



DEPARTMENT OF HEALTH & HUMAN SERVICES

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File: STN 125466/0 for Antihemophilic Human Recombinant Factor VIII

From: Randa Melhem, Ph.D., OCBQ, DMPQ, MRBII, HFM-676

Through: Marion Michaelis, Chief, OCBQ, DMPQ, MRB II, HFM-676

Subject: **Review Memo BLA:** [Novo Nordisk Inc., License # 1261]. Approval for Antihemophilic Human Recombinant Factor VIII (rFVIII) supplied as single-dose lyophilized product in vials (manufactured at Novo Nordisk facilities in Denmark), along with sterile 0.9% NaCl solution used as a diluent for reconstitution (manufactured at -----(b)(4)-----
-----).

Action Due: October 16, 2013

SUMMARY

CBER received this electronic submission on October 16, 2012. Novo Nordisk Inc. (Novo Nordisk) submitted this BLA to provide information to support US market authorization of lyophilized Antihemophilic Human Recombinant Factor VIII (NovoEight, rFVIII, also referred to as turoctocog alfa) supplied with sterile diluent - 0.9% NaCl solution. NovoEight is presented in single-dose vials containing 6 strengths of 250, 500, 1000, 1500, 2000 or 3000 International Units (IU) of lyophilized product per vial, and the sterile 0.9% NaCl diluent is supplied in a pre-filled syringe.

The reconstituted drug product solution is for intravenous injection and is indicated for treatment and prophylaxis of bleeding in patients with hemophilia A, covering on-demand treatment, prophylaxis and treatment in connection with surgery.

CBER performed Pre-License Inspection at Novo Nordisk A/S facility in ---(b)(4)--- Denmark from ---(b)(4)---, to support the review of the original BLA 125466/0. The ---(b)(4)--- site used for the manufacture of the turoctocog alfa drug substance, and the inspection findings are documented in the EIR.

SUBMISSION REVIEW

In this review memo, I cover the manufacturing process of NovoEight (rFVIII) to include the drug substance (cell culture, capture and purification) and drug product (filling and lyophilization) performed at Novo Nordisk (Denmark), as well as the manufacturing of the 0.9% NaCl sterile diluent performed at the contract manufacturer -----(b)(4)-----.

My review focused on the Facilities and Equipment, Sterilization process, Lyophilization process, Container Closure and container closure integrity testing, and the Filling of the product and diluent.

The following Facilities are associated with the manufacture of rFVIII drug substance/ product and diluent:

Facility	Manufacturing Operations	Last FDA Inspection
-----(b)(4)----- -----(b)(4)----- -----(b)(4)----- (b)(4) -----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	-----(b)(4)----- -----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	-----(b)(4)-----
Novo Nordisk Facilities are associated with the manufacture of rFVIII drug substance/ product and QC testing and packaging		
-----(b)(4)----- -----(b)(4)----- -----(b)(4)----- Denmark FEI No.: ----(b)(4)----- (merged FEI#----- (b)(4)---)	-----(b)(4)----- -----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	The Pre-License Inspection is the first inspection of this site performed -----(b)(4)----- ---
Novo Nordisk A/S -----(b)(4)----- -----(b)(4)----- -----(b)(4)----- Denmark FEI No.: -----(b)(4)-----	-----(b)(4)----- -----(b)(4)----- -----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	Last surveillance inspection performed -----(b)(4)-----
Novo Nordisk A/S -----(b)(4)----- -----(b)(4)----- Denmark FEI number: ----(b)(4)---	-----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	Last surveillance inspection performed -----(b)(4)-----
0.9% NaCl Diluent Manufacturing and QC Testing and Packaging		
-----(b)(4)----- -----(b)(4)----- -----(b)(4)----- -----(b)(4)----- --- (b)(4) --- FEI No. ----(b)(4)---	-----(b)(4)----- -----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	Last Inspection, 2012.

Overview

The blood coagulation Factor VIII is a cofactor essential for maintaining normal hemostasis. Thrombin activated Factor VIII (FVIIIa) functions as a cofactor for Factor IXa mediated activation of Factor X.

Recombinant Factor VIII is a human recombinant Factor VIII with a molecular mass of 166 kDa, produced in Chinese Hamster Ovary (CHO) cells. Once activated by thrombin cleavage the resulting rFVIIIa has the same structure as endogenous FVIIIa.

Novo Nordisk provided the nomenclature used for rFVIII which is reproduced below, and turoctocog alfa or rFVIII will be used interchangeably throughout the document:

International Nonproprietary Name	turoctocog alfa
United States Established Name	Antihemophilic Factor (Recombinant), Plasma/Albumin-Free (pending CBER approval)
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) (b) (4)peptide, glycosylated ² rFVIII NNC 0155-0000-0004 NN7008 N8
Company/laboratory code	turoctocog alfa ³
Chemical abstract service (CAS) registry number	1192451-26-5
Identification number of production strain	F8-500 1C9

¹ CAS index name

² International Nonproprietary Name description

³ Name used in this application

Turoctocog alfa Drug Substance

FACILITY FOR DRUG SUBSTANCE MANUFACTURE

This BLA was submitted to provide information to support US market authorization of lyophilized Antihemophilic Human Recombinant Factor VIII (NovoEight, rFVIII), and it was reviewed per Guidance for industry: *For the Submission of Chemistry, Manufacturing and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for in vivo Use*, August 1996.

