) rFIX (b) (4) and total impurities of the sample used for the linearity study in section 6.1.
- b. As discussed above, accuracy of PEG rFIX, PEG rFIX related product and impurities cannot be automatically inferred from the outcome of linearity, specificity and precision for this critical assay. 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 accuracy from your results of spike-recovery studies for each of rFIX, (b) (4) and total impurities for applicable ranges in reportable percentage up to their specification values for this product. Accuracy for these components may also be demonstrated by comparing the results of (b) (4) method(s).
- c. In section 6.7 you determined rFIX QL to be (b) (4) by evaluating the precision of the (b) (4). We do not agree with such approach for the determination of QL. Please provide supporting data for QL for each of total impurities, rFIX (b) (4) rFIX and rFIX separately for this assay. QL should be determined by using (b) (4) and adequate precision and accuracy of the measurement, if such samples are available. Alternatively QL can be determined from the plot of peak area against peak percent of total impurities, rFIX (b) (4), rFIX (b) (4) rFIX and rFIX, each (b) (4) levels of peak area and using the equation,  $QL = (b) (4)$  where  $\sigma$  stands for the standard deviation of the peak area and S for the slope of the linear regression.

- d. Please provide the actual test results and the statistical evaluation to support your conclusion for the robustness study in section 6.8.
4. Regarding analytical procedure (b) (4) "Identity by (b) (4) (novODOCS ID 001990709), please add acceptance criteria of column (b) (4) as part of the SST in section 11.
5. Regarding "Validation of Analytical Procedure (b) (4) Identity by (b) (4) by (b) (4)" (novODOCS ID 001990724), please provide details of test results and the statistical evaluation of the robustness study to support your conclusion in section 5.2.
6. Regarding "Validation of Analytical Procedure (b) (4) Purity of rFIX (b) (4) by (b) (4)" (novODOCS ID 002326601):
- a. Please provide the correlation coefficient value for Figure 3 (page 9) in the linearity study.
- b. Accuracy cannot be automatically inferred from the outcome of linearity and precision studies. 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 accuracy of the rFIX purity from (b) (4) studies or by comparing results obtained using an (b) (4) method.
- c. Please provide details of the test results and the statistical evaluation of the robustness study to support your conclusion in section 6.7.
7. Regarding analytical procedure (b) (4) "Product related impurities by (b) (4) (novODOCS ID 001893633), please identify the rFIX (b) (4) in the chromatograms of (b) (4), DP and control shown in appendixes B-E and provide data in support of your identification.
8. Regarding "Validation of Analytical Procedure (b) (4) Product related impurities by (b) (4)" (novODOCS ID 001893669):
- a. You plotted total peak area of (b) (4), which does not show linearity of individual impurities. This method is used for the determination of product-related impurities for rFIX (b) (4) and (b) (4) separately. Therefore, please provide linearity plots of peak area of rFIX (b) (4) and peak area of PEG rFIX (b) (4) separately, including their slopes and their respective correlation coefficients to support linearity for both impurities.

- b. You have not provided any data to demonstrate the accuracy of the assay. Please provide accuracy data from appropriately conducted studies. We suggest that you either perform (b) (4) study or use an (b) (4) method to support the accuracy of the method.
  - c. Please provide details of the test results and the statistical evaluation of the robustness study to support your conclusion in section 6.6.
9. Please provide the analytical procedure/standard operating procedure of "Water Determination by (b) (4)
10. We do not agree that Water Determination by (b) (4) is a (b) (4) method and verification (novoDOCS ID 002260532) of the method is sufficient. For a method to be (b) (4), there has to be a monograph of the article ((b) (4) drug product) in (b) (4) to which the method is referenced. Please provide a complete validation of the (b) (4) method for your drug product. The range of water determination in weight should have adequate coverage of the water level in a typical DP sample. Your validation should include results for the determination of QL of the method because this is a quantitative test for residual moisture and is used as a reference/alternative method for lot release.
11. Regarding "Validation of Analytical Procedure (b) (4) Water Determination by (b) (4)" (novoDOCS ID 002013793):
  - a. Please provide the variation ranges of matrix components, especially the contents of mannitol, sucrose and polysorbate 80 in the samples used for calibration (Table 17, page 37). It is important for the established model to have a full coverage of the proposed specification ranges (polysorbate 80 (b) (4), sucrose (b) (4) and mannitol (b) (4) for these three OH containing components in the DP matrix to demonstrate the specificity of the method. (b) (4) moisture determination is only applicable to DP samples with matrix component ranges covered by the calibration model.

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 7, 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

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