



DEPARTMENT OF HEALTH & HUMAN SERVICES

Division of Biological Standards & Quality Control, Office of Compliance & Biologics Quality,
Center for Biologics Evaluation & Research, Food & Drug Administration

MEMORANDUM

From Alfred Del Grosso, Ph.D., LACBRP/DBSQC/OCBQ HFM-682
Tao Pan, Ph.D., LACBRP/DBSQC/OCBQ HFM-682
Ritu Agarwal, Ph.D., LACBRP/DBSQC/OCBQ HFM-682
Mark Levi, Ph.D., LACBRP/DBSQC/OCBQ HFM-682
Hsiaoling Wang, Ph.D., LACBRP/DBSQC/OCBQ HFM-682
To STN 125512/0
Through Lokesh Bhattacharyya, Ph.D., Chief, LACBRP, OCBQ/DBSQC, HFM-682
William M. McCormick, Ph.D., Director, OCBQ/DBSQC, HFM-680
Sponsor Baxter Healthcare Corporation
Product Human coagulation factor VIII, OCTANATE[®], STN: 125512
Subject DBSQC Review Memo for Chemistry Related Test
Methods for Antihemophilic Factor (Recombinant),
Porcine Sequence (OBI-1) from Baxter Healthcare
Corporation, STN 125512

Review Summary and Recommendation

Specific Assays Reviewed and addressed in this memo include:

- 1) Water Content by ---(b)(4)---
- 2) Polysorbate 80 by ---(b)(4)-----
- 3) Chloride and Citrate by -----(b)(4)-----
- 4) Sodium and Calcium by -----(b)(4)-----
- 5) Protein Content and -----(b)(4)-----
- 6) Tris by (b)(4)
- 7) Sucrose by -----(b)(4)-----
- 8) -----(b)(4)-----
- 9) Physical and Chemical Attributes: Appearance, Reconstitution
Time, (b)(4)

Procedures and Validations, including Baxter's responses to CBER Information Requests for the above listed procedures have been reviewed and evaluated as adequate.

Review Narratives

1. Determination of Water Content in rpFVIII Drug Product

Reviewer: Yichuan Xu, Ph.D.

Information reviewed included:

- 125512/0.1 – Cover Letter, dated 08 November 2013
- 125512/0.1 – 3.2.P.5.1 Control of Drug Product “Specification”
- 125512/0.1 – 3.2.P.5.4 Batch Analyses
- 125512/0.1 – 3.2.P.5.2 Analytical Procedures for Water Content by –(b)(4)-----
- 125512/0.1 – 3.2.P.5.3: Method Validation Report, Determination of Water Content in
rpFVIII Drug Product (document numbers: AMV-RP-MVR(1)-
M002/M008, 112835-RPT/1.0, 114328-RPT/1.0
- 125512/0.7 - 3.2.P.5.2 Analytical Procedures: Determination of Water Content in rpFVIII
Drug Product (061486-SOP/5.0)
- 125512/0.19 – Quality Information Amendment
- 125512/0.19 – Supplemental Validation 114328-RPT
- 125512/0.19 – Supplemental Validation 112835-RPT

The ---(b)(4)---- method is used for the measurement of residual moisture of the drug product, Porcine Sequence (OBI-1). The specification for product release is proposed as (b)(4) (w/w). The sponsor provided analytical procedures (061486-SOP/5.0) and the validation report (AMV-RP-MVR(1)-M002/M008, 112835-RPT/1.0, 114328-RPT/1.0).

Method

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1 Page Determined to be Not Releasable: (b)(4)

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Conclusion:

The submitted procedure and validation information indicate that this method is acceptable.

2. Polysorbate 80 by ----- (b)(4) -----

Reviewer: Yichuan Xu, Ph.D.

Information reviewed included:

- 125512/0.1 – Cover Letter, dated 08 November 2013
- 125512/0.1 – 3.2.P.5.1 Control of Drug Product “Specification”
- 125512/0.1 – 3.2.P.5.4 Batch Analyses
- 125512/0.1 – 3.2.P.5.2 Analytical Procedure for Polysorbate 80
- 125512/0.1 – 3.2.P.5.3: Method Validation Report, Determination of Polysorbate 80 in OBI-1 by –b(4)----- (document numbers: 114326-RPT/1.0, 11687-RPT/1.