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

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----- (b)(4) -----
----- . During the PLI we observed the

changes and also requested in the 1-May- 2013 information request that the qualification documentation of the modifications be submitted to the file. Novo Nordisk reported in their May 17 response that the information will be submitted in June, 2013.

Building (b)(4) is access controlled and houses Department 050 - Biopharm API Mammalian Cell Production (Turoctocog alfa drug substance), Department 1412 - Cell Culture Pilot Plant, and Department 1201- Cell Biology. The three departments are physically separated. Building (b)(4) also houses support areas including offices, rest rooms, inventories and archives. The utilities for Department 050 are located outside the production area and are separated from those of other departments in the building.

In the production areas, walls are either glass/steel or made of painted concrete elements or gypsum building boards, ceilings are steel plates and floors are covered with epoxy. In the Grade -----(b)(4)----- areas, walls and ceilings are covered with vinyl, and floors are covered with epoxy. Novo Nordisk reported that the production area is access controlled and requires gowning prior to entry.

Novo Nordisk reported that the following products, all of which use CHO cells, are manufactured in department 050 on a campaign basis.

- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- Turoctocog alfa (rFVIII)

They added that cross-contamination between different products is prevented by using validated cleaning procedures, changeover procedures as well campaign manufacturing of the different products.

Department 050 consists of -----

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

----- . Novo nor disk provided the room classification for the different areas as shown in the table below. In addition they listed the activities that take place in the different areas in Table 3-6 of the eCTD 3.2.A.1 *Facilities and Equipment: Facility for Drug Substance Manufacture.*

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

They provided in Table 7 of the same document, the list of equipment used for the various operations (closed or open), their location and whether they are multi-use, -----

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

Novo Nordisk provided the flow diagrams and brief description for the movement personnel, process equipment and utensils, product, raw materials and solid waste. This was also looked at during the PLI and it is deemed adequate.

Novo Nordisk provided a list of the utility equipment including freezers, air compressors, air dryers, cooling compressors, process control computers, dishwasher, refrigerators, scales, feed water and WFI and clean steam production.

They also provided a schematic diagram of the water system. -----

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

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

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

Novo Nordisk reported that the facility, equipment and utilities are covered by a maintenance program as described in their SOPs. They added that manufacturing areas with adjacent washrooms, toilets, and locker facilities as well as the offices are cleaned frequently according to written procedures; and that waste material is collected in suitable containers and disposed at regular, frequent intervals.

Computer Systems

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

----- The programs have been developed and qualified according to written procedures and are 21CFR part 11 compliant. A local system specific procedure describes how changes are made in ----- (b)(4) ----- . The procedure is built upon the overall procedure for performing changes to a computer system in Novo Nordisk.

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

-----.

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

-----.

Prevention of Contamination

Novo Nordisk described the procedures in place to prevent contamination at Building (b)(4) to include room classification with proper ventilation and differential pressure to prevent ingress from the dirty to the cleaner areas, environmental monitoring to ensure proper room classification; cleaning of facilities and equipment; sterilization of equipment; virus clearance; and changeover and line clearance procedures.

Room Classifications

The open cell culture operations are performed in a Grade ----- (b)(4) ----- surrounded by a Grade (b)(4) area, and the closed cell culture operations are performed in a Grade (b)(4) area. The final purification step (b)(4) is performed in a Grade (b)(4) area. All other operations are performed in a Grade (b)(4) area. They listed the production operations and room classifications in Table 7 of the BLA submission eCTD 3.2.A.1 *Facilities and Equipment: Facility for Drug Substance Manufacture*.

All areas in the production core are supplied with HEPA filtered air. In Grade (b)(4) areas the HEPA filters are (b)(4). The HVAC system provides ventilation to create a differential pressure cascade in the classified areas. Novo Nordisk reported the differential pressure between the different areas in Appendix B of the eCTD 3.2.A.1 *Facilities and Equipment: Facility for Drug Substance Manufacture*.

Environmental Monitoring

Novo Nordisk reported that they have a microbial environmental monitoring program where they sample for and surfaces for viables. The Grade (b)(4) areas are sampled (b)(4) and the Grade (b)(4) areas are sampled (b)(4) and the Grade (b)(4) area is sampled (b)(4). They added that the gloves are also sampled for operators (b)(4). They did not report in the BLA submission about the non-viable monitoring in the different areas.

The environmental monitoring program for viables and non viables was reviewed during the PLI, and is described in the EIR.

Changeover and Line Clearance

Novo Nordisk reported that Building (b)(4) is a multi product facility and they perform manufacturing of the various products on a campaign basis. During the PLI, they stated that at this point only turoctocog alfa drug substance is manufactured in the area.

Novo Nordisk stated that they have performed risk assessment for changeover procedure to identify risks of contamination in connection with product changeover, to evaluate all product contact surfaces and to assess the robustness of the change over procedures. They confirmed the risk assessment showed that their changeover procedure minimized the risk of potential contamination and mitigated all the identified risks.

