



MEMORANDUM

From: Hsiaoling Wang, Ph.D.
CMC Reviewer
Laboratory of Analytical Chemistry and Blood Related Products (LACBRP)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To: Biologics License Application Submission Tracking Number 125671/0

Subject: Review Memo for Chemical Assays for Antihemophilic Factor (Recombinant), GlycoPEGylated

Through: Lokesh Bhattacharyya, Ph.D., Lab Chief, CBER/OCBQ/DBSQC

Maryna Eichelberger, Ph.D., Director, CBER/OCBQ/DBSQC

Applicant: Novo Nordisk Inc.

Submission Received by CBER: Feb. 27, 2018

Recommendation: Approval

Summary:

A new BLA (STN 125671/0) was submitted by Novo Nordisk for Antihemophilic Factor (Recombinant), GlycoPEGylated for use in treatment and prophylaxis of bleeding in patients with haemophilia A.

This document constitutes the Review Memo from DBSQC for the following analytical methods and their validations, which are proposed to be used for quality control lot release of the (b) (4) drug product (DP).

1. Protein Content and (b) (4) DP)
2. (b) (4) DP)
3. (b) (4) DP)

Of the two methods for (b) (4) determination, the method using (b) (4) Analysis is proposed to be the primary method. However, the (b) (4) will be

used if (b) (4) of a sample is outside of the (b) (4) calibration range or if the threshold value is higher than acceptance threshold for the (b) (4) method.

This reviewer found that all three analytical procedures were adequately described and validated for their intended uses.

Background

Antihemophilic Factor (Recombinant), GlycoPEGylated is a lyophilized powder for intravenous infusion after reconstitution with 0.9% sodium chloride solution. It is supplied in five dosage forms containing 500, 1000, 1500, 2000, and 3000 International Units (IU) per vial, respectively.

Documents Reviewed

Original submission STN 125671/0 dated Feb. 27, 2018

- Cover letter
- 2.2 Introduction
- 3.2.S.3.1 Elucidation of Structure and Other Characteristics
- 3.2.S.4.1 Specification (DS)
- 3.2.S.4.2 Analytical Procedures for Drug Substance
- 3.2.S.4.4 Batch analyses (DS)
- 3.2.S.5 Reference Standards or materials
- 3.2.P.5.1 Specifications (DP)
- 3.2.P.5.2 Analytical Procedures for Drug Product
- 3.2.P.5.3 Validation of Analytical Procedures (DP)
- 3.2.P.5.4 Batch analyses (for DP)
- 3.2.P.5.5 Characterization of Impurities
- Analytical Procedure (b) (4): Protein Content (b) (4)
- Validation of Analytical Procedure (b) (4) "Protein Content (b) (4)"
- Analytical Procedure (b) (4)
- Validation of Analytical Procedure (b) (4)

Amendment 13, dated June 27, 2018

- Response to FDA Information Request dated June 13, 2018
- Analytical Procedure (b) (4)
- Validation of Analytical Procedure (b) (4)

Amendment 18, dated July 25, 2018

- Follow-up Response to FDA Information request dated June 13, 2018

Amendment 37, dated Nov. 2, 2018

- updated 3.2.P.5.1 Specifications (DP)

Review Narrative

1. Protein Content (b) (4)

The specifications of protein content (b) (4) respectively. The protein content specifications for DP are (b) (4) for 500 IU, (b) (4) for 1000 IU, (b) (4) for 1500 IU, (b) (4) for 2000 IU and (b) (4) for 3000 IU, respectively, at release and (b) (4) for 500 IU, (b) (4) for 1000 IU, (b) (4) for 1500 IU, (b) (4) for 2000 IU and (b) (4) for 3000 IU, respectively, for shelf life. The specifications of (b) (4) for all DP presentations are (b) (4) at release and (b) (4) for shelf life.

Method

A (b) (4) method is used for the determination of protein content (b) (4)

Method Validation

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Information Request (IR) and Review of Response

The following IRs were sent to sponsor on June 13, 2018 regarding the validation report. The responses were received on June 27, 2018 in the Amendment 13 and on July 25, 2018 in the Amendment 18.

- a. A (b) (4) is clearly displayed in the figures 2 and 4 of the validation report. Please provide identification of these (b) (4) with necessary supporting data to demonstrate that they are part of active pharmaceutical ingredients of your product.

Review of the response: The sponsor identified the (b) (4) as a component of Turoctocog alfa pegol enriched with (b) (4) PEG moiety. This PEG form has been characterized by (b) (4) in module 3.2.S.3.2 of the submission. It is considered an active component because the B-domain is cleaved during thrombin activation. The response is acceptable.

- b. We do not agree that the quantitation limit (QL) for (b) (4) value of (b) (4) (section 6.6) because QL cannot be estimated by (b) (4). In addition, (b) (4) percent of a (b) (4) is affected by relative (b) (4) and their

(b) (4). You may use data in Table 5 to estimate QL by plotting the (b) (4) (reportable result) against (b) (4) area (response) or using an appropriate method of your choice and submit your results for review.

Review of the response: A new experimental data was submitted for lower level (b) (4) linearity study. The results are summarized in the method validation. LOQ determination is satisfactory. The response is acceptable.

