



Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
Silver Spring MD 20993-0002

To: Administrative File:
STN 125611/0, Coagulation GlycoPEGylated Recombinant Factor IX

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CBER/OCBQ/DMPQ/MRB2

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Edward Thompson, RPM, CBER/OBRR/RPMS

Subject: Original Biologics License Application

**Indication/
Drug Info:** For use in adults and children with hemophilia B for control and
prevention of bleeding episodes, perioperative management and routine
prophylaxis

Applicant: Novo Nordisk Inc.

License Number: 1261

Facility Site: (b) (4)

Action Due Date: June 3, 2017

Recommendation: Approval

Product Summary

This Biologics License Application (BLA) for Coagulation GlycoPEGylated Recombinant Factor IX (refers to as NONACOG BETA PEGOL in this memo) was submitted on May 16, 2016. NONACOG BETA PEGOL is a recombinant human factor IX (rFIX) with a 40 kDa polyethylene glycol (PEG) moiety covalently attached to the N-linked glycans in the activation

peptide. NONACOG BETA PEGOL is produced in Chinese Hamster Ovary (CHO) cells and the PEGylation is carried out enzymatically. NONACOG BETA PEGOL is supplied as a sterile lyophilized powder for solution for injection for intravenous use, manufactured in three different product strengths (500, 1,000 and 2,000 IU/vial), and is reconstituted in a 10 mM Histidine Solution prior to use. The Histidine Solution is manufactured by (b) (4) and is supplied in a pre-filled glass syringe co-packaged with the NONACOG BETA PEGOL Drug Product and a sterile vial adaptor. In addition to the information submitted to support licensure of NONACOG BETA PEGOL, the BLA also contains a Comparability Protocol (CP) for introduction of a (b) (4) bioreactor compared to the (b) (4) production bioreactor to be approved under this BLA. The CP proposes to submit the resultant data in a CBE-30.

Review Process Summary

This BLA was submitted on May 16, 2016, and Kevin Foley was initially assigned as the CMC/Facilities and Equipment Reviewer. Based upon his initial review of the original submission, an Information Request containing four comments was emailed to Novo Nordisk on June 7, 2016, to request additional information regarding the need to conduct pre-license inspections of the Novo Nordisk manufacturing facilities. Novo Nordisk responded to this Information Request in an amendment of June 21, 2016 (STN 125611/0/3). The responses to this Information Request are reviewed below under *Review of the Amendment of June 21, 2016 (STN 125611/0/3)*. This BLA was subsequently re-assigned on October 11, 2016. Based upon subsequent review of the original submission and of the amendment of June 21, 2016 (STN 125611/0/3), a second Information Request containing ten comments was emailed to Novo Nordisk on November 23, 2016. Novo Nordisk responded to this Information Request in an amendment of December 7, 2016 (STN 125611/0/21). The responses to this Information Request are reviewed below under *Review of the Amendment of December 7, 2016 (STN 125611/0/21)*. After additional discussion with management and based upon review of the original submission and of the amendment of December 7, 2016 (STN 125611/0/21), a third Information Request containing eight comments was emailed to Novo Nordisk on March 9, 2017. Novo Nordisk responded to this Information Request in an amendment of March 23, 2017 (STN 125611/0/43). The responses to this Information Request are reviewed below under *Review of the Amendment of March 9, 2017 (STN 125611/0/43)*. References to the comments in the Information Requests are provided throughout this memo.

This BLA was reviewed according to 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 (August 1996).

Pre-license inspections of applicable manufacturing facilities were waived for this BLA as described in two separate inspection waiver memos.

Based upon review of the original submission, amendment of June 21, 2016 (STN 125611/0/3) containing responses to the Information Request of June 7, 2016, amendment of December 7, 2016 (STN 125611/0/21) containing responses to the Information Request of November 23, 2016, and amendment of March 23, 2017 (STN 125611/0/43) containing

responses to the Information Request of March 9, 2017, approval of this BLA is recommended.

Contents of Submission

This is an electronic submission in eCTD format. The following documentation was reviewed:

Items Reviewed – Original Submission (DCC Login ID#632722)

- Section 1: Cover Letter, Form FDA 356h and Request for Categorical Exclusion from Environmental Assessment
- Section 2: Introductory Document, Quality Summaries for the Drug Substance, Drug Product, and Facilities and Equipment, and Regional Information
- Section 3.2.S: CMC Information on the Drug Substance
- Section 3.2.P: CMC Information on the Histidine Solution (diluent) and Drug Product
- Section 3.2.A.1: CMC Facilities and Equipment Information for the Drug Substance (b) (4) Facility (Building (b) (4) Drug Substance (b) (4) facility (Building (b) (4) , Drug Product manufacturing facility (Building (b) (4) , Denmark) and Histidine Solution (diluent) Manufacturing Facility (b) (4)
- Section 3.2.R: CP for Introduction of a (b) (4) Bioreactor, CMC Information on the Vial Adaptor and a Shipping Validation for Transportation of the Histidine Solution from (b) (4) to Novo Nordisk

Items Reviewed – Amendment 3 (DCC Login ID#635571)

- Section 1: Cover Letter, Form FDA 356h and Response to the Information Request of June 7, 2016

Items Reviewed – Amendment 21 (DCC Login ID#650302)

- Section 1: Cover Letter, Form FDA 356h, Letter of Authorization for the Vial Adaptor and Response to the Information Request of November 23, 2016
- Section 3.2.S: Interim Resin Lifetime Study Reports
- Section 3.2.P: A Revised List of Histidine Solution Manufacturers and Information for the (b) (4) Device
- Section 3.2.A.1: Study Reports for the Qualification of the HVAC System in Building (b) (4)

Items Reviewed – Amendment 43 (DCC Login ID#668444)

- Section 1: Cover Letter, Form FDA 356h and Response to the Information Request of March 9, 2017
- Section 3.2.S.2.4: Revised Information on Control of Critical Steps
- Section 3.2.R: Revised CP for Introduction of a (b) (4) Bioreactor

Review

Environmental Assessment

Novo Nordisk requests a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(c). They state that the supplement meets the


requirements of a categorical exclusion under 21 CFR §25.31(c) because the active pharmaceutical ingredient, rFIX, (1) qualifies as a substance that occurs naturally in the environment, (2) is expected to be readily biodegradable, (3) has no known adverse effects on humans or the environment, and (4) is considered to not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. In addition, Novo Nordisk states that, to the best of their knowledge, no extraordinary circumstances exist that would require an environmental assessment under 21 CFR part 25.21.

Reviewer's Comments: *The request for categorical exclusion from environmental assessment for NONACOG BETA PEGOL is accepted.*


Drug Substance

Drug Substance Description

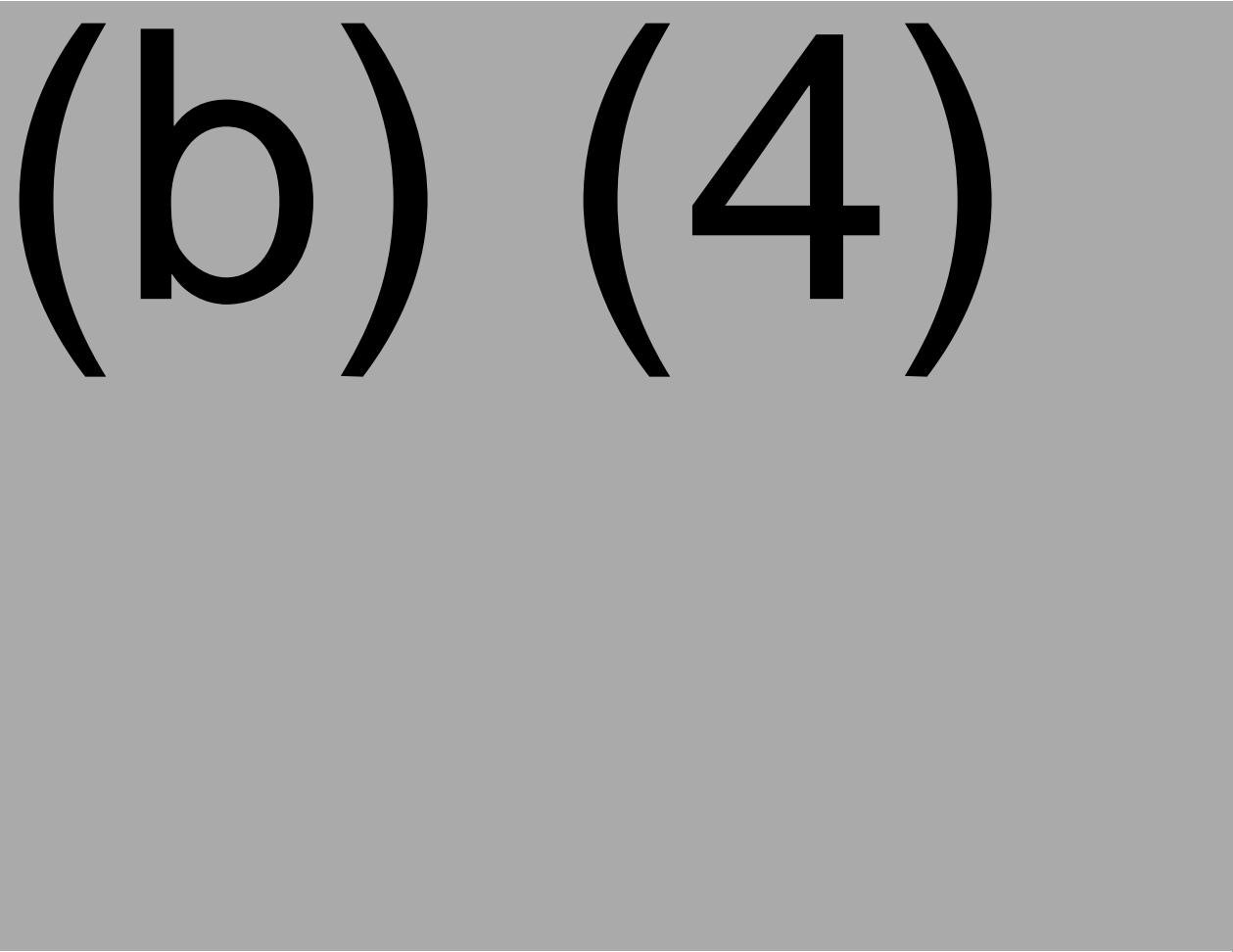
(b) (4)

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(b) (4)

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(b) (4)

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(b) (4)

(b) (4)

Histidine Solution

Histidine Solution Description

The Histidine Solution is supplied as a single-use prefilled 5 mL glass syringe containing (b)(4) of 10 mM Histidine (nominal volume is 4 mL) for the reconstitution of the lyophilized NONACOG BETA PEGOL Drug Product before use. The syringe is (b) (4) to the syringe used for Novo Nordisk's approved product NOVOEIGHT®.


