

MEMORANDUM



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



To: Administrative File (STN 125466/0) and Leigh Pracht, CSO, RPMB/DBA/OBRR

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Subject: Final Review of the CMC Information in the Original Biologics License Application from Novo Nordisk Inc., Denmark, for Antihemophilic Factor (Recombinant) [Novoeight]

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BACKGROUND

Novo Nordisk Inc., Denmark, submitted an original Biologics License Application (BLA) to seek U.S. licensure for Antihemophilic Factor (Recombinant), under the proprietary name Novoeight, with the proposed indication for use in adults and children with hemophilia A for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

Novoeight is not indicated for the treatment of von Willebrand disease. This product, with an International Nonproprietary Name of turoctocog alfa*, is currently not licensed or authorized to be marketed in any country.

Currently, several recombinant (r) Factor (F) VIII products (RECOMBINATE, KOGENATE FS, ADVATE, and XYNTHA) and plasma-derived FVIII concentrates are licensed in the U.S. for the treatment of patients with hemophilia A.

The active ingredient in Novoeight is a recombinant analogue of human FVIII modified in a way that its B-domain is truncated to a short segment of 21 amino acid residues encoding amino acids -----(b)(4)----- of the FVIII B-domain. While being similar in structure to the licensed FVIII product Xyntha, Novoeight is more close to the natural FVIII sequence as it contains native flanks of the B-domain, both adjacent to the sites of proteolytic activation of FVIII. Novoeight is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology, and purified using a process that includes two validated viral inactivation/removal steps – detergent treatment and nanofiltration. No materials of human or animal origin are used in the establishment of the CHO production cell line, manufacturing process or formulation of Novoeight.

Novoeight Final Drug Product (FDP) is manufactured as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with the diluent (0.9% sodium chloride) and is available in six dosage strengths: 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU.

Novoeight was developed for the U.S. market under IND 14059. Type C Meeting to discuss the CMC and Clinical aspects was held on 17 December 2010 and Pre-BLA Type C Meeting including discussion of multi-product facility for manufacture of Novoeight Drug Substance (DS) was held on 20 June 2012, with subsequent follow-up correspondence from FDA on 20 September 2012. The original BLA was received on 16 October 2012 and was reviewed under the PDUFA V program. Mid-Cycle communication was held on 17 April 2013; Late-Cycle Face-to-Face Meeting with the Applicant was held on 11 July 2013. Pre-License Inspection of Novo Nordisk Facility in ----(b)(4)-----, Denmark was performed on -----(b)(4)-----.

The scope of this review included development and validation of the manufacturing processes for DS and FDP with established in-process controls; control of raw materials and cell bank system; characterization of turoctocog alfa; aspects related to DS and FDP Specifications; and batch analyses.

qualified, consistent with FDA Guidance: *Monoclonal Antibodies Used as Reagents in Drug Manufacturing*.

3. The Novoeight characterization program utilized an extensive panel of state-of-the-art analytical methods to evaluate the structure and function of the rFVIII product. The primary structure, post-translational modifications (------(b)(4)-----), and the higher order structure of turoctocog alfa were confirmed and found to correspond to those reported for plasma-derived FVIII. The turoctocog alfa -----(b)(4)----- structure was found to be comparable to the published models of rFVIII molecules.
4. The biological activity of Novoeight was confirmed by its ability to support FX activation in the Chromogenic Substrate (CS) assay and to promote blood clotting in the One-Stage Clotting (OC) assay. The data in the BLA support the equivalence between the CS and OC assays in determining Potency of Novoeight, with the OC/CS ratio close to 1. Agreement was reached to use the OC assay for Potency assignment for Novoeight batches distributed in the U.S. based on the general availability of the OC assay in clinical laboratories, and comparable variability of the two assays.
5. The specifications for DS and FDP are established in accordance with ICH Guidelines Q6A and Q6B. The parameters are selected from CQAs, and their acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data. As requested by FDA in the course of the review process, additional parameters were included and acceptance criteria for some parameters were tightened, based on statistical analyses of the data, to represent manufacturing experience. The current specifications for DS and FDP are adequate to control the identity, purity, biological activity, and safety of Novoeight. The results of Batch Analyses encompass over (b)(4) DS and (b)(4) FDP commercial-scale batches and support consistency of the manufacturing process to produce Novoeight that meets pre-determined quality characteristics. In-support testing by CBER confirmed the results of batch analyses for PPQ lots reported in the BLA and suitability of test methods for their intended use.
6. Novo Nordisk has initiated a program for Continued Process Verification which includes standard monitoring for (b)(4) post-PPQ DS batches and subsequent FDP batches for reproducibility and compliance with limits. The results will be reported in Annual Product Review reports. Additional testing will be performed if needed, e.g., for verification of specification ranges as more data become available. -----(b)(5)(b)(7e)----- . Novo Nordisk committed to perform stability studies with intermediate dosage strengths of FDP (please refer to Dr. Peng's memorandum), and to include determination of additional excipients in FDP Specification as stated in their letters of 29 July 2013 and 19 September 2013, respectively.

RECOMMENDATION

The Applicant has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls in the BLA and has adequately addressed the requests from all CMC reviewers in Amendments #17, 20, 22, 23, 26, 30, and 34. In particular, the Applicant performed additional viral clearance validation studies and submitted the data; tightened acceptance criteria for some Specification parameters to reflect manufacturing experience; and revised the SOP for the analytical method for the determination of Content and -----
------(b)(4)-----.

I recommend **APPROVAL** of the BLA for Antihemophilic Factor (Recombinant) [Novoeight]. Two remaining items (related to the stability studies and FDP Specifications) will be addressed in Post Marketing Commitments listed at the end of this memorandum. The Applicant confirmed their commitment in Amendment #26 dated 29 July 2012 and Amendment #34 dated 19 September 2013, respectively.

