

**From:** Thompson, Edward  
**Sent:** Monday, February 23, 2015 6:36 AM  
**To:** 'Erik Bjornson (Erik\_Bjornson@baxter.com)'  
**Subject:** Information Request for BL 12566/0

**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 FVIII Recombinant (rAHF) Potency—(b) (4) Assay**

- a. For Analytical Procedure, NE-13-00031E/Ver.82
  - i. Please clarify which reference standard is to be used for the assay. In the analytical procedure, use of the reference standard (b) (4) is instructed. However, in the method validation report, you used reference standard lot number (b) (4). How are the two reference standards related? If they are not the same material, please provide full compositions of both standards and explain how method validation conducted using the standard lot number (b) (4) could apply to your assay, which is to be performed using a different reference standard material.
- b. For Method Validation Report 2009, (b) (4)/METHODE/(b) (4)/Ver.4
  - i. You have analyzed repeatability of your method using (b) (4) Final Container. Please provide data for your drug product, termed “HalfLife” in your validation report (FDP BAX855), for which the method is intended to be used.
  - ii. You have provided data from the standard only to demonstrate linearity of your assay. Please provide data demonstrating linearity of the drug product, FDP BAX855, at least over the range of (b) (4) of your target concentration and parallelism between the standard and drug product regression lines with this range.

- iii. We do not agree that specificity does not need to be assessed because the assay uses (b) (4). Please provide specificity data for your drug product, FDP BAX855, and demonstrate that the drug product matrix does not contribute significantly to the assay results.
- iv. The range of the assay has been assessed from accuracy, linearity and repeatability studies, which has been measured using the (b) (4). Please provide data for potency of the drug product, FDP BAX855, at least over the range of (b) (4) of your target concentration.
- v. Robustness was assessed using (b) (4) Final Container. Please provide data for the robustness of your assay using the drug product, FDP BAX855 for the parameters you have chosen.

**2. (b) (4)-FVIII binding using (b) (4) Method**

- a. Analytical Procedure for (b) (4)-FVIII binding using (b) (4), NE-13-00146
  - i. The method validation (report number 2013-BAX855-FVIII-(b) (4)-Binding-(b) (4) RFPA1/Ver.1) described that you have followed the SOP to prepare negative controls, (b) (4). However, the negative control preparation procedures are not described in the SOP. Please include the procedures in the SOP and resubmit.
  - ii. In section 5.5.4 (b) (4) step, please provide a description/composition of the (b) (4).
- b. For validation Report, 2013-BAX855-FVIII-(b) (4)-Binding-(b) (4)-RFPA1/Ver.1:
  - i. In the SOP, (b) (4) is listed as a critical reagent. Please provide the lot number of this reagent used in validation.
  - ii. You used the (b) (4) final drug product with a known FVIII (b) (4) activity as a standard. Please provide data for the standard qualification.
  - iii. In measuring intermediate precision in your validation assay, the result average CV% of parameter (b) (4) which is not conformant to the acceptable criteria (b) (4) The average CV% for parameter (b) (4) which is unacceptably high. Please provide adequate data to show that results conform to the preset acceptance criteria.

**3. Determination of Total Protein Concentration by (b) (4)**

- a. You have validated the protein assay using (b) (4) lot as a reference standard (report # 2011-TOTAL-PROTEIN-A(b) (4)-BAX855-RP1/Ver.1).

Please explain how the protein value was assigned to this reference standard and provide data for the qualification of this standard. If you obtained protein value using the same method as being validated, it is circular and some of the validation characteristics (e.g., accuracy) may not be acceptable.

- b. Your validation study includes samples (b) (4) evaluated from the calibration curve using (b) (4) reference standard. Please explain how these samples are relevant to the validation of the assay for BAX855 (current submission).
- c. In section 4.6 of your validation report, you have described the sample preparation of FDP BAX855, 1000 IU potency/strength only. However, we did not find this description in your SOP. Please explain. If applicable, please add appropriate sample preparation including reconstitution volume for samples of all strengths/potencies intended to be analyzed by this assay in the test method SOP (document #.NE-40-11-0047) and submit for review.
- d. In your linearity data presented in section 9.4.4 of your validation report, FVIII (b) (4) (b) (4) was analyzed at different concentrations. However, you have not provided linearity data for any of your DP samples for which the assay is intended. Please provide data using representative DP samples and demonstrate parallelism between the standard and sample regression lines.
- e. You have demonstrated accuracy of the method by spiking (b) (4) reference solution into (b) (4) samples containing approx. (b) (4). Thus, you have studied accuracy at one concentration level only. Please provide accuracy data using your DP samples, over the proposed assay range.
- f. You have established range of the assay based on the linearity and accuracy results of (b) (4) reference standard. The range should be supported by the data obtained from the drug product samples intended to be analyzed by this assay. Please provide appropriate linearity, accuracy and precision data using the drug product, FDP BAX855, to establish range of the assay for which the method is intended to be used (current submission).

