



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, BLA STN 125671/0

From: Hector Carrero, Facilities and Equipment Reviewer, OCBQ, DMPQ, MRBII

cc: Andrey Sarafanov, Chair and Product Reviewer, OTAT, DPPT, HB
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Through: Qiao Bobo, Ph.D., Chief, OCBQ, DMPQ, MRBII

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

Action Due: February 27, 2019

Action Recommended: Approval

SUMMARY

CBER received this electronic submission on February 27, 2018. Novo Nordisk Inc. Novo Nordisk submitted this BLA to provide information to support US market authorization of lyophilized Antihemophilic Factor (Recombinant), GlycoPEGylated ([ESPEROCT], also referred to as turoctocog alfa pegol) supplied with sterile diluent - 0.9% NaCl solution. ESPEROCT is presented in single-dose vials containing 5 strengths of 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. Also, Novo Nordisk will introduce changes to the drug substance manufacturing process, including (b) (4) [REDACTED]

[REDACTED] The manufacturing of turoctocog alfa pegol drug substance (b) (4) [REDACTED] is performed at Novo Nordisk US in (b) (4) [REDACTED] manufacturing of drug product (formulation, filling, lyophilization and inspection)

is performed at Novo Nordisk A/S in (b) (4) ; and manufacturing of diluent (formulation and filling) is performed at (b) (4) . The drug substance is shipped to Novo Nordisk (b) (4) from Novo Nordisk (b) (4)

To support this BLA, the firm provided process validation, facility information, equipment qualifications, cleaning validations, sterilization validations, and computer systems.

CBER performed a Pre-License Inspection (PLI) at Novo Nordisk (b) (4) from (b) (4) to support the review of the original BLA STN 125671/0 (turoctocog alfa pegol). The initial classification is Voluntary Action Indicated (VAI). The inspection findings will be documented in the Establishment Inspection Report (EIR).

(b) (4)

An inspection waiver recommendation for this BLA submission's Drug Product and Diluent manufacturing site was dated July 11, 2018.

As this is a recombinant product, this review was conducted under FDA's *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*. Under this guidance, limited information is required to be submitted regarding facility and equipment. As such, my review is based on this guidance document.

SUBMISSION REVIEW

In this review memo, I cover the facility and equipment, and manufacturing process of turoctocog alfa pegol (b) (4) performed at Novo Nordisk (b) (4) ; manufacturing process of drug product (formulation, filling, lyophilization and inspection) performed at Novo Nordisk A/S in (b) (4) and manufacturing of diluent performed at (b) (4) . I reviewed applicable information provided under STN 125671/0.

ENVIRONMENTAL ASSESSMENT

Novo Nordisk stated that to the best of their knowledge the firm is not aware of any extraordinary circumstances that would require an Environmental Assessment. Novo Nordisk believes that turoctocog alfa qualifies for a Categorical Exclusion under 21 CFR Part 25.31(c):

Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally

in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

The firm requests a Categorical Exclusion from submitting an environmental assessment of turoctocog alfa pegol.

Reviewer's Comments: *The request is acceptable.*

TUROCTOCOG ALFA PEGOL DRUG SUBSTANCE

(b) (4) [Redacted]

[Redacted]

[Redacted]

- [Redacted]
- [Redacted]

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

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(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

Reviewer's Comments: Overall, the facility flows described and illustrated appear to be appropriate to support the cGMP manufacturing process. Additionally, the facility flows were reviewed during the recent FDA inspection and no issues were identified for the (b) (4) facility flows.

(b) (4) [Redacted]

(b) (4) [Redacted]

[Redacted]

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4) [Redacted]

[Redacted]

[Redacted]

Reviewer's Comments: The Novo Nordisk (b) (4) site is currently manufacturing multiple products and seems to have appropriate controls and changeover procedures to prevent contamination and cross contamination. The contamination/mix-up precaution procedures were reviewed during inspection and are discussed in the EIR.

10 pages determined to be not releasable: (b)(4)

(b) (4)

[Redacted]

[Redacted]

TUROCTOCOG ALFA PEGOL DRUG PRODUCT

The following Facilities are associated with the manufacture of drug product:

Table 24 List of manufacturing activities at (b) (4)

Name/Address	Manufacturing Activities	Inspection/Waiver	Comments
Novo Nordisk A/S (b) (4)	<ul style="list-style-type: none"> • Manufacture of the Drug Product (b) (4) • Final release testing (microbiological sterility, endotoxin) 	Waived	ORA (b) (4) NAI

