

MEMORANDUM



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



Chemistry, Manufacturing and Controls Review

To: File of STN 125466, & Leigh Pracht,
OBRR/DBA/RPMB

From: Andrey Sarafanov, Ph.D., OBRR/DH/LH

Through: Mark Weinstein, PhD, Associate Deputy Director, OBRR
Basil Golding MD, Division Director, OBRR/DH

CC Timothy Lee, Ph.D., OBRR/DH/LH and Natalya Ananyeva, Ph.D., OBRR/DH/LH

Product: Antihemophilic Factor (Recombinant), Plasma/Albumin Free [NovoEight]

Subject: Final Review of CMC information related to Product Quality/Analytical Methodology
in Novo Nordisk Inc. BLA for NovoEight.

EXECUTIVE SUMMARY

This memorandum represents the final CMC review of the analytical methodology used for testing the Drug Substance (DS) and Final Drug Product (DP) in the biologics license application (BLA) from Novo Nordisk Inc. (Novo) for Antihemophilic Factor (Recombinant) [Novoeight] (N8). The following analytical procedures and their validation were included in the scope of the review: -----(b)(4)-----; Identity and Purity by ---(b)(4)---; Content and -(b)(4)- by ---(b)(4)---; Identity by ---(b)(4)---; Potency by Chromogenic Substrate Assay; FVIII Activity by One-Stage Clotting Assay; -----(b)(4)-----; Anti-FVIII mAb leakage (b)(4); Microbial Count; Bacterial Endotoxin; and Sterility testing.

During the review process, an Information Request was sent to the Applicant on April 09, 2013, with Questions 8-11 relevant to the present review. FDA requested additional information regarding (i) qualification of compendia methods, (ii) procedure for verification of the Sterility test, (iii) recovery monitoring in the validation of the Endotoxin test, and (iv) methodological procedure for (b)(4) test. In their responses submitted on May 13, and June 14, 2013, Novo addressed the questions in a satisfactory way.

Thus, all analytical methods used for characterization of identity, purity, quality and safety of N8 Drug Substance and Drug Product have been adequately validated to support the Specifications. I recommend approval of the BLA for N8 from the analytical methodology perspective. I am also providing some recommendations for the Specification parameters of N8, which Dr. Ananyeva, BLA chairperson, has reviewed.

BACKGROUND

Novoeight (N8 or turoctocog alfa), is a recombinant human coagulation factor VIII (FVIII) modified in a way that its B-domain is reduced to a short segment of 21 amino acid residues. This product is very similar in structure to Xyntha, a FVIII product already approved in the USA. The B-domain-like portion of N8 is similar to that of Xyntha, and represents native flanks of the B-domain, both adjacent to sites of FVIII thrombin activation. Within this fragment, there is also a site for -----(b)(4)----- . Upon activation of N8 by thrombin, the modified B-domain is cleaved off and the molecule acquires a structure identical to that of activated FVIII. N8 is produced in Chinese Hamster Ovary cells. The post-translational modifications of N8 include -----(b)(4)-----

----- . The proposed indication of N8 is the same as that for other FVIII products, i.e. control and prevention of bleeding episodes in FVIII-deficient individuals (having Hemophilia A). The drug product is manufactured in a lyophilized form to be reconstituted in 0.9% NaCl, at the dosages of 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU. Since the original submission, the Applicant has sent additional information. In Amendment 9, the specification limit for Polysorbate 80 was updated, and in Amendments 11 and 17, verifications of assays for Microbial Count, Bacterial Endotoxin, Sterility, Particulate Matter and ----(b)(4)---- were provided.

SUMMARY OF REVIEW

The subject of this review is validation of analytical procedures used for characterization of the final drug product (DP) N8, and also the bulk drug substance (DS) as a manufacturing intermediate. I reviewed the following sections.

3.2.S.4.2, Analytical Procedures (drug substance)

3.2.S.4.3, Validation of Analytical Procedures (drug substance)

3.2.S.5, Reference Standards

3.2.P.5.2, Analytical Procedures (drug product)

3.2.P.5.3, Validation of Analytical Procedures (drug product)

Also, other sections (such as 3.2.S.4.5; 3.2.P.4.6; and 3.2.P.5.6), relevant to the review subject were considered.

