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**To** STN: #125611/0

**Through** Lokesh Bhattacharyya, DBSQC/OCBQ  
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**Sponsor** Novo Nordisk Inc.

**Product** Coagulation Factor IX (Recombinant), glycoPEGylated

**Subject:** Primary Discipline Review Memo for Quality Control Lot-release Test Methods in BLA for Coagulation Factor IX (Recombinant), glycoPEGylated

### Summary of Review

A new BLA was submitted for Coagulation Factor IX (Recombinant), glycoPEGylated by Novo Nordisk Inc. (STN: 125611). This is the Primary Discipline Review memo for the quality control lot-release test methods for the drug Product, and includes the following analytical methods and their validations, which were used for the lot release testing of the drug product.

1. Determination of Polysorbate 80 by (b) (4)
2. Determination of Sucrose and Mannitol contents by (b) (4)
3. (b) (4)
4. Appearance of Lyophilized powder
5. Appearance of Reconstituted solution and Reconstitution time
6. (b) (4)
7. Particulate matter (b) (4)

Based on the review of the original BLA submission and subsequent responses to the information request (IR) from Novo Nordisk, it is concluded that the above mentioned methods have been described and validated adequately for their intended use.

### Background

Novo Nordisk Inc. submitted a new BLA for a drug product (Nonacog beta pegol), which is a recombinant Coagulation Factor IX, glycoPEGylated. It is indicated for use in adults and children diagnosed with hemophilia B for control and prevention of bleeding episodes, perioperative management and routine prophylaxis. The drug product is a sterile lyophilized powder for intravenous infusion after reconstitution with histidine solution.

The drug product will be available in single-use vials containing 500, 1000, or 2000 International Units (IU) per vial, and is supplied with a pre-filled diluent syringe and vial adapter. The nonacog beta pegol drug product is reconstituted in a 10 mM Histidine solution prior to use.

### Submitted Information Reviewed

This is an electronic submission. Information submitted and reviewed includes:

- 125611/0 – Cover Letters Dated May 16, 2016; September 30, 2016; February 16, 2017
- 125611/0 – 3.2.P.5.1 Specification for Drug Product
- 125611/0 – 3.2.P.5.2. Analytical Procedures
  - Overview of Analytical Procedures for Drug Product
  - SOP (b) (4) – Quantitative Determination of Polysorbate 80 by (b) (4) .
  - SOP (b) (4) – Quantitative Determination of Sucrose and Mannitol by (b) (4) .
  - SOP (b) (4) – Analytical Procedure for Appearance of Powder and Reconstitution Time.
- 125582/0.0 – 3.2.P.5.3 Validation of Analytical Procedures
  - NovoDOCS ID 001870476 – Validation of Analytical Procedure (b) (4)
  - NovoDOCS ID 002197136 – Validation of Analytical Procedure (b) (4)
  - NovoDOCS ID 001859331 – Validation of Analytical Procedure (b) (4)
  - NovoDOCS ID 002255855 – Verification of (b) (4) Procedure (b) (4)
  - NovoDOCS ID 002266024 – Verification of (b) (4) Procedure “Particulate Matter (b) (4)”
- 125611/0.11 1.11.1 Quality Information Amendment: Response to FDA information request dated 12 September 2016, Received on 30 September 2016
- 125611/0.37 1.11.1 Quality Information Amendment: Response to FDA information request dated 2 February 2017, Received on 16 February 2017
- 125611/0.44 1.11.1 Quality Information Amendment: Response to FDA information request dated 2 February 2017, Received on 24 March 2017

### Review Narrative

#### 1. Determination of Polysorbate 80 by (b) (4)

Polysorbate 80 is an excipient in nonocog beta pegol drug product. The specification is (b) (4) polysorbate 80/mL in nonocog beta pegol drug product of different strengths.

#### Method

The polysorbate 80 (PS80) in nonacog beta pegol drug product is determined by (b) (4)

(b) (4)

(b) (4)



Method Validation

This is a quantitative assay method. For the validation of this method the following characteristics were evaluated as per ICH Q2 (R1): accuracy, repeatability, intermediate precision, specificity, linearity, range, and robustness.

