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To STN 125611/0

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Product Coagulation Factor IX (Recombinant), glycoPEGylated, Nonacog beta pegol, (b) (4)

Sponsor Novo Nordisk, Inc.

Subject Primary Discipline Review Memo for Biological License Application for Quality Control Lot-Release Test Methods for the (b) (4) Drug Product for (b) (4) (Nonacog beta pegol)

Summary of Review

The Biologic License Application (BLA) for Nonacog beta pegol (STN: 125611) was submitted by Novo Nordisk, Inc. This Primary Discipline Review memo applies to the following analytical methods and validations as used for the lot release of the drug product:

1. Potency by One-stage clotting assay
2. (b) (4)

The validation was carried out by Novo Nordisk A/S. The methods have been described and validated adequately and may be used for lot-release testing of Nonacog beta pegol (b) (4) drug product.

Background

Nonacog beta pegol is proposed for treatment and prophylaxis of bleeding in patients with hemophilia B. Nonacog beta pegol is a purified recombinant human factor IX (rFIX) expressed in Chinese Hamster Ovary cells. A 40-kDa PEG moiety is attached to the N-linked glycans, with monoPEGylated rFIX being the predominant form. Three formulation potencies of 500 IU, 1000 IU and 2000 IU are proposed. The drug product is reconstituted in a 10 mM Histidine solution. Nonacog beta pegol is to be administered intravenously in a single-bolus injection.

Submitted information reviewed:

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

125611/0 – 3.2.S.4.2 Analytical Procedures

- Analytical Procedure M056 Potency by One-stage clotting assay, version 1.0
- (b) (4) Analytical Procedure (b) (4), version 1.0

125611/0 – 3.2.S.4.3 Validation of Analytical Procedures

- Validation of Analytical procedure M056 Potency by One-stage clotting assay, version 1.0
- Validation of Analytical Procedure (b) (4) version 1.0

125611/0 – 3.2.P.5.1 – Specifications

- Specification for Drug Product

125611/0 – 3.2.P.5.2 – Analytical procedures

- Overview of Analytical Procedures for Drug Product

125611/0 – 3.2.P.6 – Reference Standard or Materials

- Reference Standard or Materials for Drug Product

125611/0.11 – 1.11.1 - Quality Information Amendment

- Novo Nordisk Response to FDA Information Request dated September 13, 2016
CMC Information

125611/0.23 – 1.11.1 – Quality Information Amendment

- Novo Nordisk Response to FDA Information Request dated November 22, 2016
CMC Information

125611/0.23 – 3.2.S.4.2 Analytical Procedure

- (b) (4) Analytical Procedure (b) (4), version 3.0

125611/0.23 – 3.2.S.4.3 Validation of Analytical Procedures

- Validation of Analytical Procedure (b) (4), version 2.0

125611/0.29 – 1.11.1 Quality Information Amendment

- BLA Commitment for FDA Information Request dated November 22, 2016
Analytical Procedure (b) (4)

125611/0.29 – 3.2.S.4.3 Validation of Analytical Procedures

- Validation of Analytical Procedure (b) (4), version 3.0

1. Potency by One-stage Clotting Assay

The one-stage clotting assay, based on the (b) (4)

(b) (4) is used to measure the FIX potency of Nonacog beta pegol, Coagulation Factor IX (Recombinant), glycoPEGylated, [Rebinyn] (b) (4) drug product. The proposed lot release specifications for the drug product are 500 IU: (b) (4), 1000 IU: (b) (4), and 2000 IU: (b) (4)

(b) (4) The specifications for specific activity, calculated from the One-stage clotting assay and (b) (4) for the (b) (4) formulations. The sponsor provided an Analytical Procedure, M056, Potency by One-stage clotting assay, and

validation report, Validation of Analytical Procedure M056, Potency by One-stage clotting assay.

Method

This one-stage clotting assay is based on the ability of a FIX-containing sample to reduce the prolonged coagulation time of FIX-deficient plasma. (b) (4)

[Redacted]

Method Validation

This is a quantitative method and is validated according to ICH guidelines. The Validation of Analytical Procedure M056 Potency by One-stage clotting assay contained evaluation of the following: specificity, accuracy, linearity, range, precision (repeatability and intermediate precision) and robustness.

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

First Information Request and Review

The following IRs were submitted to the sponsor on 13 September 2016. The response was received on 30 September 2016 as Amendment 11. The IR questions, the response from the sponsor and review of the responses are discussed below.

