DEPARTMENT OF HEALTH & HUMAN SERVICES   Public Health Service

Division of Biological Standards & Quality Control, Office of Compliance & Biologics Quality,
Center for Biologics Evaluation & Research, Food & Drug Administration, MD 20993

MEMORANDUM

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To	STN 125512/0
Through	Dr. William M. McCormick, Director OCBQ/DBSQC, HFM-680
Company	Baxter Healthcare Corporation
Product	Antihemophilic Factor (recombinant), Porcine Sequence, B-domain deleted
Subject	Final Review Memo for the Lot Release Tests for the Drug Product, STN: 125512, Antihemophilic Factor (recombinant), Porcine Sequence (OBI-1)

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Summary

A new BLA was submitted for recombinant Antihemophilic Factor (rp-FVIII), Porcine Sequence with the B-domain deleted. This document constitutes the Final Review Memo from DBSQC 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)----------------------------------

The original submission and the responses to the IRs sent on 24 February 2014 and 1 April 2014 were reviewed and included in the Primary Review Memo, dated 22 April 2014, in which we indicated that the Analysis of rpFVIII by ---(b)(4)------ Analysis Using -----(b)(4)------------ is approvable. The other three test methods (# 1-3 above) had outstanding issues. This memo will provide review of the response to the IRs received as Amendment 18 (5 May 2014) and Amendment 29 (25 August 2014) for these three assays.

In conclusion, we found that the following two test methods and their validations are also approvable.

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

However, we noted that the Analysis of rp-FVIII Activity by Chromogenic Assay has significant issues both in terms of the performance of the method and the method validation. The issues were discussed with the sponsor in a teleconference, held on 22

August 2014. The sponsor proposed to withdraw this method as a lot-release test for the
------(b)(4)---------------- drug product but report the results "for information only" in the
lot-release protocol. Since the potency is also measured by the One Stage Coagulation
Assay, the review committee felt that the sponsor's proposal is acceptable. The
coagulation (clotting) assay will be used as the lot-release test for the determination of the
potency of the drug substance and the product.

Submitted Information and Documents

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

- 125512/0.1 – 3.2.S.2.6 Reference Standard Development
- 125512/0.18 – 1.11.1 Quality Information Amendment, received 5 May 2014
    - 3.2.P.5.3 Validation of Analytical Procedure, received 5 May 2014
    - Qualification of TQC-004, Analysis of rp-FVIII Activity By Chromogenic Assay
      on the -----(b)(4)----------, Technical Report Number: TCR-05-009
- 125512/0.28 – 1.11.1 Quality Information Amendment, received 13 August 2014
- 125512/0.29 – 1.11.1 Quality Information Amendment, received 25 August 2014
    - Change Protocol for MF-13-003QC, Analysis of rp-FVIII Activity By
      Chromogenic Assay on the -----(b)(4)---------, Doc CP-14-105-AA
    - Report for the Change Protocol for MF-13-003QC, Analysis of rp-FVIII Activity
      By Chromogenic Assay on the -----(b)(4)---------, Doc CP-14-105-AA-01
    - 3.2.P.5.1 Specifications

Review Narrative

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

Outstanding Information Request (sent on 17 April 2014):

The responses to the following information requests (IR) were received on 5 May 2014
(Amendment 18) and 13 August 2014 (Amendment 28), and were not addressed in the
Primary Discipline Review Memo.

a. You have demonstrated specificity of the assay by spiking known quantities of
    rpFVIII to in-process samples. Your data do not demonstrate specificity of the assay for the
    OBI-1 final container drug product (OBI-1 FCDP) because, although the FCDP contains
    more purified rpFVIII, it also contains additional excipients. Furthermore, FCDP is only
    ---(b)(4)------- 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.

b. Please provide information on what material you used to spike rpFVIII to the in-process
    sample for the specificity study in document TCR-05-009.

c. 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.

d. 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.

e. 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.

f. Please revise your SOP to include the following and submit your revised SOP for review.

    i.   Details of dilution of the samples

    ii. Acceptable potency of the control for system suitability.

