



To STN: #125671/0

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Product STN: 125671/0, Turoctocog alfa pegol

Sponsor Novo Nordisk, Inc.

Subject: Review Memo for Biological License Application for Antihemophilic Factor (Recombinant), GlycoPEGylated, STN# 125671/0, Turoctocog alfa pegol: Review of the test method and method validation report for FVIII Potency by Chromogenic Assay

Recommendation: Approval

Summary of Review

A BLA was submitted for Antihemophilic Factor (Recombinant), PEGylated, drug product, STN: 125671/0 – Turoctocog alfa pegol, by Novo Nordisk. This memo reviews the test method (b) (4) for rFVIII Potency by Chromogenic Assay and its validation for the turoctocog alfa pegol (b) (4) drug product (DP). The analytical procedure (b) (4) Potency by Chromogenic Assay has been described and validated adequately for its intended use.

Background

The DP turoctocog alfa pegol is presented as a lyophilized powder for intravenous use in five strengths: 500, 1000, 1500, 2000 and 3000 International Units (IU)/Vial. It is reconstituted in (b) (4) of 0.9% Sodium Chloride Solution before use. The DP is indicated for use in the treatment and prophylaxis of bleeding in patients with hemophilia A.

Submitted Information Reviewed

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

- 125671/0.0-3.2. S.4.2. Analytical Procedures
 - Analytical Procedure (b) (4) - Potency by Chromogenic Assay Version 1.0
- 125671/0.0-3.2. S.4.3. Validation of Analytical Procedures
 - Validation of Analytical Procedure (b) (4) - Potency by Chromogenic Assay Version 1.0
- 125671/0.0-3.2. S.4.3. Verification of Repeatability for Drug Substance Analytical Procedures, Version 1
- 125671/0.0-3.2. P.1 Description and Composition of the Drug Product, Version 1.0

- 125671/0.0-3.2. P.5.1 Specification for Drug Product, Version 1.0
- 125671/0.0-3.2. P.6. Reference Standards or Materials
- 125671/0.34 (Amendment) Response to FDA CMC IR dated Sep 20, 2018, Recd. 10/11/18
- 125671/0.36 (Amendment) Response to FDA CMC IR dated Oct 16, 2018, Recd. 10/24/18
- 125671/0.40 (Amendment) Response to FDA CMC IR dated Nov 1, 2018, Recd. 11/15/18
- 125671/0.43 (Amendment) Follow up - FDA CMC IR dated Oct 16, 2018, Recd. 11/21/18

Review Narrative

The proposed specifications for potency of the drug product by the chromogenic assay (reconstitution vol. (b) (4)

500 IU	(b) (4)
1000 IU	(b) (4)
1500 IU	(b) (4)
2000 IU	(b) (4)
3000 IU	(b) (4)

Method

The test method described in the document entitled, “Analytical Procedure (b) (4) Potency by Chromogenic Assay”, Version 1.0 is a (b) (4)

(b) (4)

. Overall the method and its acceptance criteria are suitable for determining the potency of FVIII drug product.

Method Validation

The validation report described the assessment of the following characteristics: accuracy, linearity, precision (repeatability and intermediate precision), specificity, range, and robustness (b) (4), DP (b) (4) and DP (b) (4) to (b) (4) all presentations manufactured by the sponsor.

Accuracy

The accuracy study was performed over (b) (4)

(b) (4)

method accuracy. An information request was sent on 9/20/2018.


Precision

The repeatability results from (b) (4)



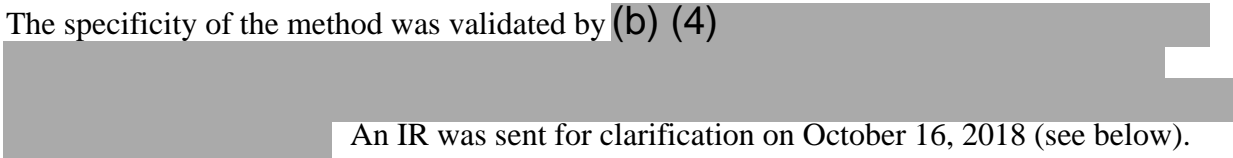
Linearity

Linearity was evaluated by (b) (4)



Specificity

The specificity of the method was validated by (b) (4)



An IR was sent for clarification on October 16, 2018 (see below).

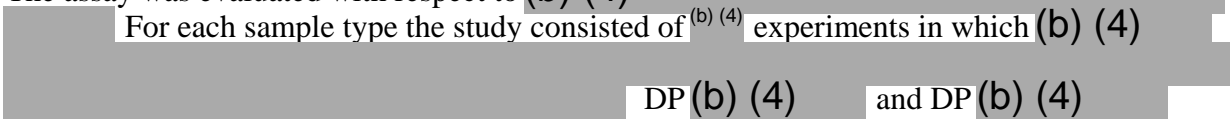
Range

The test method range is defined based on meeting the acceptance criteria for accuracy, precision and linearity studies to be from (b) (4).