- a. For accuracy, you have measured the recovery of Nonacog beta pegol reference material at (b) (4) in drug product placebo. Please provide details of the composition of the drug product placebo.

Review of Response: The sponsor provided a list of the constituents of the drug product placebo and demonstrated that the composition was identical to that of the drug product without the active ingredient. This is acceptable.

- 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.

Review of Response: The sponsor clarified that the acceptance criteria were not for each individual (b) (4) level, but the average of all (b) (4) levels. As the average recovery for all (b) (4) levels is (b) (4) and the acceptance criterion is (b) (4) this is adequate.

- c. To demonstrate your method accuracy please provide R^2 and slope of the measured potency (IU/mL) plot vs. nominal potency (IU/mL) of the reference material, presented as Figure 2 in your validation report.

Review of Response: The sponsor provided the R^2 value as (b) (4) and slope as (b) (4). This demonstrated accuracy of the method.

- d. You have demonstrated repeatability and intermediate precision by measuring (b) (4) drug product in (b) (4). 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.

Review of Response: The sponsor asserted that the use of the (b) (4) was sufficient to demonstrate both repeatability and intermediate precision as it was based on measurement of (b) (4) experimental setups and provided statistical equations to illustrate their point. We did not agree that this analysis provided an adequate measurement of repeatability, so this generated an additional IR (see 1 below).

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

Review of Response: The sponsor analyzed (b) (4) analytical setups of control measurements over a (b) (4) month period, which amounted to (b) (4) response curves. The measured potency values were normalized to the target potency to allow comparison, and plotted against the p-value for parallelism. The sponsor felt that there was no difference between the results in the range for p value for parallelism of (b) (4) to those with p-values (b) (4). They also provided plots of Weight (%) vs p-value for parallelism. The Weight is defined as the inverse variance of the \log_{10} -relative potency of the sample vs reference and is therefore an estimation of precision. (b) (4) curves had p-values below (b) (4), however the sponsor felt there was no difference between these results and all of their other data in this study, as the Weights for the (b) (4) curves were within (b) (4) of the entire data set. To further exemplify the comparison of Weight and p-value for parallelism, they provided response vs concentration curves where the p-values ranged from (b) (4), and the Weight was between (b) (4). The data points were all close to the fitted curve. Curves with higher p-value (b) (4) and low weight (b) (4) were also presented, however the data were more scattered around the fitted curve. These curves were rejected by the software. Hence the sponsor felt the combined criteria of F-test for parallelism with (b) (4) and Weight (b) (4) was more applicable than the use of parallelism at p (b) (4) alone. We did not agree that the use of the F-test for parallelism was adequate for the analysis.

Furthermore, we felt the sponsor had not demonstrated linearity of their method. This generated additional IRs (see 2 – 4 below).

- f. You examined robustness by altering the (b) (4) and the (b) (4) of the assay buffer. Please provide the data of your robustness studies.

Review of Response: The sponsor provided the table of results illustrating that the (b) (4) of the assay buffer was altered in (b) (4) combinations. The overall %RSD was (b) (4) which met the acceptance criteria of (b) (4). This is acceptable.

Second Information Request and Review

The following IRs were submitted to the sponsor on 22 November 2016. The response was received on 13 December 2016 as Amendment 23. The IR questions, the response of the sponsor and review of the responses are discussed below.

1. The modified (b) (4) analyses may address intermediate precision but not repeatability. Please provide repeatability data as previously requested.

Review of Response: The sponsor provided repeatability data where three concentrations each of the 500 IU and 2000 IU drug product over the range of the assay (b) (4) of the starting potency) in (b) (4) were measured. The %RSD for the 500 IU drug product was (b) (4), while the %RSD for the 2000 IU drug product was (b) (4). Tests were within the acceptance criteria of (b) (4). This is satisfactory.

2. It is our understanding that linearity may be determined by ANOVA analysis, but not by F-test, however, this may be a semantic issue. Please describe your method of analysis and provide representative calculations for your F-test.

Review of Response: The sponsor clarified that the F-test was not used to measure linearity, but was performed by the software to confirm the goodness of fit of the calculated curves. The sponsor provided a large set of data in response to IR#3 to further clarify this point. Please see Response to IR#3 for further details. This is adequate.

