DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

CBER REGULATORY REVIEW MEMORANDUM

Date 17 February, 2017

From Hyesuk Kong, Ph. D.
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Division of Biological Standards and Quality Control (DBSQC)
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 # 125606/0

Subject BLA: Review of Bioburden, Endotoxin, Sterility and Rabbit Pyrogen Test Methods for HAEGARDA™, C1 Esterase Inhibitor (Human)

Through James L. Kenney, D.Sc., Chief, LMIVTS
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Applicant CSL Behring's (CSLB)

Product HAEGARDA™ (C1 Esterase Inhibitor [Human])

Biologics License Application (BLA) Submission Tracking Number (STN) 125606/0

Submission Received by CBER 9 June, 2016

Review Completed 17 February, 2017

Material Reviewed

Method qualifications for: 1) bioburden and bacterial endotoxin tests performed on the (b) (4) 2) sterility test performed on the drug product (DP). In addition, procedure for rabbit pyrogen test performed for the DP; and the response to CBER's Information Request (IR) responses received 30 August and 30 November of 2016 were also reviewed.

Executive Summary

After a thorough review of this BLA, and the responses to CBER's IR (amendments 125606/0/2 and 125606/0/9), this reviewer finds CSLB's bioburden, bacterial endotoxin, and sterility test methods were qualified in accordance with (b) (4) respectively. In addition, the rabbit pyrogen test is being performed in accordance to (b) (4)

Background

On 30 June, 2016, CSL Behring (CSLB) submitted this BLA for HAEGARDA™ (CSL830: C1-Esterase Inhibitor Human [C1-INH]) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients. HAEGARDA™ is a lyophilized concentrate of human plasma-derived C1-esterase inhibitor supplied in a single-use vial containing either 2000 or 3000 international units (IU) of C1-INH. Each vial of reconstituted CSL830 contains 500 IU/mL of C1-INH, 65 mg total protein, 10 mg glycine, 8.5 mg sodium chloride and 2.5 mg sodium citrate. The HAEGARDA™ proposed dose is 60 IU per kg body weight by subcutaneous injection twice weekly (every 3 or 4 days).

The HAEGARDA™ production process is similar to CSLB's Berinert® product (STN 125287), which was approved by FDA, except for (b) (4) .

The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product (b) (4) 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: the confirmatory testing of submitted product samples; 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 following method qualifications for CSLB's bioburden, bacterial endotoxin and sterility test methods to ensure the product (b) (4) is suitable for these intended test methods and the review of rabbit pyrogen test procedure to ensure it is compliant with (b) (4)

Review

(b) (4)

(b) (4)

Sterility Test Qualification for CSL830 Drug Product (DP)

CSLB qualified their CSL830 DP (b) (4) using the (b) (4) method by performing (b) (4) qualification studies on (b) (4)) to demonstrate the CSL830 DP (b) (4) is suitable for the intended test method. Note: This (b) (4) was prepared containing 500 IU/mL C1-esterase inhibitor after reconstitution and the active and inactive ingredients are proportionally similar between two proposed final container sizes following their indicated reconstitution procedure.

(b) (4)

(b) (4)

Rabbit Pyrogen Test

The rabbit pyrogen test is a compendial test that does not require suitability qualification testing; however, the method (standard operating procedure [i.e., #10.002]) was reviewed to ensure it was performed in accordance with (b) (4) In addition, CSLB submitted the rabbit pyrogen test results for (b) (4) batch conformance lots (lots: (b) (4)) of

their CSL830 DP and the results were found to be accordance with the (b) (4) specifications, indicating an absence of pyrogens in their final container produc (b) (4)

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds CSLB's CSL830 (b) (4) DP (b) (4) are suitable for testing using their bioburden, endotoxin, and sterility testing methods, as these tests were qualified and performed in accordance with (b) (4) and (b) (4) respectively. In addition, rabbit pyrogen test on the (b) (4) is performed in accordance with (b) (4) Therefore, this reviewer finds these methods acceptable for their intended purpose.