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)

(b) (4)

First Information request: The following IR was submitted to the sponsor on 12 September 2016. The response by Novo Nordisk received as Amendment 11 on 30 September 2016, is discussed below.

*Repeatability – On page 12 and 13 of the Validation of the Analytical Procedure (b) (4), you used (b) (4) were shown for each condition. Please explain how you calculated repeatability % RSD and/or provide data for repeatability with either (b) (4) determinations at the nominal concentration or (b) (4) determinations at each of (b) (4) different concentrations as prescribed in ICH Q<sub>2</sub>(R1).*

Review of Response: The sponsor acknowledged the request for (b) (4) but insisted that using (b) (4) design gave sufficient and more accurate results with more degrees of freedom than (b) (4). We did not agree with the sponsor's answer. A second information request is necessary.

Second Information Request: The following IR was submitted to the sponsor on February 2, 2017. The response by Novo Nordisk received as Amendment 37 on February 16, 2017 is discussed below.

*Repeatability- You stated that using (b) (4) provided more accurate repeatability results than that from (b) (4). We do not agree that your results demonstrate repeatability. Please provide repeatability assessment results with either (b) (4) concentration or (b) (4) of Polysorbate 80 in nonacog beta pegol, using the experimental procedure you are validating, as was requested in our previous Information Request.*

Review of Response: Novo Nordisk has conducted additional studies to assess the repeatability of the method, (b) (4), using nonacog beta pegol 2000 IU/vial (Batch (b) (4) for (b) (4) independent determinations from (b) (4) analytical run. The statistical data provided show the average of (b) (4) polysorbate 80 concentrations to be

(b) (4)

The repeatability assessment of the method (b) (4) has been met.

Range of the method was assessed from the accuracy, linearity, and precision results , and was found to be (b) (4)

Robustness of the analytical method was established (b) (4)

Information Request: The following IR was submitted to the sponsor on 2<sup>nd</sup> September 2016. The response by Novo Nordisk received as Amendment 37 on 16 September 2017 is discussed below.

(b) (4)

Review of Response: The sponsor provided results from the robustness studies which show that the recovery of PS80 concentration is in the range of (b) (4) compared to the target analysis condition, and met the acceptance criteria of (b) (4)

The response is satisfactory.

Outstanding information request: The following IR was submitted to the sponsor on 02 May 2017. The responses have not been received yet.

*We have the following questions/comments regarding the Method validation report, Document ID 001870476:*

- i. *You have demonstrated linearity of your assay using the data obtained from polysorbate 80 standards only. Please provide the linearity data based on the*

*analysis of nonacog beta pegol samples, with at least (b) (4) data points over the proposed assay range.*

- ii. *You have indicated in sections 5.2 and 5.4 that linearity and accuracy were assessed in the range of (b) (4) of polysorbate 80 and (b) (4) of polysorbate 80, respectively. Thus, you have validated your assay in the range of (b) (4) of polysorbate 80. Please explain how this range is relevant to the specification range of (b) (4) of polysorbate 80 in nonacog beta pegol drug product.*

Conclusion: The method description is adequate. However, there are outstanding issues remaining for the method validation.

## **2. Determination of Sucrose and Mannitol contents by (b) (4)**

Sucrose and mannitol are two of the excipients used during the manufacturing of nonacog beta pegol drug product. The specification is (b) (4) for sucrose and (b) (4) for mannitol in nonocog beta pegol drug product of different strengths.

### Method

Sucrose and mannitol in are determined by (b) (4)

### Method Validation

(b) (4)

(b) (4)

(b) (4)

(b) (4)

First information request: An IR was sent to the sponsor on September 12, 2016 after initial review. Response was received on September 30, 2016 in the amendment 11, and resubmitted on November 28, 2016 in the amendment 19.

*Precision/Repeatability- On page 15 and 16 of the Validation of the Analytical Procedure (b) (4), you established repeatability based on (b) (4). However, for each condition (b) (4) you only provided (b) (4) determined values. Please provide data for repeatability with either (b) (4) determinations at the nominal concentration or (b) (4) determinations each at (b) (4) concentrations over the assay range.*

Review of Response: The sponsor referred to the response to the similar IR question raised for polysorbate 80 (PS80) assay. The response stated that the use of (b) (4) from one experimental condition (b) (4) of freedom). This is not acceptable.