Novo Nordisk stated that per procedure a memo of change of product, stating that the facility is ready for a new campaign in connection with change of product is prepared every time a product is changed. The memo addresses: (b)(4).

Equipment Cleaning

Novo Nordisk reported that the majority of equipment is (b)(4), and few are cleaned (b)(4) according to validated procedures and written SOPs. The cleaning solutions include (b)(4). They reported that for some pieces of equipment, they use different cleaning procedures between products than the procedures used to clean between batches.

Two types of cleaning processes exist at the facility:

- Critical cleaning processes which cover cleaning of (b)(4). These cleaning processes are validated.

They also provided the alert and action limits in Table-11 of eCTD 3.2.A.1 *Facilities and Equipment: Facility for Drug Substance Manufacture*. The ----(b)(4)---- acceptance limits set by the firm do not reflect process capabilities and are much (b)(4) than the (b)(4) specifications.

Reviewer's comments: During the PLI, we discussed the cleaning validation and the acceptance limits, and it was agreed that Novo Nordisk will set the acceptance limits based on process capabilities rather than ----(b)(4)----. The new acceptance criterion for -----(b)(4)-----
----- (b)(4)-----
----- . The new acceptance criterion for ----(b)(4)---- of all equipment for ----(b)(4)----. The cleaning validation and acceptance limits are reviewed in the EIR.

Novo Nordisk reported that they evaluate the cleaning process --- (b)(4) --- and during periodic system evaluation (PSE). If they determine that the process has deviated, the surfaces has changed, revalidation will be performed. They added that revalidation is also performed if there were negative trends detected during monitoring, or if there were changes to the equipment, manufacturing process or cleaning procedures.

Sterilization

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

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

Validation of the Sterilization Process

Novo Nordisk provided a brief description of the validation process. -----

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

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Reviewer's comments: During the PLI, I looked at the ----- (b)(4) ----- sterilization and they appear adequate. The sterilization is reviewed in the EIR.

Virus Clearance

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

DRUG SUBSTANCE MANUFACTURING

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

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

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

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

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

Turoctocog alfa Drug Product

FACILITIES AND EQUIPMENT

Filling of rFVIII occurs in the ----- (b)(4) -----
-----, Denmark), a ---- (b)(4) ---- building constructed in (b)(4). This is an approved
multi-product facility and is used for the manufacturing of turoctocog alfa drug product
(formulation, filling in primary packaging, lyophilization, and inspection of the finished
drug product). The area of the building is about (b)(4). The walls are painted with
washable water based acrylic paint or vinyl. Floors are covered with vinyl or two-
component joint free flooring. The following products are manufactured in the (b)(4)
building:

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

1 page redacted (b)(4)

----(b)(4)-----		----(b)(4)-----		
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Novo Nordisk also listed the equipment used in the production of turoctocog alfa drug product – some of which are located in the Class ----(b)(4)----- rooms and the others are located in the Class --- (b)(4) --- areas as summarized in the Table below:

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

They also listed the equipment critical to sterilization and aseptic processing, their functions and locations as shown in the Table below:

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

In addition they provided a list of the dedicated product contact equipment and their method of cleaning and sterilization.

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

They added that the filling machine is -----(b)(4)-----, and then it is assembled by including all the sterilized parts and subjected to (b)(4). The lyophilizer which is not dedicated is also -----(b)(4)-----.

Lyophilizer

-----:

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

-----.

Prevention of Contamination

Novo Nordisk described the procedures in place to prevent contamination at the

----- building.

- Manufacturing operations of the different products are performed in campaigns with dedicated product contact equipment.
- The flow of materials, equipment and personnel support segregation.
- The current drug products manufactured in (b)(4) bldg. are -----
-----, and thus easy to clean.
- SOPs are in place to segregate drug substance and formulated drug products during manufacturing.
- There are change over and line clearance procedures between different batches and products.
- Facility and equipment are cleaned per SOPs to prevent cross contamination between products or microbial contamination.
- Sterilization of product contact equipment by validated processes (-----
-----)
- Different area classifications are maintained by an HVAC system with appropriate air changes per room provided by several air handling units. Pressure cascades between the different classifications - A positive pressure differential of ----- Pa is maintained between adjacent rooms of differing classification, when doors are closed.
- Laminar flow for aseptic manipulations.
- Environmental monitoring of the classified areas is performed by microbial swab tests, contact plates, air-sampling for viables and non-viables according to standard operating procedures.

Change over and Line Clearance

Novo Nordisk stated that they evaluated their change over procedures and concluded that they are appropriate and adequate for their multi-production manufacturing operations. The procedures are used for formulation, filtration, filling, lyophilization, capping and inspection operations. The procedure includes:

- Removal of all used equipment and utensils

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2 pages redacted (b)(4)

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

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

Container Closure

The container closure system for the drug product consists of the following parts:

- Glass Vial
Description: 5 mL (b)(4) glass, high hydrolytic resistance; high neck
Manufacturer: ----- (b)(4) -----
----- (b)(4) -----
----- (b)(4) -----

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

----- (b)(4) -----
----- (b)(4) -----
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• Lyophilization Stopper

Description: Stopper, 13 mm, Grey, rubber compound ----- (b)(4) ----- . The coating is a solution of ----- (b)(4) ----- . The stoppers are supplied ready to be sterilized.

