



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

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

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

Cc: Natalya Ananyeva, Ph.D., OBRR/DH/LH, HFM-392
Leigh Pracht, RPM, OBRR/DBA/RPMB, HFM-380

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

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

Action Due: October 16, 2013

ACTION RECOMMENDED

Based on the information provided in the original BLA submission, and the three amendments submitted in response to the information requests, I recommend approval of this submission.

SUMMARY

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

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

In support of this original BLA 125466/0 review, CBER performed a Pre-License Inspection for the manufacturing of turoctocog alfa drug substance at Novo Nordisk A/S

1 page redacted (b)(4)

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

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

Reviewer's comment: In Document 5021235, Summary ----- (b)(4) -----, that requalification of the sterilization in --- (b)(4) -----, ----- (b)(4) ----- study was performed in September 2012, while the ----- (b)(4) ----- were performed earlier (July 2012). Novo Nordisk explained in amendment 125466/0/28 that all ----- (b)(4) ----- are qualified on a (b)(4) basis. They added that the tests are independent and there is no requirement to perform the tests in a specific sequence, as long as it is within the scheduled - (b)(4) - peiod.

You provided a summary report of the sterilization of the final product. Please describe the -- (b)(4) -- and the sterilization method. You stated that the ----- (b)(4) ----- showed no ----- (b)(4) -----, please provide a schematic diagram showing the ----- (b)(4) ----- and the justification why they represent coverage of the --- (b)(4) --- (and worst case -- (b)(4) --). Please also provide the ----- (b)(4) -----, and why these --- (b)(4) --- are considered representative (or worst case) --- (b)(4) ---.

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

5. Please list the number of (b)(4) that support the production of 0.9% NaCl diluent and their uses.

Novo Nordisk reported that there are (b)(4) used at (b)(4) for sterilization of equipment ((b)(4)), and terminal sterilization of 0.9 % NaCl PFS ((b)(4)).

6. You stated that equipment and primary packaging materials are sterilized using (b)(4). Please describe the (b)(4) and the sterilization method. Please provide the sterilization validation studies, including the different (b)(4) qualified.

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

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

They provided the most recent requalification study report reviewed in **Q4** above.

7. In section 3.2.A.1 Facilities and Equipment Report for Sodium Chloride manufacturing facility, you stated that Sodium Chloride is currently classified as a worst case substance for cleaning. Please provide results of studies performed to demonstrate that NaCl is the worst case soil, and provide summary reports of studies performed to validate the cleaning procedures.

NaCl is selected as worst case substance because it demonstrates the solubility properties representative for other inorganic substances, and solutions containing NaCl are very frequently produced at (b)(4). As described in **Q4** above, due to the physicochemical characteristics of 0.9 % Sodium Chloride (solubility of 358 g/L), the cleaning validation is covered by the worst case substances (b)(4).

8. *You stated that CIP/SIP is used for cleaning and sterilization of equipment. Please describe the parameters used, and provide the results of studies performed to validate the CIP/SIP process. Please list the equipment cleaned/sterilized by CIP/SIP.*

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

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

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9. *In the submission, there is a brief description of the facility water. As (b)(4) is used as an ingredient in the manufacture of the diluent, please describe your procedures for monitoring the quality of the (b)(4).*

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

10. *Please describe your procedures for packaging and shipping the 0.9% NaCl to Novo Nordisk facilities.*

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

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

Results of the study show that the container closure integrity is satisfactory for (b)(4) vials (and thus to (b)(4) and (b)(4) vials) closed with lyophilization stoppers, -----
----- (b)(4)-----
----- . Thus this container closure is suitable for the duration of the shelf life (36 months) ----- (b)(4)----- (normal production capping).

