

To: Review Committee Chair,

Through: Kori Francis, Team Leader, LACBRP, DBSQC, OCBQ

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From: Grainne Tobin, LACBRP, DBSQC, OCBQ

Date: 19 September, 2014

Sponsor/Product: Baxter Healthcare Corp./ Recombinant Porcine Factor VIII, B-Domain Deleted (OBI-1)

Re: STN 125512 In-support testing to measure the Factor VIII potency of OBI-1 using the -(b)(4)- Factor VIII Chromogenic Assay kit.

Background:

A request was made to measure the FVIII potency of OBI-1 using the -(b)(4)- Factor VIII Chromogenic assay kit. FVIII potency of five lots of OBI-1 product was measured using two lots of the kit.

Method:

In-support testing of five lots of OBI-1 final drug product for STN 125512 was carried out at LACBRP/ DBSQC/ CBER using the Factor VIII chromogenic assay kit -(b)(4)---- from -(b)(4)- and compared to data provided by Baxter. The method detailed in 061497-SOP / 4.0 from Baxter was used to measure OBI-1 potency using the -(b)(4)- kit, with the following modifications: (1) the standard curve was 0.03 – 0.00375 IU/ml, instead of --- (b)(4)----- (2) the potency, as measured by the intensity of the colored product, was measured using a Bio Tek microplate spectrophotometer, instead of an ----- (b)(4)----- . The reference standard, ---(b)(4)-----, and control, ---(b)(4)----, were used for the analysis. Two measurements were made using two different kit lots on two different days and the data are presented in Table 1.

Results:

- The results were calculated by linear regression analysis using the manufacturer's Reference Standard, ---(b)(4)----- . The standard curve met the validity criteria for Kit -(b)(4)- with an R2 value of (b)(4), while the standard curve using Kit (b)(4) did not meet the criteria as the R2 value was (b)(4).
- The potency of the Control, ----(b)(4)-----, was measured at 10.66 and 0.31 IU/ml on separate days, 5/21/2014 and 5/23/2014, which is ----(b)(4)----- of the manufacturer's reported value of -(b)(4)--, suggesting that there were an error in testing the control on the second day.
- The % RSD for duplicate samples met the assay validity criteria of (b)(4) for both kits. However, the average % RSD for the (b)(4) dilutions of each sample was (b)(4) for three of the five OBI-1 lots tested using Kit -(b)(4)-, and two of the five lots tested using Kit -(b)(4)-, which was above the acceptance criteria. The slope ratio between control and standard was 0.78 and 0.64, using Kits ----(b)(4)-----, respectively, which did not meet the acceptance criteria, ---(b)(4)--. The slope ratios between samples and standard for lots tested using Kit (b)(4) were between 0.87 and 1.12, and 0.95 – 1.11 for Kit (b)(4), which were within the acceptance criteria.
- The measured Factor VIII potencies are presented in Table 1.

Table 1: Summary of Results from DBSQC/ LACBRP and Comparison with Manufacturer's Results.

Lot number	Baxter Calculated Result (b)(4)	CBER FVIII Potency Value (IU/ml)	
		Kit (b)(4) 5/21/2014	Kit (b)(4) 5/23/2014
(b)(4)	270	340	279
(b)(4)	270	257	346
(b)(4)	294	335	327
(b)(4)	302	265	357
(b)(4)	286	314	305

* Values provided in 125512/0.29 1.11.1 Quality Information Amendment

- The Baxter's results for the 5 lots in Table 1 are theoretically calculated results. The sponsor has not provided experimental results for any of the 5 lots in Table 1 using (b)(4) reference standard. Baxter noted a change in the potency of successive reference standards with time. Since the batch analysis results provided for (b)(4) and (b)(4) had been carried out using reference standard, (b)(4), and the lot release data for (b)(4) had been measured using (b)(4), it was necessary to apply a correction factor to convert the measured potency results to those expected if (b)(4) had been used as the reference standard. This correction factor is necessary as (b)(4) will be the reference standard going forward. Baxter also noted that different lots of the chromogenic assay kit gave different potency results.

Conclusions:

- The results show that the potency values measured at CBER by the Factor VIII Chromogenic Assay were variable, depending on the kit used for measurement, and did not meet the acceptance criteria on some occasion.
- R² of the standard curve did not meet the validity criteria for Kit (b)(4).
- All data provided by Baxter are based on theoretical calculation using an average correction factor. The sponsor did not provide any experimental results for the 5 lots tested.

4. Since the Chromogenic Assay produced variable results at both CBER and Baxter and due to the change in potency of successive reference standards, it was decided that Baxter would continue to perform the FVIII Chromogenic assay but that the results would be reported for information purposes only. The One Stage Clotting Assay will be used as the potency assay.