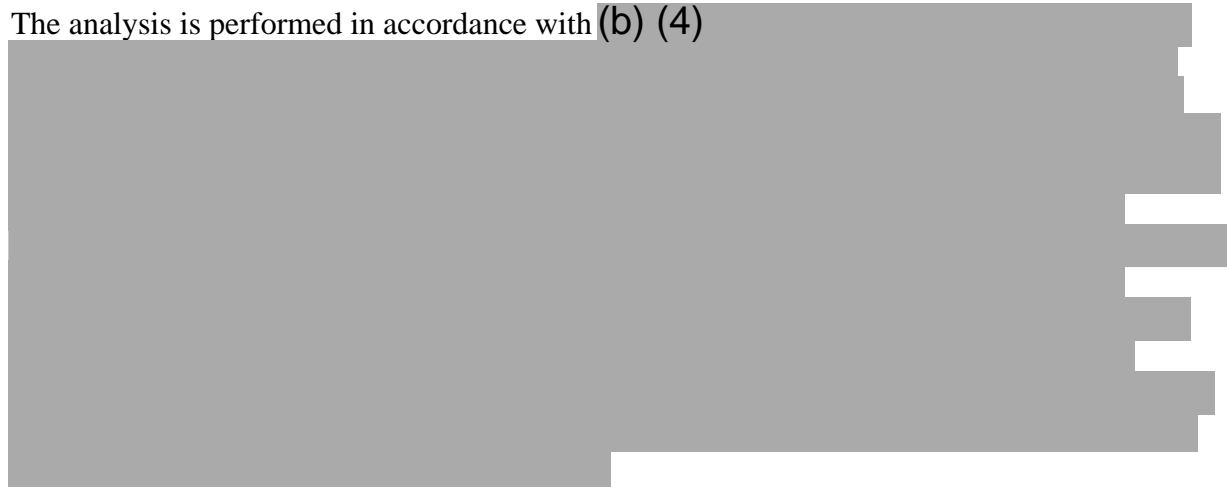
Conclusion: (b) (4) assay is adequately described and validated for the intended use.

2. (b) (4)

The proposed specifications for (b) (4) in all lyophilized presentations of DP are (b) (4) at release and (b) (4) for shelf life.




Method

The analysis is performed in accordance with (b) (4)



Method Validation

(b) (4)



(b) (4)

Information Request (IR) and Review of Response

The following IRs were sent to sponsor on June 13, 2018 regarding analytical procedure and validation report. The responses were received on June 27, 2018 in the Amendment 13.

Your analytical procedure (b) (4) cannot be considered a compendial procedure for Antihemophilic Factor (Recombinant), GlycoPEGylated because a monograph for Antihemophilic Factor (Recombinant), GlycoPEGylated is not present in (b) (4). To consider a test as compendial, there must be a monograph in (b) (4) and the assay procedure must be described or cited in the monograph. Please conduct complete validation of this method and provide us the report.

Review of the response: (b) (4) method and its validation were submitted in the response and are summarized above. The response is satisfactory.

Conclusion: The assay is adequately described and validated for the intended use.

3. (b) (4)

The proposed specifications for all presentations of DP samples are (b) (4).
Of the two methods for (b) (4) determination, the method using (b) (4) is the proposed to be the primary method. However, the (b) (4) method will be used if (b) (4) of a sample is outside of the (b) (4) calibration range (b) (4) or if the threshold value is higher than acceptance threshold for the (b) (4) method.

Method

(b) (4)

Validation

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Information Request (IR) and Review of Response

The following IRs were sent to sponsor on June 13, 2018 regarding analytical procedure and validation report. The responses were received on June 27, 2018 in the Amendment 13.

For validation report for the analytical procedure, (b) (4)

- i. In the validation report, you used only (b) (4) to demonstrate (b) (4) specificity of the method with (b) (4) value in section 5.1.1. Please provide data for at least (b) (4), preferably using products manufactured at the same manufacturing site, to evaluate the specificity of the method.
- ii. In appendix D of the validation report, Table 13 showed the model characteristics. Please provide the rationale for using (b) (4) and describe the specific (b) (4) method that was applied.
- iii. Table 13 also showed that there were (b) (4) samples left out for the model. Please provide justification for such action and modify the total number of (b) (4) used for the model establishing accordingly.
- iv. Please provide experimental data to demonstrate that the variation of concentrations of excipients within the proposed specifications (for example, sucrose (b) (4) and polysorbate 80 (b) (4) does not affect (b) (4) result of your DP sample

Review of the response:

- i. (b) (4) samples were tested and the (b) (4). The response is satisfactory.
- ii. The sponsor stated that the software (b) (4) applies (b) (4) by default. The same (b) (4) is consistently used for the method without any optimization. (b) (4) as one of widely used (b) (4) techniques could effectively (b) (4). But a blind application of a specific (b) (4) is not recommended. However, we could accept the use of this (b) (4) purely based on the satisfactory outcome of the calibration model and (b) (4) prediction in the DP samples. The response is acceptable.
- iii. The sponsor explained that (b) (4) out of total (b) (4) were excluded randomly for (b) (4) validation of the calibration model each time instead (b) (4) at a time as usual. Such (b) (4) validation is called (b) (4) validation. Thus the total number of samples is (b) (4). The response is acceptable.
- iv. It is important for the established model to have a full coverage of the proposed specifications ranged for (b) (4) containing components in the DP matrix to demonstrate the specificity of the method. The sponsor provided a list of Turoctocog alfa pegol DP samples used in the calibration model establishment with contents of protein (b) (4) mg/vial and sucrose (b) (4), which encompass the proposed specification limits of these ingredients in the DP samples. The contents of methionine (b) (4) and polysorbate 80 (b) (4) are slightly off from the proposed limits of (b) (4). But they are reasonably acceptable for such minor deviation. The response is acceptable.

Conclusion: The method is adequately validated for the intended use.