



Meeting Response Memorandum

Our Reference: CRMTS #8352
Ref. # STN 125398/0

Division of Blood Applications

TODAY'S DATE: March 8, 2012 **PAGES:** #13

TO: Mr. Robert Fischer
Novo Nordisk, Inc.
Email address: rofi@novonordisk.com

FROM: Debbie Cordaro
Regulatory Project Manager
Division of Blood Applications
OBRR
Phone number: (301) 827-6157

SUBJECT: Summary of FDA Internal Meeting

PRODUCT: Factor XIII A Subunit (Recombinant)

We completed our review of your information package for Factor XIII A Subunit (Recombinant) and are providing the following responses to the questions you posed in the package. Although we continue to reserve March 14, 2012, 11:00 am – 12:30 pm for a face-to-face with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us as soon as possible so that we may clear the meeting time. Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the review team can provide clarification during the reserved meeting time.

THANK YOU

Questions from Novo Nordisk Inc.:

9.1 Supplemental Process Validation (Item #2 from Complete Response letter)

Applicant Question 1:

For Item 2a in the Complete Response Letter, the Agency has requested (b) (4) (b) (4) for chromatography columns (b) (4) from the three PV runs and (b) (4) for the respective columns. In Section 10.1.1.1, all of the requested information is presented.

Does the Agency agree that the presented data are sufficient to address the deficiency?

FDA Response to Question 1:

The presented data appear to be sufficient. However, the adequacy of the response to Question 2a will be evaluated during the review of Novo Nordisk's official response to the CR letter.

Applicant Question 2:

For Item 2b in the Complete Response Letter, the Agency recommended to include parameters (b) (4) in the supplementary in-process control testing outlined in Amendment # 19 (Table 5 on Page 9 of 12). Novo Nordisk has conducted some preliminary testing with the current analytical method for (b) (4), and the data suggests that it will be possible to test in-process (b) (4) with the existing method. In-process samples from the supplementary process validation batches will be tested and results of (b) (4) will be included in the response to the Complete Response letter.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 2:

The presented approach is acceptable but the adequacy of the response to Question 2b will be evaluated during the review of Novo Nordisk's official response to the CR letter.

Applicant Question 3:

For Item 2c in the Complete Response Letter, the Agency has requested side-by-side comparison of the manufacturing runs for the PV and clinical batches. All of the requested information is presented in Section 10.1.1.3.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 3:

The presented data appear to be acceptable. However, the adequacy of the response to Question 2c will be evaluated during the review of Novo Nordisk's official response to the CR letter.

Applicant Question 4:

For Item 2d in the Complete Response Letter, the Agency has requested the justification of the change in the (b) (4) criterion and a risk assessment for the potential impact of the proposed change on the quality attributes of rFXIII BDS. All the requested information is presented in Section 10.1.1.4.

Does the Agency agree that the presented information is sufficient to address the Deficiency?

FDA Response to Question 4:

The presented data appear to be acceptable. However, the adequacy of the response to Question 2d will be evaluated during the review of Novo Nordisk's official response to the CR letter.

Applicant Question 5:

For Item 2e in the Complete Response Letter, the Agency has recommended to include (b) (4) monitoring of manufacturing steps (b) (4). The data for these parameters are presented in Section 10.1.1.5.

Does the Agency agree that the presented data are sufficient to address the deficiency?

FDA Response to Question 5:

The presented data appear to be acceptable. However, the adequacy of the response to Question 2e will be evaluated during the review of Novo Nordisk's official response to the CR letter.

Applicant Question 6:

For Item 2f in the Complete Response Letter, the Agency has requested the confirmation of the prerequisite limit for manufacturing step (b) (4). In Section 10.1.1.6, Novo Nordisk confirms the prerequisite limit and presents the data.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 6:

The provided information is adequate.

Applicant Question 7:

For Item 2g in the Complete Response Letter, the Agency has requested a summary of the investigation of the deviations that led to process failure. In Section 10.1.1.7, the requested information is presented.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 7:

The presented data appear to be acceptable. However, the adequacy of the response to Question 2g will be evaluated during the review of Novo Nordisk's official response to the CR letter.

9.2 Manufacturing and Inspection Issues (Item #3-10 and 14-15 from Complete Response Letter)

Applicant Question 8:

For Item 3 in the Complete Response Letter, the Agency has requested to include acceptance limits for additional in-process control parameters. (b) (4) were not critical in-process tests during the Propagation, Fermentation and Initial recovery, and were monitored with alert limits. However, it was not possible to determine parameter (b) (4) at step (b) (4). The parameter was determined at step (b) (4) as non-critical in-process test which is trended. The details of the information are presented in Section 10.2.1.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 8:

With regards to Questions 3a and 3b in the CR letter:

No, the submitted information is not sufficient to address the deficiency communicated by the Agency in Question 3. Since (b) (4) is not controlled for manufacturing Step (b) (4), the following in-process control parameters: (b) (4) should be considered as critical for the control strategy of the fermentation process. Furthermore, they can have significant effect on the performance of downstream process and quality attributes of the final product. Therefore, the

Agency reiterates its request to include Acceptance Limits for these three in-process control parameters.

