



CBER REGULATORY REVIEW MEMORANDUM

Date 20 August, 2015

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Food and Drug Administration (FDA)

To Biologics License Application Submission Tracking Number 125566/0

Subject BLA: Review of Bioburden, Sterility, and Bacterial Endotoxin Test Method Qualifications for BAX855, Antihemophilic factor (recombinant), PEGylated

Through Dr. James L. Kenney, Chief, DBSQC/OCBQ/CBER/FDA
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Applicant Baxter Healthcare Corporation (Baxter)

Product BAX 855, Antihemophilic factor (recombinant), PEGylated

Biologics License Application (BLA) Submission Tracking Number (STN) 125566/0

Submission Received by CBER 25 November, 2014

Review Completed 20 August, 2015

Material Reviewed

Method qualifications for: 1) burden performed for in process control (IPC) (b) (4) 2) (b) (4) Bacterial Endotoxin Test (b) (4) ; and 3) sterility and (b) (4) using (b) (4) performed on the drug product (DP); and Baxter's response to CBER's Information Requests (IRs: amendments 125566/0/7, 125566/0/10; and 125566/0/12; received on 1 April, 22 April, and 21 May, 2015, respectively).

Executive Summary

After a thorough review of this BLA and the responses to CBER's IRs, this reviewer finds Baxter's bioburden, (b) (4) , sterility, and (b) (4) methods were qualified in accordance with (b) (4) (b) (4) respectively, by demonstrating the tested matrixes are suitable for these intended test methods.

Background

Baxter submitted this BLA on 25 November, 2014 for BAX 855, Antihemophilic Factor (Recombinant), PEGylated. BAX855 is indicated for the control and prevention of bleeding episodes, and for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adolescent (12 to less than 18 years) and adult (greater than or equal to 18 years) patients with hemophilia A (congenital factor VIII deficiency). It is supplied as a sterile white to off-white lyophilized powder in single-dose vials containing 250, 500, 1000 or 2000 International Units (IU) per vial of PEGylated recombinant human factor VIII. BAX 855 is administered by intravenous injection after reconstitution of the lyophilized powder with 5 mL of sterile water for injection. The reconstituted solution is a clear, colourless solution, free from visible particles containing approximately nominal activity of 50, 100, 200 and 400 IU/mL, and the product also contains the following components per mL: 160 mg Mannitol, 40 mg Trehalose dihydrate, 26.3 mg Sodium chloride, 7.8 mg Histidine, 6.1 mg Tromethamine, 1.2 mg Calcium chloride dehydrate, 0.5 mg Polysorbate 80, and 0.4 mg Glutathione.

BAX855 bulk drug substance (BDS) is manufactured at the Baxter (b) (4) facility located in (b) (4). The BDS is manufactured by covalently binding a branched polyethylene glycol (PEG) reagent to ADVATE (Antihemophilic Factor, Recombinant). ADVATE is a full length human recombinant factor VIII (rFVIII) with a complete (b) (4) and is produced by recombinant DNA technology in Chinese hamster ovary cells by a plasma/albumin free-cell culture method. The BAX 855 DS manufacturing process starts with a (b) (4)



The continued BAX 855 DP manufacturing process involves the formulation of DS utilizing (b) (4)



Once the target is achieved, the product goes through sterile filtration, aseptic filling, lyophilization, capping, bulk packaging and storage before shipment of the DP from the Baxter (b) (4) facility to the Baxter (b) (4) facility for labeling and packaging.

The Division of Biological Standards and Quality Control (DBSQC) reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. Therefore, this review will focus on: 1) the bioburden and (b) (4) methods performed on their BAX 855 (b) (4) and 2) sterility and (b) (4) (b) (4) methods qualification on their BAX 855 DP, to indicate if the product matrix is suitable for testing using the intended test methods.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Sterility Test – Membrane Filtration Qualification for BAX855

Baxter qualified their BAX855 DP using their compendial sterility membrane filtration method by performing bacteriostatic and fungistatic (B&F) qualification studies on one lot of BAX855 FP 2000 IU/vial (i.e., lot number: (b) (4)) to demonstrate their DP matrix is suitable for the intended test method. Since the DP 2000 IU is the highest concentration, its qualification was considered the worst case scenario and suitable for the assessment of DP at 250, 500, and 1000 IUs.

The test was performed using a total (b) (4)

(b) (4)

(b) (4)

(b) (4)

CBER performed licensing support bacterial endotoxin testing using a (b) (4) method (equivalence of (b) (4) method) on their DP conformance lots (i.e. (b) (4) at 250 IU/vial and (b) (4) at 2000 IU/vial) using Baxter's proposed (b) (4) sample testing dilution. Baxter's qualification report – as reviewed above – supports CBER's licensing support BET results; CBER's licensing support test result memo is included in the STN file.

The bacterial endotoxin specification of (b) (4) for BAX855 DP was calculated based on the endotoxin tolerance limits for non-intrathecal from (b) (4) (i.e., (b) (4) (b) (4)). Baxter submitted endotoxin results on several non-clinical and clinical DP batches, which met their endotoxin test specification of (b) (4). Based on this information, this reviewer finds Baxter's proposed BET release specification of (b) (4) for DP acceptable.

Conclusions

After a thorough review of the information submitted in this BLA and the response to CBER's information requests (amendments 125566/0/7, 125566/0/10, and 125566/0/12), this reviewer finds Baxter's bioburden, sterility, (b) (4) methods were qualified in accordance with (b) (4) (b) (4) > respectively, by demonstrating the tested BAX855 matrixes are suitable for their intended test method. Therefore, I recommend approval of their bioburden and (b) (4) methods for testing of (b) (4) and their sterility and (b) (4) methods for testing of DP.