



Our Reference: BLA 125611/0

Novo Nordisk Inc.
Attention: Ms. Patricia D. Wilson
March 9, 2017
Sent by email

Dear Ms. Wilson:

We are reviewing your May 16, 2016 biologics license application for Coagulation Factor IX (Recombinant), GlycoPEGylated. We determined that the following information is necessary to continue our review:

1. We note that the (b) (4) bioburden results you have provided in the BLA for the PPQ and post-PPQ (b) (4) are in general well below your proposed limits (even after re-evaluation). Please consider implementing (b) (4) bioburden limits that are in-line with your process capabilities and/or implementing alert limits so that you can identify potentially significant increases in (b) (4) bioburden that are below the action limit.
2. Regarding the container closure integrity testing performed for the Histidine Solution syringes, please confirm that the positive and negative control syringes used during the testing had the expected results as this part of the testing is not described in the information provided.
3. We note that during the (b) (4) qualification for the Histidine Solution syringes container closure integrity testing was performed (b) (4) to simulate "a worst-case scenario". Please clarify if you are seeking approval of a (b) (4) of Histidine Solution syringes for syringes that fail the requirements for sterilization (b) (4).
4. We note that container closure integrity testing for the drug product was performed using (b) (4) testing. Please clarify if the drug product is (b) (4) sensitive and if so, clarify and describe if you have performed any other container closure integrity testing (such as (b) (4) analysis) that would support that integrity of the container closure prevents the entry of (b) (4).
5. We note that the stated limit for bioburden in the (b) (4) is (b) (4) used in Building (b) (4). In addition, we note that the manufacturing equipment is (b) (4) before use in Building (b) (4).

Please provide a justification for this bioburden specification that supports that it is adequate to prevent contamination of the (b) (4) .

6. We note that the list of manufacturers for the drug product that you have provided states that labeling and secondary packaging of the finished drug product is performed at the (b) (4) site, but it does not appear that this step is performed in Building (b) (4). Please clarify and describe the location where secondary labeling and packaging (kitting) is performed, if this location is currently approved to perform this manufacturing step for other US licensed products, and if this manufacturing step involves new procedures that are not currently performed for a US licensed product.
7. Regarding the submitted comparability protocol to support addition of a (b) (4) production bioreactor to be used in (b) (4) to the current (b) (4) production bioreactor to be approved under this BLA, please confirm that you will provide study reports for the validation of cleaning (and sterilization) of the (b) (4) production bioreactor in the supplement that contains the resultant data from the comparability protocol.
8. We note that in the interim report for (b) (4) provide in the amendment of December 7, 2016, the bioburden limit is stated as being "No more than (b) (4) may exceed the limit of (b) (4) While this limit appears to be in-line with microbial control data provided (the maximum bioburden results was (b) (4) please clarify how you will ensure that objectionable organisms (and their byproducts) will not be introduced into the drug substance (and potentially into the drug product) with such a high limit.

The review of this application is on-going and issues may be added, expanded upon, or modified.

Please submit your response and your notification of the shipment for this request as an amendment to this file by March 23, 2017, 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