

Our Reference: BLA 125611/0

Novo Nordisk Inc.
Attention: Ms. Patricia D. Wilson
January 17, 2017
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:

Please reference your response submitted on November 14, 2016 and November 28, 2016 that have been designated as amendments 17 and 19 respectively:

1. In the response to the question 2a of our IR dated Oct. 24, 2016, you provided a discussion of three different types of bias to justify your inference of accuracy from linearity, specificity and precision, and data to show that the constant bias is small for this assay. The figure associated with your response 2a is cut off in such a way that it is not possible for us to have an estimate of this assay constant bias . In addition, you have not provided R2 value for line B [forced through (0,0)], which did not permit us to assess correlation between line B and the actual data points. Furthermore, the three types of bias you indicated in your response assume no interaction between the analyte and the stationary phase under the elution conditions. However, there is ample literature reference indicating interactions between the (b) (4) and the stationary phases of chromatography columns. Thus, you have not provided any information that would conclusively justify inferring accuracy of this assay based on linearity, precision and specificity of the method. Please provide the complete data as we requested on Oct. 24, 2016 to permit us to complete our review on time. Furthermore, several methods have been reported in the literature to generate the (b) (4) rich sample and may be done easily. . Samples, enriched in (b) (4) , may be spiked for accuracy evaluation.
2. Please provide appropriate data to show that (b) (4) in your product are not retained by the column under the proposed chromatography condition in the analytical procedure (b) (4) "Protein Content and (b) (4) (novodoCS ID 001357555).
3. In the response to the question 2b of our IR dated Oct. 24, 2016, we do not agree with your calculation of the (b) (4) in your precision study. In addition, the formula of (b) (4) cannot be used for the LOQ

calculation from multiple measurements of the same sample. Both σ and S values are determined from a linear plot of peak area versus aggregate peak percent with at least three different aggregate peak percents in the samples. (You may consult ICH Q2(R1) (p. 12) for more details on how to determine LOQ from (b) (4). Please provide LOQ for (b) (4) from either appropriately determined (b) (4) or (b) (4). You may use the method for the determination of (b) (4) described in (b) (4) General Chapter (b) (4)

4. In the response to the question 3b of our IR dated Oct. 24, 2016, you did not provide accurate data as requested. We do not agree with your justification supporting inference of accuracy from linearity, specificity and precision, the details of which we have discussed above under question #1. Please provide the data as we requested on Oct. 24, 2016.
5. Please provide appropriate data to show that the chromatogram shows all impurities present in (b) (4) DP samples and none of them are retained by the column for the analytical procedure (b) (4) "Identity, PEG Profile and Product Related Impurities by (b) (4) (novoDOCS ID001742468).
6. In the response to the question 3c of our IR dated Oct. 24, 2016, we do not agree with the calculations for the (b) (4) and the equation (b) (4), as discussed above under Question 3. Please provide appropriate data on the determination of the LOQ values for rFIX, (b) (4) rFIX, rFIX (b) (4) and rFIX (b) (4) (all in peak percentage).
7. In the response to the question 3d of our IR dated Oct. 24, 2016, you submitted robustness study results, which show that (b) (4) has a significant influence on the results. The (b) (4) shows poor separation of (b) (4) (unknown impurity). However, your analytical procedure (b) (4) continues to allow the (b) (4), which is not supported by your robustness study. Please revise your analytical procedure (b) (4) per your robustness evaluation results.
8. In the response to the question 6b of our IR dated Oct. 24, 2016, you did not provide the accurate data as requested. We do not agree with your justification supporting inference of accuracy from linearity, specificity and precision, the details of which we have discussed above under question #1. Please provide data as we requested on Oct. 24, 2016.
9. In the response to the question 7 of our IR dated Oct. 24, 2016, you stated that you collected the (b) (4), DP and the control samples. However, you only provided the N-terminal amino acid sequence and (b) (4) test results for (b) (4). Please provide the test results from DP and the control fractions to support your conclusion.

10. In the response to the question 8b of our IR dated Oct. 24, 2016, you did not provide accurate data as requested. We do not agree with your justification supporting inference of accuracy from linearity, specificity and precision, the details of which we have discussed above under question #1. Please provide data as we requested on Oct. 24, 2016.
11. Please provide appropriate data to show that the chromatogram shows all impurities present in (b) (4)/DP samples and none of them are retained by the column for the analytical procedure (b) (4) "Product Related Impurities by (b) (4) (novoDOCS ID001893633).
12. The chromatograms you provided in the analytical procedure (b) (4) "Product Related Impurities by (b) (4) show a significant shoulder peak for the main peak of nonacog beta pegol for (b) (4) DP samples. Please identify the shoulder peak with the supporting data. Furthermore, please explain the reason that the chromatograms obtained by the analytical method (b) (4) "Identity, PEG Profile and Product Related Impurities by (b) (4) " (novoDOCS ID001742468 Figures 4 and 5) doesn't have the same peak for the nonacog beta pegol samples.
13. Please add details of your typical sample injection sequence including blank, control and sample injections and the procedure for sample mass determination to your "Analytical Procedure (b) (4) (novDOCS ID003214103) and submit for review.
14. We do not agree that (b) (4) method is a (b) (4) method as has been discussed in the question 10 of our IR dated Oct. 24, 2016. Please provide a complete validation for the method with your drug product samples.

The review of this application is on-going and issues may be added, expanded upon, or modified.

Please submit your response and your notification of the shipment for this request as an amendment to this file by January 31 2017, 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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