Our Reference: BL 125577/0

Baxter Healthcare Corporation
Attention: Maximilian Fernandez, PhD
April 23, 2015
Sent by email

Dear Dr. Fernandez:

We are reviewing your December 19, 2014, biologics license application (BLA) for von Willebrand Factor (Recombinant). We determined that the following information is necessary to continue our review:

Determination of Ristocetin Cofactor Activity

1. We have the following information request regarding your CTP, document number VN1306081TB-CTP00.05:

   a. In section 5 of your CTP, it is not clear how you fit your sample and reference curves. Please clarify if you are using linear or non-linear curve fit. If curve fitting is not linear regression, please explain the meaning of "slope" and "slope ratio" because slope of each curve changes at every point for a non-linear curve.

   b. Please provide details of calculation of parallelism for your curve fitting.

   c. (b) (4)

   d. Please revise section 5 to include acceptable range of slope ratio (based on validation and historical data) as an acceptance criterion and submit for review.

2. We have the following information request regarding your Method validation report, document number VN-13-06081TB-CVRX1.06:

   a. To demonstrate specificity of your method, please provide data to show that the matrix of the drug product (which does not contain vWF:RCo) does not affect the assay results significantly.

   b. Table 3 of your validation report shows that the results obtained with the standard curves are not valid (n.v.) for the standard (WHO (b) (4)). We do not agree that data from TE1 and TE4 can be included in the evaluation of the validation

characteristics.   Please recalculate all validation characteristics after excluding the data from TE1 and TE4 and resubmit for review.

c. (b) (4)

d. Please provide appropriate data analysis to show parallelism between the standard and samples for each experiment to demonstrate linearity of your method.

e. In section 5.8.2, your criterion for acceptance of parallelism is (b) (4)   This range is too wide. Please justify why this wide range is acceptable, with appropriate calculations and literature reference.

f. (b) (4)

g. For robustness studies in section 5.10.1.3, the report stated that "Statistical significance is obtained for the analyzers (b) (4)   but not for the reagents (b) (4)) or operators (b) (4))." Please clarify this statement indicating what your null hypothesis is, what your conclusions are and how you arrived at the conclusions (your calculations).

Determination of the (b) (4) **rVWF Samples**

3. We have the following information request regarding your Method validation report, document number VN1306101TB-CVR00.03:

(b) (4)

(b) (4)

Determination of vWF (b) (4)

4. We have the following information request regarding your Method validation report, document number VN1306136TB-CV00.02:

(b) (4)

(b) (4)

Determination of the (b) (4)

5. We have the following information request regarding your Method validation report, document number OR1100019-CVRX1.04:

(b) (4)

6. We have the following information request regarding your Method validation report, document number OR-13-00127:

(b) (4)

(b) (4)

Purity and identity by (b) (4)

7. We have the following information request regarding your Method validation report, document number OR13-00693:

(b) (4)

Determination of (b) (4) **in recombinant vWF samples by** (b) (4)

8. We have the following information request regarding your Method validation report, document number VN 13-06113TB:

(b) (4)

Determination of Polysorbate 80 by (b) (4)

9. We have the following information request for your Method validation report, document number VN1104053TB-CVRX3.02:

a. In your accuracy determinations (section 4.2), you have not specified the initial polysorbate 80 content in the rVWF drug product. Assuming the polysorbate 80 concentration to be approx. (b) (4) (from the batch analysis results), your validated range is (b) (4) . Thus, your accuracy data does not cover the lower specification limit of the product (b) (4) Please provide additional results of accuracy of the method using your drug product, evaluated at minimum (b) (4) of the target concentration.

b. Please provide the linearity plot of (b) (4)) against the analyte concentration (polysorbate 80) for your standard (section 4.6.1).

c. You have evaluated linearity and range from the accuracy results of rVWF drug product samples. Please re-evaluate these characteristics (including linear regression plots) based on the revised accuracy data as requested above, modify your validation report accordingly, and submit for review.

d. You have studied specificity (section 4.5) by measuring the response of buffer used for the preparation of polysorbate 80 standards. Please provide data obtained by the analysis of representative rVWF product matrix, which contains all components of the drug product except polysorbate 80, to demonstrate the specificity of your method and that the results are not affected by the product matrix.

e. You have evaluated intermediate precision (section 4.4) using (b) (4) which is a different product. Thus, the results are not applicable to rVWF drug product. Please provide data obtained using rVWF drug product to demonstrate that the assay variability is within the acceptable range.

f. You have not submitted the robustness data for your method. Please provide the results to permit complete review of your assay.

Determination of the Mannitol and Trehalose dihydrate content

10. We have the following information request regarding your Method SOP (NE-11-00131):

a. In the section 5.1.1 of your SOP the acceptance criterion for (b) (4) . It is not clear what you mean by percent (%). Please clarify this acceptance criterion with supporting data, including calculation or make adequate correction, if necessary.

Sodium Assay by (b) (4)

11. We have the following information request for your Method validation report, document number VN1104082TB-CVRX4.02:

a. For determination of specificity, you did not provide a list of the (b) (4) used. Please provide a list of the (b) (4) used, their concentrations, and data to show their effects on the Na concentrations.

b. For determination of robustness, you did not provide the details of the parameters which were varied. Please provide details of the parameters varied and their effects on the results of Na concentrations.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response to this information request as an amendment to this file by May 7, 2015 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

The action due date for this file is December 19, 2015.

If you have any questions, please contact me at (240) 402-8447 or cherie.ward-peralta@fda.hhs.gov.

Cherie Ward-Peralta, M.S.
Regulatory Project Manager
Office of Blood Research and Review
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
WO-71- 4254
Silver Spring, MD 20993
Phone: 240-402-8447
Email: cherie.ward-peralta@fda.hhs.gov