

Our Reference: BLA 125611/0

Novo Nordisk Inc.
Attention: Ms. Patricia D. Wilson
November 10, 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:

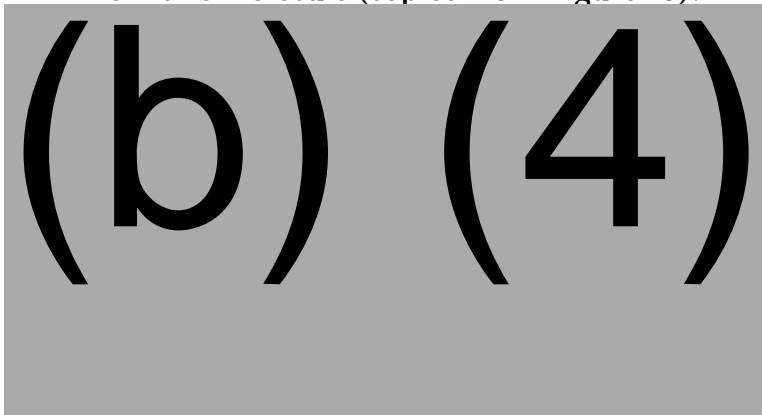
1. With regards to the DNA and protein sequences:
 - a. In Figure 2 of section 3.2.S.1.3 *General Properties* and Figures 1 and 2 of section 3.2.S.3.1 *Elucidation of Structure*, you have only provided the amino acid sequence and post-translational modifications of the fully processed form of recombinant Factor IX (rFIX), please provide the DNA sequence used for the expression of the entire rFIX molecule and its associated amino acid sequence.
 - b. Please confirm that no other plasmids, other than the one for the *f9* gene, were used to create the Master Cell Line.
 - c. Please provide data to support the genetic stability of the Master and Working Cell banks per ICH Q5B “Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products”.

2. With regards to the GlycoPEGylation process:

In section 3.2.S.3.1 *Elucidation of Structure*, you described the GlycoPEGylation process but did not provide details. Please explain in detail the chemical reactions that led to the formation of this molecule (copied from Figure 3):

(b) (4)

from this molecule (copied from Figure 10):



Furthermore, please verify that the molecule described in Figure 3 accurately represents the final product, and indicate if the structure will change when the glycan on the rFIX intermediate changes.

3. In section 2.3.S.2 *Manufacture*, you mentioned that the supplier of the 40K PEGylation reagent had been switched from (b) (4) [redacted]. The (b) (4) reagent was used in the manufacture of products for the non-clinical, phase 1 and part of phase 3 clinical trials; and the (b) (4) reagent was for products used in late phase 3 clinical trials and market production. Please provide the rationale for this change.

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 response and your notification of the shipment for this request as an amendment to this file by November 22, 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.

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/OTAT/DRPM