Second information request: The following IR was submitted to the sponsor on February 2, 2017. The response by Novo Nordisk received as Amendment 37 on February 16, 2017/2016 is discussed below.

*Precision/Repeatability- We received and reviewed your response to information request dated September 12, 2016, amendment 11. The same repeatability assessment was posted in a revisited validation of the method (b) (4) submitted on November 28, 2016, amendment 19. You stated that (b) (4) (b) (4) results provides a better estimate of repeatability of the method (b) (4) degrees of freedom. We do not agree that your results demonstrate repeatability. Please provide assessment results with either (b) (4) concentrations of both sucrose and mannitol in nonacog beta pegol, using the experimental procedure you are validating, as was requested in our previous Information Request.*

Review of Response: Novo Nordisk has conducted additional studies to assess the repeatability of the method (b) (4) using nonacog beta pegol 2000 IU/vial (Batch (b) (4) for (b) (4) independent determinations from (b) (4) analytical run. The results show that the averages of (b) (4) sucrose and mannitol concentrations to be (b) (4) (b) (4) The acceptance criteria for passing %RSD for both excipients are (b) (4) The results are acceptable.

Accuracy of the analytical method (b) (4) was inferred from linearity, specificity and precision. However, data provided on linearity, specificity and precision did not support method's accuracy. An information request was sent to the sponsor.

Information Request: An IR was sent to the sponsor on September 12, 2016 after initial review. Responses were received on September 30, 2016 in the amendment 11 and on November 28, 2016 in the amendment 19.

*Accuracy – You stated on page 16, section 5.5 that the accuracy of the method was inferred from linearity, specificity and precision. Please provide analysis of your linearity, specificity and precision data to show how you inferred accuracy of the method. Otherwise, please provide accuracy data minimally at (b) (4) levels over the assay range, including concentrations below and above the nominal concentration for both sucrose and mannitol.*

Review of Response: In amendment 11, the sponsor stated that no accuracy data were available, but will be provided by December 1, 2016.

In amendment 19, the sponsor provided the new accuracy data. Accuracy was determined by a recovery study on samples prepared by adding different amounts of sucrose and mannitol in solutions containing nonacog beta pegol (b) (4) other matrix components to represent formulations of nonacog beta pegol pegol drug product at 500 IU and 2000 IU. (b) (4) test solutions were prepared: (b) (4) with



500 IU/vial and (b) (4) others with 2000 IU/vial in the concentration levels at (b) (4) of the target value of sucrose and mannitol respectively. Each test solution was analyzed (b) (4) precision conditions. The % recoveries were reported to be (b) (4) for sucrose and (b) (4) for mannitol, which met the acceptance criteria of (b) (4) for sucrose and (b) (4) for mannitol. The accuracy assessment is acceptable.

Robustness - (b) (4)

These parameters were tested in (b) (4) different experiments. The sponsor stated that the tested parameters at high and low did not have any significant effect on the analytical results but did not provide the raw data.

Information Request: An IR was sent to the sponsor on February 2, 2017. A response was provided on February 16 2017 in the amendment 37.

*In section 5.6 of the validation of Analytical Procedure (b) (4) (Determination of sucrose and mannitol contents by (b) (4) , you stated that “The test parameters at high and low levels did not have any significant effect on the analytical results, except for (b) (4) where the effect (b) (4) was not considered to be critical.” Please provide experimental data to support the robustness assessment of the method (b) (4)*

Review of Response: In response, the sponsor submitted the robustness data. The data confirmed sponsor’s earlier conclusion that the test parameters (b) (4) did not have any significant effect on the analytical results.

*It is not clear to us what “...except for (b) (4) where the effect (b) (4) was not considered to be critical” means. Please explain.*

Review of Response: According to the sponsor, the (b) (4) is observed to have a significant effect on the results for sucrose. Based on the 95% confidence interval the effect is estimated to be less than (b) (4) when the (b) (4) is changed by (b) (4) from the method set-point. An effect of (b) (4) (corresponding to (b) (4) of the concentration of (b) (4) is not considered critical, as the % RSD for the entire data set for sucrose is (b) (4) which met the acceptance criterion of RSD (b) (4).