Robustness

The assay was evaluated with respect to (b) (4)

For each sample type the study consisted of (b) (4) experiments in which (b) (4)



DP (b) (4) and DP (b) (4) respectively, which met the acceptance criteria for robustness (same as that for precision).

Information Request and Review

The following IR were sent to the sponsor on 9/20/2018. The response was received on October 11, 2018 (125671/0.34 Amendment). The response is reviewed below:

1. While reviewing of your accuracy data, we noted that you determined nominal (expected) and measured potencies using the same method. We do not agree that the results support accuracy of your method. The accuracy should be demonstrated by either comparing results obtained using (b) (4) methods or from (b) (4) experiments, in which an authoritative standard (e.g., WHO International Standard) of known assigned potency value is (b) (4) /product under consideration and measured to evaluate accuracy (b) (4). Please provide data obtained by either of these two approaches to demonstrate accuracy of your method.

Review of the response: The sponsor reported a (b) (4) study using a secondary reference standard of the DP which was (b) (4) into a DP placebo sample. However, the issue was not resolved because the measured and expected potency values for calculating the % Recovery (accuracy) were derived from the same FVIII chromogenic method (b) (4) using the same standard. Another IR was sent on 10/16/2018 (see below).

2. In your validation report, you provided linearity data for test samples only. You did not provide data such as correlation coefficient, slope and intercept; and the acceptance criteria for the standard curves. Please provide system suitability results (as per section 11 of your test procedure (b) (4) obtained during experiments carried out for method validation. This should include data for standard and control, and formulae and results of analysis used to show parallelism and equivalence between reference curve, control and test samples.

Review of the response: The sponsor provided slope, intercept and correlation coefficient (R^2) values in Amendment 125671/0.34. R^2 values from all the three set-ups resulted in values (b) (4), which is acceptable for the linearity parameter. No further information is required for linearity; the test method meets the criteria for linearity.

The following IR were sent to the sponsor on 10/16/2018. The response was received on 10/24/2018 via amendment 125671/0.36. The response is reviewed below:

1. Question 1 of the IR has not been addressed. You have provided the % Recovery data of (b) (4) added to a drug product placebo sample based on the nominal assigned potency of a secondary standard (b) (4) and measured potency by your "Analytical Procedure (b) (4) Potency by Chromogenic Assay". Please provide comparative data for the (b) (4) using both the chromogenic assay and one stage clotting assay. Alternatively, you can use WHO international standard for (b) (4) into the drug product and measure the (b) (4) by your chromogenic assay, (b) (4). For new accuracy study, please also submit the system suitability data for your assay as per section 11 of your Analytical Procedure (3.2.S.4.2 Analytical Procedure (b) (4)

Review of the response: A teleconference was arranged on 11/1/2018 at the request by the sponsor to discuss the concerns about the accuracy data and how the study could be designed to address the IR question. During the teleconference, the sponsor proposed to use a comparative study using an (b) (4) method, one stage clotting assay, to support the accuracy of the

potency assay (b) (4) (chromogenic assay) using (b) (4) lots each of (b) (4) DP, in which DP lot is different from the DP lot used as the standard. CBER agreed to sponsor's proposal. The sponsor's response was received on 11/21/2018 as Amendment 125671/0.43, in which (b) (4) DP and (b) (4) lots were evaluated by both methods. For each sample three independent determinations were made at (b) (4) of the testing range. The percent recoveries were (b) (4) by the chromogenic assay and (b) (4) by the one stage clotting assay. The ratio between results obtained by the one stage clotting assay to the chromogenic assay were (b) (4) for the DP. This supports the accuracy of the test method (b) (4) adequately.

2. You indicated that you obtained comparable results for potency by the chromogenic assay and one-stage clotting assay for your secondary standard (b) (4). Please provide the potency data of this standard obtained by the one-stage clotting assay and explain how you found the data comparable.

Review of the response: The sponsor provided data with final values as the mean from (b) (4) measurements for both the chromogenic and clotting assays, however some of details were not provided. Therefore, an IR was sent on 11/1/18 to get more details about the study plan (see below).

3. You have used (b) (4) drug product placebo sample for (b) (4) experiment. Please clarify what this placebo sample is.

Review of the response: The sponsor provided the information and composition of these buffers, which demonstrates that these are buffers alone without any active drug product or substance. The response is satisfactory. The IR is resolved.

The following IR sent to the sponsor on 11/01/2018.

You showed (b) (4) replicate results each for potency of your secondary standard (b) (4) by the chromogenic and one-stage clotting assays. Please provide details of how the data were obtained, including how many independent sample preparations, analysts, instruments, and laboratories were involved in this study.

Review of the response: The sponsor submitted a response on 11/15/2018 as amendment 125671/0.40. The sponsor explained that the secondary reference standard was calibrated against (b) (4) WHO FVIII International Standard using both the chromogenic and one stage clotting assays. The assays were performed by more than (b) (4). Mean potency values obtained for the turoctocog alfa pegol standard were (b) (4) by chromogenic and clotting assays, respectively. A ratio of (b) (4) was obtained between chromogenic and clotting assay results which is satisfactory.

Conclusion: The test method for FVIII Potency by Chromogenic Assay was adequately described and validated for its intended use.