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

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

-----.

• Snap off Cap

Description: Plastic Snap-Off and a 13 mm aluminum cap (non-product contact)
Manufacturer:
Sampling: Sampling is based on ----- (b)(4) ----- . Supplier certificate from approved supplier may be accepted as an alternative to all or some of the tests.

• Vial Adapter for Reconstitution

Description: Sterile, disposable device packed in a blister package for the easy transfer of fluids. Puncturing of the rubber stopper in the powder vial is achieved by means of the integral plastic spike. The vial adapter has a 25µm in-line filter which allows particulate filtration and flow aspiration. Vial adapter body, spike and hub with female luer lock are made of polycarbonate.
Filter, filter disc made of ----- (b)(4) -----

Does not contain latex or parts of animal origin; no PVC components and, no DEHP and other phthalates.

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

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

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

Capping

After lyophilization, the stoppered vials are transferred to be capped with aluminum caps. The capped vials are then subjected to visual inspection and stored protected from light in a cold storage facility (2 – 8°C).

Packaging

The packaging involves the labeling of the lyophilized drug product, the labeling of the sterile 0.9% NaCl diluent, and the final packaging of the turoctocog alfa drug product vial, the syringe with 0.9% NaCl diluent (---(b)(4)---) with the vial adaptor in cartons provided with imprint of batch number and expiry date. Visual inspection is performed to assure proper labeling and packaging. After completion of the packaging operation, vial reconciliation is done. The finished product is transferred to the warehouse and stored at 2-8°C.

To ensure that the turoctocog alfa meets the specification, in process tests of the critical steps are performed and evaluated throughout the manufacturing process as presented in the Table below:

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

Novo Nordisk gave an overview of the risk assessment performed -----
 ---(b)(4)----- to evaluate their process and to identify the steps in the manufacturing process with an impact on the CQAs. They implemented process changes and in-process testing to mitigate the risks. They presented summary of the control strategy for the drug product in Table 4 of eCTD 3.2.P.5.6
Justification of Specification: turoctocog alfa Control Strategy for Drug Product.

Product Specifications

Turoctocog alfa drug product is formulated in six presentations; 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU. Novo Nordisk provided the product release specifications of the lyophilized product (appearance of powder, reconstitution time/solubility and water content) and of the reconstituted liquid product (appearance of solution/clarity, (b)(4), identity, potency, purity, ---(b)(4)---, content, (b)(4), anti-oxidant, Polysorbate-80, particulate matter, ---(b)(4)---, bacterial endotoxin and sterility). Novo Nordisk stated that they set their specifications based on data obtained from laboratory scale batches, clinical batches, process justification batches, process performance qualification batches and batches used to demonstrate the consistency in the manufacturing process and analytical procedures.

The release specifications will be described in the product review memo. Listed below are the specifications pertaining to sterility and endotoxin level.

Test item	Analytical procedure	Limits/Acceptance criteria
Bacterial endotoxin	----- (b)(4) ----- --- (b)(4) --- ----- (b)(4) ----- ----- (b)(4) ----- --- (b)(4) ---	----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) ----- ----- (b)(4) -----
Sterility	----- ----- (b)(4) ----- --- 21 CFR 610.12	Complies – absence of growth.

2 pages redacted (b)(4)

meets the acceptance criteria. This was further evaluated in the performance qualification studies at the production scale described below.

Process Validation for the Drug Product Manufacturing

Turoctocog alfa is manufactured according to GMP using non-animal derived pharmacopeia excipients, to minimize the risk for contamination with adventitious agents. The manufacturing process is kept in check through established process parameters and in process control testing. In addition the final product has to pass all the release specification testing to confirm the quality, efficacy and safety of the drug product. The specification limits have been established based on the -----(b)(4)----- for Human coagulation factor VIII (rDNA), drug product process capability, stability, relation to drug substance specification requirements and clinical relevance.

The process validation includes Process design, PPQ and Process Verification.

Novo Nordisk provided a list of all the batches manufactured which contribute the process validation. The clinical batches are manufactured at a (b)(4) scale from (b)(4). However the proposed commercial batches as demonstrated by PPQ batches are (b)(4).

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

Process Design

Novo Nordisk stated that establishment of the turoctocog alfa drug product formulation was mainly based on knowledge of stabilization of lyophilized rFVIII as described in literature and knowledge of other Novo Nordisk recombinant coagulation factors. They stated that for convenience to the patient, they wanted a product to be stored at 5-30°C, and thus they include L-Methionine as antioxidant in the formulation. L-Methionine is also used as antioxidant in other licensed pharmaceuticals for parenteral administration (e.g. NovoSeven®).

The lyophilization process was designed to ensure robustness and appropriate freeze drying:

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

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

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

The manufacturing process was developed and tested in laboratory and manufacturing scale, and there were few changes that were implemented. This is described in more detail in the product review memo.

Process Validation-Lyophilization (Justification Studies)

Turoctocog alfa drug product is produced in six different presentations; with the only difference is the active ingredient which is relatively very low compared to the rest of the excipients/buffers. Therefore, the same container closure, filled volume and lyophilization process are used for the six presentations.

