



CBER REGULATORY REVIEW MEMORANDUM

Date 08 May, 2018

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Food and Drug Administration (FDA)

To Biological License Application Submission Tracking Number # 125668/0

Subject BLA: Review of Bioburden, Sterility, Endotoxin and Diphtheria Test Method Qualifications for Cutaquig®

Through James L. Kenney, D.Sc., Chief, LMIVTS
Maryna Eichelberger, Ph.D., Director, DBSQC

Applicant Octapharma

Product Cutaquig® ((b) (4)): Immune Globulin Subcutaneous)

Biological License Application (BLA) Submission Tracking Number (STN) 125668/0

Submission Received by CBER 29 December, 2017

Review Completed 08 May, 2018

Material Reviewed

Method qualifications for: 1) bioburden, 2) sterility, 3) and endotoxin and 4) diphtheria tests performed on Cutaquig® and the responses to CBER's Information Request, received 27 February of 2017, were reviewed.

Executive Summary

After a thorough review of this BLA, this reviewer finds the bioburden, sterility, and endotoxin test methods were qualified in accordance with ((b) (4)), respectively. In addition, diphtheria potency test was qualified in accordance with 21 CFR 640.104 for Cutaquig®.

Background

On 29 December, 2017, Octapharma submitted a BLA for production of Cutaquig® (working title- (b) (4)) a 16.5% human normal Immunoglobulin G (IgG) solution for subcutaneous infusion. It is indicated for treatment of primary humoral immunodeficiency in adults. The solution contains $\geq 96\%$ IgG and has a distribution of IgG subclasses closely proportional to native human plasma. The development of (b) (4) was based on manufacturing processes of licensed products Octagam 5% and Octagam 10%, both intravenous immune globulins. Therefore, the manufacturing processes of the three products are almost identical. (b) (4) is intended to be manufactured at Octapharma's Pharmazeutika Produktionsges.m.b.H, Austria (OPG) and Dessau GmbH, Germany (ODE) sites whereas all the lot release testing will be performed at (b) (4) site.

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 release specifications for endotoxin testing to ensure they reflect process capability and meet regulatory compliance. DBSQC also produces and calibrates CBER toxin and antitoxin reference standards used in *in-vivo* and *in-vitro* test methods; therefore, DBSQC has expertise in these methods and reviews them to ensure regulatory compliance. In addition, DBSQC's review of toxin/antitoxin methods ensures reference standard use is appropriate for the intended test method and provides quality control production oversight of CBER potency standard replacement lots, if applicable. 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 qualification of bioburden, sterility, endotoxin and diphtheria test methods performed on the Cutaquig® to determine if they were appropriately qualified to indicate if its matrix is suitable for these intended test methods.

Review

Bioburden Test Qualification for (b) (4)

The bioburden qualification test ((b) (4) qualification) was performed to demonstrate (b) (4) does not (b) (4). The test was performed using (b) (4) method and (b) (4) indicator microorganisms (i.e., (b) (4)) and (b) (4) environmental isolates (i.e., (b) (4)) on (b) (4) lots of (b) (4) (i.e., (b) (4)).

The qualification test involved (b) (4)

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Sterility Test Qualification for Drug Product (DP)

The (b) (4) DP was qualified using the (b) (4) method by performing (b) (4) qualification studies to demonstrate the matrix is suitable for the intended test method. Octapharma performed the test using (b) (4) indicator microorganisms (i.e., (b) (4)) and (b) (4) known environmental strains (i.e., (b) (4)) on (b) (4) final container lots of (b) (4) DP (i.e., (b) (4)).

The test for each microorganism was performed using (b) (4) final container vials and (b) (4)

After not more than (b) (4) , all test media had turbidity comparable between the test sample and their respective PC count and the NCs showed no growth. The tests were performed and compliant with (b) (4) and the test results indicate there is no product inhibition on microorganism growth; thus, indicating the (b) (4) DP matrix is suitable for testing via their (b) (4) sterility test method.

(b) (4) Qualification for DP

Octapharma qualified their (b) (4) method for their (b) (4) DP to verify the product matrix is suitable for the intended test method in accordance with (b) (4) .

The (b) (4) was calculated to be (b) (4) by (b) (4)

Inhibition/enhancement tests were performed (b) (4) lots of (b) (4) DP (i.e., (b) (4)) to determine a suitable testing (b) (4) using (b) (4)

(b) (4) CBER finds the proposed test (b) (4) acceptable. In addition, CBER finds the bacterial endotoxin specification of (b) (4) for the (b) (4) DP acceptable, based on the results of several technical, clinical, and conformance batches. After review of (b) (4) method qualification results, this reviewer concludes this method was qualified in accordance with (b) (4) .

Diphtheria (b) (4) test for DP

Octapharma qualified their Diphtheria (b) (4) Test using (b) (4) DP final container lot (i.e., (b) (4)).

U.S. Standard Diphtheria Antitoxin / toxin preparations were prepared as follows: (b) (4)

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Test sample/toxin preparation: (b) (4)

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Octapharma also submitted diphtheria results on several technical, clinical, and conformance DP batches of (b) (4), which also met their diphtheria antibody test specification of (b) (4).

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds Octapharma (b) (4) drug product matrix is suitable for testing using their sterility, endotoxin, and diphtheria testing methods; these tests were qualified and performed in accordance with (b) (4), 21 CFR 640.104, respectively. In addition, the (b) (4) matrix is suitable for testing using their bioburden test method and the qualification was performed in accordance with (b) (4). Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.