#### **4. Residual Moisture Content by (b) (4)**

- a. For your SOP, Document VN1104033TB-CTP00.01:
  - i. Please describe the acceptable system suitability criteria for this assay in section 5.1 of your SOP.
  - ii. Please include the details of the preparation of final container samples of all drug product strengths/potencies in section 4.1 of your SOP, including the (b) (4) of the sample taken to permit calculation of percent moisture content and submit for review.

b. For the Method validation report, Document VN-11-04033TB-45-VB.01:

- i. Based on the information you provided, it is not clear if the accuracy data covers the proposed assay range. Please provide accuracy data from adequate number of points between the LOQ and the specification limit of (b) (4), including these two points. We suggest that you evaluate accuracy of your method at LOQ, specification limit, and at least one point in-between.
- ii. You have evaluated Linearity, LOQ and range from the accuracy results of the drug product samples. Please re-evaluate these characteristics (including linear regression plots) based on the revised accuracy data as requested above, and accordingly revise your validation report and submit for review.

**5. Free FVIII subunit by (b) (4)**

- a. From the accuracy data you provided in the validation report (#2011-FREEFVIIISUBUNIT-BAX855-RFPQ1/VER.2), it is unclear how the theoretical percentage value of free subunit of the spiked material was obtained. If it was obtained using the same method as being validated, the validation of accuracy is circular and is not acceptable. Please provide information on how the percentage was obtained and, if appropriate, please provide data of your method accuracy using the percentage of free subunit obtained by a different method, preferably using an orthogonal method.
- b. Please provide representative (b) (4) of blank, control and samples to demonstrate specificity of your method.

**6. FVIII identity by (b) (4)**

- a. In validation report, CCR00001796, for the test method for Identification of FVIII Recombinant and (b) (4) (SOP # NE-40-1100044) you have not provided (b) (4). Please provide the (b) (4) in support of section 7 (Results).
- b. Please amend section 5 (Evaluation) of the test method SOP # NE-40-1100044 to require inclusion of a (b) (4) in the reportable results.
- c. Please provide the lot numbers of the BAX-855 FC used for the validation study.
- d. Please provide latest version of the Test Method# NE-40-1100044.

**7. Mannitol and Trehalose Assay**

- a. In the section 5.1.1 of your SOP (NE-11-00131) "Determination of the Mannitol and Trehalose dihydrate content", the acceptance criterion for (b) (4)

It is not clear what you mean by percent (%). Please justify this acceptance criterion with supporting data, including calculation or make adequate correction, if necessary.

- b. You have not provided linearity and precision data to cover entire range of the assay for mannitol and trehalose dihydrate using BAX855 FDP samples in the validation report (2011-MAN/TRE-BAX855-RFPQ1/Ver.2). Please provide the requested data.

**8. (b) (4) total Glutathione assay**

- a. Please add number of theoretical (b) (4) as system suitability check criteria to your SOP (NE-11-00138) section 5.1 and set acceptance criteria based on your historical data.
- b. Please include the (b) (4) used for the assay in section 3.1 of the SOP and resubmit for review.
- c. The quantification limits for (b) (4) stated in section 5.2 of your SOP are inconsistent with the results in section 5.8 of your validation report (2012-GLUTATHIONE-ADVATE-BAX855-RFPQ1 / Ver.1). Please explain.
- d. You have not provided linearity and precision data in your validation report, which cover entire range of the assay for (b) (4) using BAX855 FDP samples in the validation report. Please provide the requested data.

**9. Determination of Polysorbate 80 by (b) (4)**

- a. For your Method validation report, Document 2011-POLYSORBATE80-BAX855-RFPQ1-AD1/Ver.1:
  - ii. As per the data presented in section 7.7, you have studied linearity using polysorbate 80 standards, analyzed at different concentrations. Please provide data to demonstrate linearity of the method using the drug product and parallelism of results between the standard and the drug product from regression analysis.
  - iii. You have established range of the assay (section 7.8) based on the linearity data of polysorbate 80 standards only. The range should be determined based on the linearity, accuracy and precision data obtained from the representative drug product samples. Please provide appropriate data obtained with the drug product for linearity, accuracy and precision, and the assay range.
  - iv. In section 2 under “scope”, section 7.6 “under specificity”, and section 4.0 “under validation approach”, you have indicated that validation was previously performed using BAX855 1000 IU/vial drug product, and was documented in Report 2011-POLYSORBATE-BAX855-RFPQ1/Ver.1. The above mentioned report was not included in this submission. Please provide the report for our review.