The lyophilization process was validated using filled product at the lowest (250IU), middle (1000IU) and highest (3000IU) active protein presentations. The studies cover batch size range ---(b)(4)---, which corresponds to a -----

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

-----.

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

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

Reviewer's comments:

- You have stated that during qualification you have placed (b)(4) TCs on every shelf, yet during the justification validation, the sensors were placed in -----
--(b)(4)-----. Please explain the rationale for using -----(b)(4)----- only, and why do you consider these points representative of the whole lyophilizer.
- You have stated that the lyophilization process was validated for the -----
---(b)(4)----- to cover the range. Yet you loaded shelves -----(b)(4)-----
------. So you did not provide data to support that the products lyophilized on those shelves meet the acceptance criteria. Please provide explanation/data to demonstrate that all products lyophilized on all shelves met the acceptance criteria.

Novo Nordisk provided process data for lyophilization batches under -----
--(b)(4)----- in Tables 5 and 6 respectively of eCTD 3.2.P3.5, *Process
Validation: Process Justification Summary for Drug Product*. The process was run
according to set parameters except -----

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

-----.

Novo Nordisk listed the batches used for the challenge studies in Table 2 of eCTD
3.2.P3.5, *Process Validation: Process Justification Summary for Drug Product*. They
provided the results for the (b)(4) challenge (justification) batches in Table 7 reproduced
below:

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

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

Reviewer's Comment: Potency and stability are under the purview of the product office and this issue will be addressed in the product review memo. The batches met the set specifications for moisture content (see supplementary sampling results),

endotoxin and sterility which under DMPQ purview and covered in this memo. Results show the moisture content was very low for all the batches independent of location.

Reviewer's comment: Please clarify if the current validated cycle for the lyophilization of turoctocog alfa is variable for the following parameters: time, temperature and pressure. Please also clarify how these three parameters (and their combined effect) are monitored and controlled throughout the lyophilization cycle.

Novo Nordisk also provided the results (summarized in the Table below) for the additional sampling performed during these studies to further evaluate the quality of the lyophilized drug product. -----

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

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

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

-----.

Reviewer's comment: You have stated that sampling -----
---(b)(4)----- shelf for each of the justification studies. You also stated that samples for turoctocog alfa drug product were taken from -----(b)(4)----- . Samples were also taken from placebo, ---(b)(4)--- for documentation of the lyophilization process. Please explain your

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

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

Reviewer's comment: In the justification studies, you have reported that a number of vials were discovered broken following lyophilization. Please provide the investigation for the broken vials during the lyophilization justification studies, and describe the corrective methods that were implemented.

Novo Nordisk concluded that the parameters set for lyophilization are appropriate and adequate for the lyophilization of turoctocog alfa drug product. The results show that a uniform product is produced within these parameters, and the product is in compliance with the acceptance criteria for critical in-process controls and the drug product specifications for phase 3. All results except the results for potency for ----- (b)(4) ----- and the 2 batch validation samples for purity for ---- (b)(4) ---- are within the limit for the release limit. The results have been related to the analysis and not the manufacturing process. Their studies were adequate and supportive of this conclusion.

Process Performance Qualifications (PPQ)

Novo Nordisk qualified the manufacturing process by manufacturing and testing conformance lots (PPQ batches) using released/ qualified drug substance batches. The PPQ batches covered the ----- (b)(4) ----- batch size range and included the highest strength (3000 IU), middle strength (2000 IU) and the lowest strength (250 IU).

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

They reported that the manufacturing process of the PPQ batches is similar to that established during process design, and followed during production of drug product for clinical trials and stability studies.

During the manufacturing of the PPQ batches, extended in process control sampling and parameter recording was performed to document and verify conformance to specified requirements and development data. The number of samples drawn during production differed for the three batches due to different batch sizes. Manufacturing turoctocog alfa drug product was performed using dedicated and/or disposable equipment.

Novo Nordisk described the manufacturing steps and in-process controls performed during the PPQ. The PPQ and the quality of the drug product are covered in detail in the product review memo. In this review memo ----- (b)(4) -----

1 page redacted

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

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

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

The lyophilized product was analyzed by visual inspection, moisture content, (b)(4), identity, and content, (b)(4), Anti-oxidant, (b)(4), purity, potency, particulate matter, (b)(4), endotoxin and sterility. Results provided show that the batches complied as presented in Table 12 of the eCTD 3.2.P3.5, *Process Validation: Process Performance Qualification Summary for Drug Product*. In this memo I will review the data presented for the moisture content sterility and endotoxin and visual inspection (appearance):

Test	Method	Release Specification	Batch number		
			(b)(4) (250IU)	(b)(4) (2000IU)	(b)(4) (3000IU)
Appearance of powder	Visual Inspection	white or slightly yellow powder or friable mass	Complies	Complies	Complies
Moisture content	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Endotoxin	(b)(4) (b)(4)	(b)(4) (b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)	(b)(4) (b)(4)
Sterility	----- (b)(4)	No growth	Complies	Complies	Complies

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

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

Reviewer's comments: In Table 14 of eCTD 3.2.P.3.5 *Process Validation – PPQ Summary for Drug Product*, you did not describe all the defects as was the case in the

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

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

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

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

The lyophilized product was analyzed by visual inspection, moisture content, (b)(4), identity, and content, (b)(4), Anti-oxidant, ---(b)(4)---, purity, potency, particulate matter, ---(b)(4)---, endotoxin and sterility. Results provided show that the batches complied as presented in Table 12 of the eCTD 3.2.P3.5, *Process Validation: Process Verification for Lyophilization*. Presented below are the data for the moisture content, sterility and endotoxin and visual inspection (appearance). Other specifications are covered in the product review memo.