Response from the Sponsor and Review:

a. The sponsor clarified that in the assay, the OBI-1 drug product is diluted approximately ---(b)(4)-- in assay buffer to obtain a concentration range in the middle of the standard curve ----(b)(4)---------. Furthermore, they provided data from their LOD and LOQ summary which demonstrated that there was negligible effect of the assay buffer in the assay. We agree that since the samples are extensively diluted into assay buffer prior to analysis, the effect of excipients would be negligible. The demonstration that assay buffer has no effect in the assay in the LOD/LOQ data is adequate.

b. Baxter indicated that the in-house OBI-1 reference standard (b)(4) was used to spike in-process samples, and described the method used to prepare the dilution. Since using reference standard (b)(4) as both the reference standard for the specificity assay, as well as the sample used to spike in-process samples, is circular and is not acceptable. The sponsor's response led to additional IR sent on 6 August 2014 (see later).

c. Baxter acknowledged that in the Validation Report, VR-105, the method used to establish range was circular, as reference standard (b)(4) was used as both sample and standard. They asserted that the correct method was used in Technical Report, TCR-05-009, whereby three different OBI-1 batches, ------(b)(4)----------- and ---(b)(4)--, "only 1 of which was used for the standard curve" (b)(4)--, were used to measure accuracy. However, reviewing the submission we noted that the reference standard (b)(4) was used as both the reference standard and sample at the low point of the standard curve -(b)(4) for this study. Hence the study is again circular and is not acceptable. The sponsor's response led to additional IR sent on 6 August 2014 (see later).

d. Baxter clarified that the linearity, accuracy and precision evaluated in TCR-05-009 was measured at ----(b)(4)----------- of the highest point of the standard ---(b)(4)------ and not the target potency. Hence, the range of this assay was ---(b)(4)--------------. Furthermore, in subsequent validations, presented in VR-105, the range is measured at ---(b)(4)----- of the target value of the drug ---(b)(4)---------. The actual range is therefore ----(b)(4)-----------, which spans the ----(b)(4)-------- of the target potency.

Hence the sponsor felt they had measured linearity, precision and range over the correct range. The clarification that the results are based on percentages of the highest concentration of the standard curve, and not target potency, was acceptable. However, as already noted, the data cited for the low (b)(4) point of the linearity, accuracy and precision measurements in document TCR-05-009, as well as the range measurements described in VR-105, and cited as table 2 in the current document, uses (b)(4) reference standard as both sample and reference standard, which is circular. The sponsor's response led to additional IR sent on 6 August 2014 (see later).

e. The sponsor responded that ---(b)(4)-- standard is no longer available, making it impossible to show equivalency between the two standards. The two standards, -----(b)(4)-------------------------- were calibrated against different reference standards, with ---(b)(4)---- calibrated against the previous OBI-1 reference standard, (b)(4), and ---(b)(4)---- calibrated against the WHO 8th International Standard (IS) for FVIII potency. The company provided a detailed history of the development of the reference standards, as detailed in Section 3.2.S.2.6, Reference Standard Development. It was noted that with the development of subsequent reference standards, there was a decrease in potency, as measured by both the One Stage Clotting Assay (OSCA) and the Chromogenic Assay. Also different lots of chromogenic assay reagents gave different potency values when compared to the FVIII IS. [We made similar observation in our laboratory during in-support testing using the chromogenic assay method, memo from Tobin, dated 19 September 2014.] With the development of ----(b)(4)----- it was noted that the ratio between OSCA and the Chromogenic assay had increased from ---(b)(4)--, suggesting ----(b)(4)------ had a lower potency than previous reference standards.

We are concerned that for the development of reference standard, each was calibrated against the previous reference standard, and not validated against an International Standard. In particular, reference standard (b)(4), was used for the validation studies, while ----(b)(4)------ will be used for lot release testing, and no data has been provided to demonstrate equivalency between these two reference standards. This leads to the propagation error and the results are likely to be increasingly incorrect with time. This IR has not been addressed and generated a further IR (1.c below). The response led to additional IR sent on 6 August 2014 (see later).

f. Baxter stated that although some details, such as approximate potency of sample being ---(b)(4)--, and how to dilute in appropriate buffer, are provided in the SOP, they will review and make changes to the SOP to provide more detail as appropriate. Also, as the acceptable potency for the control for system suitability may vary from lot to lot, the sponsor does not feel it is appropriate to add the acceptable potency to the SOP as it may change over time. This is adequate.

