



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

- 125512/0.7 – 3.2.P.5.2 061510-SOP/4.0: Laboratory Method for the Analysis of rp-FVIII by -----(b)(4)-----
- 125512/0.12 Response to FDA Information Request, received 3/17/2014
- 125512/0.12 TCR-06-002 Test Method Transfer Report: Transfer of 0B1-1 (rpFVIII) Purity Determination by -----(b)(4)-----
- 125512/0.15 Response to FDA Information Request, received 4/10/2014

Review Narrative

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

The method is based on the chromogenic factor VIII (FVIII) assay reference method for the assay of High Purity FVIII concentrates in the ----(b)(4)----- (2.7.4) and is used to measure FVIII potency in the final container drug product, -----
------(b)(4)-----
------. The proposed specifications for drug product are ---(b)(4)-----
and the ratio of the One Stage Clotting Assay to Chromogenic Assay to be ---(b)(4)----. The sponsor provided a Standard Operating Procedure, 061497-SOP / (b)(4) as well as validation reports, VR-105 and TCR-05-009.

Assay Procedure

This assay indirectly measures the activity of (FVIII) by the activation of a chromophoric substrate. Briefly, rp-FVIII is activated by thrombin to FVIIIa, which acts as a cofactor in the conversion of FX to FXa by FIXa in the presence of Ca²⁺ and phospholipids. The hydrolysis of the chromogenic substrate by FXa to generate p-nitroalanine (pNA) is measured photometrically at (b)(4)-. Since Ca²⁺ and phospholipids are used at an optimal concentration and FX is in excess, the intensity of the color is proportional to the amount of FVIII activity.

(b)(4)

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

-(b)(4)

-(b)(4)

Information Request and Review

The following Information Requests (IR) were submitted to the sponsor on 2/24/2014. The response was received on 3/17/2014 as Amendment 12. The SOP for the procedure, document 061497-SOP / 4.0, was provided in Amendment 07, and was received on 2/27/2014. The IR questions, the response of the sponsor and review of the responses are discussed below.

- a. Please provide the SOPs TQC-004.04 ---(b)(4)---- and -----(b)(4)-----
----- for determination of Factor VIII by chromogenic assay (also requested on 31
January 2014).

Response: The response provided to the 31 January 2014 information request (submitted as sequence 0007) contained the current version of the procedure used for chromogenic assay drug product testing (061497-SOP: The Analysis of rp-FVIII Activity by Chromogenic Assay on the -----(b)(4)-----
-----). The TQC-004.04 SOP as referenced has been superseded by this newer SOP, with new numbering based on the (b)(4) document control system.

Review: Although 061497-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 Amendment 15 (received 10 April 2014) details of the differences between documents TQC-004.04 and 061497-SOP. The primary changes include -----

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

----- However, 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-Chromogenic Assay] (3.2.P.5.2).
- i. In the Methods section, please specify the dilutions which will be made of controls and samples for analysis.

Response: The control (QCC-13-0906) is diluted as follows:

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

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

Review of response: The sponsor has provided the range and optimal test value, so this provides adequate information. 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: details of dilution of the samples
- ii. In the System Suitability section, it states "The average activity control must be within pre-determined limits". Please specify the acceptable range of the control.

Response: The controls (QCC-13-0906) were qualified, and after a period of routine use in both ----- (b)(4) ----- laboratories, the control range was reassessed and new limits of ----- (b)(4) ----- were assigned according to established procedures.

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)]

Based on the results of this collaborative study, the potency values assigned to OBI-1 Potency Reference Standard ---(b)(4)----- are:

One-Stage Clotting Method: (b)(4)--

Chromogenic Method: (b)(4)

Review of response: This response addresses the IR as it clarifies that the results presented in Table 1 represent the geometric coefficient of variation and hence take into account inter-assay variability in the use of different equipment and reagents.

- d. We have the following IR questions/comments regarding your Method Validation Report, VR-105, and Technical Report, TCR-05-009.
- iii. You propose to use the in-house reference standard, ----(b)(4)----, in your routine lot-release testing. However, this standard has not been used in evaluating any of the validation characteristics. Please provide data on all of the validation characteristics using the in-house reference standard that you propose to use in routine lot release.

Response:

(b)(4)

Review of response:

(b)(4)

Please provide comparability data showing that the two standards, ---(b)(4)--- and ---(b)(4)----- will produce equivalent results. Please provide data for at least 6 samples, preferably more. Also, please provide data showing dilution parallelism between the two standards.

- iv. The Materials and Methods section in the Technical Report TCR-05-009 lists the -----(b)(4)-----, while the Analytical Procedure 3.2.P.5.2 lists the concentration as (b)(4). Please clarify or amend accordingly.

Response:

(b)(4)

(b)(4).

(b)(4):

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

Review of response: -----
 -----(b)(4)-----.

- v. Stability studies (sections 5.1 and 5.2) and range determination (section 5.4) in the Validation Report VR-105 were carried out using ---(b)(4)---, a reference standard for Phase 1 and Phase 2 clinical Drug Product batches, and not final Drug Product. Please provide a detailed description of ---(b)(4)--- and explain why we can consider this standard as a representative final container Drug Product.

