



Our Reference: BLA 125611/0

Novo Nordisk Inc.
Attention: Ms. Patricia D. Wilson
September 13, 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:

We have reviewed the following quality control assays for the drug product and their validation reports submitted to this application.

Potency by One Stage Clotting Assay

1. Validation of Analytical Procedure, M056, Potency by One-Stage Clotting Assay
 - a. For accuracy, you have measured the recovery of nonacog beta pegol reference material at (b) (4) of the target potency (b) (4) in drug product placebo. Please provide details of the composition of the drug product placebo.
 - b. Your recovery results failed to meet your acceptance criteria at (b) (4) (Table 4, page 10 of your validation report). Please explain why the results are acceptable to demonstrate the accuracy of your method.
 - c. To demonstrate your method accuracy please provide R^2 and slope of the measured potency (U/mL) plot vs. nominal potency (U/mL) of the reference material, presented as Figure 2 in your validation report.
 - d. You have demonstrated repeatability and intermediate precision by measuring (b) (4) drug product in (b) (4) days. Please provide repeatability data from (b) (4) measurements of your drug product at the target concentration or at (b) (4) concentrations over the assay range each in (b) (4), measured under the same experimental condition.

- e. For your linearity study you set the F-test for parallelism between sample and reference curves as (b) (4). We do not agree that setting (b) (4) provides an appropriate measure of parallelism. Please provide data demonstrating parallelism of your drug product at (b) (4), as well as representative plots.
- f. You examined robustness by altering the (b) (4) of the assay buffer. Please provide the data of your robustness studies.

(b) (4) Content by (b) (4)

2. Validation of Analytical Procedure, (b) (4)

- a. In your linearity study, you provided data demonstrating linearity of your reference standard. Please provide data demonstrating linearity of your drug product over the range of the test as well as representative plots. Please demonstrate dilution parallelism between your drug product and reference standard by providing the slope ratios between reference standard and drug product.
- b. Please calculate your LOQ based on your drug product and not your reference material. Also, please note that the correct formula for LOQ calculation is:
(b) (4)
Whereby QL = Quantitation limit, σ = standard deviation of the response and S = slope of the curve (see, for example, the ICH Q2 guideline, page 12).
- c. You have measured repeatability and intermediate precision in (b) (4) independent runs performed by (b) (4) technicians using different batches of assay buffer and placebo buffer. Please provide repeatability data from (b) (4) measurements of your drug product at the target concentration or at (b) (4) concentrations of your drug product each in (b) (4), measured under the same experimental condition.
- d. You have examined robustness by altering the time for the (b) (4), and time from (b) (4) and reading the plate, as well as measuring the effect of (b) (4) on sample stability. Please provide the data of your robustness studies.

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 notification of the shipment for this request as an amendment to this file by September 30, 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.

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Thank you

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/OBRR

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Thank you