Name/Address	Manufacturing Activities	Inspection/Waiver	Comments
Novo Nordisk A/S (b) (4)	<ul style="list-style-type: none"> Final release testing (microbiological test) 	Waived	ORA (b) (4) NAI

Drug Product Manufacturing Facility

The Novo Nordisk A/S, Building (b) (4) supports the (b) (4) (b) (4) and visual inspection of turoctocog alfa pegol manufacturing. The (b) (4) site is a multi-product facility. The (b) (4) Building is a (b) (4)

The (b) (4) of recombinant (b) (4) and recombinant coagulation factor products takes place in (b) (4) on the (b) (4) floor. Filling of sterile water and sterile histidine diluents for reconstitution also takes place in (b) (4). Additionally, clinical development programs for coagulation factors are carried out on (b) (4). Inspection of vials and packaging also take place on the (b) (4). There is a (b) (4) dedicated to sterile (b) (4)

This is an approved multi-product facility. In addition to turoctocog alfa pegol drug product, the following drug products are filled by (b) (4) in building (b) (4)

- NovoSeven® Coagulation Factor VIIa (recombinant) including Histidine diluents for reconstitution (b) (4) – US Marketed Product STN 103665
- Novoeight® Coagulation Factor VIII (recombinant) – US Marketed Product STN 125466
- TRETEN® Coagulation Factor XIII (recombinant) and sterile water for reconstitution (b) (4) – US Marketed Product STN 125398
- Refixia®/Rebinyn® Coagulation Factor IX – Glyco-PEGylated (recombinant) – US Marketed Product STN 125611
- GlucaGen® including sterile water for reconstitution (b) (4) – US Marketed Product
- Norditropin Reference Sample

MANUFACTURING PROCESS

The manufacturing of turoctocog alfa pegol (N8-GP) drug product includes the following steps:

1. (b) (4)

7. Inspection - Visual inspection is performed according to a standard procedure for a lyophilized parenteral. Quality control testing is performed after visual inspection.
8. Labeling and Packaging – The product and labelling materials are collected and identified according to the packaging order. The packaging process is performed manually and/or automatically. The vial with drug product and the syringe with solvent are labelled and packed together with the vial adaptor in cartons provided with imprint of batch number and expiry date.
9. Storage - Finished drug product is stored protected from light at 2–8°C.

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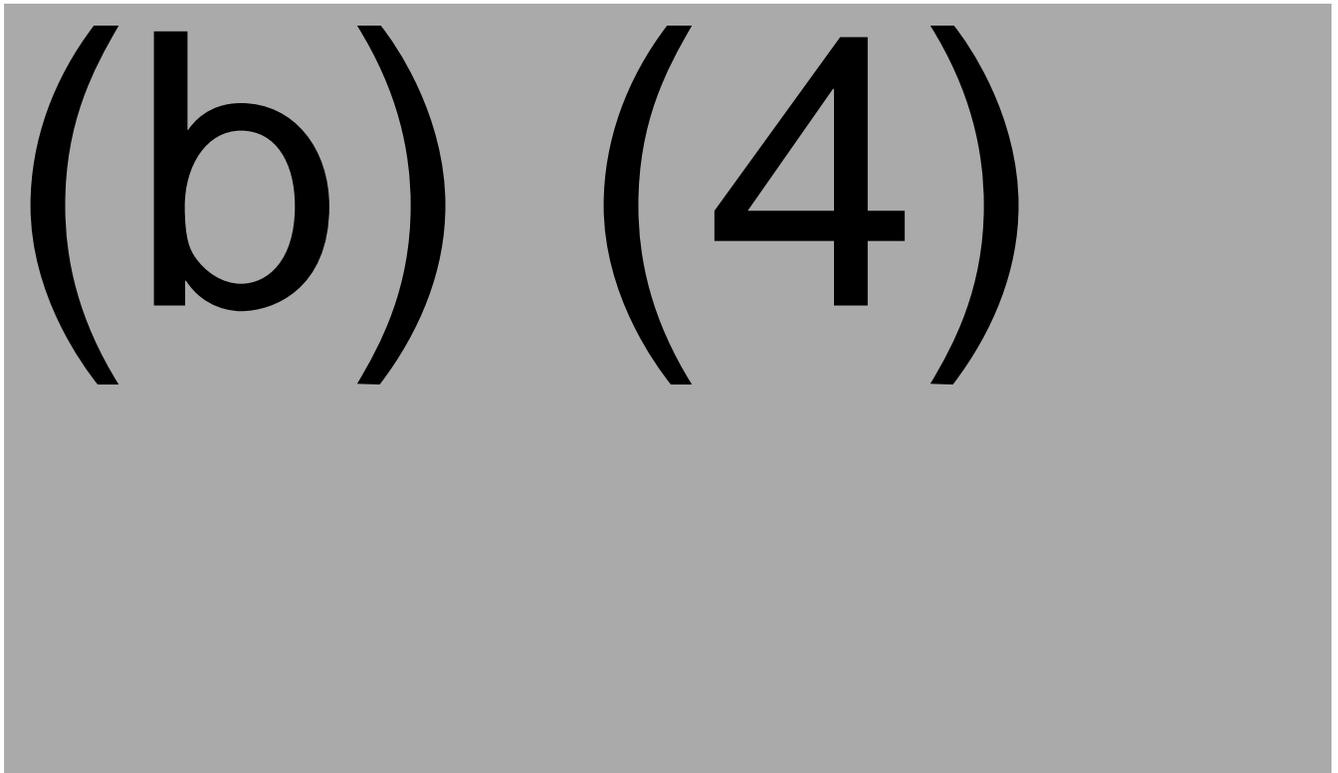
PROCESS VALIDATION/PROCESS PERFORMANCE QUALIFICATION (PPQ)