12. *During the PLI, you stated that you implemented changes to the areas used for formulation and filtration of the drug product; and that (b)(4) Batches of Turoctocog alfa for clinical trials were manufactured ----(b)(4)---- (after implementing the changes) . Please submit the qualification of the area as an amendment to BLA 125466/0.*

Novo Nordisk reported that they submitted the qualification of the DP formulation and filtration areas -----(b)(4)----- facility in Denmark as a CBE-30 to NovoSeven RT® BLA 103665 (STN 103665/5815 submitted November 30, 2012). As per FDA request they submitted the qualification of the area to this BLA (125466/0) as well as batch release data for the (b)(4) clinical batches manufactured in the renovated area. Novo Nordisk provided in the following table indicating which sections of this submission were already submitted to NovoSeven RT® BLA.

| Documents from CBE-30- NovoSeven RT® | Version included in Module 3 –turoctocog alfa |
|--|--|
| 3.2.A.1 Microbiological Monitoring of the Environment 3.2.A.1 Qualification of HVAC and room classification 3.2.A.1 Procedures and Specifications for Media Fills & Actions Concerning Product When Media Fills Fail 3.2.A.1 Equipment | Documents from Original CBE-30 submission November 30, 2012 |
| 3.2.A.1 Floor plans ---(b)(4)--- HAC | Documents updated in NovoSeven RT® BLA Annual Report (May 24, 2013) <u>Changes:</u> ----- (b)(4)----- ----- (b)(4)----- ----- (b)(4)----- ----- (b)(4)----- ---(b)(4)--- |
| 3.2.A.1 Lyophilised parenterals and diluents for reconstitution --- (b)(4)--- Filling HAC | <u>Changes:</u> ----- (b)(4)----- ----- (b)(4)----- |
| 3.2.A.1 Media fill qualification of ----- ----- (b)(4)----- ----- | ----- (b)(4)----- ----- (b)(4)----- |
| 3.2.A.1 Qualification of environmental | ----- (b)(4)----- |

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|---|---|
| Documents from CBE-30- NovoSeven RT® monitoring | Version included in Module 3 –turoctocog alfa Updated documents with minor corrections |
|---|---|

The data submitted in association with STN 103665/5815 (CBE submission and response to information request) were reviewed by CBER and it was concluded that the qualification of the area and the environmental monitoring program are acceptable.

The Batch analysis of the (b)(4) clinical batches (2000IU) listed below was provided and all results met the acceptance criteria.

| DP batch | DS used | Batch scale | Date of Manufacture | Batch size |
|--------------|--------------|------------------|---------------------|------------|
| ---(b)(4)--- | ---(b)(4)--- | Production scale | ---(b)(4)--- | (b)(4) |
| ---(b)(4)--- | ---(b)(4)--- | Production scale | ---(b)(4)--- | (b)(4) |

I summarize below the data presented for the moisture content, particulate matter, sterility and endotoxin and visual inspection (appearance):

| Test | Method | Release Specification | Batch Number | |
|---|-------------------------|---|-------------------------|------------------------|
| | | | --(b)(4)--- (2000IU) | --(b)(4)-- (2000IU) |
| Appearance of powder | Visual Inspection | white or slightly yellow powder or friable mass | Complies | Complies |
| Reconstitution time / Solubility | Visual Inspection | ------(b)(4)----- | Complies | Complies |
| Moisture content | (b)(4) | (b)(4) | (b)(4) | (b)(4) |
| Appearance of solution / clarity | Visual inspection | clear or slightly opalescent solution | Complies | Complies |
| Particulate matter | ------(b)(4)-- ----- | ----- -----(b)(4)----- ----- | (b)(4) | (b)(4) |
| | | ----- -----(b)(4)----- ----- | (b)(4) | (b)(4) |
| Endotoxin | ------(b)(4)-- ----- | -----(b)(4)--- | (b)(4) (b)(4) | (b)(4) (b)(4) |
| Sterility | Membrane filtration | No growth | Complies | Complies |
| * During the Late Cycle meeting (11-Jul-2013), Novo Nordisk agreed to tighten the Endotoxin acceptance limits to ---(b)(4)--- | | | | |

13. Please provide the EMPQ for the Grade (b)(4) areas in the (b)(4) facility, and include the frequency and acceptance criteria (alert and action limits) for routine monitoring.

Novo Nordisk provided in amendment 125466/0/22 the qualification of the Grade (b)(4) areas:

- a. Qualification of environmental monitoring Seeding laboratory (1.3.14) and person/material airlock (1.3.13)
- b. Qualification of environmental monitoring Post-viral purification room (S.3.07), person/material airlock (S.3.04.1), corridor (S.3.08) and bulk filling (S.3.09)

Qualification of environmental monitoring Seeding laboratory (1.3.14) and person/material airlock (1.3.13)

An environmental monitoring requalification was performed to demonstrate that the EM program has proper sampling of the areas to ensure appropriate room classification:

- person / material airlock (1.3.13), -----(b)(4)-----
- seeding laboratory (1.3.14), ----(b)(4)-----
- seeding laboratory (b)(4) (1.3.14), ---(b)(4)---

The EMPQ was carried out from February 02-25, 2013, and additional testing for viable airborne microorganisms from March 22 to May 05, 2013.