Setting the Parameters to Characterize the Drug Product to Ensure its Safety and Efficacy

The Applicant stated that the selection of critical parameters (specification parameters) for the DP and DS was performed in accordance with ICH guidelines Q11 (*Development and Manufacture of Drug Substance*) for DS (3.2.S.4.5) and Q8 (R2) (Pharmaceutical Development) for the DP (3.2.P.5.6). These parameters reflect the respective critical quality attributes (CQA) of the DP, identified based on characterization of the DP produced during 2007-2011, and the company's prior experience from 15 years of manufacturing another product rFVIIa (NovoSeven). To prioritize the COA parameters, their severity ranks were established. The highest ranks were assigned to such parameters as -----(b)(4)-----, because of their potential immunogenicity, and the lowest ranks were assigned to -----(b)(4)----- (3.2.S.4.5 and 3.2.P.5.6). As a result, the most important parameters were defined as specification parameters, which were established for both DS and DP.

The limits of the specification parameters were determined based on the requirements for DS and DP, the manufacturing process capability, stability, and clinical relevance (3.2.S.4.5 and 3.2.P.5.6). Process capability estimations were performed on batch release results and trends seen during the stability testing. These calculations (to assess the specification limits) were justified based on estimates of the respective mean values and standard deviation assuming that the results for each component follow normal distribution. Thus, the present review also covers the specification parameters and their ranges as grounding the respective analytical procedures used to ensure compliance of the product to its specification.

Product Specifications and Analytical Methods Used.

Table 1. Drug substance specifications and analytical methods (3.2.S.4.1)

---(b)(4)---

1 page redacted (b)(4)

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¹ Complies = the lyophilized powder appears as a white or slightly yellow powder or friable mass

² Complies = the lyophilized powder dissolves within -----(b)(4)-----, giving a clear or slightly opalescent solution
------(b)(4)-----

⁴ Complies = clear or slightly opalescent solution

⁵ Complies = comparable to reference
------(b)(4)-----

⁷ The units IU/vial and mg/vial refer to IU or mg per withdrawn volume, (4 mL)

⁸ Complies = the product meets the requirement of test for sterility in -----(b)(4)----- and 21 CFR.610.12

Development of the Analytical Methodology

The analytical methodology was developed along with the development of manufacturing to ensure compliance to the product specifications. During the manufacture development, most of the changes in analytical methodology were editorial as related to the change of the identification numbers in the documentation. For Identity by ---(b)(4)---, the acceptance criteria were narrowed without change of methodology. For Potency by chromogenic substrate assay, for the control sample, the relative standard deviation (RSD) was reduced from -----(b)(4)----. For Content and -----(b)(4)----- assay, detection was changed from -----(b)(4)----- to obtain an adequate limit of quantitation of -(b)(4)-. For -(b)(4)-, the unit of response was changed from -----(b)(4)----- relative to the N8 content (3.2.S.4.2).

Reviewer's comment

Selection of the specification parameters and their ranges complies with the ICH Q6A/Q6B guidance (*Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*). According to it, the main principles of setting these parameters are to ensure safety and efficacy of the product. These parameters should include characterization of physicochemical properties, biological activity, immunochemical properties, purity, and impurities. The respective acceptance criteria should be established and justified based on data obtained from manufacturing development and stability of the product. Specification also needs to be linked to respective analytical methods used and developed along with manufacturing development. Thus, the specification parameters for N8, their ranges (limits) and analytical methodology used is justified and relevant to the guidance.

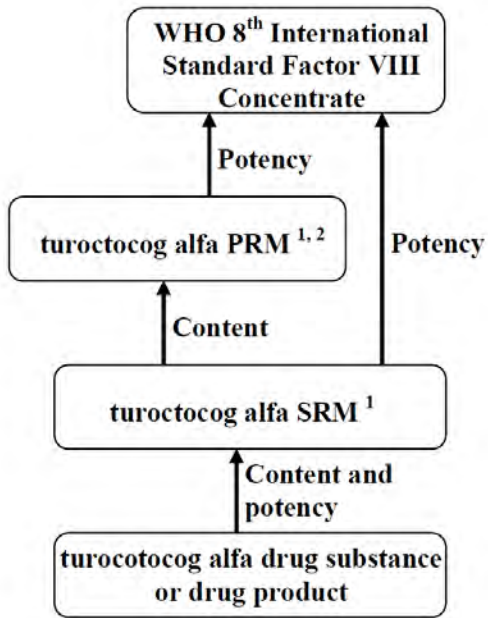
Analytical Procedures for Drug Substance

The relevant assays are described in sections 3.2.S.4.2 and 3.2.S.4.3 (validation). The validation studies were stated based on principles of the ICH Q2(R1) guidance.

