



## 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 BL 125398/0

**From:** Destry Sullivan, Team Leader, OCBQ, DMPQ, MRB II, HFM-676

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

**Subject:** **Review Memo (BLA):** Novo Nordisk, NovoThirteen Coagulation Factor XIII A Subunit (Recombinant), Original Biologics License Application (BLA)- **Review of the October 25, 2013 response to CR questions issued December 23, 2011**

**Action Due: December 25, 2013**

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### ACTION RECOMMENDED

Approval

### SUMMARY

Novo Nordisk A/S, hereafter Novo Nordisk, has submitted this Biological License Application (BLA) under BL 125398/0 for NovoThirteen Coagulation Factor XIII A Subunit (Recombinant), rFXIII 2500 IU (rFXII).

This BLA was received by CBER on February 23, 2011, and was submitted electronically in common technical document (eCTD) format. The BLA consists of Modules 1 through 5 of the eCTD. Module 1 contains administrative information and background covering previous meetings, environmental assessment, risk management plan, labeling, and a cover letter. Module 3 covers all manufacturing information for this product.

NovoThirteen is a yeast-derived intracellular recombinant protein encoding Coagulation Factor XIII A Subunit, which was cultivated, harvested, and purified before formulated and filled into final container product in their multi-product facilities in Bagsvaerd (b) (4), (b) (4)

Novo Nordisk's building (b) (4) in Bagsvaerd is utilized for propagation, fermentation and recovery of the rFXIII substance. The collected (b) (4)  
(b) (4)

Novo Nordisk's building (b) (4) is utilized to purify the rFXIII substance, package and shipped to building (b) (4) for formulation, filling, lyophilization, visual inspection and packaging in currently-licensed manufacturing areas located in (b) (4)

Novo Nordisk was issued a CR letter on December 23, 2011 for the original submission. They were again issued a CR letter on June 27, 2013 regarding lack of a validated visual inspection program/procedure for rFXIII. This review covers Novo Nordisk's October 25, 2013 response to review aspects found in the CR letter question (see below).

**CR Letter Question:**

1. You have not demonstrated that you have an acceptable, validated 100% Visual Inspection Program for rFXIII. Please provide the following:
  - a. The 100% visual inspection validation protocol, and study final results, using your updated visual inspection test defect kit. Please include validation of AQL/LQ testing as well.
  - b. Acceptance limits for each of the defect categories (critical, major, and minor sub groupings, as appropriate for your product).

**REVIEW:**

Novo Nordisk states that their visual inspection program for rFXIII is manual. The validation program consists of the following elements:

- Qualification of equipment:
  - For manual inspection: (b) (4)
- Certification of production inspection personnel performing the 100% visual inspection:
  - (b) (4)
- Certification of QA inspection personnel performing AQL/LQ sampling and visual inspection:
  - (b) (4)

Novo Nordisk has implemented a new enhanced test set for visual inspection and a new validation has been performed in order to demonstrate that Novo Nordisk has a validated 100% visual inspection program for manual inspection. Novo Nordisk uses one common test set for the three products Novothirteen, NovoSeven® and Novoeight®, as the majority of the defect types are identical for all three products. Qualification of the program included the following:

- (b) (4)

Novo Nordisk states that the certification test was performed on personnel involved in visual inspection of rFXIII using the updated test set to demonstrate that Novo Nordisk has a validated 100% visual inspection program for manual inspection. The result of the certification is summarized below:

- (b) (4)

- (b) (4)

Novo Nordisk has implemented a novel defect classification description:

- (b) (4)

(b) (4)

The severity rating for both critical\* and critical defects are identical, but as rFXIII is a product for intravenous use, sterility compromising defects and particles have been assigned a lower AQL value. Novo Nordisk's classification system, while unusual with respect to terminology, appears appropriate. Table 1 of their response illustrates defect types.