Novo Nordisk provided the diagrams with EM sampling locations during the qualification and routine monitoring: viable surface monitoring (b)(4), viable active air monitoring (b)(4), non-viable particles (----- (b)(4) -----). During the qualification, the sampling frequency and the number of sampling points were increased compared to routine monitoring as shown in the following Tables:

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

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

6 pages redacted (b)(4)

INFORMATION REQUEST SUBMITTED 2-JUNE-2013

Manufacturing Turoctocog alfa drug product at the ---(b)(4)--- Facility in Denmark

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

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

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

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The ------(b)(4)----- appears to be properly distributed -----(b)(4)-----
-----.

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

15. You stated that the sterilization (b)(4) are defined in the SOPs and validated. Please
describe the sterilization (b)(4), and justify the ------(b)(4)----- in each
validation (b)(4).

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

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

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

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

----- (b)(4) -----
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The ----- (b)(4) ----- appears to be properly distributed ----- (b)(4) -----.

16. *You reported in the BLA the sterilizing filters are sterilized ----- (b)(4) -----, please describe the ----- (b)(4) ----- used for the sterilization of the filters.*

----- (b)(4) -----
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17. *The initial validation studies for the closures included separate validations for the stoppers and the caps. Please describe the validated (b)(4), and provide additional information to demonstrate that the validations are applicable to the stoppers and caps of turoctocog alfa drug product. Please justify the ----- (b)(4) ----- in each validation (b)(4).*

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

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

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The justification for the worst case stopper and cap is acceptable.

18. *For the re-validation studies of the closure ----- (b)(4) -----, you stated maximum and minimum -(b)(4-) for closures – however you did not specify whether it was stopper or cap (b)(4). Please explain.*

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

Novo Nordisk reported that EM is performed during the media fills similar to normal production and includes: viable surface and air monitoring, personnel monitoring and non-viable particle monitoring. The results of EM performed during the filling of Batch BR40222 met the acceptance criteria and are described in the qualification of the formulation and filtration area (response to comment 13).

22. *You state in the Process Performance Qualification Summary for Drug Product report (3.2.P.3.5 Process Validation for turoctocog alfa) that “the aseptic process is qualified by media fill, see 3.2.R Procedure and Specifications for Media fills”; however, this section is not included in the submission. Please provide the information.*

Novo Nordisk stated that the reference to 3.2.R Procedure and Specification for Media fills is an error, as the information is included in eCTD 3.2.A.1.

Sterile Filtration

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

Filter validation was performed for the 250 IU and 3000 IU product by -----
--(b)(4)-----, Novo Nordisk provided the parameters for sterile filtration of turoctocog alfa, and the validation was performed under worst conditions for the critical parameters: maximum filter contact time (b)(4) and maximum pressure (b)(4).

In both filter validation studies for the two strengths a pressure of (b)(4) was achieved. A product contact time with the filter of -----(b)(4)----- has been tested in the 250 IU and 3000 IU studies respectively. The flow rate and filtration time are measured but not controlled as they are regarded as non critical; and thus variation in these two parameters is acceptable as long as the critical parameters such as the pressure and contact time are achieved.

Container Closure for turoctocog alfa

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

Novo Nordisk provided the formulation characteristics for the lyophilization 13mm (b)(4)- grey stopper made of chlorobutyl and no natural rubber latex. They added that the lyophilization Stoppers are endotoxin free which has been validated by the vendor, and they are supplied ready to sterilize.

They added that they verified the endotoxin level of the first three batches of stoppers at Novo Nordisk A/S, and that the endotoxin level is tested on a (b)(4) basis in accordance with the quality specification for the Lyophilization Stopper, 13mm, Grey. The acceptance criterion is maximum -----(b)(4)-----.

