

Application Type	Amendment, Response to CR letter
STN	125428/0.74
CBER Received Date	February 8, 2017
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Division / Office	DVRPA /OVRR
Committee Chair	Marian E. Major, Ph.D.
Project Manager	Katherine Berkhausen, Richard Daemer, Ph.D., Sudhakar Agnihothram, Ph.D.
Priority Review	No
Reviewer Name(s)	Lei Huang, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin, Ph.D. Team leader, Viral and Bioassay Team VEB, DB, OBE
	A. Dale Horne, Dr.PH Branch Chief, Vaccine Evaluation Branch DB, OBE
Applicant	Dynavax Technologies Corporation
Established Name	Hepatitis B Vaccine (Recombinant), Adjuvanted
(Proposed) Trade Name	HEPLISAV-B, HEPLISAV
Pharmacologic Class	Vaccine
Indication(s) and Intended Population(s)	Immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older

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1. EXECUTIVE SUMMARY

Dynavax submitted a full response to the deficiencies outlined in the Complete Response Letter (CRL) dated November 10, 2016 as a resubmission of a Biologics License Application (BLA125428). The reviewer considers the response to Question #48 acceptable.

2. REGULATORY BACKGROUND

HEPLISAV™ is a recombinant hepatitis B vaccine for active immunization against hepatitis B virus infection. The immunogenic component of this vaccine is hepatitis B surface antigen (HBsAg), subtype adw, which is produced in the yeast strain *Hansenula polymorpha* using recombinant technology.

CBER issued a CRL on November 10, 2016, outlining the deficiencies of the submission dated March 15, 2016. This resubmission included the applicant's responses to the questions in the CRL.

3. SOURCES OF DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

This statistical review included the following BLA/IND document:

BLA 125428/0.74 Submitted 02/08/2017

Module 1.11 Information Amendment: Information Not Covered Under Modules 2 to 5

1.11.1 Quality Information Amendment

Response to 10 November 2016 CRL, Question 48

4. APPLICANT'S RESPONSES TO CR LETTER

Question 48:

Regarding in-vivo potency determination:

- a. The DUS-SOP-QC-0204 (Software (b) (4) - HEPLISAV in-vivo potency) page 12, Section 6.6, acceptance criterion #3 (and Document VL099-Table 1, page 10 SSC) states that a 95% Confidence Interval calculation has to be performed. It is not clear whether this is 1-sided or 2-sided confidence interval for (b) (4) and relative potency calculations.

Applicant's Response:

The applicant clarified that the 95% confidence interval is two-sided.

Reviewer Comments

The response is acceptable.

- b. In the validation study for the in-vivo potency assay (VL099, page 23), lots (b) (4) were tested against a sample derived from the same lot (e.g. (b) (4) was tested against a sample ((b) (4)) derived from (b) (4)). Please confirm that reference lots (b) (4) have the same

theoretical potencies as the lots from which they were derived, (b) (4) and (b) (4) respectively. In addition, please provide the relative potencies of lots (b) (4) with respect to the reference lot that will be used for routine tests.

Applicant's Response:

The applicant confirmed that reference lots (b) (4) have the same theoretical potencies as the validation samples from lots (b) (4), respectively. The applicant also clarified that the reference lot that will be used for routine tests is (b) (4), which was derived from HEPLISAV lot (b) (4). Lot (b) (4) was tested against lot (b) (4), resulting in a geometric mean relative potency of (b) (4) based on (b) (4) tests.

Reviewer Comments

Based on the response, the relative potency of Lot (b) (4) in a routine test (with Lot (b) (4) as the reference lot). Hence, the (b) (4) potency levels of lots (b) (4) used in precision and accuracy/linearity studies cover the range of (b) (4). The reviewer considers the response acceptable.

5. CONCLUSIONS

Overall, the reviewer considers the response to Question #48 acceptable.