



CBER REGULATORY REVIEW MEMORANDUM

Date 19 July, 2016

From Hyesuk Kong, Ph.D.
Laboratory of Microbiology, *In-Vivo* Testing and Standards (LMIVTS)
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 # 125428/0

Subject BLA: Review of (b) (4) Endotoxin Test Method Qualifications for HEPLISAV™
(Hepatitis B Vaccine, Recombinant [Adjuvanted])

Through James L. Kenney, D.Sc., Chief, LMIVTS/DBSQC/OCBQ/CBER/FDA
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Applicant Dynavax Technologies Corporation (Dynavax)

Product HEPLISAV™ (Hepatitis B Vaccine, Recombinant [Adjuvanted])

Biologics License Application (BLA) Submission Tracking Number (STN) 125428/0

Submission Received by CBER 26 April, 2012

Review Completed 19 July, 2016

Material Reviewed

Method qualifications for (b) (4) endotoxin test (b) (4) performed on (b) (4) drug product (DP) for Heplisav™. In addition, the response to the information request (IR) received on 21 September, 2012 was reviewed.

Executive Summary

After a thorough review of this BLA, and the response to CBER's Information Request (Amendment 125428/0/6 - received on 21 September, 2012), this reviewer finds Dynavax's (b) (4) method was qualified in accordance with (b) (4), by demonstrating the (b) (4), and Heplisav™ DP matrixes are suitable for their intended test method.

Background

Dynavax Technologies Corporation (Dynavax) submitted an original BLA for HEPLISAV™, recombinant Hepatitis B Vaccine on April 26, 2012, with the proposed indication to prevent infection caused by all known subtypes of Hepatitis B and virus in adults 18 years of age and older. On February 22, 2013, a Complete Response (CR) letter was issued to Dynavax. This addressed deficiencies in the drug product manufacturing facility, equipment, clinical quality control, chemistry manufacturing control and testing procedures; and their responses to this CR letter were received by CBER on March 15, 2016. Note: The review for the bacterial endotoxin test was not completed prior to the CR letter.

HEPLISAV™ is a sterile, preservative-free solution intended for intramuscular injection. HEPLISAV™ is supplied as clear to slightly opalescent, colorless to slightly yellow, and essentially free of visible particles. Each 0.5 mL dose vial contains 20 µg of Hepatitis B virus surface antigen (HBsAg), 3000 µg of 1018 Adjuvant, 8 mM sodium phosphate, 154 mM sodium chloride, and 0.01% w/w polysorbate 80. The immunization schedule consists of 2 doses given 1 month apart.

Hepatitis B Surface Antigen (HBsAg) DS

HBsAg DS is manufactured at Dynavax GmbH facility located in Dusseldorf, Germany. HBsAg DS is the active pharmaceutical ingredient of HEPLISAV™, which is produced in the yeast strain *Hansenula polymorpha* using recombinant technology. The manufacturing of HBsAg is divided into (b) (4)

[REDACTED]

1018 Adjuvant (1018)

The 1018 is a 22-mer phosphorothioate molecule produced by (b) (4) oligonucleotide synthesis. The manufacturing process includes (b) (4) [REDACTED] prior to release for HEPLISAV™ DP formulation.

Manufacturing Process for HEPLISAV™ DP

HEPLISAV™ is a recombinant Hepatitis B vaccine manufactured in (b) (4) batches. Manufacturing includes (b) (4) formulation buffer that is (b) (4) [REDACTED] batch of HBsAg-1018 formulated bulk. This manufacturing process takes place at the Rentschler Biotechnologie GmbH facility located in Laupheim Germany.

(b) (4)

[REDACTED]

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 Dynavax's qualification of their (b) (4) endotoxin test methods; that is the (b) (4) test method for their (b) (4) test method for their HEPLISAV™ DP.

Review

(b) (4)

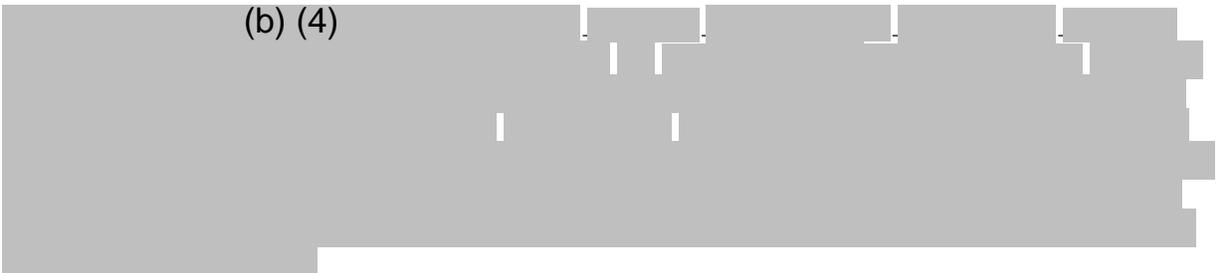
(b) (4)					

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(b) (4)



CBER finds HEPLISAV™ DP is suitable for testing using the intended test method.

Conclusions

Based on review of Dynavax’s qualification for (b) (4) in this BLA, this reviewer finds the (b) (4) test methods were qualified in accordance with (b) (4) and the final drug product HEPLISAV™ recombinant Hepatitis B vaccine, (b) (4) matrixes are suitable for their intended test methods. Therefore, this reviewer recommends approval of this test in the production of HEPLISAV™, recombinant Hepatitis B vaccine.