Test	Method	Release Specification	Batch ---(b)(4)- (2000IU)
Appearance of powder	Visual Inspection	white or slightly yellow powder or friable mass	Complies
Moisture content	(b)(4)	(b)(4)	(b)(4)
Endotoxin	----(b)(4)---- -----	----- (b)(4) -----	----(b)(4)----
Sterility	---(b)(4)---- -----	No growth	Complies

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

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

FACILITIES AND EQUIPMENT FOR FORMULATION, FILLING OF NaCl SOLUTION

Novo Nordisk reported that the 0.9 % NaCl diluent is provided in prefilled syringes (PFS) and manufactured under contract by ----- (b)(4) -----
----- . Formulation and filling are performed at the ----- (b)(4) ----- site. Visual inspection of the PFS and quality control testing is performed at one of the (b)(4) sites in ----- (b)(4) ----- . Warehousing is performed at the -----
--(b)(4)----- site. The facilities were designed as multi-product manufacturing facilities, which are approved and regularly inspected for compliance to cGMPs by FDA.

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

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

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

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

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

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

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

-----:

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

Reviewer's comments: Additional information was requested regarding the cleaning and sterilization procedures.

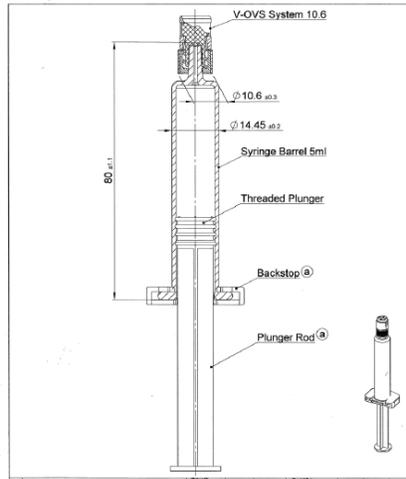
- In section 3.2.A.1 Facilities and Equipment Report for Sodium Chloride manufacturing facility, you stated that Sodium Chloride is currently classified as a -----(b)(4)----- for cleaning. Please provide results of studies performed to demonstrate that NaCl is the worst case soil, and provide summary reports of studies performed to validate the cleaning procedures.
- Please clarify if the filling equipment (or which part) is dedicated for the manufacture of 0.9% NaCl diluent. Please provide a summary of the validation studies performed to demonstrate cleaning and sterilization of the filling equipment.
- You stated that ---(b)(4)--- is used for cleaning and sterilization of equipment. Please describe the parameters used, and provide the results of studies performed to validate the ---(b)(4)--- process. Please list the equipment cleaned/sterilized by ---(b)(4)---.
- Please list the number of ---(b)(4)--- that support the production of 0.9% NaCl diluent and their uses.

Container closure system (0.9% Sodium Chloride Solution)

The final container closure system (0.9% NaCl solution) consists of the following parts:

- Syringe barrel (5.0 mL) made of a siliconized ----(b)(4)---- type (b)(4) glass in compliance with -----(b)(4)-----.
- Rubber stopper (plunger) made of bromobutyl rubber ---(b)(4)--- in compliance with -----(b)(4)-----. The rubber plunger is designed with a thread for adding the plunger rod.
- Syringe closure system consists of:
 - ♦ Tip cap of the syringe closure system (product contact part) made of (b)(4) bromobutyl rubber formulation in compliance with -----(b)(4)-----.
 - ♦ Luer lock made of -----(b)(4)----- (non product contact).
 - ♦ Plastic sleeve made of -----(b)(4)---- (non product contact).
- A backstop made of -----(b)(4)---- (non product contact).
- A plunger rod made of -----(b)(4)----- (non product contact).

Novo Nordisk provided brief description and results of studies performed to demonstrate the suitability of the container closure system: Compatibility, extractables, leachables and safety. They provided a toxicological summary which is the purview of the product office.



Stopper/Plunger

Novo Nordisk reported that the rubber plunger is manufactured by -----(b)(4)-----

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

The rubber plunger is siliconized by the supplier, and is delivered ready to sterilize. -----
 -----(b)(4)-----
 -----.

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

Syringe

The 5mL syringe barrel is manufactured by -----(b)(4)----- and complies with -----
----- (b)(4) -----

The syringe barrels are -----
----- (b)(4) -----
-----.

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

Syringe closure system

The syringe closure system has a tamper evident function and is designed to guarantee the integrity of the 5mL syringes.

The syringe closure system is designed by -----(b)(4)-----”, and it is assembled and delivered ready-to-sterilize to the manufacturing area. The sterilized, pre-assembled syringe closure system is mounted onto depyrogenated syringe barrel with a luer cone and groove. The syringe closure system snaps securely into the groove in the cone on the syringe tip.

