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Subject: Information request Baxter rVWF BLA STN125577/0
Date: Friday, May 22, 2015 3:02:00 PM
Importance: High

Our Reference: BL 125577/0
Baxter Healthcare Corporation
Attention: Nadia Agopyan, PhD

May 22, 2015
Sent by email

Dear Dr. Agopyan:

We are reviewing your December 19, 2014, biologics license application (BLA) for von Willebrand Factor (Recombinant). We determined that the following information is necessary to continue our review:

1. Regarding depyrogenation:

- Please provide the depyrogenation validation studies for the two types of vials used for the drug product, and the two types of vials used for the sWFI diluent.
- Please provide a description of all the (b) (4) that will be used for the vials.

2. Regarding lyophilization:

- Please explain your approach to validating the lyophilization cycle. Please provide a summary for the studies. Please provide the drug product eutectic temperature, collapse temperature and glass transition temperature. Please also ensure you describe your sampling method (e.g., extended sampling, sampling pattern, which shelves sampled and sample locations, number of samples taken at each location), lot size of each run, fill volume of each run, product strength of each run, and testing results (e.g., residual moisture, potency, reconstitution time).
- In your empty-chamber shelf-mapping studies, the thermocouples were placed in (b) (4). Please justify this approach.
- Please clarify if validation studies were performed using all vials from the qualified vendor. If not, please justify why this is acceptable. Please provide detailed side by side specification comparison sheet for the 30mL vials used in the validation and in routine production.
- Please confirm that the lyophilization cycle is fixed. Please provide detailed information on any changes made for any of the validation runs.
- Please clarify if fixed shelf locations will be used for both minimum and maximum loads in (b) (4) for your routine manufacturing process.

- Please explain how the filled product is physically transported to the lyophilizer and how you prevent contamination of the product during this process.
- Please provide cleaning validation and changeover procedures for (b) (4)

3. Regarding the container closure integrity testing (CCIT):

- Please provide the validation report for CCIT for the drug product and diluent.
- Please clarify if CCIT was done on all vials for the drug product.
- Please clarify if any part of the container closure system that is product contact contains latex.

4. Please clarify if (b) (4) is used as an overlay during either drug product or diluent manufacture. Please also clarify if the drug product is stoppered under a vacuum.

5. Regarding visual inspection for FDP:

- Please clarify if the inspection is manual, semi-automated, or automated.
- Please describe the visual inspection procedure performed for the drug product and diluent. Information provided should include, but not be limited to, defects evaluated, acceptance criteria, and criteria for accepting or rejecting a lot.
- Please provide the qualification of your visual inspection process.

6. Please establish a transportation time for the shipment of (b) (4) from (b) (4)

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 June 22, 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.

Kind regards,

Jie He
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