Reviewer's Comments: *It is not completely clear from the BLA is the 5 mL syringe used for the Histidine Solution co-packaged with the NONACOG BETA PEGOL Drug Product is (b) (4) as the one co-packaged with NOVOEIGHT. A clarification of this issue was therefore requested from Novo Nordisk in an Information Request. See Review of the Amendment of June 21, 2016 (STN 125611/0/3) below (comment #4).*

(b) (4)


(b) (4)

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


(b) (4)



(b) (4)



(b) (4)



Drug Product

Drug Product Description

The NONACOG BETA PEGOL Drug Product is a lyophilized powder for solution for injection for intravenous use supplied in a 12 mL type [®] glass vial with a grey chlorobutyl rubber stopper and an aluminum and plastic snap-off cap. A sterile, disposable, plastic vial adapter is provided with the Drug Product for transfer of fluids into and out of the vial. A pre-filled syringe containing (b) (4) of the Histidine Solution and equipped with a scale with a (b) (4) increment is also provided for reconstitution and administration of the Drug Product. The Drug Product is supplied in three different product strengths, containing 500, 1,000 or 2,000 IU/vial, which are all dissolved in (b) (4) of the Histidine Solution before use (the withdrawal volume is 4 mL). The final reconstituted Drug Product contains (per mL) 125 IU (b) (4) 250 IU (b) (4) or 500 IU (b) (4) NONACOG BETA PEGOL, 2.34 mg NaCl, 3.10 mg Histidine, 10 mg sucrose, 25 mg mannitol, 0.05 mg Polysorbate 80, (b) (4). The Drug Product vial has a (b) (4) and a (b) (4) overfill.

The Drug Product has a proposed shelf-life of (b) (4) at $5 \pm 3^{\circ}\text{C}$ (where the drug product may be kept at or below 30°C for a single period up to (b) (4) and in-use expiry of up to 24 hours at 5°C or up to 4 hours at $\leq 30^{\circ}\text{C}$).

Drug Product Manufacturers

The Drug Product is manufactured at the following facilities:

Facility	FEI/DUNS	Manufacturing Steps Performed
Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)
Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)
Novo Nordisk A/S Novo Allé, DK-2880 Bagsværd, Denmark	3000151819 305914798	Batch release responsible for finished drug product
Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)
Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)
Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)
Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)
Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)
Novo Nordisk A/S (b) (4)	(b) (4)	(b) (4)
Novo Nordisk A/S (b) (4)	N/A (b) (4)	(b) (4)
(b) (4)	N/A (b) (4)	(b) (4)
(b) (4)	N/A (b) (4)	(b) (4)
(b) (4)	N/A (b) (4)	(b) (4)
(b) (4)	N/A (b) (4)	(b) (4)
(b) (4)	N/A (b) (4)	(b) (4)

Drug Product Manufacturing Process Description

The Drug Product manufacturing process consists of (b) (4),
compounding of the Drug Substance with excipients, sterile filtration, filling, lyophilization
including partial stoppering, capping and visual inspection. Labelling, packaging and shipping
are performed after Quality Control analysis and batch release of the Drug Product. The Drug
Product manufacturing process is described in more detail in the following table.

(b) (4)

(b) (4)

Drug Product Microbial Reduction during Manufacture

Sterility of the Drug Product is controlled using the following strategies:

- Procedures for environmental monitoring (EM), gowning, aseptic processing including media fills, bioburden monitoring of final solution, sterilization of equipment and components, by requirements for holding time before filtration and by sterile filtration.
- Closure integrity is an (b) (4) control and the closure integrity is documented during shelf life.
- Microbial count/endotoxin testing is performed for all excipients except (b) (4).
- Testing for microbial count is included in the (b) (4) specification.
- Testing for sterility is included in the Drug Product specification.
- Sterility of the Drug Product is monitored during stability studies.

Endotoxin in the Drug Product is controlled using the following strategies:

- Endotoxin is (b) (4) control of the microbial level (b) (4) sterile filtration (via bioburden testing).
- (b) (4)
- Microbial count/endotoxin testing is performed for all excipients except (b) (4).
- Testing for microbial count is included in the (b) (4) specification.
- Testing for sterility is included in the Drug Product specification.
- Endotoxin content is monitored during stability studies.

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

More information on the microbial reduction measures in place in the Drug Product manufacturing facility is provided below under *Facilities and Equipment for the Drug Product Manufacture*.

Drug Product Control of Materials

The raw material used to manufacture the Drug Product (b) (4) Histidine, mannitol, Polysorbate 80, NaCl, (b) (4), sucrose and (b) (4) all meet the specifications described in the (b) (4). The microbial limits for these raw materials are as follows: (b) (4) Histidine, mannitol, sucrose and NaCl; (b) (4) for Polysorbate 80, and (b) (4) for (b) (4). None of these raw materials are of human or animal origin.

Drug Product Control of Critical Step and Intermediates

In-scope in-process controls parameters for each step of the Drug Product manufacturing process are provided in the above table.

(b) (4)

The processing times shown in the following table are also considered in-process control parameters.

(b) (4)

(b) (4)

Drug Product Specifications

The specifications for the Drug Product include specifications for the lyophilized Drug Product (appearance, reconstitution time and water content) and for the reconstituted Drug Product. The in-scope specifications for the reconstituted Drug Product are shown in the following table:

Parameter	Analytical Procedure (Method)	Acceptance Criteria
Endotoxin	(b) (4)	(b) (4)
Sterility	Membrane filtration (b) (4) 21 CFR 610.12)	(b) (4) 21 CFR 610.12

Drug Product Batch Analyses

The following batches of Drug Product were manufactured in support of this BLA.

PPQ Batches

Use of Batch	Batch Strength	Batch Size	Batch Scale	Drug Substance Batch Numbers	Drug Product Batch Numbers
PPQ/Clinical Trials	500 IU	(b) (4)	Commercial	(b) (4)	
PPQ	1,000 IU	(b) (4)	Commercial		
PPQ/Clinical Trials	2,000 IU	(b) (4)	Commercial		

Developmental Batches – Commercial Manufacturing Facility

Use of Batch	Batch Strength	Batch Size	Batch Scale	Drug Substance Batch Numbers	Drug Product Batch Numbers
Clinical Trials	500 IU	(b) (4)	Commercial	(b) (4)	
		(b) (4)			
Specification Setting/ Process Justification		(b) (4)	Commercial		
Clinical Trials	2,000 IU	(b) (4)	Commercial		

Developmental Batches – Pilot or Laboratory Manufacturing Facility

Use of Batch	Batch Strength	Batch Size	Batch Scale	Drug Substance Batch Numbers	Drug Product Batch Numbers
Clinical Trials/ Specification Setting	500 IU	(b) (4)	Pilot	(b) (4)	BLDP026 BLDP022 BLDP020 BLDP009 ALDP024 ALDP008 ALDP002
Specification Setting		(b) (4)		(b) (4)	(b) (4)
Stability Only		(b) (4)		(b) (4)	(b) (4)
Specification Setting		(b) (4)		(b) (4)	(b) (4)
	1,000 IU	(b) (4)	Laboratory	(b) (4)	
Clinical Trials/ Specification Setting	2,000 IU	(b) (4)	Pilot	(b) (4)	DLDP001 CLDP010 BLDP031 BLDP027 BLDP023 BLDP021 BLDP011 BLDP008 BLDP002 ALDP026 ALDP013 ALDP009 ALDP003 YLDP019
Clinical Trials/ Non-Clinical Trials				(b) (4)	XLDP002
Specification Setting/ Process Justification				(b) (4)	(b) (4) (b) (4)
Non-Clinical Trials Only				(b) (4)	CLDF012 CLDF008 001252741-01 492931-01
	2,000 IU	(b) (4)	Laboratory	(b) (4)	433-08-101 433-08-079 433-08-078
Stability Only		(b) (4)		(b) (4)	(b) (4)

The following results for in-scope microbial control testing are provided in the BLA (PPQ batches in bold; acceptance criteria provided above under *Drug Product Specifications*):

Batches	Endotoxin	Sterility
500 IU: (b) (4)	(b) (4)	Complies
1000 IU: (b) (4)	(b) (4)	Complies
2000 IU: (b) (4)	(b) (4)	Complies

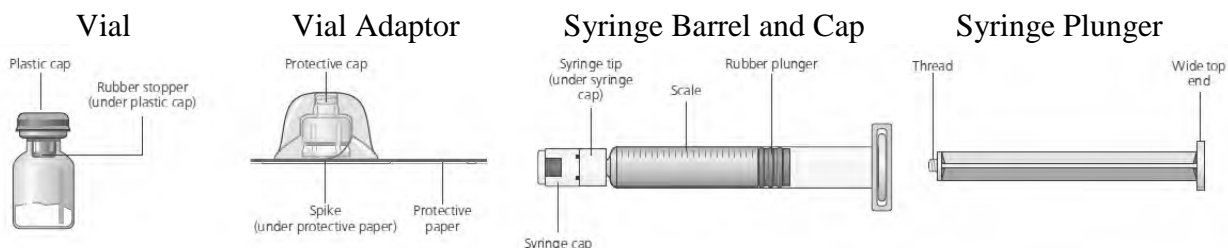
*This batch was not tested for these parameters.

Drug Product Container Closure System

The container closure system for the Drug Product consists of the following components:

- A 12 ml type ^{(b) (4)} glass vial (compliant with (b) (4) supplied by (b) (4))
- A grey chlorobutyl rubber stopper (meets the requirements of (b) (4) that is washed by the supplier (supplied by (b) (4), supplied treated with (b) (4) on the rubber surface (b) (4) and delivered “ready-to-sterilize”
- A snap-off aluminum and plastic cap supplied by Novo Nordisk and (b) (4)

The Drug Product is also supplied with a vial adapter (manufactured by (b) (4)), a sterile, disposable device packed in a blister package device (see picture below) and allows for transfer of fluids into and out of vials. The vial adaptor consists of a vial adapter body made of polycarbonate, a hub with a female luer lock made of polycarbonate, a filter with a filter disc made of high density polyethylene and filter mesh made of polyamide, and a spike made of polycarbonate. Puncturing of the rubber stopper in the vial is achieved by means of the integral plastic spike. As mentioned above, the vial adaptor has a 25 µm in-line filter for particulate filtration and flow aspiration. The vial adapter is stated as being classified as a sterile class II device cleared by FDA (K963583). The complete container closure system for the Drug Product is shown in the following figure.




The vials are release tested for the (b) (4)

(b) (4) appearance and dimensions. Results from (b) (4) lots of vials (b) (4) showing that they met all of the acceptance criteria for these tests are provided in the BLA. The stoppers are release tested for (b) (4) parameters, physical parameters (appearance and dimensions), and (b) (4) (b) (4). Results from three lots of stoppers (b) (4) showing that they met all of the acceptance criteria for these tests are provided in the BLA. The snap-off caps are release tested via visual inspection and for internal height. Results from three lots of stoppers (b) (4) showing that they met all of the acceptance criteria for these tests are provided in the BLA.

Drug Product Container Closure Integrity Testing

Container closure integrity was demonstrated by (b) (4) testing employing (b) (4) as the test (b) (4) (actual amount (b) (4)). In the study, (b) (4) vials capped with a Residual Seal Force below the rejection limit of (b) (4) were used (set at

(b) (4) vials with a (b) (4) of (b) (4) were chosen for testing. After filling at the Drug Product manufacturing facility (the (b) (4) facility in (b) (4) ; see below under *Facilities and Equipment for the NONACOG BETA PEGOL Drug Product Manufacture* for more information) with (b) (4)



Reviewer's Comments: In general, the (b) (4) testing appears to be appropriate and acceptable. However, the Drug Product is manufactured with a (b) (4) suggesting that it could be (b) (4) in which case (b) (4) testing would not be appropriate. If the Drug Product is (b) (4), a method such as (b) (4) analysis would be appropriate to confirm that the container closure integrity is adequate to support that (b) (4) will not enter the vials. Clarification of this issue was therefore requested from Novo Nordisk in an Information Request. See Review of the Amendment of March 23, 2017 (STN 125611/0/43) below (comment #4).