All inspectional issues identified during the facility inspection were satisfactorily addressed by corrective actions described in Amendment #28 dated 16 August 2013. The Clinical reviewer concludes that the clinical data adequately demonstrate the safety and efficacy of Novoeight in the proposed population and indication, and Bioresearch Monitoring inspections support the validity of the clinical data. There were no confirmed FVIII inhibitors reported for any subject in any trial.

NOMENCLATURE

United States Established Name	Antihemophilic Factor (Recombinant)
International Nonproprietary Name	turoctocog alfa
Japanese Accepted Name	turoctocog alfa
Pharmacopeial name	Human coagulation factor VIII (rDNA)
Chemical name	Blood coagulation factor VIII (synthetic human N8 heavy chain), compd. with blood-coagulation factor VIII (synthetic human turoctocog alfa light chain) ¹
Other names	Human coagulation factor VIII -----(b)(4)----- -----peptide, glycosylated ² rFVIII NNC 0155-0000-0004 NN7008 N8
Chemical abstract service (CAS) registry number	1192451-26-5
Identification number of production strain	F8-500 1C9

¹CAS index name

²International Nonproprietary Name description

MANUFACTURING FACILITIES

Facility	Manufacturing Operations
Novo Nordisk A/S ----- (b)(4) ----- ----- (b)(4) ----- Denmark ----- (b)(4) -----	----- (b)(4) ----- ----- ----- (b)(4) ----- -----
Novo Nordisk A/S ----- (b)(4) ----- ----- (b)(4) ----- Denmark ----- (b)(4) -----	----- (b)(4) ----- ----- ----- (b)(4) ----- -----
Novo Nordisk A/S ----- (b)(4) ----- ----- (b)(4) ----- Denmark ----- (b)(4) -----	----- (b)(4) ----- ----- ----- (b)(4) ----- -----
----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) -----	----- (b)(4) ----- ----- (b)(4) ----- ----- ----- (b)(4) -----

MANUFACTURE OF DRUG SUBSTANCE

The manufacturing process for turoctocog alfa Drug Substance (DS) is described in module 3.2.S.2.2 Description of Manufacturing Process and Process Controls (Process Description for Cell Culture and Process Description for Capture and Purification). The DS manufacturing process was also evaluated during the Pre-License Inspection of Novo Nordisk's Facility in --(b)(4)--, Denmark, on -----(b)(4)-----. The manufacturing process for turoctocog alfa DS is comprised of three stages: cell culture expansion (aseptic manufacturing), capture of rFVIII protein from the culture media, and purification of DS (bioburden-controlled manufacturing).

Figure 1 Manufacturing Process for Turoctocog Alfa Drug Substance

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

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4 pages redacted (b)(4)

This justifies the applicability of the process parameter ranges (established at laboratory scale) for the commercial scale -----(b)(4)----- process.

Reviewer’s Comments

In process validation, Novo Nordisk followed recommendations of ICH Guidelines Q7, Q8 and Q11 using elements of the “*Quality by Design*” approach. Process Evaluation studies (the first stage of process validation) are extensive, scientifically sound and appear adequate. Critical Quality attributes (CQAs) and Critical Process Parameters (CPPs) were identified based on risk assessments (severity ranking of quality attributes with respect to risk to patients, and Failure Mode Effects and Criticality Analysis (FMECA) with respect to process parameters at each step). The operational ranges for process parameters were established in single parameter or two-factorial design experiments and at identified worst-case conditions in laboratory scale. Robustness of the cell culture process within the established ranges for CPPs was supported by reproducible quantity and quality of rFVIII protein produced in laboratory-scale and manufacturing-scale runs.

The process control parameters and in-process control tests, with established operating ranges and acceptance criteria were also evaluated during the Pre-License Inspection (PLI) of Novo Nordisk’s facility in --(b)(4)-- (please refer to Establishment Inspection Report [EIR] for details). As a corrective action to Form FDA 483 Observation #2, Novo Nordisk extended control over the cell culture process to address potential situations of aberrant trends in process control parameters or in-process test results (Amendment #28). The SOP 119102 “*Production of Turoctocog Alfa -----(b)(4)-----*” was revised to include Alert limit for -----(b)(4)-----, in addition to Action limit of (b)(4) and quantitative Alert limits for selected nutrients and metabolites. Specifically, Alert limits are set for -----(b)(4)-----, and are based on historical data obtained from cell culture campaigns performed from 2010 to present.

The revised SOP includes a new section “*Strategy on Exceeding Process Values and on Abnormal Trends*” which specifies quantitative threshold values for process control parameters (above and below the operating ranges) established based on historical data from cell culture campaigns performed from 2010 to present. The guidelines describe possible root causes of aberrant trends, controls/checks to be performed, actions to be taken, and consequences of an incident to the cell culture campaign. These guidelines assure that the operators and process team have direct access to the necessary knowledge to act on observations and trends.

PROCESS EVALUATION FOR THE CAPTURE / PURIFICATION

Critical process parameters and in-process tests for each chromatographic step are described in section 3.2.S.2.4 Control of Critical Steps and Intermediates. In-Process Controls for the Capture and Purification Process. Evaluation of process parameters for each chromatographic step and justification of the established ranges is described in section 3.2.S.2.5 Process Validation and/or Evaluation. Process Evaluation for the Capture and Purification Process.

11 pages redacted (b)(4)

----- (b)(4) ----- . Relevant in-process stability samples were also analyzed by ----- (b)(4) ----- . The changes in different stability parameters over time were evaluated and used to establish holding and storage times that would secure the desired quality of turoctocog alfa. Of note:

- The parameter ----- (b)(4) ----- for ---- (b)(4) ---- is included in the parameter ----- (b)(4) ----- . In production, the parameter ----- (b)(4) ----- has a set point (b)(4) as early development studies indicated that ----- (b)(4) ----- could be important for product quality.

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

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

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

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

----- . The explanation is satisfactory. In production, these holding times are typically --- (b)(4) --- .