Response: -----

(b)(4)

Review of response: Please see section 1.d.iii, above for review of response.

- vi. In assessing specificity (section 5.3) in your Validation Report, VR-105, you spiked in-process samples with ---(b)(4)-- standard. When in-process samples are spiked with ---(b)(4)-- standard, the resulting sample does not represent the matrix of either the final container sample or the in-process sample. Please provide data using in-process and final Drug Product samples spiked with the reference standard that you

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

hypothesis that the variances are the same. Therefore, the data for both (b)(4) and (b)(4) was re-analyzed using a two-sample t-test (assuming equal variances) first using (b)(4) and confirmed using Excel, and the results provided in Figure 1 confirms that the statement is correct. The statistical analyses referenced in the report will be amended with the results described below (Figure 1, page 7 of 1.11.1 Quality Information Amendment).

Review of response: The response and figure provided an explanation to the discrepancy in the statistical analysis and is hence satisfactory.

Additional Information Request

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

- You evaluated 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. Please provide data to support range using a lot OBI-1 FCDP that is different from the reference standard.
- You evaluated linearity, accuracy and precision at ----(b)(4)----- of the target potency. Please provide data evaluating these validation characteristics either to cover the proposed assay range or (b)(4)--- of the target potency in the assay, whichever is wider.

Conclusion

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

2. One Stage Coagulation Assay using -----(b)(4)----- for OBI-1

The method is used to measure FVIII potency in the final container drug product. The proposed specification is ---(b)(4)-----.

Method

The method is described in details in 061499-SOP / 4.0 to permit complete review. The SOP was not submitted in the original submission but was provided as Amendment 7 in response to our IR. Activity of coagulation factor VIII is determined with the One Stage Coagulation Assay (OSCA) using -----(b)(4)-----
----- . Each sample and reference standard preparation was

(b)(4)

(b)(4)

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Information Request and Review

The following Information Requests (IR) were submitted to the sponsor on 2/24/2014. The response was received on 3/17/2014 as Amendment 12. The SOP for the procedure, document 061497-SOP / 4.0, was provided in Amendment 07, and was received on 2/27/2014. The IR questions, the response of the sponsor and review of the responses are discussed below.

- a. Please provide the SOPs TQC-004.04 -----(b)(4)--- and -----(b)(4)-----
----- for determination of Factor VIII by chromogenic assay (also requested on 31
January 2014).

Response: The response provided to the information request (submitted as sequence 0007) contained the current version of the procedure used for One Stage Coagulation Assay drug product testing (061499-SOP (One Stage Coagulation Assay using -----(b)(4)----- for OBI-1)). The 114102-SOP as referenced was a draft SOP for validation. Following the completion of the validation SOP 061499-SOP was

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.

3. Analysis of rpFVIII by -----(b)(4)-----

The proposed procedure, -----(b)(4)-----, is a quantitative
 ----(b)(4)----- method for purity determination of Final Container Drug Product
 (FCDP). The proposed specifications for the drug product are: -----(b)(4)-----
 -----.

Method

The method described in SOP number 061510-SOP/4.0 was submitted on February 13 2014 in response to an information request sent on January 31 2014. The document describes the method in sufficient details to permit review.

(b)(4)

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

(b)(4)

(b)(4)

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

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Information Request

The following IRs were submitted to the sponsor on 2/24/2014. The response was received on 3/17/2014 as Amendment 12. The IR questions, the response of the sponsor and review of the responses are discussed below.

- a. Please provide a copy of the document TCR-06-002 for precision studies in the test method transfer.

Response and Review: The document was submitted as Amendment 12, received on 3/17/2014. The document was reviewed and found to be satisfactory, as discussed above.

- b. In Accuracy determinations shown in Table 13 and Figure 7 on page 16 of document VAP-VR-127, only one concentration of Drug Product has been used. Please provide accuracy data over the proposed range of the assay. We suggest that you evaluate accuracy at the minimum at 3 concentrations over the range of the assay and with 3 replicates at each concentration, as recommended by the ICH guideline Q2(R1).

Response and Review: The sponsor responded that this data was submitted as a supplemental validation report 113226-RPT as Amendment 1. On review we found that the accuracy was determined using -----

-(b)(4)-

Therefore, this IR has not been addressed appropriately and a new IR will be submitted.

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 to address this issue.

4. Analysis of rpFVIII by -----(b)(4)-----

Baxter uses ----(b)(4)----- as a qualitative test to confirm identity of the OBI-1 drug product for release.

Method

The method described in SOP number 061510-SOP/4.0 was submitted on February 13 2014 in response to an information request sent on January 31 2014. The document describes the method in sufficient details to permit review.

-(b)(4)

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

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Information Request

The following IR was submitted to the sponsor on 2/24/2014. The response was received on 3/17/2014 as Amendment 12. The IR question, the response of the sponsor and review of the responses are discussed below.

-(b)(4)

Response:

-(b)(4).

Review: This response is acceptable.

Conclusion: This method is suitable for intended use.