



MEMORANDUM

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To STN 125512/0

Through Dr. William M. McCormick, Director OCBQ/DBSQ, HFM-680

Company Baxter Healthcare Corporation

Product Antihemophilic Factor (recombinant), Porcine Sequence, B-domain deleted

Subject Primary Review Memo for the Release Tests for the Drug Product, STN: 125512, Antihemophilic Factor (recombinant), Porcine Sequence (OBI-1)

Summary

A new BLA was submitted for recombinant Antihemophilic Factor (rFVIII), Porcine Sequence with the B-domain deleted. This document constitutes the Primary Review Memo from DBSQ for the following analytical methods and their validations, as used for lot release of the drug product.

1. The Analysis of rp-FVIII Activity By Chromogenic Assay on the -----(b)(4)-----

2. One Stage Coagulation Assay using -----(b)(4)----- for OBI-1
3. Analysis of rpFVIII by -----(b)(4)-----
4. Analysis of rpFVIII by -----(b)(4)-----

Review of the methods and their validations led to three Information Requests (IR), which were submitted on 24 February 2014, 1 April 2014 and 17 April 2014. The responses to the first two IRs were received on 1 March 2014 and 10 April 2014, respectively. The responses are reviewed and included in this memo. The response to the third IR has not been received at the time of writing this memo.

Conclusion: Based on the review of original submissions and amendments, we found Analysis of rpFVIII by -----(b)(4)----- (assay #4

above) to be approvable for quality control testing. The other three assays have outstanding issues, which have been brought to the attention of the sponsor.

Background

Recombinant Porcine Factor VIII, B-Domain Deleted (OBI-1) is manufactured by Baxter. OBI-1 is a purified recombinant porcine factor VIII, B-domain deleted protein with ----(b)(4)----- . It is expressed as a secretory protein in a baby hamster kidney (BHK) cell line. Full length porcine factor VIII is synthesized as a single chain glycoprotein with the domain structure A1-A2-B-A3- C1-C2. In OBI-1, the porcine factor VIII B-domain has been replaced with a twenty-four amino acid linker. The product is proposed to be available in the nominal strength of 500 IU/vial to prevent bleeding episodes in patients with acquired inhibitory antibodies response to human factor VIII.

Submitted Information and Documents

This is an electronic submission. Information submitted and reviewed includes:

- 125512/0.1 - 3.2.P.5.3 Specification(s)
- 125512/0.1 - 3.2.P.5.2 Analytical Procedures [Potency-Chromogenic Assay]
- 125512/0.1 - 3.2.P.5.3 VAP Factor VIII chromogenic: Validation of Analytical Procedures [Chromogenic Assay]
- 125512/0.1 - 3.2.P.5.3 VR-105 Validation Report for Test Method TQC-004: Analysis of rp-FVIII Activity by Chromogenic Assay on the ---(b)(4)-----
- 125512/0.1 - 3.2.P.5.3 TCR-05-009 Qualification of TQC-004: Analysis of rpFVIII Activity by Chromogenic Assay on the ---(b)(4)-----
- 125512/0.1 - 3.2.P.5.3 114393-RPT/1.0: Method Validation Report for Analysis of OBI-1 by One-Stage Coagulation Assay using -----(b)(4)----- Analysis
- 125512/0.1 - 3.2.P.5.3 VP-127 (Validation Protocol) Validation of Test Method TQC-007: Analysis of rpFVIII by -----(b)(4)-----
- 125512/0.1 - 3.2.P.5.3 VR-127 Report For Validation of Test Method TQC-007; 04566G-SOP: Analysis of rpFVIII by -----(b)(4)-----
- 125512/0.1 - 3.2.P.5.3 113226-RPT Supplemental Validation Report of Test Method 061510-SOP: Analysis of rpFVIII by -----(b)(4)-----
- 125512/0.1 - 3.2.P.5.3 116647-RPT Supplemental Validation Report of Test Method (Linearity, Limit of Quantitation and Limit of Detection) 061510-SOP: Analysis of rpFVIII by -----(b)(4)-----
- 125512/0 - 3.2.P.5.3 VP-126 (Validation Protocol) Validation of Test Method TQC-002: Analysis of rpFVIII by -----(b)(4)-----
- 125512/0.1 - 3.2.P.5.3 VR -126: Validation Report for Test Method TQC-002: Analysis of rpFVIII by -----(b)(4)-----
- 125512/0.7 Response to FDA Information Request, received 2/13/2014
- 125512/0.7 – 3.2.P.5.2 061497-SOP/4.0: The Analysis of rp-FVIII Activity by Chromogenic Assay on the -----(b)(4)-----
- 125512/0.7 – 3.2.P.5.2 061499-SOP/4.0: One Stage Coagulation Assay using -----(b)(4)----- for OBI-1