Outstanding Information Request (sent on 6 August 2014):

The response to the following IR was received on 25 August 2014 (Amendment 29) and was not addressed in the Primary Discipline Review Memo.

a. In response to FDA Question 1c, the sponsor acknowledges that the method used was circular and provides additional qualification data for the range in the report TCR-05-009. However it appears in figure 3 as if reference standard (b)(4) was used to generate the data for the low (b)(4) point. This again is circular. Please provide data to support the range using a lot of FDCP that is different from the reference standard at -----(b)(4)------ of the target value of the drug.

b. In response to FDA Question 1d, the sponsor refers to Table 2 of document VR-105 to justify that they have evaluated potency in the correct range ---(b)(4)----- of target drug potency). However these experiments are based on using reference standard as sample and standard, which is circular, hence the IR has not been addressed. Please evaluate linearity, accuracy and precision at ---(b)(4)---- of the target potency in the assay.

c. In response to FDA Question 1e, the sponsor states that OBI-1 reference standard ---(b)(4)---- is no longer available, and that this standard was calibrated against the reference standard (b)(4). Please provide data illustrating the validation characteristics of (b)(4) against an international standard to show its suitability as a reference standard.

Response from the Sponsor and Review:

Baxter asserted that they were re-validating the rp-FVIII Chromogenic Assay and would submit the report by 8/25/2014.

Amendment 29 was received on 8/25/2014, which contained a change protocol for analysis of rp-FVIII Activity by the Chromogenic Assay, CP-14-105-AA, a report for the change protocol, CR-14-105-AA-01, as well as a new specification, 3.2.P.5.1 and justification of specification, 3.2.P.5.6.

Revised Validation Protocol

This study was undertaken to validate drug substance and drug product using the current reference standard ----(b)(4)------. Initial validation efforts, detailed in VR-105, had used the OBI-1 reference standard ----(b)(4)---, which had been calibrated against the previous OBI-1 reference standard (b)(4). The latter standard ----(b)(4)------ manufactured by the same process, showed an approximately 50% higher potency than the current reference standard. However, since it is no longer available, it is not possible to evaluate comparability between the previous and the present reference standards and combine the results obtained with the previous standard with those obtained with the current standard, hence the need to re-validate the method against the current reference standard -----(b)(4)---------- serial dilutions of the ---(b)(4)-- FDP in the range ---(b)(4)--------- were prepared. Each sample was measured in -(b)(4) with (b)(4) analysts. The method and the new acceptance criteria were clearly described in the new validation protocol. The acceptance criteria for the assay include the following: ----b(4)------------------------------
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-----b(4)--- For range and accuracy the average result of values between ---(b)(4)------ must be within ---(b)(4)----- of the expected value, while for the ---(b)(4)----, the average result should be within ---(b)(4)---. For ---(b)(4)-- and ---(b)(4)--- precisions, the % RSD for the ---(b)(4)------ values should be (b)(4), while the (b)(4)--- sample is simply reported. The reproducibility as measured in VR-105 will stand provided the acceptance criteria for repeatability and intermediate precision are met in this validation study. The study design and acceptance criteria in the validation protocol are acceptable.

Method Validation Report

As this is a quantitative method, the method validation evaluated the following characteristics: specificity, range, linearity, repeatability and intermediate precision. This validation report (CP-14-105-AA-01) supersedes the previous validation report VR-105.

Specificity was demonstrated by comparing the ---(b)(4)----- of assay blanks to that of the -----(b)(4)---------- on the reference standard curve ---(b)(4)----. The potency values of the assay blanks, calculated from the standard curve were -(b)(4)-, suggesting that there was no interference from the assay buffer in the assay. Furthermore, serial dilutions of ----(b)(4)------------ FDP produced a concomitant decrease in potency, suggesting a lack of interference from the sample matrix. The range was determined from the linearity studies, by measuring potency of ---(b)(4)---- FDP from ----(b)(4)---- of the test concentration ----(b)(4)------. The recovery of samples between -----(b)(4)--------- were --------(b)(4)----------------------------- for the FDP, while for the ---(b)(4)-- test sample, the average result was ------------(b)(4)-------------- for the FDP. All results were therefore within acceptable limits.

Linearity was assessed by plotting the average result against the target potency of the samples. Linear plots with R^2 values -----(b)(4)------------------ FDP were obtained. However, the sponsor did not demonstrate dilution parallelism between the ----(b)(4)------ reference standard and (b)(4) or FDP.