With regards to Question 3c in the CR letter, please establish Alert Limits for the (b) (4) at manufacturing Step (b) (4)

Applicant Question 9:

For Item 4 in the Complete Response Letter, the Agency has requested Novo Nordisk to include acceptance limits for additional in-process control parameters for Recovery and Purification. The detailed control strategy (including alert limits for the requested parameters for steps (b) (4)) are presented in Section [10.2.2](#).

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 9:

No, the submitted information is not sufficient to address the deficiency outlined in Question 4. Therefore, the Agency reiterates the need to include in the control strategy for *Recovery and Purification* (Steps (b) (4)) the Acceptance Limits for the following in-process control parameters:

(b) (4)

The outlined in-process control parameters should be considered critical because deviation from their respective limits or acceptance criteria can significantly impact the performance of the purification process and quality attributes of the final product.

The Agency agrees with the proposed control strategy for the following in-process controls:

(b) (4)

Applicant Question 10:

For Item 5 in the Complete Response Letter, the Agency has recommended to include a specification for potency and (b) (4) for purity measurement in the release specification of the (b) (4) Final Drug product. Novo Nordisk has proposed release limits of the two specifications in Section [10.2.3](#).

Does the Agency agree that the proposed limits are acceptable for the two recommended specifications?

FDA Response to Question 10:

In general, the provided data are acceptable. However, the adequacy of the response, including the proposed specification limits, will be evaluated during the review of Novo Nordisk's official response to the CR letter.

Please retain *Specific Bioactivity* (b) (4) as specifications for the release of the Final Drug Product.

In addition, with reference to your response to Question 5b, please describe the calculation of *Purity* and *Impurities* for the release of the Final Drug Product, specifically, please indicate whether (b) (4) are integrated for these calculations.

Applicant Question 11:

For Item 6 in the Complete Response Letter, the Agency has recommended to include contents of L-Histidine and Polysorbate 20 in the release specification of the Final Drug Product. Novo Nordisk acknowledges the Agency's recommendation. However, analytical testing of the excipients Histidine and Polysorbate 20 is not considered to be necessary as no change is expected for these excipients during processing of the drug product. In addition, correct quality and content of excipients is assured by applied GMP procedures. Furthermore, the robustness of the formulation with respect to changes in the concentration of these excipients has been confirmed. The proposed specification for rFXIII drug product complies with ICH Q6B assuring the quality, purity and potency of the product.

Details of the control strategy of the excipients are presented in Section 10.2.4.

Does the Agency agree that the current control strategy for the two excipients is adequate, therefore the contents of the two excipients are not required to be included in the Final Drug Product Specification?

FDA Response to Question 11:

The Agency agrees that the control strategy for Histidine is acceptable. However, please include the *Level of Polysorbate 20* as a specification for the release of the Final Drug Product.

Applicant Question 12:

For Item 7 in the Complete Response Letter, the Agency has recommended to include the analysis of (b) (4) as part of the assessment of clearance for process related impurities related to the yeast extract used in the cell culture media. As described in Section 10.2.5, preliminary data of analysis indicate that the level of (b) (4) is negligible after the (b) (4) (b) (4). In addition, the clearance of (b) (4) will be evaluated in a

study, where rFXIII in-process samples are analysed. The results will be included in the assessment of clearance for impurities related to the fermentation process. Novo Nordisk considers it is not necessary to include the analysis of (b) (4) as part of the routine assessment of clearance for process related impurities.

Does the Agency agree that the analysis of (b) (4) as part of the routine assessment of clearance for process related impurities related to the yeast extract used in the cell culture media is not required?

FDA Response to Question 12:

The Agency cannot respond to your question at this time because the data demonstrating clearance of (b) (4) have not been submitted for our review.

Applicant Question 13:

For Item 8 in the Complete Response Letter, the Agency has requested manufacturing information of the Novo Nordisk rFXIII A2 BDS batches. The requested information is included in Section 10.2.6.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 13:

Yes, the Agency agrees.

Applicant Question 14:

For Item 9 in the Complete Response Letter, the Agency has some concerns over a (b) (4) (b) (4) of (b) (4) with the submitted SST sample using method M003. Detailed clarification and Novo Nordisk experience on the SST samples are included in Section 10.2.7.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 14:

The data regarding stability of the (b) (4) from reconstituted SST sample as submitted is not consistent with experience in CBER labs. Resubmission of new SST sample for further evaluation should be anticipated.

Applicant Question 15:

For Item 10 in the Complete Response Letter, the Agency has requested information on the effect of (b) (4). As described in Section 10.2.8, study data regarding dilution in (b) (4) vs. water demonstrate that (b) (4) (b) (4) does not (b) (4)

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 15:

The presented data appear to be acceptable. However, the adequacy of the response will be evaluated during the review of Novo Nordisk's official response to the CR letter.