PROCESS PERFORMANCE QUALIFICATION FOR DRUG SUBSTANCE

Summaries of the Process Performance Qualification (PPQ) studies are included in 3.2.S.2.5 Process Performance Qualification of the Cell Culture Process and 3.2.S.2.5 Process Performance Qualification of the Capture and Purification Processes. PPQ was performed by manufacturing three batches at commercial scale at each step, according to protocols covering the individual steps. The acceptance criteria included the routine in-process control testing (3.2.S.2.4 In-Process Controls for Cell Culture and 3.2.S.2.4 In-Process Controls for the Capture and Purification Process) and extended testing with acceptance criteria defined for each process step in relation to the specific purpose of the process step. In addition, the in-process data from PPQ studies were compared to the results from the preceding campaigns for the clinical materials, and a program for continued process verification was initiated.

The PPQ program comprised the manufacture at commercial scale of:

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

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

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

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

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

Reviewer's comments

I used two approaches to evaluate the results of the PPQ program: (i) review of the in-process and release data for all PPQ batches in the BLA file and (ii) verification of these data by review of executed Batch Records for each PPQ batch for each production step during the PLI of the ---(b)(4)--- facility (please refer to the EIR). Of note, each step of the manufacturing process for turoctocog alfa DS is documented in a separate Batch Record for:

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

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

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----- (b)(4) -----, was chosen for further use as its synthetic origin of phospholipid is expected to result in the most stable OC assay.

Reviewer’s comments for characterization

The Novoeight characterization program is comprehensive and utilized an extensive panel of state-of-the-art analytical methods to evaluate the structure and function of the rFVIII product. The primary structure of turoctocog alfa was confirmed to correspond to the theoretical structure of FVIII by -----

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

-----.

The post-translational modifications – ----- (b)(4) -----
----- were confirmed and found similar to plasma-derived FVIII. -----

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

The secondary and tertiary structure of turoctocog alfa was investigated by -----
--- (b)(4) ----- analysis and was comparable for the tested batches. -----

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

The physico-chemical properties of turoctocog alfa were analyzed by -----

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

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

-----.

The biological activity of Novoeight was demonstrated by its ability to support Factor X activation in the CS assay and to promote blood clotting in the OC assay. Thus, the characterization studies confirmed the expected structure and properties of turoctocog alfa.

SPECIFICATION FOR DRUG SUBSTANCE (MODULE 3.2.S.4.1)

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

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

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

JUSTIFICATION OF SPECIFICATION FOR DRUG SUBSTANCE (MODULE 3.2.S.4.5)

Control Strategy Principles

The identification of CQAs was based on characterization of turoctocog alfa, prior experience and process understanding from 15 years of manufacture of another hemophilia protein (rFVIIa, NovoSeven®), and general scientific knowledge. Severity ranking for CQAs for DS was based on assessment of risk to the patient/medical consequences (from the highest severity score S5 referring to serious adverse events with fatal outcome; to the lowest severity score S1 with no medical consequences and with dissatisfaction of quality expectation). Severity ranking for CQAs is presented below and appears adequate.

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

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

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

Failure Mode Effects and Criticality Analysis (FMECA) analysis of each individual process step and process parameter was used as a tool for assessing and controlling risks associated with excursions from process parameters (“failure modes”). Based upon the risk assessments, process parameters with a potential impact on CQA’s were studied experimentally to establish operational ranges as described under Process Evaluation.

Principles for Setting Specification Limits

The DS Specification acceptance criteria were established based on one or more of the following considerations: DS manufacturing process capability, stability, relation to FDP Specification, and clinical relevance.

Novo Nordisk defines the process capability (Cpk) of the DS production process for any given parameter as follows (with assumption that the variation in the results follows the normal distribution):

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

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

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

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

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

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

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

Reviewer’s comments for DS Specifications

The specifications for DS are established in accordance with ICH Guidelines Q6A and Q6B. The parameters are selected from the CQAs to ensure consistency of identity, purity, biological activity -----(b)(4)-----, and safety. Acceptance ranges/limits are established based on manufacturing capability, clinical outcome, analytical variability, and stability data. As requested by FDA during the review process (Information Request dated 24 June 2013), additional parameters were included and acceptance criteria for some parameters were tightened to represent manufacturing experience. These changes are described in Amendment #26 dated 29 July 2013 and are summarized below:

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

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

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

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

FVIII activity by One-stage clotting assay has been employed throughout the development as an additional test for Potency. It is not included in DS Specification as the overall control strategy for turoctocog alfa has been based on the CS assay throughout development. FVIII activity by the OC assay is included in FDP Specification as described below.

The acceptance criteria for DS specification parameters were also discussed with Dr. Nancy Kirschbaum who supported the request for tightening some of the parameters as described above. The analytical procedures used for determination of Specification parameters were reviewed by Dr. Andrey Sarafanov and found to be adequately validated.

DESCRIPTION AND COMPOSITION OF DRUG PRODUCT

Description and composition of Drug Product is presented in module 3.2.P.1. Novoeight is supplied as a white lyophilized powder in single-use glass vials of six nominal dosage strengths: 250, 500, 1000, 1500, 2000 and 3000 IU per vial. Novoeight is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with the diluent (0.9% sodium chloride).

