

# Final Memo on In-support testing - Novoeight

**To:** File: STN 125466  
**From:** Lokesh Bhattacharyya, Ph.D., Lab Chief, LACBRP, DBSQC, HFM-682  
**Subject:** Final Memo on In-support testing – Determination of Content and (b)(4)-  
by (b)(4)-- for Licensing Action  
**Thru:** William McCormick, Ph.D., Director, DBSQC, HFM-680  
**Product/Sponsor:** Antihemophilic Factor (Recombinant), [turoctocob alfa,  
NovoEight®] from Novo Nordisk  
**Recommendation:** The (b)(4) procedure described in SOP # M042, version 2.0 is  
approvable.

## Summary and Conclusions

The (b)(4) used to perform (b)(4)- procedure described in SOP # M042 failed to meet system suitability criteria. The problem was investigated by CBER and Novo Nordisk scientists working together in the Laboratory of Analytical Chemistry and Blood Related Products (LACBRP), a CBER laboratory of the Division of Biological Standard and Quality Control (DBSQC). It was concluded that the assay has robustness issues in that some of the (b)(4)- work and the others do not. The sponsor has a (b)(4)- qualification procedure in place, which is used routinely to select (b)(4)- that work with the assay procedure. This addresses CBER concern because the results met all acceptance criteria when a (b)(4)- that passes system suitability criteria is used in the assay. This also gives the assurance that there is no issue with the product quality. In addition, it was found that several steps, including the (b)(4)- qualification procedure, are not described in adequate details in the SOP (version 1.0), which was submitted with the original BLA. The SOP was revised (version 2.0) and submitted as Amendment 34. It is concluded that the entire assay procedure as described in the version 2.0 of the SOP is adequate.

It is concluded that the method as described in amendment 34 is approvable.

## Background

The review committee asked LACBRP, a laboratory of DBSQC, to perform -----  
(b)(4)----- assay for the determination of -----(b)(4)-----  
of the rFVIII product, turoctocob alfa (NovoEight®), in-support of the Licensing Action  
for a new BLA submitted by Novo Nordisk, STN: 125466, following the procedure  
submitted by the manufacturer in the BLA submission. The results from three lots, lot # -  
----- (b)(4)-----, show that there is significant interaction between the -----  
----- (b)(4)----- . The sponsor indicated that they conducted ----- (b)(4)-----  
---- of rFVIII Secondary Reference Materials (SRM) to overcome this problem but did  
not provide the procedure in the original submission. LACBRP experienced significant  
difficulty in ----- (b)(4)----- in our laboratory following a procedure provided

with the original BLA. We discussed the issues with the sponsor in a teleconference. The sponsor provided a detailed procedure on -----(b)(4)----- as amendment 12 (4 Apr 2013) at our request. We still failed to -----(b)(4)-----, following the procedure. -----

-----). Thus, the system suitability attributes did not meet the acceptance criteria proposed by the sponsor in LACBRP. Even though the results of content of rFVIII and the -----(b)(4)----- met the proposed product specifications when tested after -----(b)(4)-----, the results cannot be considered valid because of the failure to meet assay validity criteria. These results were summarized in a memo from H. Wang, Ph.D. entitled "Test Results of "Content and -----(b)(4)-----" for Novo Nordisk Recombinant Coagulation Factor VIII (rFVIII) turoctocog alfa, STN: 125466/0" dated 09 Jul 2013.

The results were discussed with the sponsor during the Late-cycle meeting on 11 Jul 2013. Novo Nordisk provided an overview of experience with the method and noted that ----(b)(4)---- is dependent on the ---(b)(4)---. It was noted that it could take -----(b)(4)----- . Novo Nordisk offered to provide technical support to FDA (CBER), including sending experts to FDA (CBER) laboratory as well as providing a translated copy of the laboratory manual, which contains additional details on operation and -----(b)(4)-----.

## Submitted Information and Documents

- 125466/0.0 – 3.2.S.4.2: Control of Drug Substance
- Analytical Procedure M042 version 1.0: Content and -----(b)(4)-----
- 125466/0.12 – 1.11.1 Quality Information Amendment
- 125466/0.30 – 1.11.1 Quality Information Amendment
- Memo from Novo Nordisk to Dr. Lokesh Bhattacharyya, Lab Chief, LACBRP
- 125466/0.34 – 1.11.1 Quality Information Amendment
- Analytical Procedure M042 version 2.0: Content and -----(b)(4)-----

## Summary and Discussion of Test Results

However, it was obvious from the above discussion that all the steps that the analysts from Novo Nordisk follow have not been included in the SOP (document number M042) for this assay. This is a concern. The sponsor requested to summarize the steps that

they follow but that were not described in the submitted SOP (document number M042, version 1.0). The sponsor submitted the summary as amendment 30 (20 Aug 2013). We also understood that Novo Nordisk scientists select the -----  
-(b)(4)----- . This is a subjective procedure, which could affect the results and determine whether a product meets specification or not. This was a concern. For example, the Novo Nordisk scientists found that the results meet specification for the -----  
-(b)(4)----- . However, when Dr. Wang of LACBRP determined the results independently, it came out to be (b)(4), which is (b)(4) the specification limit, which would be a failure to meet acceptance criteria. The sponsor should set starting and ending points of the peaks automatically using the software they use in their -----  
-(b)(4)----- data analysis. This will provide an objective approach in data calculation. Also, this is a standard feature for any -----  
-(b)(4)----- software and should not be a problem to implement. An IR was submitted on 9 Sep 2013 to address these issues. The response was received on 20 Sep 2013 as Amendment 34. The requests, response from the sponsor, and CBER review are discussed below.

### **Request 1:**

Please revise the SOP for the analytical method M042 “Determination of -----  
-(b)(4)----- and quantitative content of turoctocog alfa by ---  
-(b)(4)---” to include:

- a. The requirement to perform the qualification of ---  
-(b)(4)--- through -----  
-(b)(4)---- followed by testing for system suitability criteria
- b. The use of an objective automatic approach for -----  
-(b)(4)----- using your (b)(4) system software
- c. Description of the details of performing the assay which are critical for the outcome, based on your Visit Report (Amendment dated August 20th, 2013) and comments from DBSQC (the file is attached for your consideration)
- d. Please submit to the BLA file the updated version of the analytical procedure M042 based on the revised SOP, and with the corrected ---  
-(b)(4)--- acceptance criterion.

**CBER Review:** The revised SOP (document number 042, version 2.0) was submitted as Amendment 34. On review we found that all revisions suggested in the IR has been incorporated, which addressed all CBER concerns. It is concluded that the method as described in amendment 34 is approvable.