The composition and manufacturing process for turoctocog alfa pegol drug product is the same for all five product strengths (500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU/vial) except for the amount of active ingredient. The process validation of turoctocog alfa pegol consisted of (b) (4) batches for process design and (b) (4) batches for PPQ using a (b) (4) design of batch size and drug product strength. (b) (4) lots in the batch size range (b) (4) for lyophilization, were produced during PPQ. The maximum load (b) (4) in the lyophilizer is considered worst case. The (b) (4) were included in the PPQ matrix, (b) (4) the 1500 IU strength. The genealogy of the PPQ lots is presented in the table below:

Table 25 PPQ Batch information

Drug product	Batch size	Drug product batch no.	Date of manufacture
500 IU	(b) (4)	(b) (4)	(b) (4)
2000 IU			
3000 IU			
1000 IU			

The in-process tests controls with defined control limits performed during manufacturing of turoctocog alfa pegol drug product are presented below:



(b) (4)

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The PPQ limits and results related to DMPQ including process controls, and results from the supplementary sampling are presented in the tables below.

(b) (4)

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(b) (4)

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Table 31 Batch analysis of PPQ lots

Test parameter	Acceptance criteria for PPQ	(b) (4) 500 IU	(b) (4) 2000 IU	(b) (4) 3000 IU	(b) (4) 1000 IU	
Appearance of powder	White to off-white lyophilizate	Complies	Complies	Complies	Complies	
Reconstitution time / Solubility	(b) (4)	Complies	Complies	Complies	Complies	
Appearance of solution	Clear/colorless	Complies	Complies	Complies	Complies	
(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)	
Protein content [mg/vial]		500 IU	(b) (4)	(b) (4)	NA	
		2000 IU	NA		(b) (4)	(b) (4)
		3000 IU	NA		(b) (4)	(b) (4)
		1000 IU	NA			(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)
Identity		Complies	Complies	Complies	Complies	Complies
Potency [IU/vial]	500 IU	(b) (4)	(b) (4)	NA		
	2000 IU	NA		(b) (4)	(b) (4)	
	3000 IU	NA			(b) (4)	(b) (4)
	1000 IU	NA				(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
(b) (4) (Methionine) [mg/vial]	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Polysorbate 80 [mg/vial]	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Sucrose [mg/mL]	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Calcium [mmol/L]	(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)	(b)	(b)	(b)	(b)	
Bacterial endotoxins [EU/mL]	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Sterility	Complies (No microbial growth)	Complies	Complies	Complies	Complies	

Novo Nordisk stated that no critical alarms were encountered during the lyophilization of all (b) (4) PPQ batches. The batch analysis results and the results from extended sampling all met the acceptance criteria.

Reviewer's Comments: Results from extended sampling after lyophilization also met the criteria for appearance of powder, reconstitution time, appearance of solution and (b) (4). The supplementary samples were taken in a (b) (4) on product containing (b) (4), collecting samples from positions in the (b) (4) and assure uniformity. The evaluation of analytical results is deferred to the assigned product reviewer.