Drug Product Dosing Accuracy Qualification

This study was conducted to confirm that the scale on the 5 mL dosage syringe with attached scale label used for the reconstitution and deliver of the Drug Product is positioned correctly (based upon (b) (4) 5 mL syringes containing 4 mL of Histidine Solution were used to reconstitute the Drug Product at either the 500 IU or 2,000 IU strength. The Drug Product was reconstituted with (b) (4) of Histidine Solution as this is considered worst-case, and the (b) (4) of the reconstituted product was measured and compared against the predicted (b) (4) of (b) (4) for the 500 IU or 2,000 IU strengths, respectively. The acceptance criteria were therefore the (b) (4) syringes having a mean weight of (b) (4) for the 500 IU strength and (b) (4) for the 2,000 IU strength based upon these densities. If the results failed for either strength, then (b) (4) syringes at that strength would be tested with the same criteria. The results [mean percent \pm standard deviation (actual mean)] for the (b) (4) syringes were (b) (4) for the 500 IU strength (range (b) (4) and (b) (4) for the 2,000 IU strength (range (b) (4) which met the acceptance criteria for both strengths.

Information regarding how the label with the scale is attached to the syringe and the validation of the attachment of the scale to the Histidine Solution (which is performed at the (b) (4) facility after the filled syringes are received from (b) (4)) is provided below under *Drug Product Attachment of Scale to Syringe for Administration*.

Drug Product Usability Assessment

(b) (4) is a hemophilia drug delivery system consisting of vial containing drug, syringe containing diluent, plunger rod, vial adapter, Instructions for Use and a Patient Product Information. It forms the basis of a hemophilia drug delivery system for several Novo Nordisk coagulation factor products including (b) (4) (both approved products), and is used for the NONACOG BETA PEGOL Drug Product. Novo Nordisk states that the cumulative post-market data on adverse events and technical complaints reported to Novo Nordisk supports that (b) (4) meets the expected safety and performance requirements with respect to the intended use.

Novo Nordisk completed a development and risk management process for the NONACOG BETA PEGOL (b) (4) following (b) (4), and FDA Guidances on Medical Device Safety - Incorporating Human Factors Engineering into Risk Management and Applying Human Factors and Usability Engineering to Optimize Medical Device Design. The initial use-related risk management process included eight steps as follows: define intended use, users, and environment; identify use related hazards; estimate and prioritize the use error risk, implement risk controls; validate safety of use; determine if the risk is acceptable and/or if new risks were introduced; document the process; and implementation of post-market surveillance. Based upon the human factors engineering/risk management process Novo Nordisk concluded that there are identical considerations for human factors and use-related risks for NONACOG BETA PEGOL as for (b) (4). Therefore, Novo Nordisk concluded that the summative usability test for (b) (4) completed for (b) (4) sufficient to demonstrate that the NONACOG BETA PEGOL (b) (4) is safe and effective with regard to handling.

Reviewer's Comments: *It is not clear if Novo Nordisk has met the requirements under 21 CFR 820 for this combination product. Novo Nordisk also did not provide information for their Purchasing Controls as required under 21 CFR 820.50. The design history file, summative usability test report for (b) (4) (document UT84), and a clarification of how they meet the requirements for design and purchasing controls and CAPA were therefore requested from Novo Nordisk in an Information Request. See Review of the Amendment of June 21, 2016 (STN 125611/0/3) below (comment #6). The summative usability test was requested to assess whether functionality testing was performed as part of the testing. Review of usability testing is deferred to the assigned product reviewer.*

Novo Nordisk however did conduct a human factors validation (UT164) in 62 participants to support that the intended users of NONACOG BETA PEGOL its carton from cartons of other relevant hemophilia products from Novo Nordisk and competitor coagulation factor products. During the validation, there were three non-serious use errors (wrong strength), one close-call, no operational difficulties, and no need for parental or test administrator assistance. Finally, participants considered the task of selecting the prescribed carton from the refrigerator to be

relatively easy.

Reviewer's Comments: Review of the human factors study is deferred to the assigned reviewer from the product office.

Drug Product Stability

The Drug Product stability program includes testing of 500 IU PPQ batches (b) (4), 1,000 IU PPQ batch (b) (4), and 2,000 IU PPQ batch (b) (4) at $5 \pm 3^\circ\text{C}$ /ambient humidity/darkness at 0, 3, 6 and 9 months with 12, 18, 24 and (b) (4).

In addition, 2,000 IU PPQ batch (b) (4) was tested at $5 \pm 3^\circ\text{C}$ /ambient humidity/darkness at 0 and 3 months with 6, 9, 12, 18, 24 (b) (4).

In addition, 500 IU batches (b) (4) and 2,000 IU batches (b) (4) were tested at $5 \pm 3^\circ\text{C}$ /ambient humidity/darkness out to (b) (4).

The Drug Product stability program also includes in-use and (b) (4) testing of 500 IU batches (b) (4), and 2,000 IU batches (b) (4).

Sterility and (b) (4) were tested during long-term storage at 5°C at months 0, 24 and (b) (4) (only for primary and supportive stability batches) and 5°C /(b) (4) at months 24 (b) (4), and not during the in-use or (b) (4) studies. The results of testing for sterility and (b) (4) were reported as all being within the specifications at all of the time points measured.

Drug Product Attachment of Scale to Syringe for Administration

The Histidine Solution syringes are equipped with a scale after the filled syringes are received in bulk from (b) (4). The scale is printed on the label and the label is glued on to the syringe for administration on the packaging line. The label is placed on the syringe using an (b) (4).

The labeling process, and the label and glue are already in use for US licensed products such NOVOSEVEN RT and NOVOEIGHT.

The maximum allowable total uncertainty for the scale is (b) (4), based upon requirements in (b) (4) and corresponding to (b) (4) (i.e., a quarter of the smallest scale interval). The total uncertainty is a combination uncertainty of the label positioning (b) (4) and the uncertainty in how much the plunger position while fully inserted varies in relation to a defined

part on the syringe (b) (4) The total deviation was stated as being determined in a laboratory investigation where all results were within the required (b) (4) (results (b) (4) (b) (4) .

The attachment of the label to the syringes was investigated in a laboratory study. Since the glue reaches full adhesive strength within (b) (4) , the critical time period when a label is attached and fixed is the first (b) (4) . Therefore, a test was performed on (b) (4) syringes to verify the adhesion of the label after (b) (4) by applying an axial force on the label and subsequently examining the position of the label using a (b) (4) . Novo Nordisk states that all (b) (4) syringes met the acceptance criterion of no movement of the label.

Drug Product Lyophilization Process Development and Validation

Lyophilization of the Drug Product is performed as a (b)(4)

(b) (4) | | | | (b) (4)

All of these lyophilizers are currently approved for use to manufacture other US licensed products.

Shelf temperature mapping studies were completed in (b) (4)

(b) (4) This shelf

temperature mapping will be performed (b) (4) for each lyophilizer as an integrated element of the facility validation master plan. The shelf temperature mapping study results are shown in the following table (merged data from (b) (4) lyophilizers). The acceptance criteria for the (b) (4) positions and for the shelf variation were that the differences between (b) (4)

(b) (4) at all target temperatures and that the differences from the target temperature were (b) (4) at each target temperature.

(b) (4)

(b) (4)

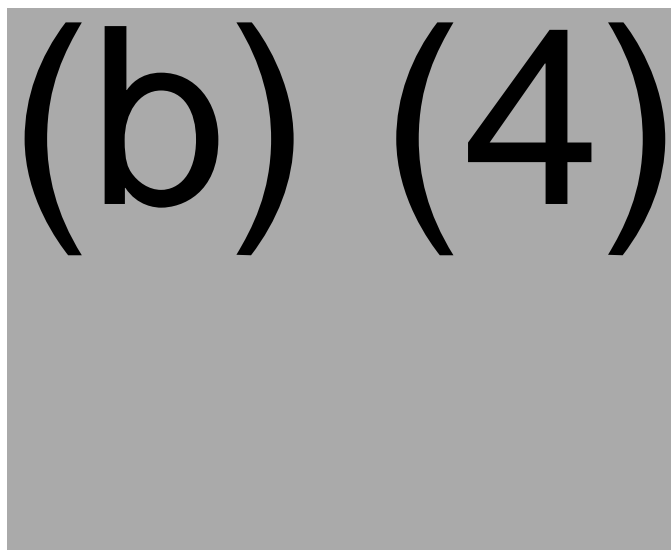
The lyophilization process for the Drug Product was initially developed at laboratory scale taking the thermal properties of the composition of the Drug Product into consideration. (b)(4)

The following cycles were used during process development as the final formulation was developed (values in parentheses were evaluated during laboratory scale developmental runs).

(b) (4)

The process (b) (4) cycle was used for the (b) (4) formulations, process (b)(4) was used for the (b) (4) formulation, and process (b)(4) was used for the (b) (4) formulation.

A formulation without (b) (4) with similar thermal lyophilization properties was employed as a surrogate for the Drug Product to achieve a full manufacturing load during lyophilization. The load pattern for the full load combination batches is shown in the following figure.



The full load for the Drug Product corresponds to the (b) (4) shelves in the lyophilizer while the minimum load corresponds to (b) (4) of the top shelf. The batches manufactured as a matrix to challenge the lyophilization process are shown in the following table.

Strength	NONACOG BETA PEGOL Batch	Surrogate Batch	Lyophilizer Load	Lyophilization Cycle Challenge
500 IU/vial	(b) (4)			
2000 IU/vial				

*Batch lyophilized in (b) (4) ; **batch lyophilized in (b) (4)

The product temperature during the lyophilization challenge batches was monitored by (b) (4) the product containing vials located in (b) (4) of the lyophilizers, as these positions are considered by Novo Nordisk to be the most likely to be affected by radiant heat and therefore are expected to show the highest variation and the largest differences between shelf temperature and product temperature. The lyophilizers were loaded in (b) (4) as shown in the above figure. The results of the product temperature mapping for these (b) (4) batches are shown in the following figures.

Reviewer's Comments: While it would be preferable that the product temperature mapping be performed not just in (b) (4) of the lyophilizer shelves, the following data/information provided by Novo Nordisk supports that this data is acceptable. First, these lyophilizers are already in use for other US licensed products supporting that they function appropriately. Second, the empty chamber mapping supports that there is no apparent difference in shelf temperature for the (b) (4) of each shelf in (b) (4) lyophilizers. Third, supplementary sample of testing for product quality was performed for these developmental batches (as described below) that sampled from (b) (4) of each shelf supporting that vial placement within the lyophilizers does not affect the resultant product quality. Fourth, extended sampling was also performed for the PPQ lots (described below under Drug Product Process Performance Qualification) that also sampled from (b) (4) of each shelf again supporting that vial placement within the lyophilizer (only (b) (4) was

used for the PPQ batches) does not affect the resultant product quality. Finally, (b) (4) visual inspection of the PPQ lots did not reveal any trends in product quality that suggest that the lyophilization cycle is not properly validated.