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 9, 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  
February 23, 2015  
Sent by email

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 FVIII Recombinant (rAHF) Potency—(b) (4) Assay**

- a. For Analytical Procedure, NE-13-00031E/Ver.82
  - i. Please clarify which reference standard is to be used for the assay. In the analytical procedure, use of the reference standard (b) (4) is instructed. However, in the method validation report, you used reference standard lot number (b) (4). How are the two reference standards related? If they are not the same material, please provide full compositions of both standards and explain how method validation conducted using the standard lot number (b) (4) could apply to your assay, which is to be performed using a different reference standard material.
- b. For Method Validation Report 2009, (b) (4)/METHOD (b) (4)/Ver.4
  - i. You have analyzed repeatability of your method using (b) (4) Final Container. Please provide data for your drug product, termed “HalfLife” in your validation report (FDP BAX855), for which the method is intended to be used.
  - ii. You have provided data from the standard only to demonstrate linearity of your assay. Please provide data demonstrating linearity of the drug product, FDP BAX855, at least over the range of (b) (4) of your target concentration and parallelism between the standard and drug product regression lines with this range.

- iii. We do not agree that specificity does not need to be assessed because the assay uses (b) (4). Please provide specificity data for your drug product, FDP BAX855, and demonstrate that the drug product matrix does not contribute significantly to the assay results.
  - iv. The range of the assay has been assessed from accuracy, linearity and repeatability studies, which has been measured using the (b) (4). Please provide data for potency of the drug product, FDP BAX855, at least over the range of (b) (4) of your target concentration.
  - v. Robustness was assessed using (b) (4) Final Container. Please provide data for the robustness of your assay using the drug product, FDP BAX855 for the parameters you have chosen.
2. (b) (4)-FVIII binding using (b) (4) Method
- a. Analytical Procedure for (b) (4)-FVIII binding using (b) (4) (b) (4), NE-13-00146
    - i. The method validation (report number 2013-BAX855-FVIII-(b) (4)-Binding-(b) (4) RFPA1/Ver.1) described that you have followed the SOP to prepare negative controls. (b) (4). However, the negative control preparation procedures are not described in the SOP. Please include the procedures in the SOP and resubmit.
    - ii. In section 5.5.4 (b) (4) step, please provide a description/composition of the (b) (4).
  - b. For validation Report, 2013-BAX855-FVIII-(b) (4)-Binding-(b) (4)-RFPA1/Ver.1:
    - i. In the SOP, (b) (4) is listed as a critical reagent. Please provide the lot number of this reagent used in validation.
    - ii. You used the (b) (4) final drug product with a known FVIII (b) (4) activity as a standard. Please provide data for the standard qualification.
    - iii. In measuring intermediate precision in your validation assay, the result average CV% of parameter (b) (4) which is not conformant to the acceptable criteria (b) (4). The average CV% for parameter (b) (4) which is unacceptably high. Please provide adequate data to show that results conform to the preset acceptance criteria.



### 3. Determination of Total Protein Concentration by (b) (4)

- a. You have validated the protein assay using (b) (4) lot as a reference standard (report # 2011-TOTAL-PROTEIN (b) (4) BAX855-RP1/Ver.1) . Please explain how the protein value was assigned to this reference standard and provide data for the qualification of this standard. If you obtained protein value using the same method as being validated, it is circular and some of the validation characteristics (e.g., accuracy) may not be acceptable.
- b. Your validation study includes samples (b) (4) evaluated from the calibration curve using (b) (4) reference standard. Please explain how these samples are relevant to the validation of the assay for BAX855 (current submission).
- c. In section 4.6 of your validation report, you have described the sample preparation of FDP BAX855, 1000 IU potency/strength only. However, we did not find this description in your SOP. Please explain. If applicable, please add appropriate sample preparation including reconstitution volume for samples of all strengths/potencies intended to be analyzed by this assay in the test method SOP (document #.NE-40-11-0047) and submit for review.
- d. In you linearity data presented in section 9.4.4 of your validation report, FVIII (b) (4) was analyzed at different concentrations. However, you have not provided linearity data for any of your DP samples for which the assay is intended. Please provide data using representative DP samples and demonstrate parallelism between the standard and sample regression lines.
- e. You have demonstrated accuracy of the method by spiking (b) (4) reference solution into (b) (4) samples containing approx. (b) (4) . Thus, you have studied accuracy at one concentration level only. Please provide accuracy data using your DP samples, over the proposed assay range.
- f. You have established range of the assay based on the linearity and accuracy results of (b) (4) reference standard. The range should be supported by the data obtained from the drug product samples intended to be analyzed by this assay. Please provide appropriate linearity, accuracy and precision data using the drug product, FDP BAX855, to establish range of the assay for which the method is intended to be used (current submission).