Reference standards (3.2.S.5)

DP batch -----(b)(4)----- of N8 was assigned to be a primary reference material (PRM). It was further used for the protein identification and characterization according to the specifications. The biological activity (potency) of N8 PRM was determined by a chromogenic substrate assay by calibration against WHO 8th International Standard (IS) of FVIII. In addition, the clotting activity of the PRM was determined by a one-stage clotting assay using calibration against the WHO 8th IS for FVIII. This PRM batch was assigned a -----(b)(4)----- and a potency of --(b)(4)-- by a chromogenic substrate assay, when reconstituted in (b)(4) of 0.9% sodium chloride. This PRM was further used for calibration for content and potency of N8 secondary reference material (SRM), derived from the same DP batch -----(b)(4)----- . The traceability chain for both PRM and SRM is shown in Fig.1. Also, a DP batch ---(b)(4)--- was aligned to -----(b)(4)----- and used as PRM and SRM.

Fig. 1 Traceability chain for N8 content and potency determinations of PRM and SRM.



¹ PRM and SRM is the same drug product batch

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Some of the methods relevant to analysis of N8 DP were reviewed under the section for (b)(4) methods, since these methods are relevant to ---(b)(4)--- DP. These methods are: Purity and -----(b)(4)-----, Content and -----(b)(4)-----, Identity ----(b)(4)----, Potency (chromogenic substrate assay) and FVIII activity (one-stage clotting assay, a supplemental test).

Descriptions, 3.2.P.5.2

Validation – 3.2.P.5.3

Appearance of Powder and Reconstitution Time

Appearance of Powder. The content of the vial is examined visually, preferably in daylight. The lyophilized powder should appear as a white or slightly yellow powder or friable mass.

Reconstitution Time. The powder should get completely dissolved in the provided solvent (0.9% Sodium Chloride) within ---(b)(4)---. Both procedures were stated as general descriptive methods, which do not require validation. Thus, no validation was provided.

Water Content (by -----(b)(4)----- analysis)

(b)(4)

----- (b)(4) -----

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----- (b)(4) -----

Reviewer's comment

For all tested parameters, the acceptance criteria were fulfilled and the method can be considered as adequately validated for determination of water content by (b)(4) in N8 DP.

---(b)(4)--- (determination of methionine by ---(b)(4)---)

The content of methionine in DP is determined by -----

----- (b)(4) -----
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----- (b)(4) -----

----- (b)(4) -----

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----- (b)(4) -----

Reviewer's comment

For all tested parameters, the acceptance criteria were fulfilled and the method can be considered as adequately validated for the determination of methionine in N8 DP.

Polysorbate 80 (by --- (b)(4) ---)

This method is to analyze the DP excipient, Polysorbate 80. The method validation and the final Specification limit for Polysorbate 80 were submitted in Amendment 9, to fulfill the commitment agreed upon in the June 13, 2012 Pre-BLA Meeting Preliminary Response. At first step, polysorbate 80 is -----

----- (b)(4) -----

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- ----- (b)(4) -----

Reviewer's comment

For all tested parameters, the acceptance criteria were fulfilled and the method can be considered as adequately validated for the determination of Polysorbate 80 in N8 DP.

Sterility (Assay Verification)

The report was provided in Amendment 11. The test is stated as performed according to -----
---- (b)(4) ----- 21 CFR § 610.12, and the provided data are verification of the test
suitability for analysis of N8 DP. The principle of the method is to -----

----- (b)(4) -----

Reviewer's Comment.

In the absence of actual filtration of the DP matrix containing the test microorganism, the
suitability of the method is questionable. If the ----- (b)(4) -----
-----, the method could be not
suitable. The performed study supports only suitability of the microorganisms' detection system
(i.e. part of the method), but not the whole method. Upon further information request, Novo
successfully verified this assay using spiking of the challenge microorganisms directly into DP
matrix, i.e. in a correct way.

Bacterial Endotoxin ----(b)(4)-----

The method validation was provided in Amendment 11 (3.2.P.5.3). The validation study was performed according to ----(b)(4)-----.

----- (b)(4) -----

----- (b)(4) -----

Reviewer's comment.

From the provided description, it is unclear how the Positive Product Control (endotoxin) was assessed for recovery in each batch of the DP. ----(b)(4)-----, but it needs to be verified with Applicant. Upon further informational request (IR) about it, Novo confirmed that Endotoxin standard was indeed spiked into the matrix in this study (Question 10 of the IR, see below).

With regard to test dilution, the correct dilution is ----(b)(4)----- as the volume (b)(4) is used for reconstitution of lyophilized product. This was noted by DBSQC during in-support testing of the PPQ batches and was conveyed to Novo Nordisk during the Pre-License Inspection and in subsequent Information Request of April 24, 2013. Novo Nordisk re-submitted the corrected results for Endotoxin testing for the three PPQ batches in Amendment 17 dated May 13th, 2013.