#### **AQL Sampling plans for lot-by-lot inspection**

After the 100% visual inspection of each batch is completed, AQL samples are randomly selected and visually inspected by QA certified personnel. The AQL values for the different defect categories are shown in Table 1. Novo Nordisk states that the AQL sampling is performed so the consumer's risk quality (CRQ) is at least as good or better than recommended in ISO standard 2859-1 (*Sampling procedures for inspection by attributes – Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection*) under tightened inspection and general inspection level II. The Novo Nordisk AQL sample size is (b) (4) vials with no critical\* or critical defects allowed. The Operating Characteristic (OC) curve for the sampling plan of size (b) (4) with acceptance number 0 is shown in Figure 1 of the submission. It is visible from the OC curve that if the defect rate for instance is (b) (4) then there is only (b) (4) probability of finding 0 defects in a sample consisting of (b) (4) items.

#### **LQ Sampling plans for isolated batches**

Novo Nordisk states that batches considered in isolation, i.e. batches that for instance are involved in a non-conformity, must comply with ISO 2859-2 (*Sampling procedures for inspection by attributes – Part 2: Sampling plans indexed by limiting quality (LQ) for isolated lot inspection*). The ISO 2859-2 sampling plans are indexed by LQ (Limiting Quality). In other standards the LQ may be also denoted as LTPD (Lot Tolerance Percent Defective). Therefore for each defect category an LQ (LTPD) value is also assigned (see Table 1). The lowest LQ value in ISO 2859-2 is 0.5%, however, Novo Nordisk has assigned LQ values as low as (b) (4) and (b) (4). The LQ sample size related to a critical\* defect is (b) (4) for all other defect categories the LQ sample size is (b) (4). For both sample sizes no critical\* or critical defects are allowed in the sample. The OC curve for the sampling plan of size (b) (4) with an acceptance number of 0 is shown in Figure 2. It is visible from the OC curve that if

the defect rate for instance is (b) (4) then there is only (b) (4) probability of finding 0 defects in a sample consisting of (b) (4) items.

**Qualification:**

Novo Nordisk has implemented a new enhanced test set for visual inspection. The new test set has (b) (4) defective vials and the total number of vials is (b) (4). 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 (b) (4) fixed + (b) (4) random defective vials will be varied for each inspection personal prior to each certification or (b) (4) re-certification. The test set description may be found on page 10 of 15 of the protocol (Attachment 1 for the submission). This test set is more than adequate for a visual inspection program, particularly for a lyophilized product.

Results of the qualification are as follows:

Two of the production inspection personnel failed their 1st attempt (see Table 2 of the final report). One of the production inspection personnel ((b) (6)) found all defects, but did not categorize all the critical defects in the correct defect category according to Table 4 in Appendix A. Although (b) (6) had two attempts in accordance with the acceptance criteria, the process was assessed and evaluated. It was evaluated that no further actions were needed before the 2nd attempt. (b) (6) passed in the 2nd attempt. The other production inspection personnel ((b) (6)) missed one critical\* defect. (b) (6) overlooked a glass particle in the size of 5.0 mm in diameter inside the vial in the 1st attempt. Although (b) (6) had two attempts in accordance with the acceptance criteria, the process was assessed and evaluated. It was decided to further document that (b) (6) is consistently capable of detecting all critical defects, as (b) (6) had to pass two consecutive tests. (b) (6) passed the two consecutive tests successfully. All other inspectors, including QA personnel required to be able to perform the testing, passed within the acceptance criteria.

**Conclusions:**

With respect to visual inspection validation, there is some concern about missing any critical defect, the defect in fact missed was a critical\* defect, which could compromise integrity of the vial or patient safety. However, the inspector passed a second examination, and this could potentially be considered an isolated event. Of greater importance is that Novo Nordisk omitted providing the results of at least one AQL validation trial/run. However, Novo Nordisk has been performing this type of inspection for some time, (b) (5), (b) (7)(E)

For this reason, it is unnecessary to issue any inspectional follow up for visual inspection issues at this time. The Visual Inspection program for rFXIII is adequate.