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Review of response: This is an adequate response. However, this information is not included in the SOP, 061497-SOP, document. The following Information Request was submitted to the sponsor on 17 April 2014.

- Please revise your SOP to include the following and submit your revised SOP for review: acceptable potency of the control for system suitability.
- c. You propose to use an in-house reference standard, ---(b)(4)----, in your routine lot-release testing (3.2.P.5.2). In section 3.2.S.5: Ref Std or Materials, you mentioned that the suitability of this standard was established based on a collaborative study between 5 labs and WHO 8th IS for VIII (07/350) was used as the standard in the collaborative study. Please provide data from this collaborative study to show that the in-house reference standard, ---(b)(4)----, is adequately qualified for this assay. If data from the collaborative study is not available, please provide qualification data generated in your laboratory using an appropriate international standard.

Response: -----

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

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

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

[(b)(4)]

intend to use in your routine lot-release testing ---(b)(4)----- . We suggest that you spike the samples with the available international standards.

Response: As per response 1.d.iii, the ---(b)(4)----- is not substantially different from (b)(4)---- since both start out as OBI-1 (b)(4). In both cases, the active product is OBI-1 material.

(b)(4)

Review of response: Although the specificity test is set up to examine the worst case scenario with respect to impurities interfering with OBI-1 drug product, as described in section d.iii and d.v, we do not feel that the data demonstrate specificity of the assay for the final container drug product (FCDP) because, although the FCDP contains more purified rpFVIII, it also contains additional excipients. Therefore, the results do not evaluate any potential impact of the excipients present in FCDP and, thus, do not demonstrate specificity of the assay in FCDP. Furthermore, FCDP is only -(b)(4)- diluted in the assay buffer for potency measurements. Hence the effect of excipient on final drug product potency cannot be considered negligible due to dilution. This has generated the following IRs, which was submitted to the sponsor on 17 April 2014.

- You have demonstrated specificity of the assay by spiking known quantities of rpFVIII to in-process samples. Your data does not demonstrate specificity of the assay for the final container drug product (FCDP) because, although the FCDP contains more purified rpFVIII, it also contains additional excipients. Furthermore, FCDP is only -(b)(4)- diluted in the assay buffer for potency measurements. Hence the effect of excipient on final drug product potency cannot be considered negligible due to dilution. Please provide data to demonstrate specificity in FCDP. We recommend that you also submit results of the assay of the Assay/Dilution Buffer showing negligible contribution from this buffer to demonstrate specificity of your assay.

vii. With reference to the specificity study in the technical report TCR-05-009, please provide details of the reference material used to spike the (b)(4) in-process samples.

Response: -----

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

Review of response: This IR is adequately addressed.

- viii. In section 5.5 of VR-105, Intermediate Precision and Reproducibility, two data values are presented for Check Std and QCC-05-0103 in some cells of Tables 5.5.1 (page 10 of VR – 105) and 5.5.6 (page 11 of the same report). For example, you included 1.02/0.97 in the second row/second column of Table 5.5.1. Please explain why two data values are included.

Response: -----

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

Review of response: This answer adequately explains the IR.

