

From: Thompson, Edward
Sent: Friday, February 27, 2015 2:05 PM
To: 'Erik Bjornson (Erik_Bjornson@baxter.com)'
Subject: Information Request for BL 125566/0

Contacts: Erik Bjornson - Baxter Healthcare Corporation

Dear Mr. Bjornson:

We are reviewing your November 25, 2014 biologics license application (BLA) for Antihemophilic Factor (Recombinant), PEGylated. We are providing the following comments and request for additional information to continue our review:

1. Determination of recombinant Factor VIII potency by clotting method

- a. We have reviewed your SOP, document number NE-40-1300032-CTP/Ver.4, and have the following information requests.
 - i. Your SOP for the factor VIII clotting assay does not provide any details of the calculation of the factor VIII potency, including construction of the calibration curve, the sample and control dilution curves, and parallel line analysis of the data. Please revise your document to add the details and submit for review.
 - ii. You are calculating potency from parallel line analysis. However, section 5.1 of your SOP does not have any acceptance criteria on parallel line analysis. Please revise the document to include adequate acceptance criteria regarding acceptance of the results of parallel line analysis and submit for review.
- b. We have the following information requests for your method validation report, document number 2009 (b) (4)/METHODE/CLOTting/Ver.3
 - i. For linearity study you have provided only r^2 value of the standard curve (Table 4 of the validation report, document number 2009 (b) (4)/METHODE/CLOTting/Ver.3) but no details. Furthermore, you have not provided linearity data from the control and the drug product BAX855. Please provide linearity data of the standard, control and sample, including the plots, their respective slopes, and results of parallel line analysis to show that they are parallel at a predefined confidence interval.
 - ii. You have not assessed repeatability and robustness using the drug product "HalfLife" (BAX855) for which the assay is intended. Please provide data using the drug product "HalfLife" (BAX855).
 - iii. You have assessed accuracy of your method by spiking the control (b) (4) to the drug product. However, it is not clear what (b) (4) is and how you calculated recovery. Please provide details of the description and composition of (b) (4), and calculation of recovery.

- iv. How did you measure activity of (b) (4) for your accuracy study? If you used the same method as being validated, your accuracy assessment is circular and the results do not show accuracy of your assay method. In that case, please provide results of your accuracy assessment either (1) by spiking your final drug product with a suitable International Standard or (2) from comparison of results of BAX855 obtained by the current method (being validated) and an orthogonal method.
- v. You have not assessed specificity of the method reasoning that you used FVIII (b) (4) for the assay. Please provide data to show that the product matrix (all components of the product except the active component, FVIII) show no or negligibly small activity to demonstrate specificity of your assay.
- vi. You have determined your assay range based on linearity, accuracy and precision, which were obtained using either the standard or a different product, as discussed above. Please recalculate your assay range based on the linearity, accuracy and precision results, as requested above, using the actual drug product.

2. Determination of FVIII Recombinant (rAHF) Potency by (b) (4)

In the Method Validation Report 2009 (b) (4)/METHODE/(b) (4)/Ver.4, you have assessed accuracy of the method by mixing BAX855 with Advate final container, and the potencies of both materials and when they are mixed are measured by the same FVIII (b) (4) assay. This is circular and does not show accuracy of your method. Please provide accuracy data either (1) by spiking your final drug product with a suitable International Standard or (2) from comparison of results of BAX855 obtained by the current method (being validated) and an orthogonal method.



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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 March 13, 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.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is November 25, 2015.

Please send an acknowledgement for receipt of this request.

If you have any questions, please contact me at (240) 402-8443.

Sincerely,

Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/RPMS

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Our Reference: BL 125566/0

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