Table 25: Composition of Novoeight Final Drug Product

Name of components	Quantity per mL before lyophilization	Quantity (nominal) Per vial of lyophilized powder ²	Quantity per mL in the withdrawal volume	Function
Active substance				
turoctocog alfa drug substance	250 IU ¹	250 IU	62.5 IU	Active ingredient
turoctocog alfa drug substance	500 IU ¹	500 IU	125 IU	Active ingredient
turoctocog alfa drug substance	1000 IU ¹	1000 IU	250 IU	Active ingredient
turoctocog alfa drug substance	1500 IU ¹	1500 IU	375 IU	Active ingredient
turoctocog alfa drug substance	2000 IU ¹	2000 IU	500 IU	Active ingredient
turoctocog alfa drug substance	3000 IU ¹	3000 IU	750 IU	Active ingredient
Excipients				

L-Histidine	6 mg	6 mg	1.5 mg	---(b)(4)---
Sucrose	12 mg	12 mg	3 mg	---(b)(4)---
Polysorbate 80	0.4 mg	0.4 mg	0.1 mg	----- (b)(4)-----
Sodium Chloride	36 mg	36 mg	18 mg ³	---(b)(4)---
L-Methionine	0.22 mg	0.22 mg	0.055 mg	---(b)(4)---
Calcium chloride dihydrate	1.0 mg	1.0 mg	0.25 mg	---(b)(4)---
Water for injections	To final volume	-	To final volume	---(b)(4)---
----- (b)(4) -----	(b)(4)	(b)(4)	(b)(4)	-----(b)(4)-----
----- (b)(4) -----	(b)(4)	(b)(4)	(b)(4)	----- (b)(4) -----
----- (b)(4) -----				
---(b)(4)---	(b)(4)	(b)(4)	(b)(4)	---(b)(4)---

¹ An average of (b)(4) turoctocog alfa drug substance is added

² Nominal quantity per vial refers to the quantity per 4 mL

³ The amount of sodium chloride originates from 9 mg from the formulation and 9 mg from the solvent 0.9% Sodium Chloride Solution used for reconstitution

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

Container and Closure

The Novoeight vial is made of (b)(4) glass, high hydrolytic resistance, in compliance with Ph Eur, USP and JP. The vial is closed with a chlorobutyl rubber stopper, not made with natural rubber latex, and sealed with an aluminum cap. The rubber meets the requirements of Ph Eur (Rubber closures for aqueous preparations for parenteral use, (b)(4)) and USP (Elastomeric Closures for Injections).

For all dosage presentations, each carton contains a 5-mL pre-filled glass syringe with the diluent (manufactured by ----- (b)(4) -----) and a vial adapter which serves as a needleless reconstitution system. The 5-mL pre-filled diluent syringes are made of glass, with a siliconized bromobutyl rubber plunger, not made with rubber latex. The vial adapter is a sterile, disposable, FDA 510 K cleared device. The adapter has an integral plastic spike for puncturing the stopper of the drug product vial, and a 25µm in-line filter for particulate filtration and flow aspiration. Please refer to the memorandum of the DMPQ reviewer for further details.

DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS FOR DRUG PRODUCT

Manufacturing of turoctocog alfa DP is performed at the Novo Nordisk facility in ---(b)(4)---, Denmark. Manufacturing Process for Drug Product is described in module 3.2.P.3.3 Manufacturing Process and Controls and includes the following steps:

1 page redacted (b)(4)

Lyophilization

Lyophilization is designed to achieve a consistent lyophilized cake appearance and low moisture content in turoctocog alfa DP. Aseptic conditions during filling and lyophilization of turoctocog alfa DP were verified in simulated media fill studies using a -----(b)(4)-----
----- . The lyophilization conditions are the following:

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

Capping and visual inspection

The tightness of the capped vials is controlled by a closure integrity test.

Labelling, packaging and shipping

Before the packaging, the product is stored in (b)(4) storage facility (b)(4). The packaging process is performed manually and/or automatically. The vial with DP and the syringe with the solvent are labeled and packed together with the vial adaptor in cartons provided with imprint of batch number and expiry date. In-process control of labeling and packaging is performed.

PROCESS VALIDATION OVERVIEW FOR DRUG PRODUCT

Similarly to Drug Substance, the process validation for turoctocog alfa Drug Product consists of three stages: Process Design, Process Performance Qualification, and Continued Process Verification.

Process Design

Process design of the manufacturing process includes developmental activities (described in module 3.2.P.2.3 Manufacturing Process Development for turoctocog alfa Drug Product), process justification (module 3.2.P.3.5 Process Justification Summary of Drug Product), and process verification studies (module 3.2.P.3.5 Process Verification for Lyophilisation).

Manufacturing Process Development for Drug Product

The developmental studies were performed to establish the final manufacturing process parameters and conditions for turoctocog alfa 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU. Based on these studies, the following changes were implemented:

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

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

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

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

- -----

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

- -----

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

Reviewer’s comments

The release data and stability data for the different formulations (b)(4) and manufacturing processes (----(b)(4)----) and ----(b)(4)---- lyophilizers (----- (b)(4) -----) were comparable for ----(b)(4)-----, Purity, Potency and Water Content. This confirms that the quality and biological properties of the Drug Product have been maintained during development and justifies the manufacturing changes.

Process Justification

Process justification studies were performed in full manufacturing scale to justify the process parameters established for the Lyophilization step. Based on risk assessment, the lyophilization process of turoctocog alfa DP is identified as a ----(b)(4)----- process. Therefore, a process justification study was performed as part of the Process Design. The study was performed at challenged set point conditions for the lyophilization time, pressure and temperature. Worst-case conditions were created by combinations of ----- (b)(4) ----- manufacturing process. The lyophilization studies were performed using a --- (b)(4) --- approach, ----- (b)(4) ----- --- batches of turoctocog alfa were produced in ----- (b)(4) ----- at challenged set points for lyophilization.

Reviewer’s comments

BLA contains results of batch analyses for -----(b)(4)----- lots of commercial-scale Drug Product (module 3.2.P.5.4 Batch Analysis for Turoctocog Alfa Drug Product) and includes a complete set of validation data for three PPQ batches representing three dosage strengths - -----(b)(4)----- . All in-process controls (parameters and tests) were within the specified ranges for -----

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

-----.

All lyophilized batches met the acceptance criteria according to the proposed release specifications. Notably, the Potency values determined by both the chromogenic and one-stage clotting assay are similar; with the ratio close to 1. The results obtained for the PPQ batches were also comparable to the results from process design batches.