Reviewer's comment: Novo Nordisk clarified in amendment 125466/0/28 that their statement that the lyophilization stopper is received endotoxin free is erroneous. The vendor tests the endotoxin level on all batches as part of the release control with an acceptance criterion of is (b)(4) endotoxin unit/rubber stopper.

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

Novo Nordisk explained that the effectiveness of the rinsing process is verified by

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

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

Lyophilization process

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

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

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

27. *In the Justification validation report you stated that during qualification you have placed --(b)(4)-- on every shelf, yet during the justification validation, the sensors were placed in the -----(b)(4)----- . Please explain the rationale for using the ----- --(b)(4)----- only, and why do you consider these points representative of the whole lyophilizer.*

Reviewer’s comment: Novo Nordisk provided in amendment 125466/0/28 additional information and data to demonstrate that all products lyophilized on all (b)(4) shelves met the acceptance criteria. This is reviewed in Q35 below.

28. *In the Justification process validation studies you reported that the lyophilization process was validated for the lowest, middle and highest concentration to cover the range (shelves ---(b)(4)--). Yet you loaded shelves -----(b)(4)----- . So you did not provide data to support that the products lyophilized on those shelves meet the acceptance criteria. Please provide explanation/data to demonstrate that all products lyophilized on all shelves met the acceptance criteria.*

Novo Nordisk explained that shelf position in the lyophilizer may -----(b)(4)--- ----- and provided justification for placing turoctocog alfa products on shelves -(b)(4)-. The (b)(4) shelf (shelf (b)(4)) is regarded as --(b)(4)-- as the vials are -----(b)(4)----- . The vials also ---

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

Novo Nordisk stated that batch BR40215 (2000 IU), (b)(4) was formulated from (b)(4) drug substance batches (------(b)(4)-----) and filled into (b)(4) vials on 25-Jun-2012 used for clinical trials. The reports provide summary data for ---(b)(4)--- drug substance, formulation, sterile filtration and filling (including in-process control parameters and results), chemical stability of the formulated product (prior to lyophilization), the lyophilization parameters and the data obtained from analysis of samples collected, as well as capping and visual inspection. All results met the acceptance criteria. I reviewed the summary results for appearance, solubility, water content, particulate matter, sterility and endotoxin (presented in the Table below). Other results pertaining to (b)(4), identification, content------(b)(4)-----, purity and potency are reviewed and documented in the product review addendum memo.

| Test | Method | Release Specification | Batch number BR40215 (2000IU) |
|----------------------------------|-----------------------|--|--|
| Appearance of powder | Visual Inspection | white or slightly yellow powder or friable mass | Complies |
| Reconstitution time / solubility | | dissolves within -----(b)(4)--- ----- | Complies |
| Appearance of solution / clarity | Visual Inspection | clear or slightly opalescent solution | Complies |
| Moisture content | (b)(4) | (b)(4) | (b)(4) |
| Particulate matter | ---(b)(4)--- | ------(b)(4)----- (b)(4) ------(b)(4)----- | ------(b)(4)----- ------(b)(4)----- |
| Endotoxin | ---(b)(4)--- ----- | ------(b)(4)----- | ------(b)(4)----- |
| Sterility | ---(b)(4)--- | ---(b)(4)--- | Complies |
| | | | ------(b)(4)----- |

Novo Nordisk provided the results for the visual inspection and reported that 202 vials were rejected as summarized in Table 22 of the report as reproduced below:

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

Novo Nordisk reported that the 190 vials in the “other” category, have been investigated and the vials are found to be a non-critical error related to the lyophilization cake.

Reviewer’s comment: Novo Nordisk provided in amendment 125466/0/28 clarification for not categorizing the 190 “other errors” as Lyo-cake non-critical errors. This is reviewed in Q37 below.

Novo Nordisk reported that the manufacturing of the verification batch was executed according to their standard procedures and within the limits of all the process controls and critical process control parameters, and no deviations were reported; thus confirming (b)(4) can produce turoctocog alfa drug product of the required quality with respect to drug product specification parameters and batch uniformity.

Placement of scale on the Prefilled Syringe at ----(b)(4)--- facility in Denmark

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

In addition to validating the accurate placement of the scale, Novo Nordisk reported that they validated the durability of the scale placement by performing an aging study on -----(b)(4)-----.

After storage, the position of the labels on the syringes were measured (using a -----(b)(4)-----).