The residual (b) (4) of the capped vials was tested at (b) (4). Inprocess sampling for (b) (4) test was also performed (b) (4) when the duration of the process exceeded (b) (4). All capping results are within the operational limits and listed in the table below:

(b) (4)

All visual inspection (VI) results were within the operational limits except for batch (b) (4) where the number of loose capsules is above the action limit, Batch (b) (4) was corrected per deviation #3042366 and no defects were found. The total number of inspected vials is the number vials unloaded from the lyophilizer minus the process scrap from the capping process. The standard AQL sample size is (b) (4) vials. VI results are presented in the tables below:

(b) (4)

(b) (4)

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Deviations

Two deviations were encountered during the execution of the PPQ:

- Deviation # 3042366 - The number of loose capsules is above the action limit for Batch (b) (4). The batch was corrected; no defects were found after the correction. It was determined by the firm to be no impact to the product quality.
- Deviation # 3044485 – The air viables Class (b) (4) environmental monitoring limit in room (b) (4) was exceeded during filtration of batch (b) (4). A trend analysis was performed and found satisfactory. In addition, no microorganism was seen in adjacent room in the week of the occurrence. The remaining batch samples were below the limit. No product or PPQ impact was determined by Novo Nordisk.

The commercial manufacturing process is reviewed and verified on a (b) (4) basis. The firm stated that a batch of turoctocog alfa pegol 1500 IU will be manufactured as a post PPQ batch and monitored in on-going stability.

***Reviewer's Comments:** The PPQ appears to have been appropriately performed and is adequate to support the manufacture of turoctocog alfa pegol DP at the Novo Nordisk (b) (4) facility. The PPQ lots met all the required acceptance criteria for process control and release testing. Evaluation of the acceptability of the other testing and parameters for these lots is deferred to the assigned product reviewer. In general, the deviations do not appear to have had any adverse effect on the PPQ or the manufactured lots, but final review of these deviations is deferred to the assigned product reviewer.*

Facilities and Equipment

HVAC

The production area is divided into a (b) (4) and sterile Filtration rooms surrounded by a (b) (4) area. The compounding takes place in a (b) (4) area. Manual visual inspection of filled product and labeling and packaging are performed in a Controlled Not Classified area. The personnel are restricted to (b) (4) during filling operations.

The (b) (4).
The air supply to the (b) (4) area is filtered through (b) (4) filters (b) (4) placed at the air inlets to the rooms. The filling machine and filtration room have a unit providing (b) (4) air flow of (b) (4) filtered air, resulting in a (b) (4) area.

The (b) (4) area is ventilated with an air change of approximately (b) (4) per hour. The air is filtered through (b) (4) filters placed in the ventilation shafts or through (b) (4)-filters in the ceiling.

The pressure differentials are (b) (4)

Routine environmental monitoring (EM) in classified areas is performed per existing procedures. The environmental monitoring program includes testing at designated locations for non-viables (airborne particles) and viables in controlled, aseptic rooms including filling line. Environmental monitoring of viable particles includes (b) (4)

Alert limits, action limits and testing frequency for the different classified rooms were provided. The environmental monitoring program at Novo Nordisk includes:

- (b) (4)

The firm stated that the plates used in the microbiological monitoring program are transported safely to the microbiology department as soon as possible after use. They also provided the conditions for (b) (4)

(b) (4)

Additionally, there are procedures in place regarding investigations and actions taken when specifications are exceeded.

Reviewer's Comments: The (b) (4) System at the (b) (4) site used for turoctocog alfa pegol appears to be acceptable.

PREVENTION OF CONTAMINATION/CROSS CONTAMINATION

Manufacturing is performed in (b) (4) to prevent cross contamination and direct product contact processing equipment is dedicated. Cleaning of the equipment is performed (b) (4) to prevent carry-over of product residues between batches. The cleaning procedures for dedicated equipment have been validated. Product contact equipment is marked with a (b) (4). The firm also has specific (b) (4)

(b) (4)

