



MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: File of STN 125398/0 & Jiahua Qian

From: Zuben Sauna
Chair of Review Committee & CMC reviewer

Through: Timothy Lee
Acting Chief, Laboratory of Hemostasis/DH/OBRR

Subject: Addendum to review of CMC information in the Biologics License Application by Novo Nordisk Inc. for recombinant human Coagulation Factor XIII A₂ Subunit (rFXIII-A₂) [Novothirteen®] expressed in yeast cells (*Saccharomyces cerevisiae*) – Review of Novo Nordisk's resubmission addressing FDA's Complete Response Letter

This biologics license application (BLA) was previously reviewed by a committee that included the following CBER reviewers:

Dr. Roman Drews (Chair of Review Committee and CMC), Dr. Harold Boxenbaum (Clinical Pharmacology), Mr. Michael Brony (Advertising and Labeling), Dr. La'Nissa Brown-Baker (Pharmacology/Toxicology), Ms. Karen Campbell (Lot Release/Analytical Methods), Deborah Cordaro (Administrative/Regulatory), Dr. Al Del-Grosso (CMC/Analytical Methods), Ms. Grace Deneke (CMC/Facility), Mr. Anthony Hawkins (Bioresearch monitoring), Dr. Nisha Jain (Clinical), Ms. Carla Jordan (Bioresearch monitoring), Dr. Charles Maplethorpe (Clinical), Dr. Alan Ou (Epidemiology), Dr. Zuben Sauna (CMC/Immunogenicity methods), Mr. Destry Sullivan (CMC/Facility), Dr. Jean Wang (Biostatistics)

The pre-licensure inspections were conducted at the following production facilities: Novo Nordisk A/S for the up-stream production of drug substance (Bagsvaerd, Denmark), and Novo Nordisk A/S for the down-stream production of drug substance and final drug product ((b) (4)).

Several CMC (Product and Facility) and Clinical deficiencies in addition to outstanding issues resulting from the pre-approval inspections have not been resolved during the first review cycle of this BLA. Thus, based on the recommendation of the review committee, a Complete Response (CR) letter

dated December 23rd 2011, listing all the deficiencies in the BLA, was issued to Novo Nordisk.

At the request of Novo Nordisk, FDA participated in two type C meetings to discuss the chemistry, manufacturing and controls (CMC) and clinical deficiencies in the CR letter on March 14th and 15th, 2012, respectively.

Novo Nordisk responded to the CR letter on December 27th 2013. The resubmission included responses to the CMC and Clinical deficiencies and to the observations during pre-license inspections.

This review addresses Novo Nordisk's responses to CMC deficiencies identified in the CR letter from the perspective of product reviewer. The CMC/Facility related issues will be reviewed separately by Mr. Destry Sullivan of DMPQ. Although there are currently no unresolved CMC product-related issues in this BLA, the submission cannot be approved pending the review of an inspection of Novo Nordisk's (b) (4) facility conducted from (b) (4). In addition, Mr. Sullivan still found deficiencies in the validation of the visual inspection program, which he included in the second CR letter.

Review of CMC related deficiencies in the CR letter

(Numbers denote the deficiency items as they appeared in the CR letter)

2. With regard to the process validation (PV) studies for the manufacture of bulk drug substance (BDS) that were reported in BLA amendments # 10, # 17 and # 19 dated October 20, November 21, and December 9, 2011, respectively:

a. Please provide copies of the (b) (4) for chromatography columns (b) (4) from the three PV runs. In addition, please include copies of the (b) (4) (b) (4) (b) (4) for the respective columns.

Reviewer's comment: The manufacturer has submitted an updated version of the document Supplementary Process Validation for Purification. This document (module 3.2.S.2.5) now includes the following additional information for the validation batches (b) (4)

(b) (4)

i) (b) (4) for chromatography columns (b) (4) (b) (4) and comparison with a reference (phase 3b batches (b) (4)

ii) (b) (4)

iii) (b) (4)

The (b) (4) of validation and clinical batches during chromatography are comparable though not identical. The explanation

that this is due (b) (4) for the validation is reasonable and these data are acceptable.

b. Please include the following parameters in the supplementary in-process control testing outlined in Amendment # 19 (Table 5 on Page 9 of 12): (b) (4)

(b) (4)

Reviewer's comment: It was noted that there was a loss of (b) (4) (b) (4) from Steps (b) (4) (Table 6 in updated version of 3.2.S.2.5 Supplementary Process Validation for Purification). The explanation provided by Novo Nordisk was that this is due to lower (b) (4) in Step (b) (4). However it was not clear whether (b) (4) was used for the calculation of "(b) (4)" or the (b) (4) estimated from (b) (4). If (b) (4) is calculated based on (b) (4) (b) (4) (and thus the (b) (4) (b) (4)) should have increased from Step (b) (4). An information request was submitted to Novo Nordisk for clarification. The response (March 27th 2013) included calculation of (b) (4) calculated both with respect to (b) (4) (b) (4). The rFXIII is essentially purified by Step (b) (4) and the apparent loss in (b) (4) of three batches was shown to be within the normal variation of (b) (4) in the drug substance. The additional data and explanation provided by Novo Nordisk are satisfactory.

c. Please provide, in a tabulated form, a summary of side-by-side comparison of the manufacturing runs for the PV and clinical batches. The data should include, but not be limited to, results of in-process control testing, supplementary in-process control testing, and rFXIII BDS release testing. In addition, please submit (b) (4) (b) (4) for chromatography columns (b) (4) from the manufacture of the PV and clinical batches.