(b) (4)

(b) (4)

In addition, a supplementary sampling program (extended sampling) was applied for the challenge batches, collecting samples from the (b) (4) of each shelf and one additional position. These samples were tested for appearance of powder, solubility (reconstitution time), water content, appearance of solution, (b) (4), content, (b) (4), potency, (b) (4), specific activity, (b) (4), mono-PEG rFIX, (b) (4) rFIX (b) (4) and rFIX (b) (4). The results for water content ranged from (b) (4) to

(b) (4) for these (b) (4) lyophilization challenge batches. All other testing results also met the specifications.

Reviewer's Comments: Review of the product quality testing for the extended sampling during the lyophilization challenge studies is deferred to the assigned product reviewer.

Capping and inspection for the lyophilization challenge batches (product and surrogate batches) were performed according to the standard procedures and acceptance criteria for lyophilized parenterals at the Novo Nordisk facility in (b) (4). The control parameters for these steps were for (b) (4) (limit (b) (4) and process time from unloading of the lyophilizer and capping to end of inspection (limit (b) (4)). The visual inspection quality limits and results (range for the product and surrogate batches) are shown in the following table.

Type	Category	Quality Limit	Results
Cap/Snap-Off	Loose cap (critical)	(b) (4)	(4)
	Fixed cap defects (critical)		
	Non-critical cap snap-off defects		
Stoppers	Missing stopper (critical)		
	Non-critical defect at stopper		
Vials	Chips and cracks (critical)		
	Non-critical vials defects		
Content	Glass particulates (critical)		
	Dark particulates (critical)		
	Other Particulates (critical)		
Filling Volume	Height of freeze drying cake (critical)		
	Empty vial (critical)		
Lyophilization Cake	Critical lyophilization defects		
	Non-critical lyophilization defects		
Other Defect	N/A		
Dropped on the Floor	N/A		
Total	N/A		
Number of Vials Inspected	N/A	(b)(4)	(b)(4) (b)(4) (b)(4) (b)(4)

*The particulate found in one vial from batch (b) (4) was concluded to originate from an autoclave plastic bag.

Finally, the lyophilization challenge batches (b) (4) along with other non-challenge batches (500 IU batches (b) (4), and 2000 IU batches (b) (4) that were lyophilized at the set points were placed on stability at $5 \pm 3^{\circ}\text{C}$ /ambient humidity/darkness, $5 \pm 3^{\circ}\text{C}$ /ambient humidity/darkness followed by (b) (4).

Reviewer's Comments: Overall, the development of the lyophilization cycle for the NONACOG BETA PEGOL Drug Product appears to be adequate and acceptable.

Drug Product Process Performance Qualification

Novo Nordisk's strategy for process validation of the Drug Product was comprised of process design, PPQ and future continued process verification. Process design was based upon the clinical lots manufactured in the pilot scale manufacturing facility (see above under *Drug Product Batch Analyses*). The PPQ consisted of the manufacture of (b) (4) Drug Product batches:

500 IU batches (b) (4), and 2,000 IU batches (b) (4) (see above under *Drug Product Batch Analyses*). All of these Drug Product PPQ batches were manufactured in Building (b) (4) in the (b) (4) facility (see below under *Facilities and Equipment for the Drug Product Manufacture*) and were lyophilized in (b) (4). The PPQ included extended sampling for homogeneity after mixing (see below for details), for chemical stability prior to lyophilization (no in-scope testing was performed; all acceptance criteria met), and from the (b) (4) on each shelf after lyophilization (again no in-scope testing was performed; all acceptance criteria met including for moisture content) for maximum size batches (b) (4) samples were collected for all sections of the shelf for minimum size batches; see above under *Drug Product Batch Analyses* for the batch sizes).

Reviewer's Comments: All of the Drug Product PPQ batches were lyophilized in (b) (4). However, the empty chamber mapping data presented for (b) (4) lyophilizers and the results of the developmental runs which were performed in (b) (4) lyophilizers (see above under Drug Product Lyophilization Process Development and Validation) supports that the (b) (4) lyophilizers are functional equivalent. In addition, (b) (4) these lyophilizers are already currently approved as being equivalent for several other licensed products. Therefore, presentation of data from Drug Product batches lyophilized in (b) (4) is considered adequate to support the use of (b) (4) for the lyophilization of NONACOG BETA PEGOL.

The range of results from the PPQ that were provided in the BLA are shown in the following table. In addition, the table shows the range of results for some of the developmental batches (500 IU Drug Product batches (b) (4) IU Drug Product batches (b) (4) that were used to set the limits for the PPQ batches.

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

The Drug Product developmental and PPQ batches were then release tested and the in-scope results are shown in the following table (the specifications are provide above under *Drug Product Specifications*):

Parameter	Results (range)
Endotoxin*	(b) (4)
Sterility	Complies

*Tested at the (b) (4) of filling for the PPQ batches.

Homogeneity studies (b) (4) sterile filtration were integrated for all batches manufactured for justification of process design. For the developmental batches, challenge studies for homogeneity were performed at (b) (4) for large batch sizes (b) (4) and at (b) (4) for medium and small batch sizes (b) (4). Protein content and (b) (4) and met the required specifications (b) (4) for protein content and (b) (4) for all of the batches. (b) (4) was measured at each (b) (4) adjustment and in the final formulation. For the PPQ batches, protein content and (b) (4) were tested for samples (b) (4).

samples for each batch) obtained from the (b) (4) of the tank during the (b) (4) and all of the samples met the required specifications (b) (4) for protein content for 500, 1,000 and 2,000 IU formulation, respectively, and (b) (4) for all formulations).

Novo Nordisk reports that there were three non-conformities during the PPQ that are described below.

- Reconstituted samples for sucrose and mannitol were (b) (4). New samples were sent for analysis and they were analyzed (b) (4). Novo Nordisk determined that this incident did not affect the outcome of the PPQ.
- (b) (4). The root cause was operator error as the operators chose the (b) (4) test method for (b) (4) instead of the test method for vials. However, the only difference between the (b) (4) test methods is the maximum RSF value that can be measured (and all results were above the operational limit of (b) (4) and therefore Novo Nordisk determined that this incident did not affect the outcome of the PPQ.
- A new lyophilization defect type was identified during manual visual inspection. During the PPQ, there were (b) (4) vials from batch (b) (4) identified as having (b) (4) lyophilization cakes. Novo Nordisk concluded that the defects represent a non-critical cosmetic defect and that the number of defective vials is well below the inspection control and quality limit of (b) (4) for this category. In addition, no lyophilization defects were identified during random AQL sampling. Novo Nordisk determined that this incident did not affect the outcome of the PPQ.

After completion of the PPQ, several of the Drug Product specification limits were modified but the limits for sterility and endotoxin remained unchanged.

Reviewer's Comments: *None of the reported non-conformances appear to have affected the acceptability of the PPQ or the quality of the Drug Product batches manufactured during the PPQ.*

Drug Product Sterile Filtration

The Drug Product is sterile filtered using (b) (4)



Studies were performed for qualification of the (b) (4)
The (b) (4) were validated for filtration of batch sizes of (b) (4)
Bacterial retention studies were performed using (b) (4) challenged with (b) (4)
in the Drug Product at the (b) (4) strengths.
(b) (4) is stated as having been found to be viable in (b) (4) strengths and thus to
be suitable for bacterial retention test. The (b) (4) are of the same composition (b) (4)
as the (b) (4) but have a (b) (4)
. Three lots of each (b) (4) were tested and the studies were performed at
(b) (4) The studies were performed using worst-case conditions of the (b) (4)

No deviations were reported.

Manufacturing Facilities and Equipment

Facilities and Equipment for the NONACOG BETA PEGOL Drug Substance Manufacture
(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

Reviewer's Comments: *As the Histidine Solution is already manufactured as the diluent for other licensed products, the existing sterile filtration procedures are acceptable and no additional information is required.*

Facilities and Equipment for the NONACOG BETA PEGOL Drug Product Manufacture

Building (b) (4) Description

Compounding, filling and inspection of the Drug Product are performed in the (b) (4) Building (b) (4) in the (b) (4) facility. Building (b) (4) is a licensed multiproduct facility and manufactures products for both clinical investigation as well as licensed products. The following Drug Products are also compounded and filled (and lyophilized) on (b) (4) on the (b) (4) of Building (b) (4) that used for the NONACOG BETA PEGOL Drug Product:

- (b) (4)

A separate filling line in Building (b) (4) is dedicated to (b)(4)

. Inspection of vials for (b) (4), recombinant coagulation factor products, sterile water and histidine diluents is performed on the (b) (4) of Building (b) (4). The packaging department for (b) (4) and recombinant coagulation factor products is also located in Building (b) (4). The layout of the (b) (4) and (b) (4) manufacturing areas in Building (b) (4) used for the NONACOG BETA PEGOL Drug Product are shown in the following figures.

Primary labeling and packaging of Drug Product for (b) (4) are performed in Building (b) (4). Solvents for reconstitution of these products are also labelled and packaged in the facility. All the labelling and packaging activities are performed in (b) (4) areas.

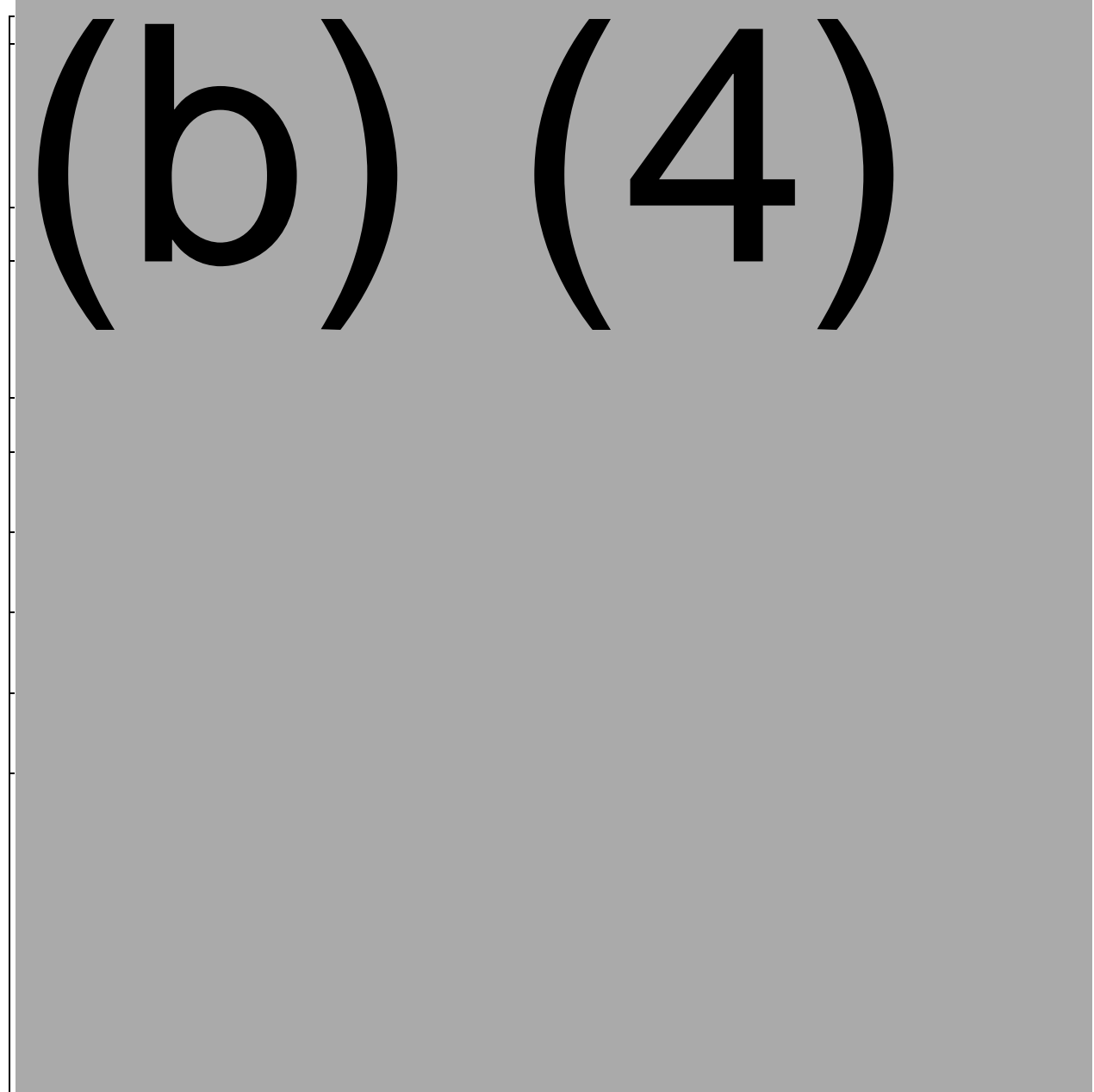
(b) (4)

