



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

Our Reference: BL 125566/0

Baxter Healthcare Corporation  
Attention: Mr. Erik Bjornson  
July 6, 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. Please provide a list describing all supplements currently under review for ADVATE (with Action Due Dates).
2. Please provide a table that clarifies where the release testing for the BAX 855 Drug Product is performed, as it is not clear if quality control testing refers to in-process or to release testing.
3. Please provide a copy of CAPA Investigation PR 96953 along with the results of the effectiveness check confirming that (b) (4).
4. Please submit the study report for the validation of the (b) (4) PEG (b) (4) (document (b) (4)-67-1093P009).
5. Regarding the resin regeneration studies for the (b) (4) manufacturing steps,
  - a. Please submit the study reports for the resin regeneration studies (documents (b) (4) 67-1093P018 and (b) (4)-67-1093P020).
  - b. We note that only data supporting resin regeneration collected from a “mock elution” performed (b) (4) step and (b) (4) uses for the (b) (4) step was submitted. As it is possible that protein could come off these resins after earlier uses and regenerations, please submit a justification that supports why data supporting that resin regenerations after earlier uses meet the acceptance criteria are not necessary.
  - c. We note that you have only submitted data from one validation run each to support resin regeneration for the (b) (4) steps but state that (b) (4) additional

runs each will be performed. Please submit the final study reports containing data from three runs per step (or provide an update on the status of these remaining runs if they have not already been completed).

6. Regarding lyophilization of BAX 855,

- a. Please provide a table containing information (such as make, model, etc.) on the (b) (4) lyophilizers to be used for BAX 855 that supports that they are equivalent. Please also provide the study reports and protocols for empty mapping studies for these (b) (4) lyophilizers.
- b. Please provide a description of the studies that were performed to develop the lyophilization cycle for BAX 855, including the study report for the initial scale-up study (document Lyo(b) (4) ), and well as a rationale for why this cycle is appropriate. Use of the same cycle as is used for ADVATE should be based upon data derived from studies of BAX 855.
- c. During the Process Performance Qualification study (document 2013-BAX855/FF-RFPPQ) to validate the lyophilization of the BAX 855 Drug Product, we note that you have not performed runs containing a maximum and minimum load (based upon number of vials) for at least the maximum and minimum potencies in each of the (b) (4) freeze-dryers. Please provide a description of your validation strategy for lyophilization of BAX 855 Drug Product in order to assist us in understanding why the runs you have provided are sufficient.

7. Regarding validation of shipping,

- a. The shipping validation for ADVATE BDS as described document 2013-BDS-SHIPPING-(b) (4)-RFPV1 was performed in April. Please provide a justification for why this validation represents worst-case conditions in term of shipping during summer and winter.
  - b. Shipping validation studies for ADVATE bulk drug substance (document (b) (4)-68-0385V) and drug product (document 2005-FF-SHIPPINGVALIDATION-RP1) have been submitted to support shipping of BAX 855 bulk drug substance and drug product. Please clarify (and describe) if the shipping containers, procedures, conditions and configurations are the same for ADVATE and BAX 855, to support that these studies are relevant to BAX 855.
8. Please provide a description of how all of the utility systems in Suite (b) (4) are monitored that includes the frequency of monitoring and the acceptance criteria used. Please also provide the results of monitoring of these utility systems over a recent six month period.
9. Please provide the full study report (including all attachments) for the qualification of Suite (b) (4) (document (b) (4)-61-0865N).

10. The study report for the validation of the (b) (4) of the (b) (4) (b) (4) (document (b) (4) -61-0854N) states that swab samples were not obtained in this validation due to limitations in the size of the cleaning pathway access. Please clarify.

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 July 20, 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