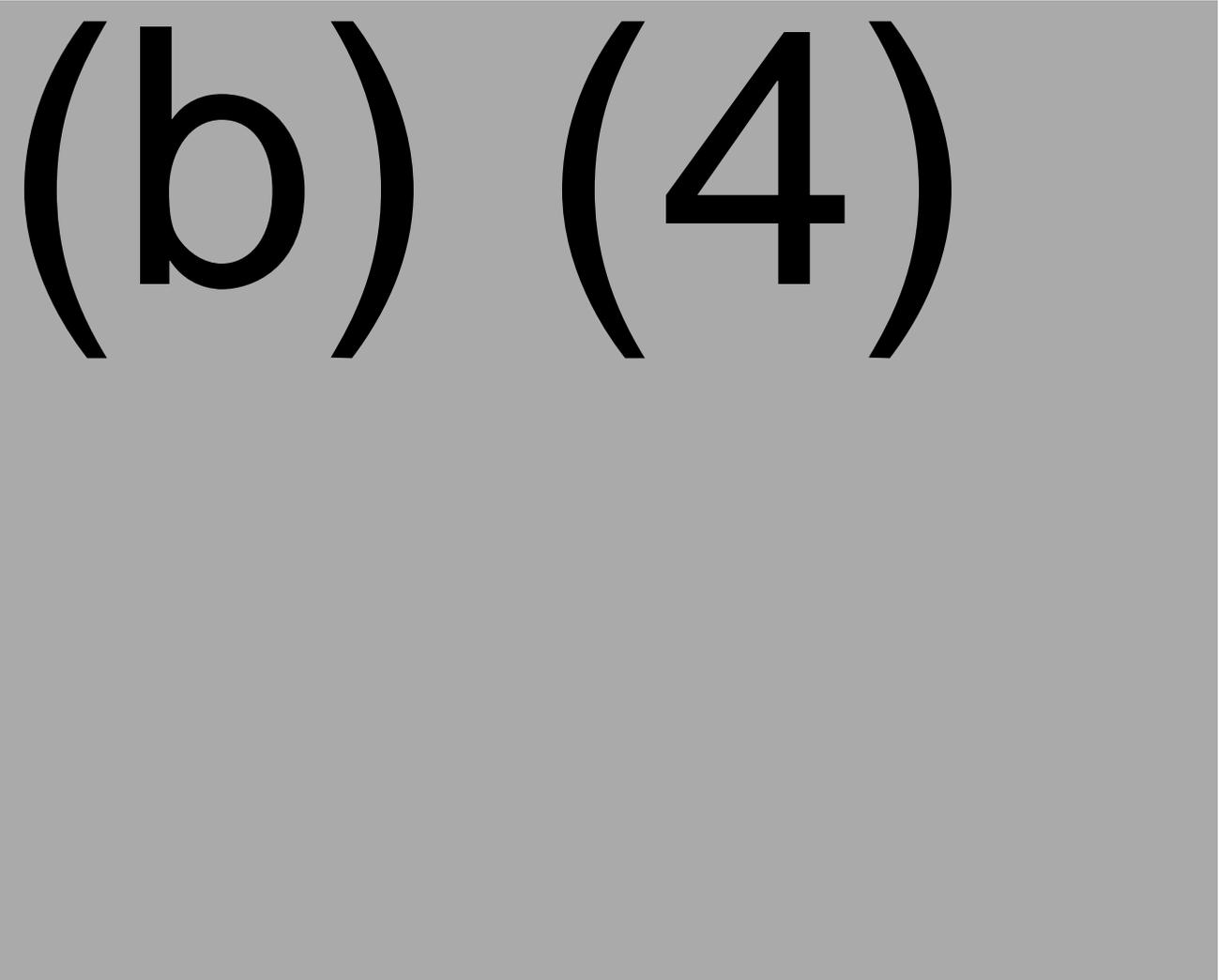
(b) (4) :

- (b) (4) [Redacted]

Reviewer's Comments: The Novo Nordisk (b) (4) site is currently manufacturing multiple US marketed products and seems to have appropriate controls and changeover procedures to prevent contamination and cross contamination.

Equipment

All equipment with direct product contact is dedicated to production of turoctocog alfa pegol drug product.



(b) (4)

Equipment Cleaning

Cleaning procedures are performed (b) (4) manufacturing operation (b) (4)

[Redacted]