Building (b) (4) Room Classifications

The production area in Building (b) (4) is divided into (b) (4) sections which are a Grade (b) (4) area, a

Grade (b) (4) area and a surrounding Grade (b) (4) area, respectively. The Class (b) (4) area comprises (b) (4) filling lines which are themselves surrounded by a Class (b) (4) area. The Class (b) (4) area comprises all of the remaining areas. In addition, some inspection activities are performed in a (b) (4) areas.

EM is performed in the classified areas according to existing SOPs as follows.




Reviewer's Comments: As Building (b) (4) is already a multi-product facility used to manufacture other licensed products, the information provided regarding the EM program is adequate.

Reviewer's Comments: *Novo Nordisk did not provide any information on how Building (b) (4) is cleaned. However, as Building (b) (4) is already a multi-product facility used to manufacture other licensed products, the facility cleaning procedures already in place would be adequate to support the manufacture of the NONACOG BETA PEGOL Drug Product.*

Building (b) (4) Flow Descriptions


Flow diagrams for personnel, raw materials, equipment, the Drug Product and waste are provided in the BLA.

(b) (4)



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(b) (4)



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Building (b) (4) HVAC System

The HVAC System in Building (b) (4) supplies HEPA filtered air to the Class (b) (4) areas. In addition, (b) (4) have a unit providing the critical steps in the filling

operations with (b) (4) air flow of HEPA filtered air resulting in Class (b) (4) areas. There is (b) (4)

rooms that is monitored. The temperature and humidity in the classified areas is held within specified limits.

Reviewer's Comments: As Building (b) (4) is already a multi-product facility used to manufacture other licensed products, the information provided regarding the HVAC system is adequate.

Building (b) (4) Utility Systems

The following utility systems supply the production areas in Building (b) (4):

- (b) (4)

Reviewer's Comments: As Building (b) (4) is already a multi-product facility used to manufacture other licensed products, the information provided regarding the utility systems is adequate.

Building (b) (4) Changeover Procedures


Changeover is performed (b) (4) every unit operation (compounding, filtration, filling, lyophilization, capping and inspection) according to established SOPs. The changeover procedures include (b) (4) according to SOPs, cleaning of equipment with in-direct product contact according to SOPs, and cleaning of rooms according to SOPs.

Building (b) (4) Process Equipment

Compounding, filtration and filling of the Drug Product is carried out with (b) (4) product contact equipment. The production processes for each product manufactured in the facility are performed in campaigns based upon the cellular source of the (b) (4)

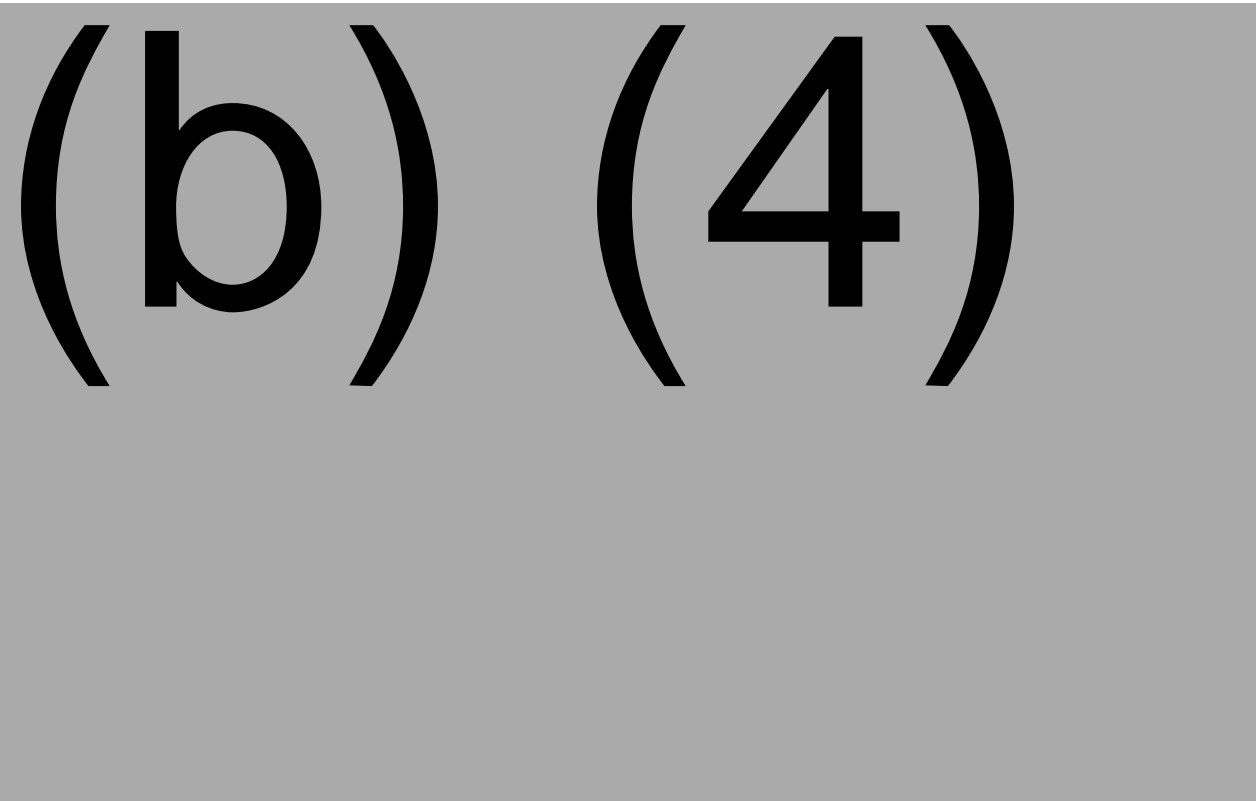
(b) (4)

(b) (4)


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The manufacture of the Drug Product (and other lyophilized Drug Products) is performed in the following rooms using the following equipment in Building (b) (4)

(b) (4)

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(b) (4)

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(b) (4)

Building (b) (4) Cleaning of Equipment

For each product manufacture in Building (b) (4), there are individual cleaning recipes or cleaning methods for the equipment. The (b) (4).

Cleaning procedures are performed consecutively at completion of each unit operation for manufacturing of each drug product. SOPs for cleaning in the facility are differentiated between three cleaning categories:

- (b) (4)

(b) (4)

All cleaning methods have been validated using worst-case conditions with regards to hold time, equipment, product concentration and washing time (for automatic cleanings). The 2,000 IU/vial strength is the highest concentration and therefore is worst-case with regard to the amount of protein present on equipment surfaces. All of the initial validations were carried out via (b) (4)

n. The worst-case conditions for the validation of cleaning of the lyophilizer were simulated by product contamination on specific positions in the lyophilizer to simulate potential spillage from broken/turned over vials.

(b) (4)

- (b) (4)

(b) (4)

Reviewer's Comments: As the majority of equipment used in the Building (b) (4) to manufacture the NONACOG BETA PEGOL Drug Product is either dedicated or disposable, and the manufacturing steps performed for the Drug Product are similar to those performed for other licensed products (see below under Review of the Amendment of June 21, 2016 (STN 125611/0/3), the information provided regarding the cleaning of equipment in this facility is adequate. In addition, though there does appear to be some shared product contact equipment (the (b) (4)) that could pose a risk of cross-contamination if not cleaned appropriately especially since it appears that the NONACOG BETA PEGOL Drug Product at the 2,000 IU/vial strength is the worst-case soil, the information provided regarding the approach to cleaning validation is adequate to support that the cleaning of the (b) (4) is acceptable.


Building (b) (4) Sterilization of Equipment

All equipment, utensils, machine parts and closures are sterilized by (b)(4).


Building (b) (4) Sterilization of Utensils, Machine Parts and Closures

Utensils, machine parts and closures are sterilized using (b) (4)

(b) (4)

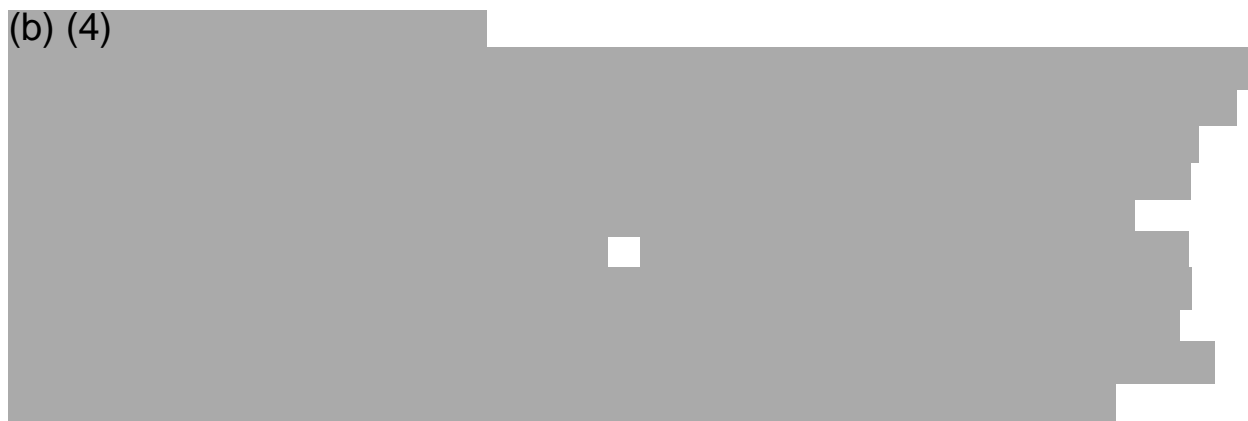
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(b) (4)


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Reviewer's Comments: All of these pieces of equipment in Building (b) (4) are already in use for other licensed products or similar to other pieces of equipment already in use for other licensed products in Building (b) (4). The submitted validations and requalifications are all acceptable.

(b) (4)


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(b) (4)





Reviewer's Comments: The (b) (4) in Building (b) (4) are already in use for other licensed products. The submitted validations are all acceptable.