- ix. Statistical analyses of the results for reproducibility in section 6.6 of VR-105 state, “Statistical comparison of the FDP results fails to reject the null hypothesis, and the means are equal with 95% confidence.” However, in Attachment 2, comparison of reproducibility of lots ---(b)(4)-----, you show statistically significant difference in measurement of lot (b)(4)-- (P-value 0.039) between the two laboratories and you concluded that “equality is not as strong”. Your null hypothesis is that variances between the two labs are the same (equivalency). We do not agree that failing to reject a null hypothesis of equivalency establishes equivalency between the two results. Please submit statistical analysis of your data showing that a null hypothesis of non-equivalency is rejected.

Response: Baxter acknowledges that the statement “Statistical comparison of the FDP results fails to reject the null hypothesis, and the means are equal with 95% confidence” appears to be incorrect based on the statistical analyses referenced in the Validation report. The original analyses assumed equal variances between labs for --(b)(4)-- and unequal variances for --(b)(4)--. This was not appropriate given that both the F-test (normal distribution) and the Levine’s test (non-normal distributions), performed prior to the analysis and included in the Attachment 2, support the null

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revised to include the new method and the recommendations from the validation report.

Review: The SOP was submitted as amendment 7 (31 January 2014) and is reviewed (see above). Although the SOP gives adequate technical information regarding the procedure, questions were raised about the extent of revisions between the old and new SOPs. Hence, the following Information Request was submitted to the sponsor on 4/1/2014:

- We requested documents TQC-004.04 for the chromogenic assay and 114102-SOP for the One Stage Coagulation Assay because you referenced these documents as the SOPs for the respective test method procedures in your corresponding method validation reports. Your latest versions of the documents for these two assays, 061497-SOP and 061499-SOP, instead of the documents requested, are acceptable as test method SOPs. However, it raises the question about the nature and extent of the changes between the versions referenced in the validation reports and the current versions. This is important because you mentioned "procedure revisions" in your e-mail communication. We need to make an assessment whether the "procedure revisions" require complete or partial revalidation of the methods. Please provide the details of the changes between TQC-004.04 and 061497-SOP (chromogenic assay) and that between 114102-SOP and 061499-SOP (One Stage Coagulation Assay).

Response and Review: In response the sponsor outlined in details between in Amendment 15 (received 10 April 2014) documents 114102-SOP and 061499-SOP. The primary changes include addition of ----(b)(4)----- in 061499-SOP. We conclude that the sponsor has adequately addressed the IR and this change should not require any revalidation of the method.

- b. Please address the following questions regarding your Analytical Procedure [Potency – One Stage Coagulation Assay] (3.2.P.5.2).
 - i. In the Method section, the control sample is defined as OBI-1 Control. Please describe the difference between the OBI-1 Control and the OBI-1 reference standard, including the detailed compositions of both materials.

Response: -----

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

Review of response: This IR was addressed adequately.

- c. We have the following IR questions/comments regarding your Method Validation Report, 114393-RPT/1.0.

- i. Accuracy (section 4.1) experiment was done using reference standard ---(b)(4)--- (DP) and not “validation sample” as was defined in section 3.3, that Batch (b)(4)-- of OBI-1 was used during execution of validation protocol, 114165-PTL. Please provide data for the validation sample.

Response: Batch (b)(4)-- was used in the validation to assess precision as repeatability and intermediate precision as detailed in the validation protocol. For the accuracy and range experiment it was necessary to use a sample with a defined potency value, in order to calculate % recovery therefore as detailed in the validation protocol reference standard ---(b)(4)---- (DP) was used. For the OSCA assay the reference standard is dilute preparation of FDP lot (b)(4) and is considered suitable for determining these validation parameters.

Review of response: According to sponsor the material ---(b)(4)---- used as reference standard, is also a final formulated drug product. Therefore, the results should be acceptable. We do not agree because the reference standard used in accuracy determination is also ---(b)(4)----. This is circular. The following IR has been submitted to the sponsor to address this deficiency on 17 April 2014. The IR also addresses the deficiency discussed under IR 2.c.ii.