3. Your parallelism criterion of p (b) (4) is too relaxed as is obvious from the Response to Information Requests, Amendment 11, Fig. 3. Please provide the actual p-values you obtained to date for the lot-release testing and stability studies of your drug. Please let us know how many of the analyses would have been invalid if the p-value is set at (b) (4).

Review of Response: The sponsor provided data covering the time period 1 (b) (4). This covered the first PPQ drug batch manufactured and released, and stability batches. A large number of p-values (b) (4) were provided, corresponding to (b) (4) samples and (b) (4) controls, each in (b) (4). Since (b) (4) different software programs had been used to generate the data, the sponsor also provided either the potency (IU/mL) or % relative potency data and RSD for each of the (b) (4) measurements. It was found that (b) (4) out of (b) (4) results had p-values between (b) (4), which represents (b) (4) rejection. The rules for rejection of samples based on parallelism constraints state that if one or more p-values of the (b) (4) measurements of sample does not comply, the results for that sample are rejected, while if one or more p-value of the (b) (4) measurement of control does not comply, the results of the entire sample set (control and four test samples) are rejected. If the parallelism criterion was changed from (b) (4) a total of 91 test samples out of (b) (4) samples measured would be rejected, corresponding to a rejection rate of (b) (4).

The sponsor noted that for all the test results, the %RSD values between the (b) (4) measurements were within the acceptance criteria of (b) (4), regardless of the p-value for parallelism. If it is assumed that the potencies of results with p-values of parallelism between (b) (4) are quantitatively different than results with p-values (b) (4), this would be expected to affect the RSD between the (b) (4) measurements. A comparison of the lowest p-value of the (b) (4) measurements vs %RSD was carried out, and the results divided into two groups, (b) (4) and (b) (4). A one-way ANOVA analysis demonstrated there was no difference between the two groups. This suggests that a criterion for parallelism of p(b) (4) would not alter the results compared to the already used p(b) (4). Hence, the sponsor concluded that it was acceptable to keep the criterion for parallelism of p(b) (4) and criterion of Weight of (b) (4) to demonstrate goodness of fit of the calculated plots.

4. Please provide a comparison of the upper and lower asymptotes and the slope ratio between the test sample and standard to demonstrate method linearity.

Review of Response: The sponsor provided data examining the ratio of the upper or lower asymptotes of test samples to reference standard, and slope ratios of test sample to standard. The ratios of upper asymptotes of sample to standard were between (b) (4), the ratios of lower asymptote of sample to standard were between (b) (4) and the slope ratios of sample to standard were between (b) (4). This demonstrated linearity and parallelism of the sample to the reference standard. The sponsor was asked to include these parameters as acceptance criteria for the assay, and this generated an additional IR (see i. below).

Third Information Request and Review

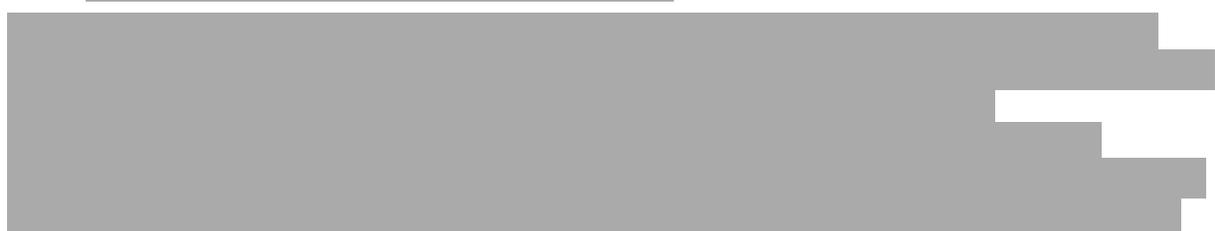
The following IR was submitted to the sponsor on 4 May 2017. The response is requested by 12 May 2017.

- i. In your response to the Information Request question 1d, provided in Amendment 23, received 13 December 2016 (Section 2.1.8), you provided data demonstrating linearity and parallelism of your method by comparing the upper and lower asymptotes and the slope ratios between test sample and standard. Please include these acceptance criteria for a valid assay in your SOP. Please note, this is the only acceptable way in which you have shown linearity and parallelism of your assay. Please provide your updated SOP by 12 May 2017.

Conclusion

The SOP and validation studies indicate that this method is suitable for use for lot-release testing.

2.(b) (4)



4 Pages determined to be not releasable: (b)(4)

Conclusion

The SOP and validation studies indicate that this method is suitable for use for lot-release testing.