Statistical (Bioassay) Review and Evaluation
BLA

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Subject STN 125428/0
Hepatitis B Vaccine (Recombinant) [HEPLISAV]
Dynavax Technologies Corporation

cc: Chron file
HFM-217/A. Dale Horne
HFM-215/Estelle Russek-Cohen

Executive Summary: This original Biologics License Application (BLA) is for HEPLISAV [Hepatitis B Vaccine (Recombinant)]. HEPLISAV is indicated for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 through 70 years of age.

This review focuses on the report of Analysis of Stability Data in Stability Program Overview (Section 3.2.S.7.3 of the submission).

It appears that the results of the long-term   **(b) (4)**   stability data met the proposed commercial specification for the three attributes: **(b) (4)**   .

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I. BACKGROUND

HEPLISAV is a hepatitis B vaccine comprised of recombinant HBsAg and the proprietary adjuvant developed by Dynavax (the applicant), 1018 ISS.

The recombinant HBsAg is a 22 nm particle containing the *adw* subtype of the hepatitis B virus HBV) protein S and lipids, and is produced in Hansenula polymorpha yeast cells. This particle resembles the noninfectious, HBsAg-containing particles that are secreted by human hepatocytes during natural HBV infection.

In earlier clinical studies, the (b) (4) was used to measure anti-HBsAg levels. The phase 3 trials HBV-10 and HBV-16 were conducted with the final proposed commercial formulation of HEPLISAV (F3). This formulation was also used in the supportive phase 2 trial HBV-14. In all 3 trials, the (b) (4) was used. Both assays are (b) (4) that quantitatively measure total antibody to HBsAg. The (b) (4) was performed by (b) (4) for HBV-14 and HBV-10, and by (b) (4) for HBV-16. Validations of these two assays are not discussed in this review.

This review focuses on the report of Analysis of Stability Data in Stability Program Overview (Section 3.2.S.7.3 of the submission).

II. STATISTICAL REVIEW

Stability data for (b) (4) HBsAg Drug Substance lots manufactured at commercial scale are included in this submission. Long-term (b) (4) stability data for individual HBsAg Drug Substance lots (n (b) (4)) are presented in Table 1 (Table 3.2.S.7.3-1 in the submission). The remaining (b) (of the (b) (4) lots are not included in the pooled statistical analysis because there were not enough stability data available for the statistical evaluation.

II.a Stability Data

**Table 1: HBsAg Drug Substance Lots Evaluated for Stability**

(b) (4)

II.b Stability Parameters

The following parameters were historically monitored to assess stability of HBsAg Drug Substance: (b) (4) Not all parameters were evaluated on all [(b) (4)] lots as some assays were only recently introduced into the program. The proposed retest period of (b) (4) for HBsAg Drug Substance stored under (b) (4) condition is based on the results of analyses performed on the compiled stability data for each of these attributes. After reviewing the data, the applicant concluded that the attributes of (b) (4) are critical for ensuring the stability and, therefore, the quality of HBsAg Drug Substance. These three attributes are discussed in Section II.d.

II.c Statistical Method

(b) (4)
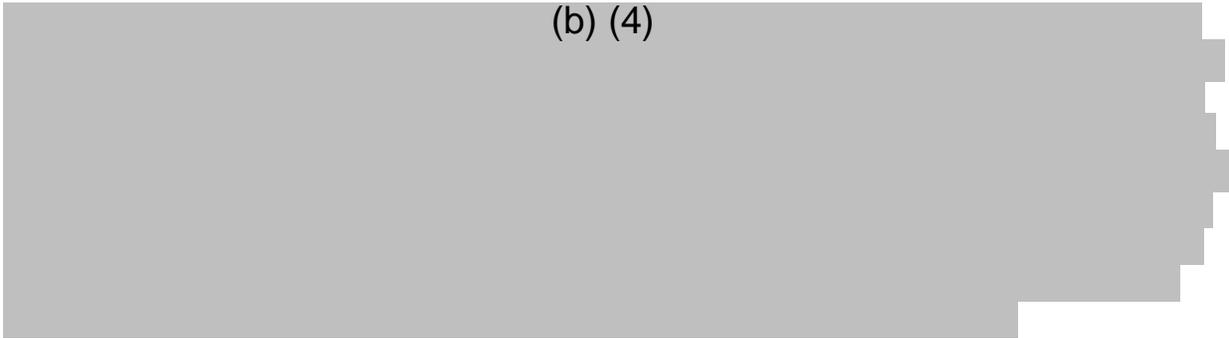
(b) (4)
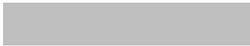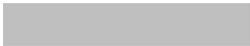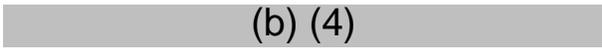
(b) (4)

III. RECOMMENDATION

From statistical point of view, it appears that the results of the long-term and the (b) (4) stability data met the proposed commercial specification for the three attributes (b) (4)

IV. COMMENTS AND QUESTIONS TO REVIEW COMMITTEE

None

V. COMMENTS AND QUESTIONS TO SPONSOR

- In the future submission, please provide the stability data and the analysis information with the software programs you use so that we can verify the results.