Polysorbate 80 is an excipient in the OBI-1 drug product (DP). The specification limit is (b)(4)----- . The sponsor provided analytical procedures and the validation report (114326-RPT/1.0, 11687-RPT/1.0).

Method

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1 Page Determined to be Not Releasable: (b)(4)

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

Conclusion

The method is described in sufficient detail and has been adequately validated for its intended use.

3. Chloride and Citrate by ----- (b)(4) -----

Reviewer: Tao Pan, Ph.D.

Chloride and citrate ions present in the drug product -----
----- (b)(4) -----
----- . A detailed SOP and
validation report were provided for this analytical method.

Submitted Information reviewed:

3.2.P.5.1. Control of Drug Product, Specifications
3.2.P.5.2 Control of Drug Product, Analytical Procedures,
AP Chloride and Citrate
3.2.P.5.3 Control of Drug Product, Validation of Analytical Procedures,
VAP Citrate and Chloride
VAP PPD 042142-01-02 Validation Report for the Analysis of Chloride and Citrate
Ions in rp FVIII ObI-1 ----- (b)(4) ----- ObI-1 Final Drug
Product-and ----- (b)(4) -----
Amendment 0.28 CR-14-0193-AA-01 Supplemental Method Validation Chloride and
Citrate Ions –b(4)---

For the final OBI-1 drug product, chloride and citrate -----
----- (b)(4) -----
----- , and that for
citrate is --- (b)(4) ----- . The chloride and citrate concentrations in OBI-I final products
were determined using an ----- (b)(4) ----- .

Method

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

3 Pages Determined to be Not Releasable: (b)(4)

The procedure as described is satisfactory. Based on the data provided in both the original BLA and subsequent amendment, the assay has been validated for its intended use, and is approvable for the determination of chloride and citrate in final drug product.

Reviewer: Ritu Agarwal, Ph.D.
Submitted Information and Documents

- 125512/0 – Cover letter, dated 08 Nov 2013
- 125512/0 – 3.2.P.5.1 Control of Drug Product “Specification”
- 125512/0 – 3.2.P.5.4 Batch Analyses
- 125512/0 – Application - Original BLA: Antihemophilic Factor (Recombinant)
- 125512/0 – 3.2.P.5.2: Analytical Procedure – Sodium and Calcium by ----(b)(4)-----

- 125512/0 – 3.2.P.5.3: Validation of Analytical Procedure – Method Validation report,
Document number 042142-01-01: Sodium and Calcium by -----(b)(4)-----

- 125512/0 – 3.2.P.5.3: Validation of Analytical Procedure – SOP for Analytical
determination, Document number M2934: Sodium and Calcium by -----(b)(4)-----

- 125512/0.12 – 1.11.1. Response to FDA information request dated 24 Feb 2014, Received
on 17 March 2014
- 125512/0.18 – 1.11.1. Response to FDA information request dated 17 April 2014,
Received on 05 May 2014
- 125512/0.28 – 1.11.1. Response to FDA information request dated 6 August 2014,
Received on 13 August 2014

6 Pages Determined to be Not Releasable: (b)(4)

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5. Protein Concentration -----(b)(4)-----

----(b)(4)----- Protein Concentration in rp-FVIII by ---(b)(4)----

- Document 061445-SOP from (b)(4) "Analysis of ---(b)(4)-- and Protein Concentration in rp-FVIII by ---(b)(4)-----"

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2 Pages Determined to be Not Releasable: (b)(4)

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Review: The method is adequately described and has been sufficiently validated.

Reviewer: Hsiaoling Wang, Ph.D.