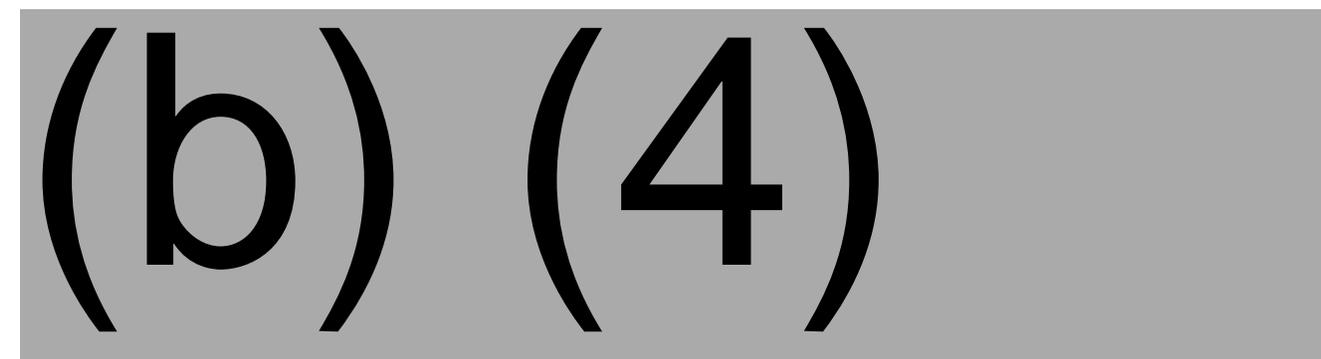
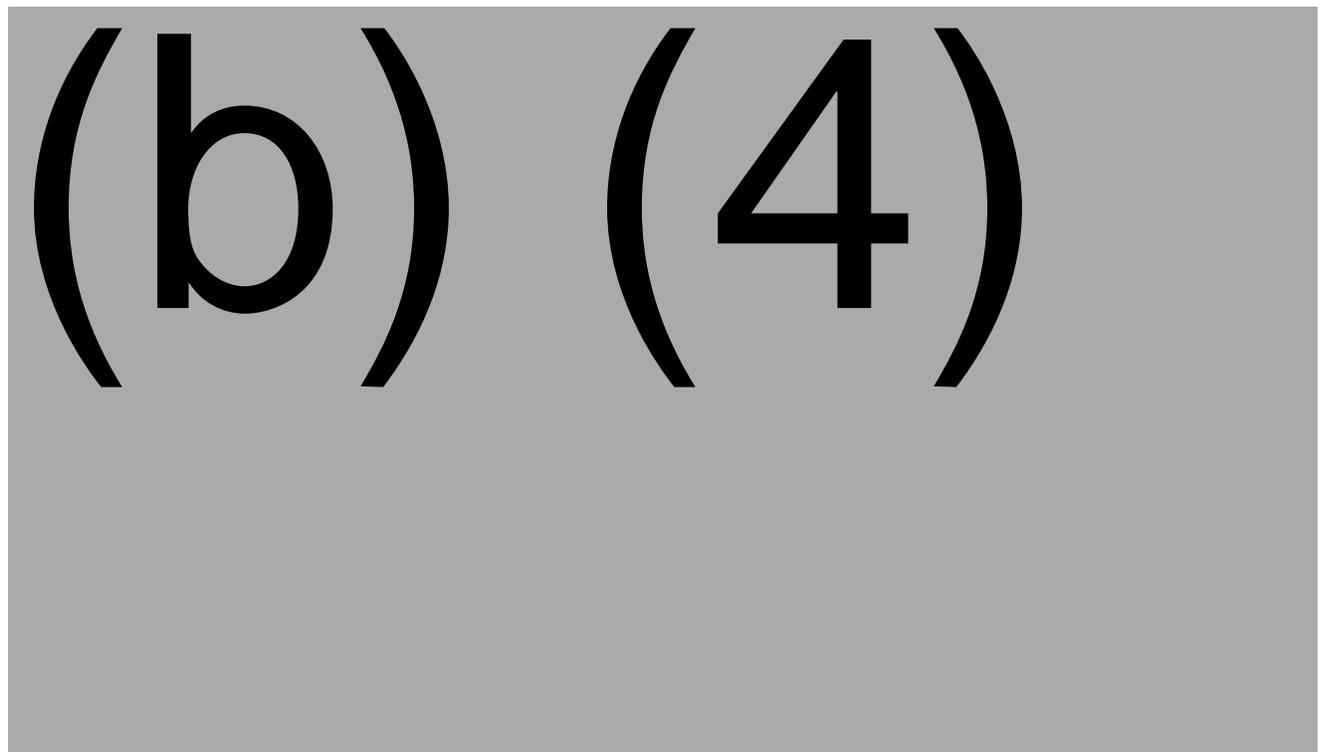
(b) (4)

Cleaning Validation

The cleaning validation program was performed per approved protocols and (b) (4)



Cleaning monitoring and revalidation are performed per standard operation procedures. The following criteria were used during validation:



(b) (4)

(b) (4)

Reviewer's Comments: The cleaning validation and routine cleaning processes appear to be appropriate. The validation study results show that the cleaning procedures established by Novo Nordisk are effective in cleaning the respective equipment.

Equipment Sterilization

(b) (4)

(b) (4)

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Utilities

Water Systems

(b) (4) is used for production. The (b) (4) is stored in a (b) (4) is controlled per standard operating procedures and specifications. (b) (4). The firm provided testing frequency and acceptance limits (microbial control and endotoxin) regarding the water system monitoring program.

(b) (4) is prepared continuously from (b) (4). The (b) (4) is distributed using (b) (4). The (b) (4) is controlled per standard operating procedures, instructions, and specifications.

Gas System

The (b) (4) is received from an external supplier. The (b) (4) is controlled according to standard operating procedures, instructions and specifications.