Particulate Matter (Assay Verification)

This information was submitted in Amendment 17 (3.2.P.5.3, Verification of Compendial Procedure Particulate Matter), in response to the FDA information request (Question 8). The procedure is performed in accordance to -----

----- (b)(4) -----

----- The acceptance criteria corresponded to the Particulate Matter specification values and were met. Therefore, the procedure was found suitable for use for the release testing of N8 DP.

Reviewer's Comment.

In the provided documentation, under Materials, the batch --(b)(4)--- is mistakenly marked as of 2000 IU strength, though it is actually of 3000 IU strength.

------(b)(4)-----

------(b)(4)-----

-----.

SUMMARY OF REVIEWER'S COMMENTS UPON THE INITIAL REVIEW

Some of -----(b)(4)----- methods used for DP analysis were not validated or verified (3.2.P.5.2, Table 1). These methods were relevant to analysis of the following specification parameters: i) Visual Evaluation of Clarity, ii) (b)(4), iii) Particulate Matter and iv) ---(b)(4)---. According to the Applicant, full validation of a compendia analytical procedure is not required according to the ICH guideline (Q2 (R1), step 4 version) (3.2.S.4.3, Validation of analytical procedures y9439, P. 7). However, current version of this guideline does not contain such statement; in addition, according to FDA Guidance for Industry, Bioanalytical Method Validation (2001), full validation is important for a new drug entity.

For Sterility assay (DP), the assay verification was not appropriately performed. The test microorganisms were not spiked into the DP matrix, but instead added to the -----(b)(4)----. Thus, only the performance of the microbial detection system was verified, i.e. growth on selective media.

Regarding validation of Bacterial Endotoxin assays for ---(b)(4)--- DP, Positive Product Control and assessment of endotoxin recovery in each tested batch of the (b)(4) DP were not sufficiently explained.

INFORMATION REQUESTS

On March 27, 2013, an information request initiated by CBER analytical group (OCBQ/DBSQC/QAB, Dr. Lokesh Bhattacharyya) was sent to the Applicant, to provide more details on the analytical methodology for --(b)(4)-- used to control Content and (b)(4) parameter. The Applicant responded on April 4, 2013. Please refer to the respective section of this review.

At Mid-Cycle, Information Request was sent to Novo Nordisk on April 09, 2013 with Questions 8-11 relevant to present review. The responses were submitted in Amendment 17 dated May 13th, 2013, (Module 1.11.1) and are reviewed below.

FDA Question 8

Please provide qualification reports for (b)(4), Particulate Matter and ----(b)(4)---- that verify their suitability under actual conditions of use.

Response

1. A suitability study of (b)(4) (compendial procedure) has not been performed as it is not considered relevant, based on the rationale given in ---(b)(4)---. It is stated that (b)(4) measurements have been routinely performed for several years on all sample types, including N8 (b)(4) DP, in the QC laboratory. All ingredients are commonly used for protein formulations and are judged very unlikely to affect the (b)(4) measurement.

Reviewer's comment.

Under -----(b)(4)-----, verification is not required for basic compendial test procedures that are routinely performed unless there is an indication that the compendial procedure is not appropriate for the article under test. Since Novo has been routinely using this procedure on all sample types, there is no indication that the method is not appropriate for the aimed purpose. It is expected that regular calibration of the ---(b)(4)--- is performed. Thus, the response is acceptable.

2. The suitability of Particulate Matter (compendial procedure) was studied on three strengths of the DP the entire range of strengths; -----(b)(4)-----

As stated, specifications were met and the analytical procedure was concluded to be suitable for all strengths. The qualification report is provided in 3.2.P.5.3 Verification of Compendial Procedure Particulate Matter.

Reviewer's comment.

I reviewed the Qualification Report and find the response to be acceptable.

3. The suitability of ---(b)(4)--- (compendial procedure) was studied on a DP 2000 IU/vial batch, assessed to be representative for all strengths of the DP. As stated, specifications and system suitability test parameters were met and the method was concluded to be suitable for the release testing of the DP. The qualification report is provided in 3.2.P.5.3 Verification of Compendial Procedure ---(b)(4)---.

Reviewer's Comment.

I reviewed the Qualification Report and find the response to be acceptable.

FDA Question 9

The provided verification data for Sterility of the final drug product (DP) only support the system's capability to detect microorganisms. To verify its capability to assess sterility in the DP, the test

organisms should be spiked into the reconstituted DP -----(b)(4)-----.
Please comment.