Applicant Question 16:

For Item 14 in the Complete Response Letter, the Agency has requested detailed descriptions of all connections between rFXIII process equipment. A detailed description of all connections and bioburden analysis data are presented in Section 10.2.9.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 16:

With respect to CR item 14b, we agree that the (b) (4) step appears to be conducted in a (b) (4) system. Therefore, performance of your (b) (4) process in a (b) (4) environment may be appropriate.

For other aspects of your manufacturing process, you still have not provided sufficiently detailed information regarding how your equipment is assembled prior to use, and at what condition it is held post cleaning, thus for us to make a determination regarding the system as (b) (4). However, since you state in Table 22 that you only intend to claim that the system(s) is/are (b) (4) with respect to (b) (4), you no longer need to provide validation data that demonstrates that the respective systems are in fact (b) (4) except for (b) (4). With respect to that column, use of sanitization procedures coupled with a cleaning validation that has to date been viewed as inappropriate and/or not validated do not support your claim that this system is (b) (4).

Please also consider that information you have provided as part of your meeting package is inadequate and it does not provide an assessment or justification for the selected manufacturing processes, considering the in-process bioburden data. In-process bioburden obtained from only one processing step cannot satisfy this question.

Applicant Question 17:

For Item 15 in the Complete Response Letter, the Agency has requested additional information on the 100% Visual Inspection Program for rFXIII. The requested information is presented in Section 10.2.10.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 17:

The final review of the visual inspection issues will be made when you submit your complete response. However, please consider the following:

- a. What color is your normal lyophilization cake? There should be a category for this under your section entitled, “Freeze drying cake” so as to ensure that cake color is considered.
- b. Your defect set does not account for particulates adhered to the inside of the vial.
- c. A defect set should often include more than one defect of the same type, when a defect may manifest in varying degree for detection. For instance, particulates can be very large, or barely visible. Your defect set, as described, includes only one particulate of an undefined size and therefore does not span a range of potential particulate sizes that could be encountered, to include particulates that are both of large and barely visible sizes.
- d. Please submit documents that describe your entire visual inspection program, to include data that demonstrates that you have validated the program.

9.3 Lyophilization Qualification (Item #16-17 from Complete Response Letter)

Applicant Question 18:

For Item 16 in the Complete Response Letter, the Agency has recommended to include more samples taken from all shelves from (b) (4) production lyophilizers for Lyophilization qualification. As described in Section 10.3.1, Novo Nordisk agrees to perform a study to include more sampling from all (b) (4) shelves during manufacturing of the batch for process confirmation employing drug substance manufactured in the Supplementary Process Validation on Purification. The study protocol is included in the meeting package (Appendix B). A final study report for (b) (4) lyophilizer will be submitted in the complete response to the CR Letter. (b) (4) lyophilizer will be similarly qualified and taken into use when necessary to meet market demand.

Does the Agency agree that the presented information and the proposed study protocol and validation approach are sufficient to address the deficiency on lyophilization qualification?

FDA Response to Question 18:

With respect to your amended lyophilization sampling plan, we reiterate our comments made on February 29, 2012 to Mr. Robert Fischer via teleconference. Your sampling

plan is acceptable provided you include sampling of alternate locations outside of the selected (b) (4) for critical lyophilization parameters such as cake appearance, residual moisture, potency/bioactivity, and reconstitution time.

With respect to the use of statistical methodology to evaluate lyophilization performance, we do not agree that use of a 95% confidence interval for (b) (4) is appropriate, particularly with respect to residual moisture acceptance criteria.

We do not agree that, in order to qualify lyophilizer (b) (4) for manufacture of rFXIII, manufacturing of a second batch of rFXIII in lyophilizer (b) (4) based on market demand and using the results from extended sampling from this batch, is appropriate. Should you wish to use lyophilizer number (b) (4) you will either have to:

- a. Perform the studies outlined previously using lyophilizer (b) (4) and submit the results of these studies as part of your complete response, or
- b. perform the studies outlined previously using lyophilizer (b) (4) and submit the results of these studies as a supplement to an approved application, or
- c. submit a complete plan for validation of lyophilizer (b) (4) as part of your complete response. Your plan should describe in detail the tests and studies to be performed on your commercial-scale manufacturing batch and your plan for assessing the potential effect of implementation of lyophilizer (b) (4) on product quality. This implementation plan should include your control strategy for commercial production; acceptance criteria for the expected results, and any non-routine tests or sampling that may be pertinent to the plan. Potential reporting categories for this change can be discussed after your complete response is received. Please note that we do not believe that this change (b) (4) lyophilizer) is necessarily within the scope of annual reportable changes.

Applicant Question 19:

For Item 17 in the Complete Response Letter, the Agency has requested the final container release information for drug product manufactured with drug substance from the Supplementary Process Validation study. The requested information will be submitted as part of the process confirmation report from manufacturing of rFXIII drug product employing drug substance from the supplementary process validation on purification in the complete response to the CR Letter.

Does the Agency agree that the presented information is sufficient to address the deficiency?

FDA Response to Question 19:

Yes

END