The supplementary sampling program for characterization of the lyophilization batches was performed for the PPQ batches, to secure sampling from -----(b)(4)----- in the lyophilizer for batches -----(b)(4)----- in the lyophilizer for batch -----(b)(4)----- . All results from the supplementary testing for stability-indicating parameters (Water Content, Content, Purity, (b)(4), Potency and -----(b)(4)-----) were at the comparable levels -----(b)(4)-----.

The statistical metric used to evaluate batch uniformity was the process capability index (Cpk) which compares the distance of the mean of the process to the nearest specification limit with the process variation (presented in Appendix D). The Cpk was estimated within each PPQ batch and across a series of batches manufactured for clinical trials and the PPQ batches (total – (b)(4) batches were used for calculations). In the statistical calculations of the inter-batch process capability for -----(b)(4)-----, Purity and Water Content, analyses were conducted on the merged data for all dosage strengths, as no statistically significant differences were found between strengths. For Content and Potency, calculations were conducted for each dosage strength separately. For all stability indicating parameters for the PPQ batches, Cpk was above 1.33, which indicates a well-performing process within the limits of the proposed specifications.

In summary, process validation activities provide evidence that the developed manufacturing process is capable of consistently and reproducibly producing turoctocog alfa Drug Product of the required quality at full manufacturing scale at the Novo Nordisk facility in -----(b)(4)-----, Denmark.

The Laboratory of Analytical Chemistry and Blood Related Products of the Division of Biological Standards and Quality Control (DBSQC) performed in-support testing of the 3 PPQ batches for the following parameters:

DRUG PRODUCT SPECIFICATIONS (MODULE 3.2.P.5.1)

Test Parameter	Analytical Procedure	Acceptance Criteria
Solid state		
Appearance of powder	Visual inspection (F7-200)	Complies ¹
Reconstitution time / Solubility	Visual inspection (F7-200)	Complies ²
Water content	------(b)(4)----- -----	------(b)(4)----- -----
Liquid state		
Appearance of solution	Visual inspection Ph Eur, JP	Complies ⁴
(b)(4)	------(b)(4)-----	-----(b)(4)----
Identification	------(b)(4)----- -----	Complies ⁵
Potency, IU/vial ^{6,7}	Chromogenic Substrate assay (Y9-439)	------(b)(4)----- -----
		------(b)(4)----- -----
*FVIII Activity, IU/vial ^{6,7}	One-Stage Clotting assay (Y9-440)	------(b)(4)----- -----
		------(b)(4)----- -----
Content, mg/vial ⁷	------(b)(4)-----	------(b)(4)----- -----
		------(b)(4)----- -----
Specific Activity	Calculated from Potency and Content	------(b)(4)-----
Purity	-----(b)(4)-----	-----(b)(4)----- -----(b)(4)-----
-----(b)(4)-----	-----(b)(4)-----	-----(b)(4)----- -----(b)(4)-----
------(b)(4)----- -----	-----(b)(4)-----	-----(b)(4)----- -----(b)(4)----- -----(b)(4)-----

Antioxidant (L-Methionine)	----(b)(4)-----	----(b)(4)-----
Polysorbate 80	----(b)(4)-----	----(b)(4)-----
Particulate matter, particles per container	----(b)(4)----- ----(b)(4)-----	----(b)(4)----- ----(b)(4)-----
----(b)(4)-----	----(b)(4)----- ----(b)(4)-----	----(b)(4)-----
Bacterial Endotoxins	----- (b)(4) -----	----(b)(4)-----
Sterility	----(b)(4)----- ----- (b)(4) -----	Complies ⁸

¹ A white or slightly yellow powder or friable mass

² The lyophilized powder dissolves within (b)(4) minutes at 20-25°C, giving a clear or slightly opalescent solution

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

⁴ Clear or slightly opalescent solution

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

⁶ The mean of three separate measurements

⁷ The units IU/vial and mg/vial refer to IU or mg per withdrawable volume, (per 4 mL volume), and reflect what is available for the patient

⁸ The product meets the requirement of test for sterility per -----(b)(4)----- 21 CFR.610.12

* values in bold relate to parameters revised according to FDA recommendations

JUSTIFICATION OF DRUG PRODUCT SPECIFICATIONS (MODULE 3.2.P.5.6)

Control Strategy Principles

Similar to Drug Substance, the Control Strategy for turoctocog alfa Drug Product was developed in accordance with the ICH Q8 (R2) Guideline “Pharmaceutical Development”, and includes input from FDA (20 June 2012 Type C meeting). The identification of CQAs was based on comprehensive characterization of turoctocog alfa, prior experience and process understanding from 15 years of manufacture of another hemophilia protein (rFVIIa, NovoSeven®), and general scientific knowledge. The CQAs were evaluated by risk to the patient and assigned a severity ranking.

Risk assessments were performed to identify the steps in the manufacturing process with an impact on the CQAs. The risk assessments were based on the experience gained from manufacturing DP batches for clinical trials. Failure Mode Effects and Criticality Analysis (FMECA) of each individual process step and process parameter was used as a tool for assessing and controlling risks associated with excursions from defined ranges or set-point for process parameters (“failure modes”). Based on risk assessments, critical process parameters were identified, and mitigating actions (in-process tests) were established in process design, justification and verification studies described above.