Range of the method was assessed based on the linearity range of (b) (4) . However, this assessment did not take into consideration the accuracy, precision and specificity of the method. An information request was sent to the sponsor.

Information request: An IR was sent to the sponsor on September 12, 2016 after initial review. Responses were received on September 30, 2016 in the amendment 11 and on November 28, 2016 in amendment 19.

*Range – You stated that the range for the method was determined on the basis of linear results. We do not agree. The range should be based on the assessment from linearity, accuracy, precision and specificity. Please reevaluate your data to determine range of your method based on linearity, accuracy, precision and specificity and submit for review.*

Review of Response: In the response from amendment 11, the sponsor stated that range based on linearity, accuracy, precision and specificity will be provided by December 1, 2016.

In response to CBER IR, received on November 28, 2016 amendment 19, the sponsor explained that range is defined as the load interval in which the method is demonstrated to be specific, precise, accurate and linear. Successful specificity, intermediate precision, and linearity in the range of (b) (4) for both sucrose and mannitol, was demonstrated in the original submission. Based on the data submitted in amendment 19, accuracy was demonstrated in load intervals (b) (4) for sucrose and (b) (4) for mannitol. Thus, the range of the method (b) (4) is successfully demonstrated to be (b) (4) for sucrose and (b) (4) for mannitol.

Outstanding Information request: The following IR was submitted to the sponsor on 02 May 2017. The responses have not been received yet.

- i. *Regarding your Method validation report, Document ID 002197136: You have demonstrated linearity of your assay using the data obtained from reference standards only. Please provide linearity data and plots of analyte concentration vs. peak area to show linearity of sucrose and mannitol response in nonacog beta pegol drug product.*

Conclusion: The description of the method, (b) (4), is adequate. However, there are minor issues remaining with the method validation.

### 3. Determination of (b) (4)

The specification for the drug product is (b) (4)

#### Method

(b) (4)

(b) (4)

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Method Verification

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

Conclusion: This method of (b) (4) determination is a (b) (4) method. The validation of the method is adequate for the intended use.

#### 4. Determination of Particulate matter

(b) (4)

##### Method

(b) (4)

Method Verification

(b) (4)

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Information request: An IR was sent to the sponsor on February 2, 2017 after initial review.  
Responses were received on March 24, 2017 as Amendment 44.

(b) (4)

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(b) (4)

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(b) (4)

(b) (4)

Conclusion: This method of determination of particulate matter is a (b) (4) method. The validation of the method is adequate for the intended use.

## 5. Appearance of Lyophilized powder

The visual inspection of the lyophilized powder is performed in order to ensure that the drug product appears as a “white to off-white lyophilisate”.

### Method

The visual inspection is performed according to (b) (4). Each sample vial is checked against a (b) (4). Visual inspection is appropriate to verify appearance of the lyophilized cake, and validation of this method is not necessary.

Conclusion: The assay is approvable as a release test for nonacog beta pegol drug product. No additional information is required.

## 6. Appearance of Reconstituted solution and Reconstitution time/solubility

The visual inspection of the reconstituted product is performed to ensure that the product is clear, without any coloration or presence of foreign material, which would compromise the quality of the drug product. The specification limit is that the reconstituted solution appears as a clear and colorless liquid and free from clearly detectable particles.

For Reconstitution time, the specification is that the lyophilized powder dissolves within 10 minutes at 20-25°C in accordance with (b) (4) requirements for human coagulation factor IX.

### Method

Appearance of reconstituted product is in accordance with (b) (4). The solvent (b) (4) is added to the lyophilized sample at room temperature. The timing is started immediately after addition of full volume of (b) (4), and is stopped after complete dissolution of the sample (by visual inspection). The exact reconstitution time is noted in seconds. The characteristic of the solution is examined visually for (b) (4). Visual inspection is appropriate to

verify the solubility and appearance of solution, and validation of this method is not necessary.

Conclusion: The assay is approvable as a release test for nonacog beta pegol drug product

7. (b) (4)

(b) (4)

Method

(b) (4)

Method Verification

(b) (4)

(b) (4)

(b) (4)

Conclusion: The assay is approvable as a release test for nonacog beta pegol drug product.