



From: Alfred Del Grosso, Ph.D. LACBRP/DBSQC HFM-682

Subject: Review Memo

To: File STN 125398 Coagulation Factor XIII A Subunit (recombinant),
NovoThirteen®

Through: Lokesh Bhattacharyya, Ph.D. Chief LACBRP /DBSQC HFM-682
William McCormick, Ph.D. Director DBSQC/OCBQ HFM-680

Recommendation: Generally approvable on Basis of the Methods Reviewed.
One item for Complete Review letter.

Summary of Review

The analytical methods reviewed for Identity, Purity and Impurities by (b) (4), and Content and (b) (4) are in general adequate along with the submitted validation information.

In the case of Method M003 “Content and (b) (4), a stability issue for the reconstituted control sample was encountered during the replication of this procedure at CBER/DBSQC. Concerns were also raised about the effects that dilution in (b) (4) might have on (b) (4) and measured (b) (4).

Recommendation for inclusion in CR Letter:

- 1) During our performance of the (b) (4) method M003 “Content and (b) (4) a (b) (4) was observed for the (b) (4) of the (b) (4) sample, Batch nr. (b) (4) that you had submitted for our use as an SST sample. Please confirm that this is consistent with your experience and if so, modify the procedure to include a time limit for the determination of the SST sample following reconstitution.
- 2) Dilution of the sample in (b) (4) could (b) (4) (b) (4) and results could show artificially low (b) (4). Please provide information on this issue (effect of (b) (4)) to demonstrate that (b) (4) does not reduce the (b) (4) and give lower than actual (b) (4).

Review Narrative

This BLA from Novo Nordisk Inc. is for a Coagulation Factor XIII A Subunit (recombinant), NovoThirteen® intended for routine prophylaxis. It is supplied as a lyophilized powder in a single use vial containing 2500 IU (15mg) Coagulation Factor XIII Subunit (recombinant) and is reconstituted for use with sterile WFI.

Information reviewed concerned the following (b) (4) Drug Product analytical procedures and supporting information:

1. 3.2.S.4.1 Specification for rFXIII (b) (4)
2. 3.2.P.5.1 rFXIII 2500 IU Drug product specifications
3. 3.2.S.4.2 Analytical Procedures
 - a. Analytical Procedure for M002 Identity, Purity and Impurities
 - b. Analytical Procedure for M003 Content and (b) (4)
4. 3.2.S.4.3 Validation of Analytical Procedures
 - a. Validation of M002 Identity, Purity and Impurities, NovoDOCS ID 465704
 - b. Validation of M003 Content and (b) (4) NovoDOCS ID 486982
5. 3.2.P.5.2 Analytical Procedures
 - a. Overview of Analytical Procedures for Drug Product
6. 3.2.P.5.3 Validation of Analytical Procedure
 - a. Validation Statement for Drug Product

The procedures for Identity, Purity and Impurities by (b) (4) and Content and (b) (4) are utilized in (b) (4) Drug Product testing.

The Identity, Purity and Impurities procedure M002 is by (b) (4)

[Redacted]

The Content and (b) (4)

[Redacted]

Validation of the (b) (4) procedure for Identity, Purity and Impurities was evaluated with respect to the analytical characteristics of specificity, linearity, range, quantitation limit for impurities and precision. Table 1 summarizes validation results, as extracted from the submitted report.

Validation of the (b) (4) procedure for Content and (b) (4) was evaluated for specificity, linearity, range, accuracy, precision and quantitation limit for (b) (4)

(b) (4) [REDACTED] rFXIII 2500 (FC). Table 2 summarizes validation results for this procedure.

Initial reviews indicated that these procedures were adequately detailed. Validations were generally judged to be satisfactory. Both procedures M002 and M003 made references regarding (b) (4) system suitability that system suitability samples must be "... within established limits" without providing actual criteria. Procedure M003, for Content and (b) (4) additionally directed to prepare a system suitability test solution by using a process to "(b) (4) .." without further information.

In a CBER information request of August 8, 2011 it was asked that the above details be submitted. Novo Nordisk responded on August 19th (Amendment 125398/0.3). The sponsor stated that acceptance criteria for system suitability samples had been established for percentage purity and impurities for procedure M002 and for content and (b) (4) for procedure M003. These criteria were described as specific to the individual lot of SST sample, and it was explained that they were not described specifically in the procedures. New (b) (4) suitability criteria were adopted for (b) (4) in procedure M002 and for (b) (4) of the (b) (4) in procedure M003.

In the course of replicating procedure M003 at DBSQC, an attempt was made to (b) (4) the rFXIII_{(b) (4)} drug product as described in Section 7 of the method by "...
.."

However samples treated in this manner showed little evidence of (b) (4). In a telecon on September 28th, 2011 a clarification was requested. Novo Nordisk responded that the current version of M003 was in error, that the suitability standard was intended to be developed from the (b) (4) material rather than the drug product. DBSQC additionally requested that (b) (4) material for use as a SST sample along with acceptance criteria be submitted in order to allow the replication of this procedure at CBER.

Subsequently a quality amendment (125398/0.7) was received on October 25, 2011 in which procedure M003 was revised to correct the error regarding SST sample preparation. Batch nr. (b) (4) (b) (4) (b) (4) for use as SST sample, was received at DBSQC on October 17, 2011 along with acceptance criteria for content and (b) (4).

In the course of implementing procedure M003 at DBSQC it was observed that the (b) (4) (b) (4) SST sample (b) (4) (b) (4) while this effect was not observed in normal test samples. If this is observed in normal assay performance, a time limit for the determination of the SST sample following reconstitution should be established.

DBSQC test results for Identity, Purity and Impurities; Content and (b) (4) along with (b) (4), pH and other tests will be reported in a separate test memo.

Conclusion: The procedural descriptions and validations are satisfactory with the exception of the previously stated criteria for time stability of the system suitability sample used in the Content and (b) (4) procedure by (b) (4) .