Principles for Setting Specification Limits

Novo Nordisk's strategy in setting the specification limits is based on the following principles:

1. For parameters described in the pharmacopeia, specification limits are based on the monograph given in Ph. Eur. This applies to -----(b)(4)-----.
2. For parameters which are not expected to change during shelf life of the product, only one specification limit is defined. This applies to ---(b)(4)---, Antioxidant, Identification, Bacterial Endotoxin, Particulate Matter, Sterility, Appearance of Powder, Appearance of Solution, Content, Reconstitution time, Polysorbate 80, and (b)(4).
 - a. The target Content value is calculated based on the nominal Potency and the average Specific Activity of DP (---(b)(4)---, determined from historical DP release data) to account for (b)(4) loss of potency during freeze-drying. Specification limits for Content are statistically calculated considering process capability and analytical variation. The contribution from storage was found statistically insignificant.
3. For parameters which are expected to change during product storage, both release and shelf life limits are defined.
 - a. Release limits for -----(b)(4)----- and Purity are calculated based on Specification limits for Drug Substance, adding relevant contribution due to manufacturing and handling (inspection, packaging and distribution) of the Drug Product and including analytical variation.
 - b. Release limit for Water Content is based on extended sampling results and release results from batches manufactured in full scale taking into account process variation and measurement variation.
 - c. Release limits (b)(4) for Potency are estimated with the use of -----(b)(4)----- based on the monograph shelf-life limits.

The following parameters were statistically evaluated to calculate the release and / or shelf life limits: Potency, Content, Purity, -----(b)(4)-----, Polysorbate 80 and Water Content.

The statistically estimated contributions used for calculation of release and shelf life limits are:

- contribution from the manufacturing process (from DS to DP); this contribution was applied to -----(b)(4)----- (release);
- calculation of process capability (if a parameter is not in DS Specification or is adjusted during formulation); this contribution was applied to Water Content and Content;
- contribution from handling (inspection, packaging and shipment) estimated based on stability data from (b)(4) of storage at (b)(4); this contribution was applied to -----(b)(4)---- and Purity (release);
- contribution from storage (-----)(b)(4)----- was used to estimate the difference between the release and the shelf life limits)

The difference between release and shelf life was estimated by calculating the degradation/change in the parameter during ---(b)(4)--- of storage at (b)(4) adding a calculated degradation/change during ---(b)(4)--- storage at (b)(4).

No statistically significant difference was found in the stability profile for the six strengths for any of the investigated parameters at any of the investigated temperatures. Therefore, the calculations of various contributions were merged for six strengths and analyzed combined with the exception of Content and Potency. For Potency the contribution from the manufacturing process and change during storage has been calculated for merged strengths using the relative response (result/strength).

The necessary difference between the release limit and the shelf-life limit for the parameters with one-sided specification limits was estimated based on a 0.95 probability level. Parameters -----(b)(4)-----, Purity and Water content showed a statistically significant change over time. For two-sided specification analyses (Content and Potency), two sets of differences are relevant, corresponding to the lower and upper limit, respectively. The necessary difference between the lower release limit and the lower shelf life limit for Potency was determined with a probability of 0.80 (due to the variability in the biological assay). For the calculation of Content, the difference between release and shelf life limit was determined with a probability of 0.95 and no statistically significant decrease was observed over time.

Reviewer's comments for DP Specifications

The specifications for FDP are established in accordance with ICH Guidelines Q6A and Q6B. The parameters are selected from the CQAs to ensure consistency of identity, purity, biological activity (potency, content, specific activity), and safety. Acceptance ranges/limits are established based on manufacturing capability, analytical variability, and stability data. Acceptance ranges/limits for all parameters were qualified in clinical trials. As requested by FDA during the review process (Information Requests dated 24 June 2013 and 9 September 2013), additional parameters were included and acceptance criteria for some parameters were tightened to represent manufacturing experience. These changes are described in Amendments #26 and #34 and are summarized below:

- Potency: initially, the parameter “*Potency*” by the CS assay was included in DP Specification. The Shelf-life limits are proposed within -----(b)(4)---- of the nominal value in accordance with (b)(4) The lower Release limits are calculated back from the Shelf-life limits and are ---(b)(4)---, based on statistical analysis of the DP stability data reflecting a ---(b)(4)--- during storage. The upper Release limits are set equal to the upper Shelf-life limit. FDA and Novo Nordisk agreed to include additional parameter “*FVIII Activity*” determined by the OC assay as discussed below. The acceptance ranges for “*FVIII activity*” are set within -----(b)(4)---- of the nominal value and are supported by the data in the BLA demonstrating equivalence of the two assays.
- The parameter “*Specific Activity*” was included in DP Specification to monitor process consistency and product purity, in line with other approved rFVIII products (ADVATE, XYNTHA). The limit of -----(b)(4)---- was established using the same approach as for

----- (b)(4) ----- . The calculations were done for each dosage strengths (example for ----- (b)(4) -----).

- The Specification limits for “Purity” were revised as a consequence of tightening the respective limit for (b)(4): the release limit from ----- (b)(4) -----, and the shelf-life limit from ----- (b)(4) ----- . The release limit for DP --(b)(4)-- is based on the revised (b)(4) specification limit of (b)(4), with consideration of potential losses due to the manufacture (b)(4) and handling (b)(4) The shelf-life limit -(b)(4)- reflects the changes in purity during storage (mainly due to the increase in -----(b)(4)----) contributing to --- (b)(4) --- as assessed by the statistical analysis of the stability data.
- The parameter (b)(4) was replaced by ----- (b)(4) -----, consistent with the change for DS. The release --(b)(4)-- and the shelf-life --(b)(4)-- acceptance limits for DP are based on the release limit for DS -(b)(4)-, estimated contribution from DP manufacture (b)(4) and changes during storage calculated by ----- (b)(4) ----- . The in-use acceptance limit for ----- (b)(4) ----- is set based on a new in-use stability study with the PPQ batches and statistical analysis of historical data. This limit relates to product handling after reconstitution as reflected in the Prescribing Information: “Use Novoeight within 4 hours after reconstitution when stored at room temperature.”

The calculations of the release limit for -----(b)(4)---- are based on -(b)(4)- DP batches manufactured from DS manufactured after the -----(b)(4)----- . The shelf life limit is based on stability data of all batches manufactured from 2010 until present. The proposed limits for -----(b)(4)---- were qualified in non-clinical studies during development, and were also evaluated with respect to clinical qualification (the same clinical qualification level was obtained for -----(b)(4)---- as for -----(b)(4)----). Novo Nordisk intends to verify the limits for --- (b)(4) --- after more experience is obtained.