- You evaluated accuracy and range by assaying the reference standard at ----- ---(b)(4)----- of the target concentration. But you used the same material as the reference standard in this evaluation. This is circular. Therefore, we do not agree that accuracy and range have been adequately evaluated. Please provide data to support range using a lot OBI-1 FCDP that is different from the reference standard.
- ii. The validated range of the assay, ---(b)(4)-----, was set using reference standard and not validation sample (Batch --(b)(4)--- of OBI-1). Please provide data for the validation sample.

Response: As with the previous question, batch --(b)(4)-- was used in the validation to assess precision as repeatability and intermediate precision as detailed in the validation protocol. For the accuracy and range experiment it was necessary to use a sample with a defined potency value, in order to calculate % recovery. Therefore, reference standard ---(b)(4)----- (DP) was used. For the OSCA assay the reference standard is a previously manufactured batch of DP and is therefore considered suitable for determining these validation parameters

Review of response: As discussed above under the review of response for IR question (2.c.i), we do not agree because the reference standard used to evaluate assay range is also ---(b)(4)-----. This is circular. The IR described under 2.c.i also present this deficiency to the sponsor.

- iii. You indicated in section 6: Linearity that linearity was assessed using OBI-1 drug product. However, in section 6.1: Procedure, you indicated that OBI-1 reference was diluted to obtain concentrations in the range of ---(b)(4)-----. Please explain this discrepancy. Please provide linearity data with the standard and the Drug Product over the proposed assay range and demonstrate parallelism between the standard and the Drug Product.

Response: As stated in the response for (2.g.xi), the reference standard is a previously manufactured batch of drug product and therefore the statement in Section 6, regarding linearity, is correct. It was unnecessary to generate linearity data with both the reference standard and drug substance and demonstrate parallelism. Parallelism between ---(b)(4)----- and batch --(b)(4)-- was satisfactorily demonstrated in sections 7: Precision as Repeatability and in section 8: Intermediate Precision as it forms part of the system suitability criteria for the assays.

Review of response: The sponsor has not presented any data analysis in sections 7 and 8 of the validation report (114393-RPT/1.0), which demonstrate parallelism. The following IR has been sent to the sponsor on 17 April 2014.

- In response to our previous IR (dated 24 February 2014) you indicated that parallelism data has been shown in sections 7 and 8 of your validation report (114393-RPT/1.0). We did not find the data and their analyses in these sections. Please provide the data and analyses to demonstrate parallelism between standard and FCDP samples. Also, please provide slopes, intercepts and distribution of residuals of the dilution curves of the standard and OBI-1 FCDP samples for the data presented in this section.
- iv. Your results in section 9: Robustness shows that (b)(4) containers should be used for sample preparation. Please revise your SOP (document 114102-SOP) to clarify this requirement.

Response: The document used for release testing is 061499-SOP. Procedure 114102-SOP is a draft document that was only used in validation; all recommendations from the validation were incorporated into procedure 061499-SOP (as provided in the information amendment, sequence 0007). The use of (b)(4) containers is detailed in procedure 061499-SOP section 12 step 2b and section 13 step 3.

Review of response: Sponsor responded adequately.

Additional Information Request

In addition to those discussed above, the following IRs were sent to the sponsor on 17 April 2014.

- Please provide qualification data for the Positive Control ---(b)(4)----- used in this assay.
- Please provide data to demonstrate repeatability (precision) of the assay over the assay range. We suggest that you use at least three concentration levels.
- Please revise your SOP to include acceptable potency of the control for system suitability.

Conclusion

The method is clearly described. However there are outstanding issues, which need to be addressed. A new Information Request has been submitted to the sponsor on 17 April 2014 to address these issues.

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

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Review: This response is acceptable.

Conclusion: This method is suitable for intended use.