Response

The Applicant clarified that the verification was carried out according to the guidelines and requirements of 21 CFR 610.12, -----(b)(4)----- . In the suitability verification study, viable microorganisms (not more than -(b)(4)-) were added to the -----
---(b)(4)----- . Novo Nordisk is aware of the final rule revising the sterility requirements for most biological products, effective June 4, 2012, as published in the Federal Register, Vol. 77, No. 86, p. 26162 – 26175, stating that challenge organisms be added directly to the product prior to membrane filtration. As the verification of the test for sterility was carried out prior to the final rule, challenge organisms were not added directly to the product. In order to comply with the final rule of 21 CFR 610.12, Novo Nordisk committed to carry out a new verification of the test for sterility.

Reviewer's comment.

Novo committed to perform the new verification of the Sterility test according to the requirements of the final rule of 21 CFR 610.12 Sterility, (Revised on April 1, 2012) that the verification must be performed with challenge organisms added directly to the product prior to membrane filtration and must demonstrate the method's capability to consistently detect the presence of viable contaminating microorganisms. Thus, the response is acceptable. By June 15th, 2013, Novo submitted new assay verification data (see below).

FDA Question 10

With reference to the validation of assays for Bacterial Endotoxin for -----(b)(4)-----
--- final drug product, please clarify if an Endotoxin standard was spiked into the matrix as a positive control, and used to measure recovery. In addition, please submit the validation protocols for these studies.

Response

Novo explained that the endotoxin standard was spiked into the sample matrix as a positive product control and these samples were used to measure the recovery. The standard protocol (SOP) for these studies was provided in Generic Validation Protocol Analytical Procedure YM-400/YM-450 Bacterial Endotoxin test.

Reviewer's Comment.

I reviewed the document and find the response to be acceptable.

FDA Question 11

With reference to your Response to Request 1 in the amendment dated 4 April 2013, you stated that the -----(b)(4)----- by injections of SRM or "other sample material". Please clarify what the "other sample material" is.

Response

Novo explained that they use the same protein, N8, for the -----(b)(4)----- . In particular, this can be a pool of already analyzed samples. They also explained that do not have experience of using -----(b)(4)-----.

Reviewer's Comment.

The response is acceptable. Considering that -----(b)(4)----- requires substantial amounts of N8 for multiple injections; that the method was custom-optimized by the Applicant and method validation appears to be adequate, this reviewer reiterates that N8 can be exempt from the Post-Licensure testing by CBER

Reviewer's Comment.

I reviewed the document and find the response to be acceptable.

On informational request sent to Novo on April 09, 2013 about the sterility assay issue (Question 9), on June 14, 2013 Novo responded as follows.

FDA Question #9 from April 9, 2013 Information Request

The provided verification data for Sterility of the final drug product (DP) only support the system's capability to detect microorganisms. To verify its capability to assess sterility in the DP, the test organisms should be spiked into the reconstituted DP prior to the filtration -----(b)(4)----- . Please comment.

Response.

In the provided response, (Module 3.2.P.5.3) Novo presented data for sterility assay verification. The challenge microorganisms (-----
--(b)(4)-----) at different combinations were spiked directly in the DP (3000 IU/vial) processed further according to the compendial protocol with relevant controls. The data supported suitability of the sterility test used for N8 DP release.

Reviewer's Comment.

I reviewed the document and find the response to be acceptable. In addition, the assay design and data presented by Novo support possible revision of the current --- (b)(4) --- in a way to correctly describe the assay.

SUMMARY OF FINAL COMMENTS OF REVIEWER

In general, the selected Specification parameters for N8 and their established acceptance ranges (limits) seem justified. Further recommendations regarding Specifications are provided in Dr. Ananyeva's review memorandum. All analytical methods used for characterization of identity, purity, quality and safety of N8 Drug Substance and Drug Product are adequately validated to support the Specifications. Based on my review of analytical methods, I have the following recommendations regarding the DS and DP Specifications.

1. A combined content of -----(b)(4)-----, instead of (b)(4) only, would provide a more accurate representation of (b)(4) impurities in -----(b)(4)-----
--- Drug Product.
2. Assessment of the -----(b)(4)----- may be a tool to monitor the presence of -----(b)(4)----- impurity. Novo Nordisk should provide justification of not performing this assessment or FDA can require including this parameter in Specification for (b)(4) DP and in Stability Programs.

RECOMMENDATION

From the analytical methodology perspective, I recommend approval of the BLA for Antihemophilic Factor (Recombinant) with the proprietary name Novoeight.