All results were within the specification limit (label movement (b)(4)) and below the measurement uncertainty of approximately (b)(4).

The validation studies provided demonstrate that the scale label is durable, and the process of the placement is well controlled.

INFORMATION REQUEST SUBMITTED 5-AUGUST-2013

35. *In your responses to comments 14, 15 and 16 of information request dated June 18, 2013 (which corresponds to comments 28, 29 & 30 in this memo), you did not provide data to demonstrate that all products lyophilized on all (b)(4) shelves met the acceptance criteria. You stated that in the initial qualification (temperature mapping) you monitored the temperature in a -----(b)(4)----- . In addition, you stated that in the -(b)(4)- certification studies, you sample every shelf (----(b)(4)----) of the loaded chamber. Please provide summary of the data to demonstrate that all products lyophilized on all shelves meet the acceptance criteria for -----(b)(4)-----.*

Novo Nordisk explained that the qualification/validation of the lyophilization process of turoctocog alfa consists of qualification of the temperature distribution in the empty chamber mapping (performed ---(b)(4)---), process justification of product quality during lyophilization process at time, temperature and pressure limits (validation), and verification studies with samples from all shelves of the lyophilizer, to demonstrate that results from samples on all shelves are comparable. They clarified that verification studies are performed -----(b)(4)-----.

The justification studies are based on ---(b)(4)--- and include -----(b)(4)----- and is reviewed in the primary memo and also in the responses to comments 28, 29 and 30.

In the verification studies, Novo Nordisk collected samples from -----(b)(4)----- of each of the (b)(4) shelves of -----(b)(4)----- samples from each position were collected for lyophilization batch uniformity parameters (moisture content, content, appearance and solubility), and (b)(4) samples from each position were collected for testing product specific parameters and stability parameters (purity, -----(b)(4)-----, antioxidant and potency). They provided a summary of the samples tests results in Tables 1- 8 of amendment 125466/0/28.

All the test results from the samples collected met the acceptance release criteria, and there was very little variation between the results of the samples located in different positions on the different shelves. There was a little variation between the samples collected from -----(b)(4)----- with regard to (b)(4); however, results of samples collected from -----(b)(4)----- were below the acceptance release limits of (b)(4).

36. Please justify the specification of (b)(4)/ lyophilization stopper for turoctocog alfa drug product considering the vendor states it is endotoxin free.

Novo Nordisk clarified that the stoppers are not endotoxin free, and the statement to that effect was an error.

37. In your response to comment 19 of Information Request dated June 18, 2013 (correspond to comment 33 in this memo) you stated that the 190 “other errors” were Lyo-cake non-critical errors, so why were they labeled as “other errors” and not included in the “Lyo-cake non-critical” errors. Please explain.

Novo Nordisk explained that they implemented a revised inspection setup of drug product in November 2011. In the revised setup (b)(4) main categories were defined with corresponding defect categories and defect types (presented in Table 14 of amendment 125466/0/24) . In case a defect is observed which is not described as a defect type, the vials are categorized as “Other error” and handled as non-conformity.

They added that during the production of verification batch in (b)(4) (June 2012), a -----(b)(4)----- was observed, which is not described in the (b)(4)-defect-types. Thus the 190 -----(b)(4)----- were considered as “other error” and not non-critical lyo-cake defect. As the other error is considered non-conformity, and an evaluation was performed and -----(b)(4)----- was evaluated as non-critical as it does not have influence on the quality of the product. They added that as of October 2012, the standard procedure for visual inspection was updated with the defect type -----(b)(4)----- in the defect category “non-critical lyophilization defect”.

38. You reported in Document 5021235, Summary -----(b)(4)-----, that requalification of the sterilization in -----(b)(4)----- included -----(b)(4)-----, and -----(b)(4)-----, and -----(b)(4)----- . In the report the -----(b)(4)----- study was performed in September, 2012, while the -----(b)(4)----- ----- were performed earlier (July 2012). Please justify the time line.

Novo Nordisk explained that all -----(b)(4)----- are qualified on a (b)(4) basis. They added that the tests are independent and there is no requirement to perform the tests in a specific sequence. The ----(b)(4)---- study, the ----(b)(4)---- and -----(b)(4)----- ----- were performed within the required ----(b)(4)---- time period.