Reviewer's Comments: *The firm briefly described the (b) (4) and (b) (4) systems (including routing microbial monitoring test frequencies and specifications for (b) (4)). The (b) (4) and gas systems appear appropriate to support cGMP manufacturing of ESPEROCT. The (b) (4) system and gas system are already approved for other US marketed products.*

Validation of Sterile Filtration

Turoctocog alfa pegol drug product is manufactured in five different product presentations: 500 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU, which differ only in the concentration of the active ingredient. They are validated for filtration of batch sizes in the range (b) (4). The drug product is (b) (4). Novo Nordisk provided the results of the validation of the following (b) (4) used for sterile filtration of (b) (4)

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The results demonstrate the retention capability of the (b) (4) filter used for sterile filtration of turoctocog alfa pegol. The following acceptance criteria were met: (b) (4). Based on the studies performed, a maximum filter contact time of (b) (4)

Reviewer's comment: The sterile filter validations appears adequate. The extractables and leachables, compatibility of filter with drug product and (b) (4) studies performed as part of the filter validation are under the purview of the product office, and will be addressed by the product office.

Media Fill

Novo Nordisk stated that media fills are performed in the (b) (4)

[Redacted]

The initial qualification consisted of (b) (4) media fill runs. The media (b) (4)

[Redacted]

(b) (4)

(b) (4)

(b) (4)

All intact vials are (b) (4)

- (b) (4)

Environmental monitoring (EM) was performed during the media fills and consisted of viable and non-viable particle air monitoring. In addition, sampling of critical surfaces and personnel for viables were performed. The firm provided the alert limits, action limits and testing frequency for airborne, surface and personnel monitoring. Viable and non-viable EM results for all three most recent media fill simulation lots did not show any excursions. Exceeded action levels are handled according to approved procedures. Novo Nordisk provided a summary of the EM results in the following table:

(b) (4)

Reviewer's Comments: The Media Fill program appears appropriate.

Lyophilization

The lyophilization is a (b) (4)

[Redacted text block]

(b) (4)

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(b) (4)

(b) (4)

Container Closure System

The container closure system for the drug product includes the drug vial, vial adapter and pre-filled diluent syringe, all packaged together. The (b) (4) is approved for several Novo Nordisk coagulation products: NovoSeven® RT (STN 103665), Novoeight® (STN 125466), and REBINYN (STN 125611). The drug product is filled into 5mL (b) (4) glass vial with 13mm chlorobutyl rubber lyophilization stopper, aluminum cap, and plastic snap-off. Each vial contains a single 4-mL dose after reconstitution. The vial adapter is a sterile, plastic disposable device in a blister package (Class II medical device, 510(K) number (b) (4) . For the (b) (4) turoctocog alfa pegol product, Novo Nordisk stated that they followed the streamlined approach for combination products as described in 21 CFR 4.4(b)(1). The approach was based on compliance to the drug cGMP regulation and the selected provisions of the device Quality System Regulations (QSR) regulation 21 CFR 820, as detailed in the “Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products.” The drug delivery system was designed in accordance with 21 CFR 820.30.

The container closure system parts for the drug product are listed below:

Table 49 Packaging components

Component	Description	Reference to monograph	Manufacturer
Vial 5 ml (b) (4)	Colorless glass with (b) (4)	• (b) (4)	• (b) (4)

Component	Description	Reference to monograph	Manufacturer
Lyophilization Stopper 13 mm Grey	Chlorobutyl rubber, (b) (4)	• (b) (4)	(b) (4)
Vial Adapter	Sterile, plastic fluid transfer device, in a blister package	(b) (4)	(b) (4)

Preparation of the container closure

Vials are cleaned by (b) (4). Afterwards the vials are (b) (4)

Rubber Stoppers are bought as “Ready to sterilize.” The stoppers are sterilized (b) (4)

Aluminium Caps with snap-off are sterilized by (b) (4)

All cleaning and sterilization processes mentioned are validated.

Container Closure Integrity Testing

The container closure integrity testing (CCIT) was conducted using a (b) (4) during the test. Vials were (b) (4)

The CCIT results met the acceptance criteria. All (b) (4) exposed test vials showed no growth after the microbial challenge test. The (b) (4)

All the prerequisites (b) (4)

(b) (4)

were met.

Packaging

Labelling, packaging and shipping are executed according to procedures. The drug product vial and the syringe with solvent are labelled and packed together with the vial adaptor in cartons provided with imprint of batch number and expiry date. During the packaging, visual in-process control is performed. After packaging, vial reconciliation is performed. The finished product is transferred to the warehouse and stored at 2-8°C.