- Acceptance limit for “Bacterial Endotoxin” was initially calculated based on requirements of ----- (b)(4) ----- which results in increasing acceptance limits for higher dosage strengths (e.g., from ----- (b)(4) -----).

To better ensure product safety and represent manufacturing capability, the acceptance limits for “Bacterial Endotoxin” were revised based on the release and stability data for the highest dosage strength (3000 IU). The limit of -----(b)(4)---- is calculated according to (b)(4) for the lowest dosage strengths (250 IU) and is used for all dosage strengths, consistent with manufacturing experience.

- Initially, the quantitative analysis of Excipients in FDP was limited to Polysorbate 80 (---(b)(4)---) and L-Methionine (---(b)(4)---). The accuracy of the excipients’ concentration in the buffer solution is secured by ----- (b)(4) ----- during the formulation. Novo Nordisk reasoned that the measured parameter --- (b)(4) --- is an adequate indicator of the buffer solution

composition and excipients' concentrations (Specification was tightened from -----
---(b)(4)-----), and (b)(4) as an indicator for correct concentration of
Histidine. FDA disagreed with these extrapolations as these parameters do not provide
the information on the relative content of excipients.

Following FDA request, Novo Nordisk committed to establish the methods for
quantitative measurement of the excipients calcium chloride and sucrose in the FDP, and
will include these parameters with acceptance criteria in the FDP Specification (Post-
Marketing commitment).

Polysorbate 80 was included in DP Specification based on FDA recommendation from
the pre-BLA stage. Content of Polysorbate 80 was determined by the --(b)(4)-- method
for (b)(4) commercial-scale batches including clinical, PPQ and stability batches. The
Specification limits of -----(b)(4)----- were established taking into account the
process capability and analytical variation, and correspond to --(b)(4)-- of target content
of Polysorbate 80 in reconstituted DP.

Specification limits for L-Methionine -----(b)(4)----- are set based on the optimal
content of L-Methionine determined in developmental studies -----(b)(4)-----, in
alignment with the (b)(4) monograph for human coagulation factor VIII (rDNA).

Parameters not included in the Specifications represent in-process controls for the filling process
----- (b)(4) -----, are controlled via the DS
Specification ----- (b)(4) -----, or are at very low levels and do not
represent toxicological concern based on safety evaluation (histidine-related impurity).

The acceptance criteria for FDP specification parameters were also discussed with Drs. Nancy
Kirschbaum, Ze Peng and Lokesh Bhattacharrya who supported the requests for tightening
some of the parameters as described above. The current specifications for FDP are adequate to
control the identity, purity, biological activity, and safety of Novoeight.

Potency: Control Strategy and Labeling

The Potency assignment for turoctocog alfa was discussed throughout the review process
(Information Requests dated 24 June 2013 and 9 September 2013) and at the Late-Cycle Meeting
on 11 July 2013. Novo Nordisk initially proposed to use the Chromogenic Substrate assay as the
Potency assay for turoctocog alfa (b)(4) and FDP release, labeling and stability testing based on the
following justifications summarized in module 3.2.S.3.1 Elucidation of Structure and other
Characteristics (Biological Activity) and Amendment #26 dated 29 July 2013:

1. In the control strategy, the CS assay has been used throughout the development, and the
complete package of documentation for the BLA was compiled for the CS assay (which
is a method recommended by Ph Eur for Potency determination). The OS assay, used for
measurements of plasma samples in the clinical setting, has been employed throughout
the development as an additional test for turoctocog alfa (b)(4) and FDP.

2. In comparative studies with the two assays, Novo Nordisk obtained consistent results for the ratio of FVIII activity determined by the OC and CS assays which is close to 1. These studies appear to support the equivalence between the CS and OC assays as demonstrated for:
 - Reference Material using both the 7th and the 8th WHO International Standard for FVIII for calibration of the potency assay (ratio from ---(b)(4)--- for three calibrated batches);
 - Novoeight (b)(4) batches) and FDP ((b)(4) batches), with the FVIII activity OC/CS ratio being close to 1 and with an acceptable standard deviation (----- (b)(4) -----, respectively);
 - Two assays were compared in Potency determination for turoctocog alfa (B-domain-truncated rFVIII) and ADVATE (full-length rFVIII) in an international, multicentre, randomized and blinded study of simulated post-infusion samples with participation of 36 laboratories from 19 countries (Viuff D et al. *Haemophilia* 2011; 17: 695-702). The OC/CS ratio for FVIII activity was close to 1 for both turoctocog alfa and ADVATE, with similar assay variability for the two proteins.
3. Results from a forced degradation study suggest similar behavior of the two assays under stressed conditions ----- (b)(4) ----- . The average OC/CS ratio of Potency values was (b)(4) with SD = (b)(4) (n = (b)(4)).
4. Comparable Potency results were obtained with the CS and OC assays in stability testing.

Table 28: Potency Measured by Chromogenic and Clotting Assays for Reference Material

Reference material batch (intended use)	Implementation date	WHO FVIII IS	Assay for calibration	Potency By the OC assay	Potency By the CS assay	Ratio ¹
----- (b)(4) -----	May-2009	7th IS	Clotting	----- (b)(4) -----	----- (b)(4) -----	(b)(4)
----- (b)(4) -----	Jul-2010	8th IS	Chromogenic	----- (b)(4) -----	----- (b)(4) -----	(b)(4)
----- (b)(4) -----	Recalibration Mar-2012 (FIO)	8th IS	Chromogenic	----- (b)(4) -----	----- (b)(4) -----	(b)(4)
7008_PRM09 10 (market) ³	Dec-2011	8th IS	Chromogenic	----- (b)(4) -----	----- (b)(4) -----	(b)(4)

¹ Ratio of FVIII activity in the One-Stage Clotting and Chromogenic Substrate assays

² 95% relative confidence intervals

³ PRM batch 7008_PRM0910 and SRM batch 7008_SRM0910 were derived from the same FDP batch

5. In Novo Nordisk's studies, the CS assay showed a lower variation for (b)(4) and DP -----(b)(4)----- respectively, compared to the corresponding variation for the OC assay - -----(b)(4)-----, and the OC assay was sensitive to aPTT reagents. In the Field study, a dose-dependence was noted for the OC-measured Potency values: the values were above (b)(4) of target at the lowest concentration (over-estimation) and were -----(b)(4)----- of target at the highest concentration (under-estimation). In contrast, the values obtained with CS assay were close to the target and more consistent at various concentrations.

