

Dehdashti, Seameen (Jean)

From: Dehdashti, Seameen (Jean)
Sent: Friday, August 31, 2018 3:24 PM
To: 'BDV (Barbara Davies)'; HPAW (Hiral Palkhiwala)
Cc: Dehdashti, Seameen (Jean)
Subject: FDA Information Request (IR)-CMC: BLA 125671/0

Importance: High

Good afternoon Barbara and Hiral,

Reference is made to Novo Nordisk, Inc., original BLA 125671 submission, dated February 27, 2018. We are reviewing your BLA submission for Antihemophilic factor, GlycoPEGylated (STN125671) and have the following information request (IR), outlined in **bold text** below. Please provide your response by Friday, September 28, 2018, and let me know if you are not able to meet the requested due date.

FDA CMC IR:

Information Request regarding *Deficiencies identified in release specifications, potency standards, and stability studies.*

1. Regarding the Final Drug Product (FDP) stability studies, please
 - a. Re-analyze the stability data using (b) (4) of the actual (not nominal) *Potency* at release as the new stability specification limits.
 - b. Investigate the biochemical root causes for the following changes in FDP quality attributes observed during the 12-month storage at +30°C in the primary and supportive stability studies:
 - i. An up to a (b) (4)
 - ii. An up to a (b) (4)
 - iii. A decrease in *Purity* (down to (b) (4))
 - iv. An increase in (b) (4)
 - c. Develop new release specification limits and stability specification limits to address the adverse stability trends for parameters such as (b) (4) and *Purity*.
 - d. Revise the storage conditions in the label to indicate that the FDP should not be returned to refrigeration after storage at room temperature, or provide data under the worst-case scenario for room temperature storage, which would be 12 months at +30°C followed by (b) (4).
2. Regarding the (b) (4) stability studies, please
 - a. Explain the increase in (b) (4) *Potency* and (b) (4) in the stability studies, and conduct additional analysis of the stability study samples using an (b) (4) method, e.g., one-stage clotting assay.
 - b. Provide copies of the Investigation Reports for all the out-of-specification results and deviations encountered in the (b) (4) stability study.
3. Please provide data to bridge the primary reference material (PRM) batch (b) (4) and the three former secondary reference materials (SRM): batch (b) (4) implemented in (b) (4), batch (b) (4) implemented in (b) (4), and batch (b) (4) implemented in (b) (4). Specifically, please use validated one-stage clotting and chromogenic substrate-based assays to test these batches in parallel with the (b) (4) WHO International Standard for Factor VIII Concentrate (b) (4).

Please confirm receipt of my e-mail, and do not hesitate to contact me, should you have any questions and/or concerns.

Warm regards,

Jean Dehdashti, MSc, RAC
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