BLA APPROVAL

Our STN: BL 125428

Dynavax Technologies Corporation
Attention: Elaine Alambra
2929 Seventh Street
Suite 100
Berkleley, CA 94710

November 9, 2017

Dear Ms. Alambra:

Please refer to your Biologics License Application (BLA) for Hepatitis B Vaccine (Recombinant), Adjuvanted dated April 26, 2012, received April 26, 2012, submitted under section 351(a) of the Public Health Service Act (PHS Act).

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 1883 to Dynavax Technologies Corporation, Berkeley, CA, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Hepatitis B Vaccine (Recombinant), Adjuvanted which is indicated for immunizaton against infection caused by all known subtypes of hepatitis B virus. Hepatitis B Vaccine (Recombinant), Adjuvanted is approved for use in adults 18 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT 00435812, NCT 00511095, NCT 01005407, NCT 01999699, NCT 02117934.

Under this license, you are approved to manufacture Hepatitis B Vaccine (Recombinant), Adjuvanted. The hepatitis B surface antigen (HBsAg) drug substance will be manufactured at Dynavax GmbH, Düsseldorf, Germany. The final formulated product, which consists of HBsAg drug substance and CpG 1018 adjuvant, will be manufactured and filled at Rentschler Biotechnologie GmbH & Co. KG, Laupheim Germany. Hepatitis B Vaccine (Recombinant), Adjuvanted will be labeled, packaged and stored at (b) (4)

You may label your product with the proprietary name HEPLISAV-B and market it in prefilled vials containing a single dose of vaccine.

DATING PERIOD

The dating period for Hepatitis B Vaccine (Recombinant), Adjuvanted shall be 36 months from the date of manufacture when stored at 5°C ± 3°C. The date of manufacture shall be defined as the date on which the active pharmaceutical ingredient (HBsAg) is added during formulation. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your HBsAg drug substance shall be (b) (4) when stored at (b) (4) .

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Hepatitis B Vaccine (Recombinant), Adjuvanted, or in the manufacturing facilities.

LABELING

We hereby approve the final draft package insert labeling submitted under amendment 112, dated November 8, 2017, the draft carton labeling submtitted under amendment 112, dated November 8, 2017, and the container labeling submitted under amendment 111, dated November 8, 2017.

Please provide your final content of labeling including the carton and container labels in Structured Product Labeling (SPL) format. All final labeling should be submitted as Product Correspondence to this BLA 125428 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at http://www.fda.gov/forindustry/electronicsubmissionsgateway/ucm387293.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of acute myocardial infarction.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following study:

1. "Post-Marketing Observational Study to Evaluate the Occurrence of Acute Myocardial Infarction in Adults 18 Years of Age and Older Who Receive HEPLISAV-B Compared with Another Hepatitis B Vaccine." As outlined in your submission dated October 8, 2017, using a non-randomized clustered design, the study conducted in Kaiser Permanente Southern California, will evaluate approximately 25,000 patients who receive HEPLISAV-B and approximately 25,000 patients who receive another hepatitis B vaccine.

We acknowledge the timetable you submitted on October 17, 2017, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: December 31, 2017

First Interim Analysis Report Submission: August 31, 2019

Second Interim Analysis Report Submission: February 29, 2020

Study Completion Date: May 31, 2020

Final Analysis of Unconfirmed Events Report Submission: September 30, 2020

Final Report Submission: June 30, 2021.

Please submit the protocol to your IND 12692, with a cross-reference letter to this BLA 125428 explaining that this protocol was submitted to the IND. Please refer to the sequential number for each study and the submission number as shown in this letter.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement to this BLA 125428. For administrative purposes, all submissions related to this postmarketing study required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letters of October 8, 2017 and October 17, 2017 as outlined below:

2. To conduct the following study: "Post-Marketing Observational Surveillance of the Safety of HEPLISAV-B in Adults 18 Years of Age and Older to Evaluate the Incidence of New Onset Immune-mediated Diseases, Herpes Zoster, and Anaphylaxis."

   Final Protocol Submission: May 31, 2018

   Study Completion: August 31, 2020

   Final Report Submission: February 28, 2022

3. To establish a pregnancy registry for providing information on outcomes following pregnancy exposure to HEPLISAV-B. Data in this registry will be used to assess risks relevant to pregnancy, including pregnancy outcomes of pre-term births, major congenital malformations, spontaneous abortions, and still births. The registry will collect information on 250-300 pregnant women.

   Final Protocol Submission: February 9, 2018

   Study Completion: August 9, 2023

   Final Report Submission: December 31, 2023

Please submit clinical protocols to your IND 12692, and a cross-reference letter to this BLA 125428 explaining that these protocol(s) were submitted to the IND.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely yours,

Mary A. Malarkey
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research

Marion F. Gruber, Ph.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research