(b) (4)



(b) (4)



(b) (4)

Reviewer's Comments: (b) (4) in Building (b) (4) is already in use for other licensed products. The information submitted regarding the media fill program is acceptable.

Building (b) (4) Manual Visual Inspection

Visual inspection for the Drug Product is manual and performed on (b) (4) of vials. The validation program for manual visual inspection consists of:

- Qualification of equipment: light source and inspection background (b) (4)
- Certification of operations inspection personnel: ophthalmic vision test, training before certification using a defect set, certification using the test set and feedback training
- Certification of Quality Assurance inspection personnel performing AQL (Acceptance Quality Limit) sampling and visual inspection: ophthalmic vision test, training before certification using a defect set, training in random selection of samples, certification in visual inspection using the test set and feedback training

Novo Nordisk uses one common test set for all the Hemophilia products (which includes NONACOG BETA PEGOL). The test set consists of (b) (4) defective vials within (b) (4) total vials. The (b) (4) defective vials consist of (b) (4) fixed defective vials representing all defect types and (b) (4) defective vials which are randomly selected from a complete set of defective vials containing all defect types.

The feedback training is a verification of the certification and is performed after the certification. The (b) (4)

Novo Nordisk distinguishes between three defect classifications: Critical* defects (can compromise sterility and include particles), Critical defects (critical for patients but not related to sterility) and Minor defects (cosmetic defects). After the (b) (4) visual inspection of each batch is completed, (b) (4) AQL samples are (b) (4) selected and visually inspected by certified Quality Assurance personnel (performed per (b) (4)). No Critical* or Critical defects are allowed for the AQL samples. In addition, batches that are involved in a non-conformity investigation (or other batches considered in isolation) must comply with (b) (4) with a Limiting Quality (LQ) sample size of (b) (4) vials related to Critical* defects and of (b) (4) vials related to all other defect categories. Again, for both sample sizes, no Critical* or Critical defects are allowed in the sample. The following defect types, AQLs and LQs are used for lyophilized Drug Products (including NONACOG BETA PEGOL) manufactured in Building (b) (4).

(b) (4)

Reviewer's Comments: The manual visual inspection program in Building (b) (4) is already in use for other licensed products. The information submitted regarding the media fill program is acceptable.

Reviewer's Comments: The list of manufacturers for the Drug Product states that secondary labeling and packaging of the finished Drug Product is performed at the (b) (4) site (see Drug Product Manufacturers above), but this step is not listed in the manufacturing process description (see Drug Product Manufacturing Process Description above) or in the information provided regarding Building (b) (4) (see Facilities and Equipment for the NONACOG BETA PEGOL Drug Product Manufacture above). Therefore, the location where secondary labeling and packaging (kitting) is performed (and if this manufacturing step involves new procedures) was requested from Novo Nordisk in an Information Request. See Review of the Amendment of March 23, 2017 (STN 125611/0/43) below (comment #6).


Comparability Protocol

Summary and Reporting Category

Novo Nordisk A/S intends to add a (b) (4) production bioreactor to be used in (b) (4) to the current (b) (4) production bioreactor to be approved under this BLA. To document the comparability of quality between NONACOG BETA PEGOL produced from the (b) (4) scale and NONACOG BETA PEGOL produced from the (b) (4) scale, this CP is established. Novo Nordisk proposes to submit the comparability data from this CP in a CBE-30 (with the stability results from the long-term stability program provided in annual reports).

Description of the Change



(b) (4)



Novo Nordisk states that when they designed the process in the commercial facility for the (b) (4) steps of the NONACOG BETA PEGOL manufacturing process, the (b) (4) were (b) (4) to a capacity suitable for commercial production in (b) (4). Therefore, there are no changes to the operating ranges for the (b) (4) steps for the (b) (4) scale compared to the (b) (4) scale. However, if necessary, extension of holding times will be documented.

Comparability Study

The comparability study will include the manufacture of (b) (4)



(b) (4)

***Reviewer's Comments:** The submitted CP appears to be adequate and acceptable for implementation of (b) (4) bioreactor train in terms of supporting comparability. Submission of the comparability data from this CP in a CBE-30 (with the stability results from the long-term stability program provided in annual reports) is also acceptable.*

***Reviewer's Comments:** The CP does not mention that cleaning and sterilization of the (b) (4) bioreactor will be validated. Novo Nordisk was therefore advised to submit the study reports for these validations with the data in an Information Request. See Review of the Amendment of March 23, 2016 (STN 125611/0/43) below (comment #7).*

Review of the Amendment of June 21, 2016 (STN 125611/0/3)

Based upon review of the original submission for this BLA, an Information Request containing four comments was emailed to Novo Nordisk on June 7, 2016 to request additional information regarding the need to conduct pre-license inspections of the Novo Nordisk manufacturing facilities, and a response to this Information Request was received in an amendment on June 21, 2016 (STN 125611/0/3). Novo Nordisk's responses to the comments in this Information Request are reviewed below. The comments from the Information Request are in **bold text**, Novo Nordisk's responses are in normal text, and reviewer's comments are in *italicized text*.

1. Are any of the processes and equipment with regards to STN 125611.0 new or novel to your facility?

Novo Nordisk provided the status of processes and equipment for NONACOG BETA PEGOL production facilities, including whether they are new or novel, as shown in the

following table.

(b) (4)

***Reviewer's Comments:** The response is acceptable and supports the potential to waive inspection of these manufacturing facilities.*

- 2. Are licensed US products currently manufactured in/on any rooms/areas, equipment or manufacturing lines in this submission?**

Novo Nordisk states that no other licensed US products are manufactured in Building (b) (4) where the (b) (4) steps for NONACOG BETA PEGOL are performed. Building (b) (4), where the Purification and PEGylation steps for NONACOG BETA PEGOL are performed, is a shared facility which also manufactures (b) (4). The NONACOG BETA PEGOL Drug Product facility in (b) (4) (Building (b) (4)) is also a shared facility for the formulation, filling in primary packaging, lyophilization, and inspection of (b) (4).

Novo Nordisk states that dedicated equipment is used where equipment has direct product contact with NONACOG BETA PEGOL.


***Reviewer's Comments:** The response is acceptable and supports the potential to waive inspection of these manufacturing facilities.*

- 3. In a tabular format, please indicate the site, building, rooms or areas, and process steps which are shared amongst licensed US products (please indicate the licensed US product(s)). Please cross-correlate the steps to your process flow in the submission.**

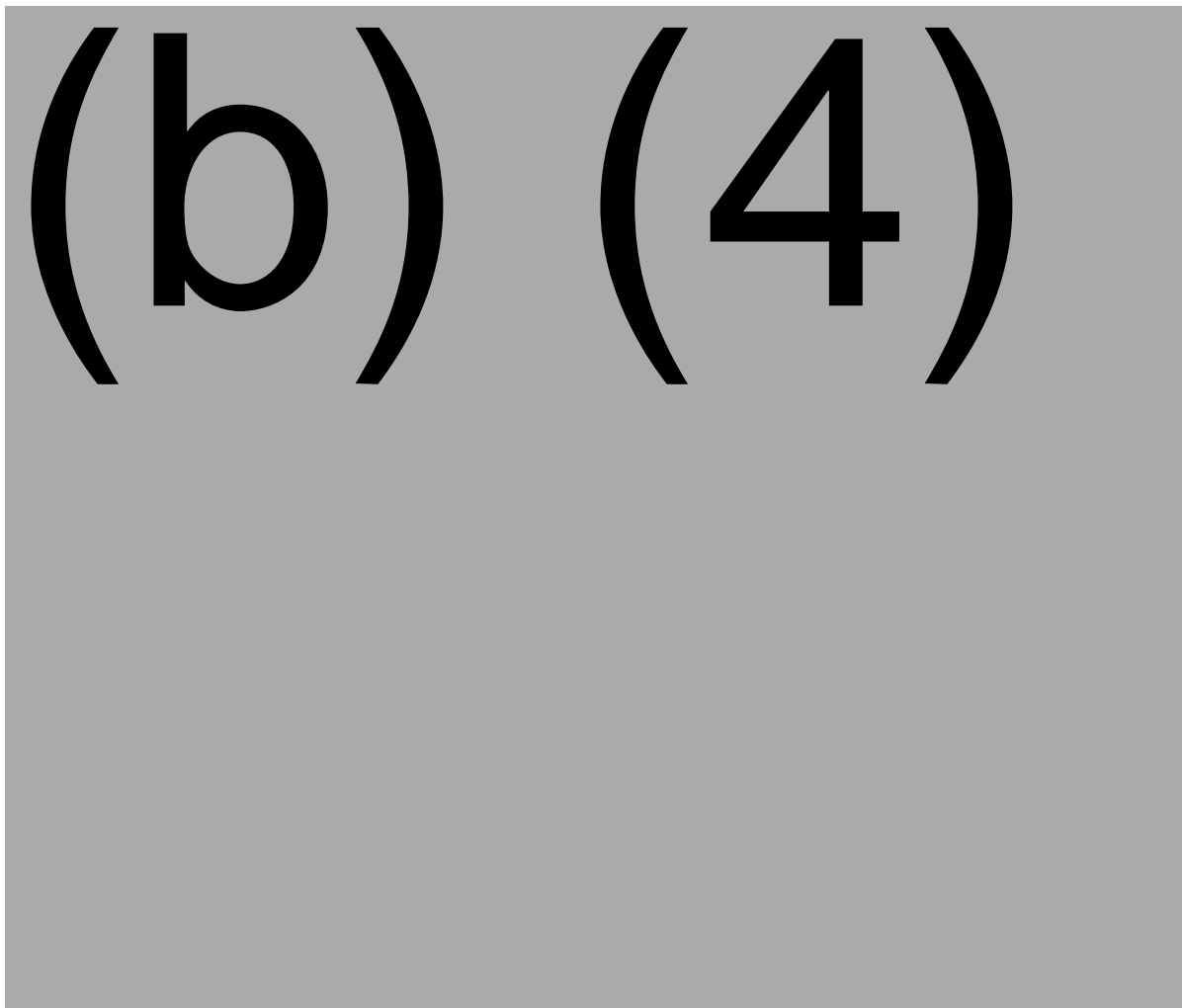
Novo Nordisk provides the following information about the NONACOG BETA PEGOL manufacturing facilities.

(b) (4)

(b) (4)



(b) (4)



***Reviewer's Comments:** The response is acceptable and supports the potential to waive inspection of these manufacturing facilities.*

- 4. Are any of your bioreactors in these areas used for either mammalian and bacterial cell lines? If this is the case, please indicate within the submission justification for this use with regards to risk mitigation.**

Novo Nordisk states that NONACOG BETA PEGOL is produced in CHO cells (mammalian cells) and the production equipment in Building (b) (4) for the (b) (4) steps is dedicated for production of the rFIX (b) (4).

***Reviewer's Comments:** The response is acceptable and supports the potential to waive inspection of these manufacturing facilities.*

Review of the Amendment of December 7, 2016 (STN 125611/0/21)

Based upon review of the original submission and of the amendment of June 21, 2016 (STN 125611/0/3) for this BLA, an Information Request containing ten comments was emailed to Novo Nordisk on November 23, 2016, and a response to this Information Request was received in an amendment on December 7, 2016 (STN 125611/0/21). Novo Nordisk's responses to the comments in this Information Request are reviewed below. The comments from the Information Request are in **bold text**, Novo Nordisk's responses are in normal text, and reviewer's comments are in *italicized text*.

