

Dehdashti, Seameen (Jean)

From: Dehdashti, Seameen (Jean)
Sent: Friday, September 07, 2018 10:55 AM
To: BDV (Barbara Davies)
Cc: Dehdashti, Seameen (Jean)
Subject: FDA Information Request (IR)-CMC: BLA 125671/0

Importance: High

Good morning Barbara,

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, October 5, 2018, and let me know if you are not able to meet the requested due date.

FDA CMC IR:

- 1) The following IRs are for the identity/purity by (b) (4) method for turoctocog alfa pegol (b) (4) drug product.
 - i) You validated the linearity of the method for the lower part of the range with the drug product, and the upper part of the range with the (b) (4), indicating that the linearity was validated for drug product (b) (4) over the entire range of the assay. Please provide linearity results for the drug product (b) (4) over the respective applicable ranges of the assay.
 - ii) Your acceptance criterion for linearity is (b) (4). This is not acceptable. The acceptance criteria of a quantitative assay should be quantitative. Please revise the validation report to express the linearity validation criterion in terms of statistically meaningful parameters, such as R or R² values.
 - iii) Different acceptance criteria for precision, including both repeatability and intermediate precision were listed for different components in (b) (4) drug product. Please provide justifications.

- 2) The following IR is for the validation of (b) (4).

In your submission, (b) (4) was validated partly as an identity and partly as a characterization method. However, this is a critical lot-release test with numerical release specification. Therefore, it is essential that you fully validate the method as a quantitative assay. Please provide additional validation data for accuracy, linearity, and range of the method. You indicated that you could not perform accuracy because of the difficulty to "establish a true or accepted value with respect to (b) (4)". We suggest that you evaluate accuracy using an (b) (4) method such as (b) (4), or evaluated by (b) (4) studies using well characterized (b) (4) reference materials (many of which are available commercially).

- 3) The following IR is for the validation of Methionine by (b) (4) method for drug product.

In the validation report, your acceptance criterion for linearity is (b) (4). This is not acceptable. The acceptance criteria of a quantitative assays should be quantitative. Please provided statistically meaningful data associated with the validation of linearity, such as Coefficient of Correlation (R) or Coefficient of Determination (R²); and make adjustments to the current acceptance criterion of (b) (4) based on the statistical result.

- 4) The following IR is for the validation of Polysorbate 80 by (b) (4) method for drug product.

The validation acceptance criterion for linearity (b) (4) being (b) (4) is vague and not statistically meaningful, please use statistically meaningful data, such as Coefficient of Correlation (R) or Coefficient of Determination (R^2), as acceptance criterion, and provide justification.

5) The following IR is for the validation of (b) (4) method for drug product.

In the validation of analytical procedure (b) (4) the linearity of the method should be validated by (b) (4)

Please provide the (b) (4) and statistically meaningful results, including R or R^2 values.

Please confirm receipt of this communication, 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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