 ---(b)(4)----- precision (repeatability) was measured by comparing the %RSD values of samples from the linearity study. The %RSD values for the ---(b)(4)----- FDP met the acceptance criteria of (b)(4), except that the RSD values for the (b)(4)- samples were between ------------(b)(4)------------------------ for the FDP, however, there were no acceptance criteria for this sample and the results were simply reported. Intermediate precision was measured for -----(b)(4)------ FDP in -(b)(4)-. The acceptance criteria of RSD (b)(4) were met for all samples except for the ----(b)(4)-------, which showed an RSD of (b)(4). Both results suggest that the limit of quantitation for the assay should be set at a concentration greater than --(b)(4)-- Thus, the sponsor should reassess the range of this assay.

Method (In-Support Testing Results)

The FVIII potencies of five lots of OBI-1 were measured using the method described in the sponsor's SOP # 061497-SOP, ver. 4.0 using ---(b)(4)------ as the reference standard and ----(b)(4)-------, as the control and the results are summarized in Testing Memo –

FVIII chromogenic potency assay STN 125512 [memo from Tobin, dated 19 September 2014.] Measurements were made on two different days using two different kit lots. The potency values show significant variability between the two kit lots. Also, the acceptance criteria for a number of assay validity criteria were not met. These include: the R^2 value for the standard curve using Kit (b)(4) was (b)(4), which is below the acceptance criteria of (b)(4), and the slope ratios between control and standard were -----(b)(4)-----, using Kits (b)(4) and (b)(4) respectively, which are also below the acceptance criteria of ---------- (b)(4). In addition, the % RSD of the (b)(4) serial dilutions of the samples were greater than the acceptance criteria of -----(b)(4)—for three of the five lots tested using Kit (b)(4), and two of the five lots tested using Kit (b)(4).

In a teleconference on 8/22/2014 between the FDA and the sponsor, Baxter presented data illustrating that with the development of successive reference standards, there was a progressive decrease in potency of the standard. This shift was attributed to using the previous lot of the standard to qualify the subsequent lot, which resulted in a propagation of error and led to a Correction Factor to be applied to enable comparison of previous data with recent results. At the initial stage, the sponsor calibrated their reference standard against the WHO International Standard (IS) but found that, when tested against the WHO IS, the reference standards showed significant lot-to-lot variation. Thus, a direct comparison of results obtained at different times is not possible. To address this issue Baxter provided chromogenic assay results that are based on a theoretical calculation from the results obtained from the clotting assay using a conversion factor, which changes with time. Furthermore, the sponsor also reported lot-to-lot variation in potency determination of the drug product samples using the chromogenic assay and found the variability to be much greater when using the WHO FVIII International Standard compared to OBI-1 as the reference standard.

Conclusions

The method is clearly described and the method validation performed as per the revised validation protocol is adequate. However, the intermediate precision failed to meet acceptance criteria. The validation data also suggest that the lowest point of the assay range should be greater than -(b)(4), compared to -(b)(4)- indicated by the sponsor in their SOP. If this method is to be used in future, the sponsor should reassess the range of this assay. In addition, as stated in the Justification of Specifications, 3.2.P.5.6, which was submitted as part of amendment 29, significantly different potency values have been reported for the same product lot with successive lots of reference standards. In addition, some of the standards have not been calibrated against the primary standard (WHO International Standard) but against the previous lot of the standard, which led to the propagation of error. Thus, the results obtained by this method are not reliable. In addition, the assay shows different results with different lots of reagents, an observation which is also consistent with the observation made at LACBRP of DBSQC. Consequently, Baxter has proposed to research and develop the chromogenic method further and withdraw the use of this method for lot release. The OSCA (clotting) method will be used to determine potency as a lot-release test of the product and reported in the lot-release protocol. In addition, ratio of potency obtained by OSCA method to that obtained by the Chromogenic Assay method will not be reported. The sponsor's proposal is acceptable to CBER.

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

Outstanding Information Request:

The response to the following information requests (IR) was received on 5 May 2014 (Amendment 18) and was not addressed in the Primary Discipline Review Memo.

a. Please provide qualification data for the Positive Control (OCC-13-0906) used in this assay.

b. 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.

c. Please provide data to demonstrate repeatability (precision) of the assay over the assay range. We suggest that you use at least three concentration levels.

d. Please revise your SOP to include acceptable potency of the control for system suitability.

e. 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.