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

2 pages redacted (b)(4)

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

Reviewer's comment: Additional information was requested about the visual inspection. You stated that visual inspection of the final product is performed per (b)(4) SOPs. Please describe the visual inspection procedure, what defects are being evaluated, what are the acceptance criteria, and the criteria for accepting or rejecting a lot. Please clarify if the inspection is manual, semi automated or automated.

• ---(b)(4)---

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

• ----- (b)(4) -----,

• ----- (b)(4) -----,

• ----- (b)(4) -----

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

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

-----:

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

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

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

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

Reviewer Comments

The information reviewed in this memo was provided in the initial BLA submitted on October 16, 2012. Additional information was needed to complete the review as noted throughout the body of the memo.

This is the summary of all the questions/ comments communicated to the sponsor; and the additional information/clarification provided by the sponsor would be reviewed in a subsequent memo.

INFORMATION REQUEST SENT ON MAY 1, 2013, AND RESPONSES RECEIVED IN AMENDEMENTS 125466/0/18 (MAY 17, 2013), 125466/0/21 (JUNE 12, 2013), AND 125466/0/22 (JUNE 14, 2013).

Manufacturing of the 0.9% NaCl diluent at -----(b)(4)-----

- 1. You stated that visual inspection of the final product is performed per (b)(4) SOPs. Please describe the visual inspection procedure, what defects are being evaluated, what are the acceptance criteria, and the criteria for accepting or rejecting a lot. Please clarify if the inspection is manual, semi automated or automated.*
- 2. You stated that container closure integrity ---(b)(4)--- test was performed on 0.9% NaCl PFS containing (b)(4) that had been subjected to -----(b)(4)----- to cover a worst case scenario, and that no -----(b)(4)----- was detected by visual inspection. Please provide the studies performed to demonstrate the validation of this method – conditions under which ----(b)(4)---- was performed as well as positive and negative controls.*
- 3. Please clarify if any part of the container closure system that is product contact contains latex. Aside from the depyrogenation of the syringe, do you evaluate and mitigate the endotoxin level of other product contact parts of the container closure? Please explain.*
- 4. Please clarify if the filling equipment (or which part) is dedicated for the manufacture of 0.9% NaCl diluent. Please provide a summary of the validation studies performed to demonstrate cleaning and sterilization of the filling equipment.*
- 5. You provided a summary report of the sterilization of the final product. Please describe the ---(b)(4)--- and the sterilization method. You stated that the -----(b)(4)----- showed no ----(b)(4)----, please provide a*

schematic diagram showing the -----(b)(4)----- and the justification why they represent -----(b)(4)----- (and worst case ---(b)(4)---). Please also provide the -----(b)(4)----- in the (b)(4), and why these ---(b)(4)--- are considered representative (or worst case) ---(b)(4)---.

6. Please list the number of ---(b)(4)--- that support the production of 0.9% NaCl diluent and their uses.
7. You stated that equipment and primary packaging materials are sterilized using -----(b)(4)-----. Please describe the --(b)(4)-- and the sterilization method. Please provide the sterilization validation studies, including the different (b)(4) qualified.
8. In section 3.2.A.1 Facilities and Equipment Report for Sodium Chloride manufacturing facility, you stated that Sodium Chloride is currently classified as a worst case substance for cleaning. Please provide results of studies performed to demonstrate that NaCl is the worst case soil, and provide summary reports of studies performed to validate the cleaning procedures.
9. You stated that (b)(4) is used for cleaning and sterilization of equipment. Please describe the parameters used, and provide the results of studies performed to validate the (b)(4) process. Please list the equipment cleaned/sterilized by (b)(4).
10. In the submission, there is a brief description of the facility water. As (b)(4) is used as an ingredient in the manufacture of the diluent, please describe your procedures for monitoring the quality of the (b)(4).
11. Please describe your procedures for packaging and shipping the 0.9% NaCl to Novo Nordisk facilities.

Manufacturing of turoctocog alfa drug substance and drug product at Novo Nordisk facilities in Denmark

12. Please submit the container closure testing performed to demonstrate the integrity of the container closure of the final drug product.
13. During the PLL, you stated that you implemented changes to the areas used for formulation and filtration of the drug product; and that (b)(4) Batches of Turoctocog alfa for clinical trials were manufactured in week 10, 2013 (after implementing the changes) . Please submit the qualification of the area as an amendment to BLA 125466/0.
14. Please provide the EMPQ for the Grade (b)(4) areas in the (b)(4) facility, and include the frequency and acceptance criteria (alert and action limits) for routine monitoring.

LETTER READY COMMENTS REQUESTING ADDITIONAL INFORMATION

Turoctocog alfa drug product.

1. For the (b)(4) sterilization (-(b)(4)-, Denmark), please provide the -----(b)(4)-----, and justify why they are representative (worst case) of -----(b)(4)-----.