In the course of negotiations, FDA (Information Request from 9 September 2013) and Novo Nordisk (Amendment #34) agreed that the parameter “FVIII Activity” by the OC assay will be included in FDP Specification, in addition to “Potency” by the CS assay, and will be used for product labeling. This FDA request is based on the following rationale:

1. The OC assay is generally available and has been historically used for testing post-infusion plasma samples in clinical practice world-wide. The current thinking of SSC and Group of Experts 6B is that labeling of Potency needs to correlate with methods used in clinical laboratories.
2. Based on the results from the recent collaborative study to establish the 8th IS for FVIII concentrates, the OC and CS assays showed similar variability – both intra-laboratory (< 10% for majority of the laboratories and <5% for the 8th IS) and inter-laboratory (6.1 % for the OC assay and 4.1 % for the CS assay for the 8th IS) (Raut S. *J Thromb Haemost* 2012; 10: 1175-6). Therefore, with better understanding of method principle and requirements for assay reagents, internal quality control procedures appear to be a more important factor in determining reproducible results rather than the method used.
3. Higher Potency values obtained with the CS assay compared to the OC assay is a well-known phenomenon for recombinant FVIII products. In Novo Nordisk studies, statistical analysis indicated that the Potency values in the CS assay are on average -----(b)(4)----- than the values obtained with the OC assay. In-support testing of the PPQ lots of Novoeight FDP by CBER/DBSQC also revealed that the Potency values obtained by the CS method were 12-23% higher than those obtained by the OC method. The difference was ascribed to assay sensitivity to the use of different standards and aPTT reagents, as summarized in a review by Barrowcliffe et al. (*Haemophilia* 2012; 18 (Suppl. 4): 61–65). The use of the OC assay for Novoeight labeling will provide a more conservative assessment of FVIII activity.
4. At this stage of scientific knowledge and clinical experience with the use of the two assays world-wide, inclusion of both the OC and CS assays in the FDP Specification will allow for prospective monitoring of the OC/CS ratio for future lots of Novoeight. Novo Nordisk proposes to include these data in Annual Reports. The proposed Specification limits for the parameter FVIII activity (OC) correspond to (b)(4) of the nominal FVIII activity (OC) and are acceptable. Release results for FVIII activity (OC) will be reflected

in the Certificate of Analysis and will be used to state actual value for FVIII activity on the vial and carton for product distribution in the U.S.

The control strategy for turoctocog alfa FDP (all in-process testing, calculation of Specific Activity for (b)(4) and FDP, and control of stability) will remain to be based on the CS assay. This is consistent with the control strategy employed by Novo Nordisk during the entire development, including all batches manufactured for clinical trials. The use of only the CS assay for control of stability is supported by comparative statistical analysis of the stability data for FVIII activity (OC) and Potency (CS) for (b)(4) primary and supportive stability batches. This analysis reflects similar trends in the OC and CS values with similar 95% confidence intervals and justifies the use of one assay (CS) in the stability monitoring. As the extensive data provided in the BLA supports the equivalence of the OC and CS assays for turoctocog alfa, the proposed control strategy is acceptable for FDA. For product distribution, the actual FVIII activity value determined by the OC assay will be printed on the label.

CONCLUSION

The manufacturing process for Antihemophilic Factor (Recombinant) [Novoeight] is validated at the commercial scale and is adequately controlled to assure consistent manufacture of the biologically-active product that meets release Specifications.

The analytical methods for determination of specification parameters are adequately validated, as concluded by Dr. Sarafanov.

The implemented control strategy for the cell bank system and the developed manufacturing process for Drug Substance and Final Drug Product provide acceptable safety profile regarding adventitious agents, as reflected in the memorandum of Dr. Peng.

Assays used to evaluate the development of FVIII inhibitory antibodies in clinical trials were found adequately validated and suitable for intended use, as stated in Dr. Sauna's memorandum. This validates the outcome of the clinical trials that no confirmed FVIII inhibitors were reported for any subject in any trial, and supports the safety of Novoeight with regard to immunogenicity.

Thus, the information on Chemistry, Manufacturing, and Controls is sufficient and satisfactory, and I recommend **APPROVAL** of Novo Nordisk's BLA for Novoeight. This recommendation is shared by all members of the review committee.

Novo Nordisk committed to the following Post-Marketing Studies on 29 July 2013 and 19 September 2013 which will be included in the Approval Letter:

1. To include at least one commercial batch each of 500 IU, 1000 IU, and 1500 IU dosage strengths in their stability study, and these batches should be monitored under the referenced storage conditions as described on page 4 of 11 in the BLA section 3.2.P.8.2 Stability Protocol and Stability Commitment for PPQ and Confirming Batches for Drug Product (novoDOCS: 001161237). The interim stability data from these batches will be

submitted as annual updates (PMC Submission – Status Update) through the dating period, and the final report will be submitted within 3 months of completion of the study (PMC Submission – Final Study Report).

2. To develop the methods for quantitative measurement of excipients calcium chloride and sucrose in the Final Drug Product, and include these parameters with acceptance criteria in Drug Product Specification. The results will be submitted as PMC Submission – Final Study Report by October 16, 2014.