



CBER REGULATORY REVIEW MEMORANDUM

Date 14 December, 2018

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Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To Biologics License Application Submission Tracking Number # 125671/0

Subject BLA: Review of Sterility, Bioburden, Bacterial Endotoxin Test Method Qualification for Antihemophilic Factor (Recombinant), GlycoPEGylated

Through James L. Kenney, D.Sc., Chief, LMIVTS

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Applicant Novo Nordisk Inc.

Product Antihemophilic Factor (Recombinant), PEGylated

Biologics License Application (BLA) Submission Tracking Number (STN) 125671/0

Submission Received by CBER 27 February, 2018

Review Completed 14 December, 2018

Material Reviewed

Method qualifications for: 1) bioburden; 2) sterility; and 3) bacterial endotoxin test (BET) (b) (4) performed on Antihemophilic Factor (recombinant), GlycoPEGylated; and the responses to CBER's Information Requests (IRs), received 06 August and 11 December of 2018, were reviewed.

Executive Summary

After a thorough review of this BLA and the responses to CBER's IRs, this reviewer finds the bioburden, sterility, and (b) (4)-BET methods were qualified in accordance with (b) (4) and (b) (4) respectively, by demonstrating Antihemophilic Factor (recombinant), GlycoPEGylated is suitable for the intended test methods.

Background

On 27 February, 2018, Novo Nordisk submitted this BLA for their Antihemophilic Factor, PEGylated B-domain deleted recombinant human factor VIII (rFVIII) with a (b) (4) polyethylene-glycol-maleimide conjugated to the protein. It is indicated for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital factor VIII deficiency) for 1) on-demand treatment and control of bleeding episodes; 2) perioperative management of bleeding; and 3) routine prophylaxis to reduce the frequency of bleeding episodes.

Antihemophilic Factor (recombinant), GlycoPEGylated is formulated as a sterile lyophilized powder for reconstitution with 0.9% sodium chloride solution as diluent for intravenous administration.

Antihemophilic Factor (recombinant), GlycoPEGylated is available in single use glass vials of 500, 1,000, 1,500, 2,000, or 3,000 international units (IU) in (b) (4) fill size. The drug product is reconstituted with a prefilled syringe of (b) (4) 0.9% sodium chloride solution.

The 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 endotoxin release specifications 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 the 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 the method qualifications for Novo Nordisk's bioburden, sterility, and endotoxin test methods performed on the Antihemophilic Factor (recombinant), GlycoPEGylated (b) (4) Drug Product (DP), to determine if they were appropriately qualified to indicate if its matrix is suitable for these intended test methods.

Review

Bioburden Test Qualification (b) (4)

(b) (4)

(b) (4)

(b) (4)

Sterility Test Qualification for DP

The Antihemophilic Factor (recombinant), GlycoPEGylated DP was qualified using the (b) (4) qualification studies to demonstrate the matrix is suitable for the intended test method. Novo Nordisk performed the test using (b) (4) indicator microorganisms (b) (4) on (b) (4) final containers (FC) of Antihemophilic Factor (recombinant), GlycoPEGylated DP (i.e., lot numbers: (b) (4)). On 06 August, 2018, CBER requested Novo Nordisk qualify their sterility test using known environmental isolates from their Denmark facility, Novo Nordisk replied (125671/0.20), that environmental monitoring will be finalized early 2019 and results will be provided to the FDA. CBER expects these results to be submitted in their annual report.

The test for each microorganism was performed using (b) (4)

(b) (4)

Bacterial Endotoxin Test (b) (4) BET) Method Qualification for DP

The same type of (b) (4) -BET qualification was used for the Antihemophilic Factor (recombinant), GlycoPEGylated DP and it was tested as mentioned above for (b) (4) on (b) (4) lots of DP dosages (i.e., lot numbers: (b) (4)).

(b) (4)

CBER finds the bacterial endotoxin specification of (b) (4) acceptable. After review of (b) (4)-BET method qualification results for the Antihemophilic Factor (recombinant), GlycoPEGylated (b) (4) DP, this reviewer concludes this method was qualified in accordance with (b) (4)

Conclusions

After a thorough review of this BLA and the responses to CBER's IR, this reviewer finds the Novo Nordisk's Antihemophilic Factor (recombinant), GlycoPEGylated matrix is suitable for testing using their proposed bioburden, sterility and bacterial endotoxin test methods, as they were qualified and performed in accordance with (b) (4) respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.