For (b)(4) sterilization (---(b)(4)---),

2. You stated that the sterilization (b)(4) are defined in the SOPs and validated. Please describe the sterilization –(b)(4)--, and justify the -----(b)(4)----- in each validation (b)(4).
3. You reported in the BLA the -----(b)(4)----- are sterilized in the ---(b)(4)---, please describe the ----(b)(4)---- used for the sterilization of the (b)(4).
4. The initial validation studies for the closures included separate validations for the stoppers and the caps. Please describe the validated (b)(4), and provide additional information to demonstrate that the validations are applicable to the stoppers and caps of turoctocog alfa drug product. Please justify the -----(b)(4)----- --- in each validation (b)(4).
5. For the re-validation studies of the closure cycle for ---(b)(4)---, you stated maximum and minimum (b)(4) for closures – however you did not specify whether it was stopper or closure (b)(4). Please explain.
6. Please explain why the initial validation of the closures for ---(b)(4)--- was performed in 2011, and clarify whether this is the first validation of the closure (b)(4) in this ---(b)(4)---.
7. For -----(b)(4)-----, please clarify what you mean by “the latest initial validation” performed for (b)(4) in 2012, and explain what prompted this validation. Please clarify if you performed -----(b)(4)----- to identify the worst case -----(b)(4)----- . Please justify your response.

Media Fills

8. You have submitted the media fill using the (b)(4) vials. Since the submission of the BLA you must have performed a media fill using (b)(4) vials. Please provide the most recent media fill using the (b)(4) vials. Also provide the environmental monitoring data collected during the media fill. Alternatively, please provide data from medial filled vials that bracket the (b)(4) size, provided that such vials use the same stopper/vial neck dimensions.
9. You state in the Process Performance Qualification Summary for Drug Product report (3.2.P.3.5 Process Validation for turoctocog alfa) that “the aseptic process is qualified by media fill, see [3.2.R Procedure and Specifications for Media fills](#)”; however, this section is not included in the submission. Please provide the information.

Sterile Filtration

10. During validation of sterile filtration, two studies were performed for the bacterial retention evaluations: one using the 250 IU product and the other using the 3000 IU product. Please clarify why the two processes are run at different durations and flow rates.

Container Closure for turoctocog alfa

11. Please clarify if the stoppers are latex free and provide documentation to support that. Are the stoppers endotoxin free and has that been validated by the vendor and verified by Novo Nordisk (sampling of lots)?

12. You state that vials (used for filling) are cleaned by -----(b)(4)----- . Please provide the tests performed to ensure that the vials are free of particles prior to depyrogenation.

Lyophilization process

13. Please clarify if the current validated cycle for the lyophilization of turoctocog alfa is variable for the following parameters: time, temperature and pressure, and clarify how these three parameters (and their combined effect) are monitored and controlled throughout the lyophilization cycle.
14. In the Justification validation report you stated that during qualification you have placed (b)(4) TCs on every shelf, yet during the justification validation, the sensors were placed in -----(b)(4)----- . Please explain the rationale for using the -----(b)(4)----- only, and why do you consider these points representative of the whole lyophilizer.
15. In the Justification process validation studies you reported that the lyophilization process was validated for the lowest, middle and highest concentration to cover the range (shelves -(b)(4)-). Yet you loaded shelves -----(b)(4)----- . So you did not provide data to support that the products lyophilized on those shelves meet the acceptance criteria. Please provide explanation/data to demonstrate that all products lyophilized on all shelves met the acceptance criteria.
16. You stated that sampling in duplicates was performed in a -----(b)(4)----- of the shelf for each of the justification studies. You also stated that samples for turoctocog alfa drug product were taken from shelf -----(b)(4)----- . Samples were also taken from --- (b)(4)----- for documentation of the lyophilization process. Please explain your rationale for not collecting samples from the other -----(b)(4)----- . In addition you sampled the challenged (---(b)(4)---) lyophilized turoctocog alfa drug product for water content, (b)(4), content, purity, (b)(4), anti-oxidant and -----(b)(4)---- . Please explain why you only tested these parameters, and not all the parameters tested during release of the product.
17. In the justification studies, you have reported that a number of vials were discovered broken following lyophilization. Please provide the investigation for the broken vials during the lyophilization justification studies, and describe the corrective methods that were implemented.
18. In Table 14 of eCTD 3.2.P.3.5 *Process Validation – PPQ Summary for Drug Product*, you did not describe all the defects as was the case in the justification studies. Please describe what you mean by the critical and non critical errors for stoppers, vials, capsules and lyophilized cake, and justify your characterization. Please provide the number of lyo cakes that are collapsed or melted.
19. In Table 22 of eCTD 3.2.P3.5, *Process Validation: Process Verification for Lyophilization*. Some defects (visual inspection) that were listed in the justification studies were not included in the verification study. Please provide the data for those defects. There are some defects described in the justification studies that were not included. Please provide the number of defective lyo cakes.

20. All the PPQ batches and the verification batches used (b)(4) for lyophilization. In addition you stated that “the latest initial validation” performed for --(b)(4)--- was in 2012. Please describe the modifications to (b)(4) and whether they have been submitted to the agency. Please clarify whether you have revalidated (b)(4) for the manufacture of turoctocog alfa, and submit the relevant data.

Placement of scale on the Prefilled Syringe

21. The lab studies to verify that the attachment of the label to the syringe is accurate and durable are not sufficient to validate the process. During the PLI, Novo Nordisk stated that they completed the validation studies in 2013. Please provide the validation studies for the placement of the scale on the syringe.
