

Application Type	Amendment, Response to CR letter
STN	125428/0.42
CBER Received Date	March 15, 2016
PDUFA Goal Date	December 15, 2016
Division / Office	OVRR
Committee Chair	Marian E. Major
Project Manager	Katherine Berkhausen; Richard Daemer
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
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Applicant	Dynavax Technologies Corporation
Established Name	Hepatitis B Vaccine (Recombinant), Adjuvanted
(Proposed) Trade Name	HEPLISAV-B, HEPLISAV
Pharmacologic Class	Vaccine

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1. EXECUTIVE SUMMARY

The serology assay for Dynavax's HEPLISAV™ hepatitis B vaccine was already reviewed during the IND stage. On October 31, 2016, the statistical reviewer received a request from the product reviewer to calculate the relative potency based on an in-vivo potency test. The reviewer reviewed the validation report of the in-vivo potency test and performed the calculation. The resulting relative potency met the lot release criteria. However, the statistical reviewer identified some issues in the validation report, described in this review in Section 4.1. The statistical reviewer defers to the product reviewer regarding adequacy of the evidence.

2. REGULATORY BACKGROUND

CBER received an amendment for the BLA for HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)] under Amendment #125428/0.42 (DATS# 628039) on March 15, 2016. This amendment contains responses to a Complete Response (CR) letter that was issued to Dynavax on February 22, 2013, as well as updates to the BLA.

HEPLISAV™ is a recombinant hepatitis B vaccine for active immunization against hepatitis B virus infection. Dynavax explains that 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. The firm indicates that the HBsAg Drug Substance is formulated with 1018 ISS Adjuvant to produce HEPLISAV™ Drug Product. There are no changes in the manufacturing processes of the HBsAg Drug Substance and HEPLISAV™ Drug Product.

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

3.1 Review Strategy

This statistical review focuses on the method validation report (VL099) and standard operating procedure (DUS-SOP-QC-0089).

3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

BLA	125428/0.42	Submitted 03/15/2016
Module	3.2.P.5	Control of Drug Product
	3.2.P.5.3	Validation of Analytical Procedures
		Method Validation Report VL099 – HEPLISAV in vivo Potency Assay
BLA	125428/0.58	Submitted 08/16/2016
Module	3.2.P.5	Control of Drug Product
	3.2.P.5.2	Analytical Procedures
		DUS-SOP-QC-0089, In Vivo Potency Assay Part III: Measurement of titers

(b) (4)

4.2 Relative Potency Calculation

Three Drug Product lots were submitted for in-vivo potency tests as part of the BLA. On October 31, the product reviewer requested the statistical reviewer to calculate the relative potency of Lot 1033385 (Reference Lot (b) (4)), based on sero-conversion rate of vaccinated (b) (4) (Table 2).

Table 2 – Sero-Conversion Rate (Lot 1033385)

Dose	(b) (4) ng/ml	(b) (4) ng/ml	(b) (4) ng/ml	(b) (4) ng/ml	(b) (4) ng/ml
Reference Standard	15/16	13/16	5/15	2/16	2/16
Test Sample	16/16	14/16	7/16	2/15	1/16

Source: Provided by the product reviewer.

The statistical reviewer performed a probit analysis on the data. Figure 1 presents the fitted dose-response curves with and without the parallelism restriction.

(b) (4)

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(b) (4)

5. CONCLUSIONS

Lot 1033385 met the release specification based on the in-vivo potency assay. The statistical reviewer identified some issues, described in Section 4.1 above, in the validation report for the in-vivo potency assay. The statistical reviewer defers to the product reviewer regarding adequacy of the evidence.