

Our Reference: BLA 125611/0

Novo Nordisk Inc.
Attention: Ms. Patricia D. Wilson
December 6, 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:

We reviewed your responses of November 22, 2016 to the information request (IR) from the Agency, which were sent on November 10, 2016; and have the following comments:

With reference to *Appendix A* in section 3.2.S.2.3 *Source, History and Generation of the Cell Substrate*, the recombinant Factor IX (rFIX) coding region in the rFIX expression (b) (4) contains a missense mutation at (b) (4). This amino acid residue is located within the (b) (4), resulting in a mature rFIX protein with an intact primary sequence which is the same as (b) (4).

However, this missense mutation may influence the overall structure and function of rFIX, and may have consequences, as discussed earlier in Bezemer *et al.*, *Haematologica*, 2009; and Greiff *et al.*, *Acta Anaesthesiologica Scandinavica*, 2015.

Please provide your rationale for introducing this missense mutation in the rFIX sequence and your assessment, specifically in light of the referenced articles and the results of the prediction tools, such as (b) (4).

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 for this request as an amendment to this file by December 19, 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