Reviewer's comment: The requested information has been provided and is satisfactory.

d. Please justify the change in the (b) (4) criterion for (b) (4) from one that is (b) (4) to one based on a (b) (4), and provide a risk assessment for the potential impact of the proposed change on the quality attributes of rFXIII BDS.

Reviewer's comment: The justification is satisfactory and is supported by the data provided in the risk-assessment. Three criteria, (b) (4) (b) (4) were evaluated in batches that were manufactured using a (b) (4) criterion and those where the (b) (4) from (b) (4). These data show that while the quality

of the product (in terms of these criteria) was not affected there was a reduction in the variability suggesting that the criterion adopted is more robust.

e. Please include (b) (4) in the monitoring of manufacturing steps (b) (4)

Reviewer's comment: The requested information has been provided.

f. Please confirm that the prerequisite limit for manufacturing step (b) (4) of approximately (b) (4), which corresponds to approximately (b) (4) of BDS, has been maintained during the PV runs.

Reviewer's comment: Novo Nordisk has confirmed that this prerequisite was fulfilled; i.e. a minimum of (b) (4) after step (b) (4) must be obtained in order to proceed to step (b) (4)

g. As stated in Part 3 (Scope) of the Process Validation (PV) protocol dated 18 August 2011 "The PV of the rFXIII will comprise 3 consecutive batches". The results for the first validation batch were submitted to the FDA on 21 November 2011 (BLA Amendment # 17). However, the submission of the validation data for the two remaining batches was delayed until 9 December 2011 (BLA Amendment # 19) because of failure of the manufacturing process (as per information provided to FDA during the teleconferences on October 5 and 20, 2011). Please provide a summary of the investigation of the deviations that led to process failure, which should include identification of root cause(s), and corrective and preventive actions that eventually resulted in the manufacture of the three (3) consecutive BDS batches required for the demonstration of process consistency in the PV studies.

Reviewer's comment: Novo Nordisk has clarified that while there was a manufacturing process failure, it did not occur during the manufacture of the three (3) consecutive validation batches, (b) (4) Novo Nordisk has also provided details of the deviation and a summary of the root cause analysis. The response is satisfactory.

3. With regard to the in-process controls for Propagation, Fermentation and Initial Recovery, please include the Acceptance Limits for the following in-process control parameters:

(b) (4)

Reviewer's comment: As requested Novo Nordisk has set the in-process control parameters. These were set based on historical norms and are as

(b) (4)

4. With regard to the in-process controls for Recovery and Purification, please include the Acceptance Limits for the following in-process control parameters:

(b) (4)

Reviewer's comment: Novo Nordisk has set Alert and/or Acceptance limits for all the parameters requested. Table 5 (Novo Nordisk's CMC Response to Complete Response Letter Dated 23 Dec 2011) summarizes the control strategy and includes the rationale for the choice of the Alert and/or Acceptance limits. The response is adequate.

5. With regard to the release specifications of the (b) (4) Final Drug Product:

a. Please include a specification for Potency based on the M005 bioactivity assay and establish acceptance limits based on manufacturing and clinical experience.

b. For Purity measured by the M002 (b) (4) test, please include (b) (4) (b) (4) as a specification with an acceptance criterion derived from manufacturing experience, and include an assessment of the (b) (4) (b) (4) for the calculation of either % purity or % impurity.

Furthermore, in the Meeting Response Memorandum from FDA dated March 8, 2012 included the following requests:

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

Please describe the calculation of Purity and Impurities for the release of the Final Drug Product, specifically, please indicate whether (b) (4)

Reviewer's comment: Novo Nordisk has proposed the following release specifications for the rFXIII drug substance and drug product.

Drug Substance		
Parameter	Procedure	Proposed limit
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Drug Product		
Total bioactivity (IU/mL)	rFXIII bioactivity assay (M005)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Polysorbate 20 (b) (4)	(b) (4)	(b) (4)

Novo Nordisk has provided adequate justification for these specifications.

With respect to residual (b) (4) Novo Nordisk contends that the measurement of (b) (4) in steps (b) (4) of the manufacturing process shows removal of (b) (4) to a level below the limit of detection (b) (4) (b) (4)). Data from (b) (4) rFXIII drug substance batches has been provided to support this observation. Novo Nordisk has also provided the results of a (b) (4) experiment with and (b) (4) (b) (4) used in step (b) (4) of the manufacturing process. The data show a minimum of (b) (4) in (b) (4) levels. Based on this these results Novo Nordisk suggests that levels of (b) (4) need not be part of the final specifications which is acceptable to this reviewer.