- Cover letters, dated Oct. 8, 2013 and Nov. 8, 2013 respectively
- 3.2.P.1 Description and Composition of Drug Product [OBI-1]
- 3.2.P.5.1 Specifications
- 3.2.P.5.2 Analytical Procedures “Tris (trishydroxymethylaminomethane)”
- 3.2.P.5.4 Batch Analyses
- 3.2.P.5.6 Justification of Specification (s) [Tris]
- SOP “Method for the Analysis of Tris in rp-FVIII (OBI) ----(b)(4)-----,
Lyophilized Finished Product, -----(b)(4)-----
-----”
- Validation Report for the Analysis of Tris in rp-FVIII (OBI-1) ----(b)(4)-----
Substance, OBI-1 Final Drug Product, -----(b)(4)-----

- 1.11.1 Quality Information Amendment 125512/0.19, received May 9, 2014
- Updated SOP M2937.04 “Method for the Analysis of Tris in rp-FVIII (OBI-1)
----- (b)(4) -----, Lyophilized Finished Product, -----
----- (b)(4) -----”
- 1.11.1 Quality Information Amendment 125512/0.28 (dated Aug. 13, 2014)

- Updated SOP M2937.05 “Method for the Analysis of Tris in rp-FVIII (OBI-1)
----- (b)(4) -----, Lyophilized Finished Product, ----- (b)(4) -----
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Drug Product (DP) specification for excipient Tris is –b(4)–. The sponsor provided the method description in 3.2.P.5.2 and the validation report (SOP version 03 as attachment 1 in the validation report).

Method

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Conclusion: The procedure for TRIS is adequately described and validated for the intended use.

7. Sucrose by ----- (b)(4) -----

Reviewer: Hsiaoling Wang, Ph.D.

Drug Product (DP) specification for the excipient sucrose is --- (b)(4) ---- The sponsor provided the method description in 3.2.P.5.2 and the validation report (SOP version 01as attachment 1 in the validation report).

Documents Reviewed

- 3.2.P.5.2 Analytical Procedures “Sucrose”
- 3.2.P.5.4 Batch Analyses
- 3.2.P.5.6 Justification of Specification (s) [Sucrose]
- SOP “Method for the Analysis of Sucrose in rp-FVIII (OBI-1) -----(b)(4)-----
-----, Lyophilized Finished Product, -----(b)(4)-----
-----”
- Validation Report for the Analysis of Sucrose in rp-FVIII (OBI-1) -----(b)(4)-----
-----, OBI-1 Final Drug Product, -----(b)(4)-----

- 1.11.1 Quality Information Amendment 125512/0.19, received May 9, 2014
Drug Product (DP) specification for the excipient sucrose is ----(b)(4)----- . The sponsor
provided the method description in 3.2.P.5.2 and the validation report (SOP version 03
as attachment 1 in the validation report).
- 1.11.1 Quality Information Amendment 125512/0.28 (dated Aug. 13, 2014)
- New version SOP M2936.06 “Method for the Analysis of Sucrose in rp-FVIII (OBI-1)
----- (b)(4) -----, Lyophilized Finished Product, -----(b)(4)-----
-----”
- CR-14-0192-AA-01: Supplemental Validation Report for the Analysis of the Sucrose in
rp-FVIII (OBI-1) ----- (b)(4) -----

Method

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4 Pages Determined to be Not Releasable: (b)(4)

8. Physical and Chemical Attributes

Reviewer: Alfred Del Grosso, Ph.D

- a. Appearance**
- b. Reconstitution Time**
- c. (b)(4)**

Specifications for Appearance (Pre-Reconstitution) is described as “white cake”,
Appearance (Post-Reconstitution) is “Clear, colorless solutions, essentially free of visible
particules. Reconstitution time is specified as -----(b)(4)-----
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Documents Reviewed

- 3.2.P.5.2 Analytical Procedures “Appearance”, “Visible Particles”, “Reconstitution
Time and Appearance”, “(b)(4)”
- 3.2.P.5.4 Batch Analyses
- 3.2.P.5.6 Justification of Specifications
- 3.2.P.5.3 Validation of Analytical Procedures
- AMV-RP-MVR(1)-M002/M045 Method Validation Report for the Determination of
(b)(4) in rpFVIII Drug Product

Appearance of the sample before reconstitution is performed in accordance with ---(b)(4)-
----- using a viewing station with white and dark panels and comparison to a reference
photograph.

For post-reconstitution appearance and reconstitution time, -----

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Comparison post-reconstitution is made against WFI
or purified water. (b)(4) is determined in accordance with ---(b)(4)----- after reconstitution
with -----(b)(4)-----.

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Conclusion: Procedures for “Appearance”, “Visible Particles”, “Reconstitution Time and
Appearance” and “(b)(4)” are adequately described and acceptable for use.