

From: Thompson, Edward
Sent: Friday, May 01, 2015 11:46 AM
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 have reviewed your responses to our IR, received on 11 March 2015, 3 April 2015, and 20 April 2015, and the associated documents (SOPs and Validation Reports) and request additional information to continue our review:

1. Determination of FVIII Recombinant (rAHF) Potency by (b) (4)
 - a. Please provide response to the following information requests regarding the validation report, document number 2014-(b) (4) /Clotting-(b) (4) - RFPQ1/Ver.2
 - i. In section 5.3: PQ03 Accuracy (WHO^{(b) (4)} Spiked Samples) of the validation report, you reported measurement of accuracy by preparing (b) (4) . However, you did not cover the range of the assay. In section 5.4: PQ04 Accuracy (Standard over the range), you provided additional accuracy data whereby the standard (b) (4) was prepared at (b) (4) and evaluated against the same standard. This is circular. Furthermore, the standard, (b) (4), is not the drug product for which this test is intended to be used for lot-release testing. In the Quality Information Amendment 8, you stated that accuracy was assessed by spiking BAX 855 drug product with (b) (4) different concentrations (b) (4) of the (b) (4) International Standard. However, we could not find this data in your validation report or anywhere else in your submission. Please provide the accuracy data that you reported to have assessed by spiking BAX 855 drug product with (b) (4) different concentrations ((b) (4)) of the (b) (4) International Standard.
 - ii. Please clarify how in section 5.4: PQ04 Accuracy of the validation report, you prepared (b) (4) samples of potency (b) (4) however the measured values ranged from (b) (4) .
 - iii. In section 5.7: PQ07 Specificity of the validation report, you reported specificity by comparing results obtained with (b) (4) . However, in the Quality Information Amendment 8, you stated that specificity was measured comparing BAX 855 FDP and (b) (4) . We could not find this data in your validation report or anywhere else in your submission. Please provide the data in which you compared results at different dilutions of

BAX 855 FDP and (b) (4) to demonstrate method specificity. Please note that (b) (4) is not the drug product for which this test is intended to be used for lot-release testing.

- iv. In section 5.8: PQ08 Linearity of the validation report, you assessed linearity by comparing the calibration curves generated for the Intermediate Precision study using (b) (4). However, in the Quality Information Amendment 8, Received 3 April 2015, you stated that linearity and parallelism between the standard and BAX 855 was measured and the comparability of results was analyzed by ANOVA test. We could not find this data and details of your ANOVA test in your validation report or anywhere else in your submission. Please provide the data demonstrating linearity of the standard and the drug product and parallelism between the two dilution curves, including details of your ANOVA test.
- v. It is not clear to us how you can demonstrate dilution parallelism between standard and drug product from ANOVA test. Please explain with adequate literature reference
- vi. Please reassess your assay range based on the accuracy and linearity data as per the comments above and submit for review.

2. Determination of Total Protein Concentration by (b) (4)

- a. We have the following information request regarding the validation report, Document 2015-Total Protein-BAX855-RFPQ1/Ver.1.
 - i. You have not provided the requested linearity data but just said that the results for R, y-intercept, slope and slope ratios were within the specified limits. Please submit the results and representative plots of the standard and samples obtained for the linearity evaluations.
 - ii. In your accuracy determinations, you have defined the assay range as (b) (4) protein/ml of the drug product. However, you have mixed the drug product with the same amount of spiking material (FDP BAX 855 (b) (4)), and have measured the combined accuracy in the range of (b) (4). Although, the results met the acceptance criteria, please note that only one concentration is within your proposed assay range. Thus, we cannot conclude that accuracy was adequately demonstrated for your assay range. Please provide additional data, at least at three concentration levels covering the intended assay range, to demonstrate accuracy of the method for the drug product, BAX 855. Also, if required, please re-evaluate your assay range based on the revised accuracy data.