- 1. The information provided in the BLA regarding your column lifetimes studies for performance indicator parameters is not sufficient for us to understand how these studies are being conducted as you have not provided clear criteria that will be used to determine how the acceptability of re-use of the resins will be determined. Please provide the acceptance criteria and current results for the column lifetime studies for the columns used for the NONACOG BETA PEGOL (b) (4)**

Novo Nordisk performed (b)(4) column lifetime studies for the manufacture of the NONACOG BETA PEGOL (b) (4). One study covering the column/resin (b)(4)

A description of these studies is provided below.

Novo Nordisk notes that the limits used for these studies are aligned for all column lifetime study parameters, which are also part of in-process controls used in routine production, additional sampling and specification testing. They further note that regarding (b) (4), the acceptance criterion is that the (b) (4)

(b) (4) Lifetime Study of Manufacturing Step

This interim report describes the results of the lifetime study of the columns used for the (b) (4) in the NONACOG BETA PEGOL manufacturing process performed in Building (b) (4). The lifetime for these columns is currently set to (b) (4)

based on virus clearance studies. The following acceptance criteria were used for this study:

(b) (4)

The results for the following (b)(4) columns are provided in the report:

(b) (4)

All of the results for these runs for (b) (4) were within the specifications described in the above table with no significant trends. There were no deviations reported.

Reviewer's Comments: The (b) (4) limit of (b) (4) for the (b)(4) columns appears to be high, though the data submitted in the study report supports that this limit is in-line with the results obtained (the maximum (b) (4) results was (b) (4)). In addition, with this level of (b) (4) in the resins before use, it is not clear how Novo Nordisk will ensure that objectionable organisms (and their byproducts) will not be introduced into the Drug Product. An explanation was therefore requested from Novo Nordisk in an Information Request. See Review of the Amendment of March 23, 2017 (STN 125611/0/43) below (comment #8).

Resin Lifetime Study for Manufacturing Steps (b) (4)

This interim report describes the results of the lifetime study of the columns (b)(4)

(b) (4)

The resins used for this study were either new or have

previously been used only for this same manufacturing process and for the same
(b) (4) step. The following acceptance criteria were used for this study:

(b) (4)

The results and proposed lifetimes for the following column resins are provided in the report:

(b) (4)

All of the results for these runs for the parameters listed in the above table were within the specifications described in the above table with no significant trends (except for some yield results which were not related to the resin performance; see deviations below).

There were five deviations during the lifetime study: (b) (4)

. All were
assessed to have no impact on the acceptability of the study.

***Reviewer's Comments:** The response is acceptable. All of the column/resin lifetime studies appear to appropriate with the currently available data supporting the proposed lifetimes for the columns/resins. The reported deviations do not appear to impact the acceptability of the second study or the proposed re-use of these resins.*

2. **Please clarify and describe if a study was performed to support that the NONACOG BETA PEGOL (b) (4) remains at temperature during shipping from your production facility in (b) (4) to the purification site in (b) (4), or provide a rationale for why such a study is not necessary.**

Novo Nordisk states that a validation study was performed which consisted of (b) (4)

(b) (4)

Reviewer's Comments: *The response is acceptable as the described shipping study appears to be adequate and to have been performed under reasonable worst-case conditions* (b) (4)

3. Please clarify and describe if a study was performed to support that the NONACOG BETA PEGOL (b) (4) remains at temperature during shipping from the (b) (4) production facility to the Drug Product production facility in (b) (4), or provide a rationale for why such a study is not necessary.

Novo Nordisk states that a validation study was performed which included (b) (4)

(b) (4)

Reviewer's Comments: *The response is acceptable as the described shipping study appears to be adequate and to have been performed under reasonable worst-case conditions* (b) (4)

4. Please clarify and describe if the container closure system used for the Histidine Solution co-packaged with NONACOG BETA PEGOL is (b) (4) to the one co-packaged with NOVOEIGHT or provide a description of (b) (4).

Novo Nordisk states that the container closure system with product contact used for the Histidine Solution co-packaged with NONACOG BETA PEGOL is (b) (4) to the container closure system used for the NaCl Solution co-packaged with NOVOEIGHT. The (b) (4)

(b) (4)

Reviewer's Comments: *The response is acceptable and* (b)(4)

(b) (4)

5. Please clarify if the microbiological and chemical quality control testing stated to be performed at the (b) (4) facilities in (b) (4) and (b) (4) is release testing for the Histidine Solution in the final container or in-process testing.

Novo Nordisk clarifies that chemical and microbiological release testing as well as

microbiological in-process testing is performed at both of the above mentioned (b) (4) facilities.

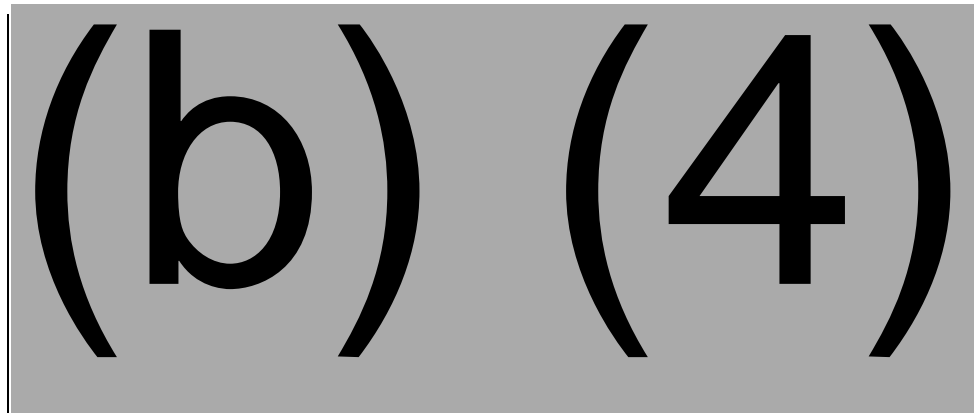
Reviewer's Comments: *The response is acceptable and confirms that these two facilities will need to be included in the inspection waiver memo for the (b) (4) sites.*

6. Please provide the following information regarding the complete NONACOG BETA PEGOL combination product including the vialled drug product, diluent in a prefilled syringe and vial adaptor:

a. The design history file

Novo Nordisk clarifies that the Design History File is a compilation of documents that describe the design history of a finished product [as described in 21 CFR 820.30 (j)]. Since the design history file references the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of 21 CFR 820.30 (j), demonstration of how the process was applied for NONACOG BETA PEGOL is relevant to this BLA. Therefore, Novo Nordisk has provided an Overview of Design History File for NONACOG BETA PEGOL, which contains a comprehensive description of the design history, in the amendment. This summary includes the following information:

- A description of the NONACOG BETA PEGOL (b) (4) including a comparison with the (b) (4) used for NOVOSEVEN RT and NOVOEIGHT
- The Design Plan organized around decision points and milestones, and including specification of design requirements, design verification, design validation readiness, submission of this BLA, launch readiness pending approval, and launch completion after approval
- The Design Inputs/Functional Design Requirements including the items shown in the following table as reported by Novo Nordisk:



(b) (4)

***Reviewer's Comments:** The summary of the design history file appears to be appropriate and comprehensive, and to take into account any potential issues related to the uses of the (b) (4) for NONACOG BETA PEGOL.*

b. The summative usability test for (b) (4) (document UT84)

Novo Nordisk notes that the summative usability test for (b) (4) (document UT84) was conducted in February 2012 and previously submitted and reviewed under in the (b) (4). The test report consists of three documents, the (b) (4) Usability Specification, Summative Usability Test Plan (b) (4) -UT-84-2012, and Human Factor Validation Test Conclusive Report, which were provided in the amendment (described below). Novo Nordisk further notes that in previous email correspondence from FDA on usability testing for the NONACOG BETA PEGOL (b) (4) there was agreement that a differentiation test would be the only required additional summative usability testing. The results of the differentiation test (document UT164) were provided in the BLA.

(b) (4) Usability Specification

The usability specification was established via a risk management assessment process that identified potential hazards to the users when using the pre-filled syringe, caused either by faults of the product itself, or by unintended use or use error. The specification provides input to the usability test by providing a list of prioritized critical tasks to be assessed. The following hazards were identified to be assessed during the usability test:

- **Receiving (b) (4):** pharmacist or healthcare provider dispense drug kit
- **Preparing the Drug:** verifying the drug type, checking the expiry date, removal of the plastic cap on the vial, cleaning of the rubber stopper on the vial, removal of the protective paper, assembly of the vial and vial adapter, removal of the protective cap, mounting of the plunger rod on the syringe, removal of the syringe cap, and mounting of the syringe on the vial adapter
- **Mixing:** injection of the diluent into the vial, swirling of the solution,

drawing out of the mixed solution in syringe (exact amount), removal of air bubbles from the syringe, and disassembly of the syringe from the vial adapter

Additional identified hazards (storage of the drug, attaching the syringe to the infusion set, injection of the dose, and disposal of the device) were excluded from the usability test with justifications provided.

Summative Usability Test Plan and Human Factor Validation Test Report

The summative usability test consisted of a differentiation scenario (choose the (b) (4)) and a handling scenario (assemble the (b) (4) and reconstitute including a full and calculated dose).

***Reviewer's Comments:** The (b) (4) Usability Specification appears to be comprehensive and to consider the potential hazards to the use of this combination product. Assessment of the acceptability of the specifications and the risk of the hazards that were not assessed in the usability test is deferred to the assigned product reviewer. The summative usability test for (b) (4) was previously reviewed under the BLA for NOVOEIGHT which uses the same container closure as NONACOG BETA PEGOL (see the response to comment #4 above). Review of this test is also deferred to the assigned product office reviewer and was requested for information only.*

c. A summary of how you comply with the requirements for design controls under 21 CFR 820.30 (for the combination product and for each device and device component)

Novo Nordisk provided a document entitled 21 CFR Part 820 Quality System Information for Devices in the amendment that provides a summary of how Novo Nordisk complies with 21 CFR Part 820.30. Novo Nordisk further notes that the following set of SOPs is in place in the Novo Nordisk Quality Management System to handle design controls:

- Medical Device Project Manual (021503)
- Requirements Engineering for Medical Devices (145504)
- Design Reviews in Medical Device Development Projects (029116)
- Design Verification of Medical Devices (037172)
- Design Validation of Medical Devices (129525)
- Usability Tests with Medical Devices (037254)
- Design Transfer of Medical Devices (172875)
- Change Control (007532)
- Configuration Management of Device Development Documents (029100)

***Reviewer's Comments:** The response is acceptable and supports that Novo Nordisk complies with the requirements under 21 CFR 820.30. This document actually states and describes compliance with 21 CFR 820.20 Management*

Responsibility, 21 CFR 820.30 Design Controls, 21 CFR 820.50 Purchasing Controls, 21 CFR 820.100 Corrective and Preventive Actions, 21 CFR 820.170 Installation, and 21 CFR 820.200 Servicing, and therefore supports that Novo Nordisk complies with the other requirements under 21 CFR 820.

d. A summary of how you comply with the requirements for purchasing controls under 21 CFR 820.50 (for the combination product and for each device and device component)

Novo Nordisk provided a document entitled 21 CFR Part 820 Quality System Information for Devices in the amendment that provides a summary of how Novo Nordisk complies with 21 CFR Part 820.50. Novo Nordisk further notes that the following set of SOPs is in place in the Novo Nordisk Quality Management System to handle design controls:

- Selection and Approval of Direct Spend Suppliers (103259)
- Re-evaluation of Suppliers - Direct Spend (103203)
- Sourcing - Direct Spend (019443)
- Contract Manufacture (019438)

Reviewer's Comments: The response is acceptable and supports that Novo Nordisk complies with the requirements under 21 CFR 820.50.

e. A summary of how you comply with the requirements for corrective and preventative action under 21 CFR 820.100 (for the combination product and for each device and device component)

Novo Nordisk provided a document entitled 21 CFR Part 820 Quality System Information for Devices in the amendment that provides a summary of how Novo Nordisk complies with 21 CFR Part 820.100. Novo Nordisk further notes that the following set of SOPs is in place in the Novo Nordisk Quality Management System to handle design controls:

- CAPA System (181356)
- CAPA Handling (181502)

Reviewer's Comments: The response is acceptable and supports that Novo Nordisk complies with the requirements under 21 CFR 820.100.