6. With regard to the release specification for the Final Drug Product, please include the contents of the following excipients: L-Histidine and Polysorbate 20.

Reviewer's comment: At the Type C Meeting on March 14, 2012 Novo Nordisk stated that during manufacturing of drug product no change in excipients was expected and that establishment of the limits for histidine would be covered by the tests for pH (b) (4). FDA concurred with this rationale. Novo Nordisk has established and validated a new analytical method for determining the polysorbate 20 content in the final drug product. The proposed release specifications are (b) (4) which is acceptable.

7. Please 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.

Reviewer's comment: Novo Nordisk has provided data showing that the (b) (4) of manufacturing process) reduces (b) (4) level to (b) (4) of rFXIII. The (b) (4) step (step (b) (4) of manufacturing process) further reduces the level of (b) (4) of rFXIII. The (b) (4) step is also expected to reduce (b) (4) levels. However as the input levels of (b) (4) are already below the level of detection, a (b) (4) experiment was used to show a (b) (4) in (b) (4) levels at this step. These results satisfactorily resolve the query.

8. *At the time of this review, at least (b) (4) batches of rFXIII A2 BDS were manufactured by Novo Nordisk after the transfer of the manufacturing process from (b) (4). Please provide, in a tabulated form, the following information regarding the manufacture of these batches: date of manufacture, disposition with regard to the outcome of in-process control and final release testing, and reason(s) for process failure or batch rejection.*

Reviewer's comment: Novo Nordisk has provided the requested information.

Items 9-10 in the CR letter were requested and reviewed by Dr. Al Del-Grosso (CMC/Analytical Methods) and Novo Nordisk's response was determined by him to be adequate.

11. *With reference to the assessment of freeze-thaw stability of quality control (QC) reagents described in Module 5.3.1.4.3, ("Final report: validation of an (b) (4) for the detection of anti-FXIII antibodies in human plasma (EDTA) and primate serum using (b) (4) Section 3.6, Pg. 17), please describe the handling of patient samples, specifically the number of freeze/thaw cycles they have experienced, and limit the number of freeze/thaw cycles for the QC reagents and samples to (b) (4) in subsequent studies.*

Reviewer's comment: Novo Nordisk responded that 98.9% (622/629) of the patient samples from the pivotal phase 3 clinical trial (F13CD-1725) were freeze/thawed (b) (4) times (upon baseline thawing). The remaining seven samples were freeze/thawed (b) (4) times. This is acceptable.

12. *With reference to Module 5.3.1.4.3, ("Analysis of anti-FXIII inhibitors in antibody screening positive samples from Trial ID: F13CD-1725", Section 3, Table 1, Pg. 9) which reports on the analysis of anti-FXIII inhibitors in antibody screening positive samples:*

a. Please specify the duration at which the samples were taken, and the number of doses the patient has received.

Reviewer's comment: The information was requested for clarification as immunogenicity is the primary end point of the clinical study. Novo Nordisk has provided the requested information and collection of samples were determined to be consistent with the study design.

b. Novo Nordisk states "All test results come from (b) (4) individual runs performed." Please clarify if additional multiple replicates were performed for the data presented in this section, and if any of those samples were tested positive for FXIII-neutralizing activity.

Reviewer's comment: Novo Nordisk did not perform additional replicates and there are no unreported results of samples that tested positive for FXIII-neutralizing activity.

13. With reference to the determination of anti-FXIII antibodies in human plasma (EDTA) using (b) (4), Clinical Study F13CD-1725 provided in Module 5.3.1.4.3 (Determination of anti-FXIII Antibodies in Human plasma (EDTA) Using (b) (4) section 2.13.1, Pg. 21), please describe the derivation of the normalization factor (b) (4) using negative control (b) (4)

Reviewer's comment: Novo Nordisk has described the derivation of the normalization factor and is satisfactory.

Responses to Items 9-10 in the CR letter are reviewed by Mr. Destry Sullivan (DMPQ) in a separate memo.

Conclusions and Recommendations

From the perspective of this product reviewer, there are no unresolved CMC issues with Novo Nordisk's BLA for recombinant human Coagulation Factor XIII A₂ Subunit (rFXIII-A₂) [Novothirteen®] expressed in *Saccharomyces cerevisiae* (STN 125398/0). However, the BLA cannot be approved in this review cycle due to the following reasons:

A recent inspection of Novo Nordisk Inc, located at (b) (4) (b) (4)) was conducted from (b) (4) (b) (4). The TeamBio inspector recommended potential Official Action Indicated. This inspection is currently under review by the Division of Case Management (DCM) in the Office of Compliance and Biologics Quality (OCBQ). Therefore, OCBQ, DCM does not recommend approval of this supplement. In addition, Mr. Sullivan found deficiencies in the validation of the visual inspection program. Thus, a second CR letter will be issued describing these deficiencies.