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

- a. For your SOP, Document VN1104033TB-CTP00.01:
  - i. Please describe the acceptable system suitability criteria for this assay in section 5.1 of your SOP.

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- ii. Please include the details of the preparation of final container samples of all drug product strengths/potencies in section 4.1 of your SOP, including the (b) (4) of the sample taken to permit calculation of percent moisture content and submit for review.
- b. For the Method validation report, Document VN-11-04033TB-45-VB.01:
- i. Based on the information you provided, it is not clear if the accuracy data covers the proposed assay range. Please provide accuracy data from adequate number of points between the LOQ and the specification limit of (b) (4) including these two points. We suggest that you evaluate accuracy of your method at LOQ, specification limit, and at least one point in-between.
  - ii. You have evaluated Linearity, LOQ and range from the accuracy results of the drug product samples. Please re-evaluate these characteristics (including linear regression plots) based on the revised accuracy data as requested above, and accordingly revise your validation report and submit for review.

**5. Free FVIII subunit by (b) (4)**

- a. From the accuracy data you provided in the validation report (#2011-FREEFVIISUBUNIT-BAX855-RFPQ1/VER.2), it is unclear how the theoretical percentage value of free subunit of the spiked material was obtained. If it was obtained using the same method as being validated, the validation of accuracy is circular and is not acceptable. Please provide information on how the percentage was obtained and, if appropriate, please provide data of your method accuracy using the percentage of free subunit obtained by a different method, preferably using an orthogonal method.
- b. Please provide representative (b) (4) of blank, control and samples to demonstrate specificity of your method.

**6. FVIII identity by (b) (4)**

- a. In validation report, CCR00001796, for the test method for Identification of FVIII Recombinant and (b) (4) (SOP # NE-40-1100044) you have not provided (b) (4). Please provide the (b) (4) (b) (4) in support of section 7 (Results).
- b. Please amend section 5 (Evaluation) of the test method SOP # NE-40-1100044 to require inclusion of a (b) (4) in the reportable results.
- c. Please provide the lot numbers of the BAX-855 FC used for the validation study.
- d. Please provide latest version of the Test Method# NE-40-1100044.

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## 7. Mannitol and Trehalose Assay

- a. In the section 5.1.1 of your SOP (NE-11-00131) "Determination of the Mannitol and Trehalose dihydrate content", the acceptance criterion for (b) (4) is not clear what you mean by percent (%). Please justify this acceptance criterion with supporting data, including calculation or make adequate correction, if necessary.
- b. You have not provided linearity and precision data to cover entire range of the assay for mannitol and trehalose dihydrate using BAX855 FDP samples in the validation report (2011-MAN/TRE-BAX855-RFPQ1/Ver.2). Please provide the requested data.

## 8. (b) (4) total Glutathione assay

- a. Please add number of theoretical (b) (4) as system suitability check criteria to your SOP (NE-11-00138) section 5.1 and set acceptance criteria based on your historical data.
- b. Please include the (b) (4) used for the assay in section 3.1 of the SOP and resubmit for review.
- c. The quantification limits for (b) (4) stated in section 5.2 of your SOP are inconsistent with the results in section 5.8 of your validation report (2012-GLUTATHIONE-ADVATE-BAX855-RFPQ1 / Ver.1). Please explain.
- d. You have not provided linearity and precision data in your validation report, which cover entire range of the assay for (b) (4) using BAX855 FDP samples in the validation report. Please provide the requested data.

## 9. Determination of Polysorbate 80 by (b) (4)

- a. For your Method validation report, Document 2011-POLYSORBATE80-BAX855-RFPQ1-AD1/Ver.1:
  - ii. As per the data presented in section 7.7, you have studied linearity using polysorbate 80 standards, analyzed at different concentrations. Please provide data to demonstrate linearity of the method using the drug product and parallelism of results between the standard and the drug product from regression analysis.
  - iii. You have established range of the assay (section 7.8) based on the linearity data of polysorbate 80 standards only. The range should be determined based on the linearity, accuracy and precision data obtained from the representative drug product samples. Please provide appropriate data obtained with the drug product for linearity, accuracy and precision, and the assay range.

- iv. In section 2 under “scope”, section 7.6 “under specificity”, and section 4.0 “under validation approach”, you have indicated that validation was previously performed using BAX855 1000 IU/vial drug product, and was documented in Report 2011-POLYSORBATE-BAX855-RFPQ1/Ver.1. The above mentioned report was not included in this submission. Please provide the report for our review.

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

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

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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/PPMS