7. Please provide the limits for the microbial environmental monitoring program in the classified manufacturing areas in Building (b) (4) used to manufacture the NONACOG BETA PEGOL Drug Substance.

Novo Nordisk notes that the EM program in Building (b) (4) includes microbial monitoring performed on air samples and on surfaces as well as personnel microbial monitoring performed on gloves used in Grade (b) (4) as described in the BLA (see above under *Building*

(b) (4) *Room Classifications*). They provided the following action limits for the microbial EM program in Building (b) (4) in the amendment.

(b) (4)

Novo Nordisk notes that the action levels used in Building (b) (4) correspond to the limits in their other facilities which produce hemostasis products (e.g., (b) (4)), and that alert levels are also implement in these facilities but are variable parameters (as they are based on historical data) that are set at (b) (4) of the action levels.

Reviewer's Comments: The response is acceptable as the limits are reasonable.

8. **Please provide a summary of how the rooms in Building (b) (4) used to manufacture the NONACOG BETA PEGOL Drug Substance are cleaned. Please also clarify if disinfectant effectiveness studies covering the materials of construction in these manufacturing areas have been performed. Please provide a brief summary of these studies if they were performed or a rationale for why they are not necessary if they were not conducted.**

Facility Cleaning Program

Novo Nordisk states that cleaning and disinfection of the rooms in Building (b) (4) used for the manufacture of NONACOG BETA PEGOL is done by trained personnel according to written procedures having stated methods and frequencies for each room/area. (b) (4) types of cleaning/disinfection are used: (b) (4)
(b) (4) of Building (b) (4) is performed as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Disinfectant Effectiveness Studies

Novo Nordisk states that the effectiveness of the disinfectants used in Building (b) (4) was demonstrated via surface challenge testing (b) (4)

***Reviewer's Comments:** The response is acceptable. The frequency of cleaning/disinfection appears to be appropriate and the effectiveness of the disinfectants used appears to have been appropriately demonstrated.*

9. Please provide a summary description of the environmental monitoring performance qualification performed to qualify the HVAC system and classified rooms in Building (b) (4) used to manufacture NONACOG BETA PEGOL.

Novo Nordisk states that the EMPQ performed to qualify the HVAC system and classified rooms in Building (b) (4) used to manufacture NONOCOG BETA PEGOL consisted of an Operational Qualification (OQ) of the HVAC system for the manufacturing area and a Performance Qualification (PQ) of classified areas. As described in a document entitled Qualification of HVAC in Classified and Controlled Areas, which was provided in the amendment, during the OQ, the HVAC system in the Grade (b) (4) Grade (b) (4) and (b) (4) areas were qualified for (b) (4)

All of the specifications for this testing were met during the OQ with no deviations reported. In addition, Novo Nordisk notes that temperature, pressure and humidity are monitored by the Facility Monitoring System in Building (b) (4), and this monitoring was qualified.

The PQ is described in documents entitled Qualification of Environmental Monitoring

(b) (4)

(b) (4) During the PQ, the classified areas were qualified for monitoring of (b) (4) in operation. Diagrams of the monitoring locations are provided in the documents and appear to identify worst-case locations. There were five deviations during the PQ which were all considered to be isolated incidents as there were no trends identified (four were action limit excursions and one was an invalid sample that was replaced by an extra sample).

Reviewer's Comments: The response is acceptable with the EMPQ having been appropriately performed.

10. Please clarify how the initial cleaning validation for the (b) (4) bioreactor used for (b) (4) in Building (b) (4) was performed so that it was under worst-case conditions compared to routine production which can include up to (b) (4) of continuous (b) (4) in this bioreactor.

Novo Nordisk states that cleaning validation for the (b) (4) bioreactor (Step (b) (4)) was performed on worst-case conditions compared to routine production for (b) (4)

Reviewer's Comments: This response is acceptable and supports that the cleaning validation for the (b) (4) bioreactor was performed under worst-case conditions.

Review of the Amendment of March 23, 2017 (STN 125611/0/43)

After additional discussion with management and based upon review of the original submission and of the amendment of December 7, 2016 (STN 125611/0/21), an Information Request containing eight comments was emailed to Novo Nordisk on March 9, 2017, and a response to this Information Request was received in an amendment on March 23, 2017 (STN 125611/0/43). Novo Nordisk's responses to the comments in this Information Request are reviewed below. The comments from the Information Request are in **bold text**, Novo Nordisk's responses are in normal text, and reviewer's comments are in *italicized text*.

1. We note that the (b) (4) bioburden results you have provided in the BLA for the PPQ and post-PPQ (b) (4) batches are in general well below your proposed limits (even after re-evaluation). Please consider implementing (b) (4) bioburden limits that are in-line with your process capabilities and/or implementing alert limits so that you can identify potentially significant increases in (b) (4)

bioburden that are below the action limit.

Novo Nordisk states that they agree to implement an alert limit of (b) (4) for (b) (4) bioburden for the (b) (4)

which will be monitored according to current Novo Nordisk procedures. The current bioburden (b) (4) limits of (b) (4) are maintained for these steps. In addition, they have (b) (4)

. The associated CMC documents have been undated to include these new and revised limits and were provided in the amendment. In addition, the alert limit for bioburden for Step (b) (4) in these documents, in accordance with the response to comment #3 in the information request of July 19, 2016, submitted on August 1, 2016 (STN 125611/0/4; not reviewed in this memo as the Information request was from another reviewer assigned to this BLA).

Reviewer's Comments: This response is acceptable.

- 2. Regarding the container closure integrity testing performed for the Histidine Solution syringes, please confirm that the positive and negative control syringes used during the testing had the expected results as this part of the testing is not described in the information provided.**

Novo Nordisk confirms that all of the results of positive and negative control syringes analyzed during CCIT of the Histidine Solution syringes met the acceptance criteria (b) (4)

Reviewer's Comments: This response is acceptable.

- 3. We note that during the (b) (4) sterilization qualification for the Histidine Solution syringes container closure integrity testing was performed after (b) (4) of sterilization to simulate "a worst-case scenario". Please clarify if you are seeking approval of a (b) (4) of terminal sterilization of Histidine Solution syringes for syringes that fail the requirements for sterilization (b) (4).**

Novo Nordisk clarifies that they are not seeking approval of a (b) (4) of terminal sterilization of Histidine Solution syringes for syringes that fail the requirements for sterilization (b) (4).

Reviewer's Comments: This response is acceptable.

- 4. We note that container closure integrity testing for the drug product was performed using (b) (4) testing. Please clarify if the drug product is (b) (4) and if so, clarify and describe if you have performed any other container closure integrity testing (such as (b) (4)) that would support that**

integrity of the container closure prevents the entry of (b) (4).

Novo Nordisk clarifies that the NONACOG BETA PEGOL Drug Product was shown during formulation development to not be (b) (4). They note that (b) (4), since NONACOG BETA PEGOL contains potential sites for (b) (4). However, (b) (4) was followed during a stability study by (b) (4), and no changes were observed for any of the formulations, showing that NONACOG BETA PEGOL is not (b) (4). Other data, such as potency, (b) (4) and total impurities were also followed during stability and supported that NONACOG BETA PEGOL Drug Product is not sensitive to (b) (4). Finally, Novo Nordisk notes that (b) (4) was excluded from the formulation from the start of the (b) (4).

***Reviewer's Comments:** This response is acceptable and supports that the NONACOG BETA PEGOL Drug Product is not sensitive to (b) (4), and therefore use of (b) (4) testing for CCIT is acceptable and appropriate.*

5. **We note that the stated limit for bioburden in the (b) (4) for equipment used in Building (b) (4). In addition, we note that the manufacturing equipment is not sterilized before use in Building (b) (4). Please provide a justification for this bioburden specification that supports that it is adequate to prevent contamination of the (b) (4).**

Novo Nordisk clarifies that the limit for bioburden in the (b) (4) in Building (b) (4). They further note that for routine cleaning monitoring, an alert limit of (b) (4) is used, depending on the equipment type.

***Reviewer's Comments:** This response is acceptable. After additional review of the information provided in the BLA, it is confirmed that the limit for bioburden in the (b) (4) in Building (b) (4). The limit of (b) (4) is actually for Building (b) (4).*

6. **We note that the list of manufacturers for the drug product that you have provided states that labeling and secondary packaging of the finished drug product is performed at the (b) (4) site, but it does not appear that this step is performed in Building (b) (4). Please clarify and describe the location where secondary labeling and packaging (kitting) is performed, if this location is currently approved to perform this manufacturing step for other US licensed products, and if this manufacturing step involves new procedures that are not currently performed for a US licensed product.**

Novo Nordisk clarifies that secondary labeling and packaging (kitting) are performed in Building (b) (4) in areas segregated from aseptic filling operations. They further note that the kitting process for NONACOG BETA PEGOL is similar to the process for NOVOSEVEN and NOVOEIGHT, and that it involves no new operations that are not

currently performed for these products.

Reviewer's Comments: This response is acceptable.

7. Regarding the submitted comparability protocol to support addition of a (b) (4) production bioreactor to be used in (b) (4) to the current (b) (4) production bioreactor to be approved under this BLA, please confirm that you will provide study reports for the validation of cleaning (and sterilization) of the (b) (4) production bioreactor in the supplement that contains the resultant data from the comparability protocol.

Novo Nordisk confirms that summary study reports covering both cleaning and sterilization validation of the (b) (4) production bioreactor will be provided as part of the supplement to support production at this scale. They submitted a revised CP that includes this information (in Section 5 Reporting) in the amendment.

Reviewer's Comments: This response is acceptable.

8. We note that in the interim report for (b) (4) provide in the amendment of December 7, 2016, the bioburden limit is stated as being "No more than (b) (4) may exceed the limit of (b) (4)". While this limit appears to be in-line with microbial control data provided (the maximum bioburden results was (b) (4) please clarify how you will ensure that objectionable organisms (and their byproducts) will not be introduced into the (b) (4) drug product) with such a high limit.

As described above in the response to comment #1, Novo Nordisk has re-evaluated the proposed (b) (4) bioburden limit for process Step (b) (4) and adjusted it from (b) (4) to reflect the manufacturing process capability. They have also implemented an alert limit of (b) (4) for this step. The associated CMC documents have been undated to include these new and revised limits and were provided in the amendment.

Reviewer's Comments: This response is acceptable.