

From: Rana, Pratibha  
Sent: Wednesday, October 21, 2015 8:31 PM  
To: 'Vicki Chen'  
Subject: 125574/0 Information Request

Dear Ms. Chen:

We are reviewing your submission to your BLA for Antihemophilic Factor (Recombinant), submitted on December 16, 2014. We are providing the following comments and request for additional information to continue our review.

CMC Information Request

1. Report PDR-PR-CH-0033.02 "Process Development Report for KGPf (BAY 81-8973) Small Scale (b) (4) Lifecycle Study" does not appear to support maximum of (b) (4) cycles

for the (b) (4). This is evidenced by (b) (4) reduction in HCP clearance (b) (4) drop in Specific Activity of FVIII in the (b) (4) reduction in viral clearance ability in terms of (b) (4) performance (b) (4)

The data from your small-scale study reliably support a (b) (4) Use Life of (b) (4). Please be advised to take this into consideration in your planned concurrent validation at commercial scale (Protocol PVP-PR-CH-0035.01).

2. Please provide the first 10-year Stability Reports for Master Cell Bank and Working Cell Bank. Please also confirm that the HSP-70 gene is integrated in the cell genome (versus being present in the cell as a separate plasmid).

3. Regarding Drug Product Specification: we note that the proposed specification range for the parameter Total Protein represents calculated extreme values and is not acceptable. We understand that limited data for each fill size do not allow you to reliably perform analyses of the manufacturing data. Please re-calculate and tighten the acceptance range for Total Protein using nominal values for Potency and the lower and upper limits for Specific Activity. This approach is more accurate considering that the established range for Specific Activity already reflects variability of your manufacturing data for both Potency and Total Protein. Please commit to re-establish the ranges for Total Protein in Drug Product Specification based on statistical analysis of manufacturing data when sufficient number of Drug Product lots are manufactured, and project the expected time period.

4. Please provide your plan for Continued Process Verification, or indicate respective section in the BLA if it was submitted.

5. Please revise the TRD S.2.2.70 to reflect the limit of (b) (4) for (b) (4) storage time at (b) (4)

6. In the amendment 22 response to question 2 of the information request dated June 29, 2015, you proposed an (b) (4) endotoxin specification of (b) (4) IU based on requirements in the (b) (4). In the amendment 22 response to question 5 of the information request dated July 10, 2015, you proposed a (b) (4) endotoxin specification of (b) (4). Please align the (b) (4) endotoxin limit with that established for (b) (4), if feasible.

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 November 9, 2015 referencing the date of this request.

The action due date for this file is March 16, 2016.

If you have any questions, please contact me at Prati bha.rana@fda.hhs.gov or (240) 402-8433.

Prati bha Rana

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