3. Residual Moisture Content by (b) (4)

- a. Please address the following questions regarding your revised SOP, Document VN1104033TB-CTP00.04

- i. In section 5.1 of your method SOP, please clarify which water standard and control sample is to be used for the assay.
 - ii. Please specify the acceptable limits (Assay Validity Criteria) for the control sample.
 - b. We have the following information request for the method validation report, Document VN-11-04033TB-45-VB.01
 - i. In response to Question 4b.i of the IR submitted on 23 Feb 2015, you indicated that the three data points ((b) (4)) analyzed in the accuracy studies cover the intended assay range. We could not understand how you have evaluated the range from the above data. Based on our analysis of the submitted data, two of the moisture levels, (b) (4) (corresponding to approx. (b) (4) moisture), are well above the proposed specification limit of (b) (4). Please provide adequate explanation or submit data for accuracy evaluation at the LOQ level, and at least at two additional moisture levels between the LOQ and the proposed specification limit to demonstrate accuracy of the method.
 - ii. In response Question 4b.ii of the IR submitted on 23 Feb 2015, you indicated that LOQ is the lowest validated amount in the accuracy studies and have reported this value as (b) (4). Your linearity plots range from (b) (4) content, and you evaluated accuracy at (b) (4). Please provide appropriate explanation, and if required, re-evaluate the LOQ, linearity (data and plots), accuracy (as requested above) and range of the assay, and modify your validation report accordingly, and submit for review.
4. Determination of Polysorbate 80 by (b) (4)
 - a. We have the following information request for the validation report, Document 2011-Polysorbate80-BAX855-RFPQ1-AD1/Ver.1.
 - i. In our previous IR (Question 9a.i, sent on 23 Feb 2015), we requested linearity data for the drug product. In response, you provided an explanation to support that the data obtained with polysorbate 80 standard as representative of that from the drug product samples because the method involves (b) (4) ((b) (4)). This response is not acceptable because the drug product matrix contains other components, which may not be removed by the (b) (4) step. At least, you have not presented any data to show that they are removed. Therefore, such components may impact on the assay results. Please provide appropriate linearity data obtained using the drug product, and demonstrate parallelism of results between the standard and samples by regression analysis, as requested in the previous IR.

- ii. As requested in the previous IR question (9a.ii, sent on 23 Feb 2015), please re-evaluate range of the assay based on the revised linearity, accuracy and precision data obtained using representative drug product samples, revise your validation report accordingly and submit for review.
- iii. We could not find the robustness data in the validation reports (documents 2011-POLYSORBATE80 -BAX855-RFPQ1/Ver.1 and 2011-POLYSORBATE80 -BAX855-RFPQ1-AD1/Ver.1) submitted by you. The summary section of the validation report refers to robustness assessed using a product (Advate), which is different from the product under consideration in the current submission (BAX855). Please provide appropriate results for the robustness of your method using BAX 855 drug product.



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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 May 14, 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

Baxter Healthcare Corporation
Attention: Mr. Erik Bjornson
May 1, 2015
Sent by email

Dear Mr. Bjornson:

We are reviewing your November 25, 2014 biologics license application (BLA) for Antihemophilic Factor (Recombinant), PEGylated. We have reviewed your responses to our IR, received on 11 March 2015, 3 April 2015, and 20 April 2015, and the associated documents (SOPs and Validation Reports) and request additional information to continue our review:

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 - iv. In section 5.8: PQ08 Linearity of the validation report, you assessed linearity by comparing the calibration curves generated for the Intermediate Precision study using (b) (4). However, in the Quality Information Amendment 8, Received 3 April 2015, you stated that linearity and parallelism between the standard and BAX 855 was measured and the comparability of results was analyzed by ANOVA test. We could not find this data and details of your ANOVA test in your validation report or anywhere else in your submission. Please provide the data demonstrating linearity of the standard and the drug product and parallelism between the two dilution curves, including details of your ANOVA test.
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demonstrate accuracy of the method for the drug product, BAX 855. Also, if required, please re-evaluate your assay range based on the revised accuracy data.

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other components, which may not be removed by the (b) (4) step. At least, you have not presented any data to show that they are removed. Therefore, such components may impact on the assay results. Please provide appropriate linearity data obtained using the drug product, and demonstrate parallelism of results between the standard and samples by regression analysis, as requested in the previous IR.

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