Visual Inspection

Novo Nordisk provided a description of the visual inspection process (VI) and the validation strategy. (b) (4) Manual Visual Inspection of the prefilled vials is performed. AQL (Acceptance Quality Limit) sampling of the acceptable pre-filled vials from the (b) (4) Manual Visual Inspection is performed.

The VI qualification consists of different phases: training of manual inspectors, qualification of manual inspectors, training and qualification of personnel performing AQL, and qualification of equipment.

Novo Nordisk established three defect classifications: (b) (4)

- (b) (4)

After the (b) (4) visual inspection of each batch, AQL samples are randomly selected and visually inspected by certified QA personnel. The AQL values for the different defect categories were provided. AQL sampling at Novo Nordisk is performed to meet the consumer's risk quality

(CRQ) recommended in ISO standard 2859-1 (Sampling procedures for inspection by attributes – Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection). The Novo Nordisk AQL sample size is (b) (4) vials with no critical* or critical defects allowed.

Reviewer’s Comments: The visual inspection process and validation appear to have been appropriately performed and to be adequate to support the evaluation of prefilled vials.

Stability

Evaluation of the acceptability of the stability data and the overall plan is deferred to the assigned product reviewer. Novo Nordisk committed to submit sterility and endotoxin long-term stability data for the four PPQ batches to support a drug product shelf life of up to (b) (4) .

DRUG PRODUCT – DILUENT

The 0.9% Sodium Chloride (NaCl) diluent, presented in a 5mL glass prefilled syringe (PFS) is single use, and is manufactured under contract by (b) (4) facility. The facilities were designed as multi-product manufacturing facilities, which are approved and regularly inspected for compliance to cGMPs by FDA. The NaCl diluent (4mL filling volume) is used for reconstitution of the lyophilized turoctocog alpha pegol drug product before intravenous administration. The composition of the diluent solution is sodium chloride and (b) (4) . The diluent PFS is part of the (b) (4) approved for several Novo Nordisk coagulation products: NovoSeven® RT (STN 103665), Novoeight® (STN 125466), and REBINYN (STN 125611).

The following Facilities are associated with the manufacture of turoctocog alfa pegol diluent:

Table 50 Diluent Manufacturing Facilities

Name/Address	Manufacturing Activities	Inspection/Waiver	Comments
(b) (4)	<ul style="list-style-type: none"> (b) (4) 	Waived	ORA (b) (4) NAI

Name/Address	Manufacturing Activities	Inspection/Waiver	Comments
(b) (4)	<ul style="list-style-type: none"> (b) (4) 	Waived	IOG/CDER (b) (4) VAI
(b) (4)	<ul style="list-style-type: none"> (b) (4) 	Waived	ORA (b) (4) NAI

Diluent Container Closure System and Integrity Testing

The container closure system for the 0.9% sodium chloride solution consists of a 5 mL (b) (4) glass syringe barrel (b) (4), a 5 mL Bromobutyl rubber plunger and bromobutyl rubber tip cap (b) (4). (b) (4) conducted the CCIT of the pre-filled syringes at the (b) (4) site using a validated (b) (4) method. The CCIT was performed using 0.9% NaCl PFS containing (b) (4) that had been subjected to (b) (4) to cover a worst case scenario. (b) (4) syringes were tested by visual inspection, and they stated that all showed no (b) (4).

The firm submitted a (b) (4) re-qualification summary report (b) (4) document 5053025, approved 21-Nov-2016) which I review below:

The drug product is (b) (4)

(b) (4) The maximum load is a defined and approved load and is distributed among (b) (4).

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

- (b) (4)

The firm provided diagrams with the location of validation (b) (4)

(b) (4) The diagrams provided show that the (b) (4) . All results met the acceptance criteria of no growth of (b) (4) distribution throughout the (b) (4) . The results demonstrated a (b) (4) sterilization of the product.

Attachment of scale to syringe for administration

The syringe for solvent is labelled in the same facility used for the labelling and packaging of turoctocog alfa pegol drug product in (b) (4) . The label with the scale is placed accurately on the syringe and controlled using an (b) (4) system. The in-process control for the step includes the position the label with scale on the syringe. A total uncertainty tolerance of (b) (4) is allowed, in alignment with the indications of ISO 7886-1. The verification checks the scale label is accurately placed at correct position on the syringe, dosing accuracy and that label is permanently attached.

Reviewer's Comments: *The manufacture of the diluent appears to be adequate as this product is currently used for other US marketed products. The process validation of the 0.9% NaCl diluent at (b) (4), including container closure, (b) (4) method validation, (b) (4) sterilization, visual inspection and hold times of pre-filled syringes, as well as the facilities, were reviewed and approved under BLA STN 125466/0.*