Response from the Sponsor and Review:

a. The sponsor provided data for the qualification of the positive control obtained at ----(b)(4)-------- sites with ----(b)(4)--- replicate determinations, respectively. One of (b)(4) data points at (b)(4) was an outlier. The remainder data was used to determine the acceptable range of the positive control. The data provided by the sponsor constitutes an example of how they qualified the positive control (OCC-13-0906) used in the method validation and how they qualified and continue to qualify the positive control. The response is adequate.

b. In response to our IR, the sponsor indicated, "As the reference standard was the only analyte of known purity available at the time of the validation it was used to prepare the standard curve and the range and accuracy solutions, this was considered to be satisfactory as the preparations were independent and the precision as repeatability and intermediate precision testing was performed on a separate batch of drug product (b)(4)----- …. In addition to the validation work performed the inclusion of an assessment of parallelism between DP and reference standard during routine analysis can also show evidence of accuracy, precision and linearity over the full range of the assay ----(b)(4)------ of nominal potency)." The sponsor's statement does not adequately address the IR issue. It is difficult to accept that the sponsor did not have actual product to use for method validation. In addition, we do not agree that demonstration of parallelism addresses accuracy and precision of the assay.

However, we noted that, in response to the IR # c., the sponsor provided data on the % recovery at --------(b)(4)------------ of the target concentration of the sample using the drug product OBI-1 in Table 5 of the Quality Information Amendment (1.11.1) document. Although the purpose of the data is to demonstrate repeatability, the same data can be used to assess accuracy and range of the assay. The results show that the % recoveries are ----------------(b)(4)---------------------, which met the acceptance criteria of (b)(4) recovery for accuracy. The results also show that acceptable linearity (validation report: 114393-RPT/1.0), repeatability and accuracy demonstrating (b)(4)---- of the target concentration as the acceptable range of the assay, which met the minimum requirement of ---(b)(4)-- of the target concentration.

c. In response to our IR, the sponsor provided results of repeatability data at -----(b)(4)----------- of the target concentration of the sample (table 5 of Quality Information Amendment, 1.11.1). The results of (b)(4) replicate analyses at each concentration using OBI-1 batch ---(b)(4)-- show RSD to be -----(b)(4)--------------- respectively, which met the acceptance criteria of (b)(4).

d. In response to our IR, the sponsor stated that the acceptable potency range of the control for system suitability varies from lot to lot of the control. Therefore, it is not practical to indicate the acceptable potency of the Control for system suitability in the SOP. However, the data are available and the supervisors know what the acceptable range is at a given time, but did not provide the details. Even though the IR was not adequately addressed, we decided to accept the response because in response to our IR # a., the sponsor provided detailed procedure and data to illustrate how the acceptable potency range was determined. This shows that the sponsor knows how to establish the acceptable range for the control.

e. In response to our IR, the sponsor presented data in Table 6 – Table 17 and Figure 2 – Figure 13 providing slopes, slopes, intercepts and distribution of residuals for both standard and DP samples demonstrating parallelism between the respective dilution curves. These results were obtained during the study of repeatability and intermediate precision and adequately address the IR.

Conclusion:

Based on the initial submissions and the response to our IRs, we conclude that the One-stage Coagulation assay has been adequately validated and the method can be approved for lot release of the drug product.

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

Outstanding Information Request: In response to our previous IR (dated 24 February 2014) you indicated that you assessed accuracy in the supplemental validation report, 113226-RPT. We found that you used (b)(4). However, (b)(4) is not your product. Please provide accuracy data over the proposed range of the assay, as requested previously, using OBI- FCDP.

Response from the Sponsor and Review: In the response dated April 17 2014 the Sponsor presented results of accuracy determinations using Drug Product by reanalysis of data from linearity studies initially presented in Validation Report 116647-RPT. The response vs ----(b)(4)---------- in Figures 1, 2 and 3 of 116647-RPT were combined to

make a single graph in Figure 15 of Quality Information Amendment (1.11.1). ------------
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---(b)(4)---

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

Conclusion:

Based on the initial submissions and the response to our IRs, we conclude that the
method for the Analysis of rpFVIII by ------(b)(4)------------------------------- has been
adequately validated and the method can be approved for lot release of the drug product.