Our STN: **BL 125428/0**   **BLA COMPLETE RESPONSE**

Dynavax Technologies Corporation
Attention: Ms. Elaine Alambra
2929 Seventh Street
Suite 100
Berkeley, CA 94710

Dear Ms. Alambra:

This letter is in regard to your biologics license application (BLA) for Hepatitis B Vaccine
(Recombinant), Adjuvanted, manufactured at your Dynavax GmbH, Düsseldorf, Germany
location (a wholly owned subsidiary of Dynavax Technologies Corporation, USA) and at your
contract manufacturing location, Rentschler Biotechnologie GmbH, Laupheim, Germany and
submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA with
the exception of the extensive information in the amendments dated September 23, 2016,
October 2, 2016, October 5, 2016, October 7, 2016, October 8, 2016, and October 12, 2016.
After our complete review, we have concluded that we cannot grant final approval because of the
deficiencies outlined below.

CLINICAL ITEMS

Items 1-25 are a reiteration of our information request dated September 9, 2016 to which you
submitted responses on September 23, 2016, October 2, 2016, October 7, 2016, and October 8,
2016, as noted above. You may refer to those responses in your response to this letter; please
note that additional items below also pertain to data from your safety study, HBV-23.
Incomplete information, as reflected in the comments below, preclude a determination of the
risk/benefit profile for the vaccine at this time. We remain concerned about the cardiac events
observed in that study which may require additional consultations, discussions and analysis after
our review of your responses to this letter.

Regarding Study HBV-23:

1.   For study HBV-23, please provide narratives and CRFs for all subjects who reported a
        serious adverse event (SAE) with a System Organ Class (SOC) of Cardiac Disorders.
        Please ensure there is a full narrative that describes each cardiac SAE that was reported.
        For example, a narrative for subject 140-099 was submitted for the SAEs of cardiac
        failure, atrial fibrillation, cardiac ventricular thrombosis, pneumonia, pleural effusion,
        pulmonary embolism, sepsis, and ischemic hepatitis. However, you did not provide a
        narrative for the SAE of acute myocardial infarction for subject 140-099, which was
        reported at a different time than the events listed above. The narratives should include at

a minimum the cardiac diagnosis, basis for diagnosis, temporal relationship to vaccination, all co-morbid conditions, the treatment and outcome.

2. We acknowledge your analysis of the imbalance in SAEs with an SOC of Cardiac Disorders and the imbalance in acute myocardial infarction observed in HBV-23 in the CSR on page 104 and your analysis of these events in the Summary of Clinical Safety on page 82. Please submit any other analyses you have performed or are performing in order to assess these imbalances.

3. For subject 140-099, who reported the SAEs of acute coronary syndrome, acute myocardial infarction, and later cardiac ventricular thrombosis, among others, please clarify how many events of cardiac ventricular thrombosis occurred during the study. One SAE of cardiac ventricular thrombosis is noted in the datasets. The narrative provided for this subject for the SAEs of cardiac failure, atrial fibrillation, cardiac ventricular thrombosis, pneumonia, pleural effusion, pulmonary embolism, sepsis, and ischemic hepatitis notes that he had a "prior history of left ventricular thrombosis". Please clarify when this subject acquired a history of left ventricular thrombosis – prior to study enrollment, coincident with the ST elevation MI as seems to be implied from the description of events on page 82 of the CSR, or another time. If another event of cardiac ventricular thrombosis occurred while the subject was enrolled in the study, please clarify why this was not reported as an AE. Please also provide the narrative for the SAE of acute myocardial infarction, as requested in #1 above.

4. Please provide a brief narrative and the CRFs for the following subjects reporting non-serious cardiac MAE:

    a. Subject 122-631, who received Engerix-B and reported the non-serious MAE with an investigator term of "cocaine induced coronary vaso spasm", which was coded as the preferred term "drug abuse." Please also state your rationale for selecting the preferred term of "drug abuse" instead of "arteriospasm coronary."

    b. Subject 125-359, who received Engerix-B and reported the non-serious MAEs of chest pain and "catheterisation cardiac".

    c. Please also provide the total number from each arm of the study all cardiac MAE's not considered to be SAE's.

5. We note an imbalance in new-onset adverse events of special interest (AESIs), including autoimmune events, between study groups in study HBV-23. We acknowledge the Safety Evaluation and Adjudication Committee's assessment of these events and your analyses of this imbalance presented in the CSR and the Clincal Summary of Safety. Please submit any other analyses you have performed or are performing in order to assess this imbalance.

6. Subject 131-035 reported the treatment-emergent AE of granulomatous dermatitis, for which sarcoidosis was a primary diagnosis in the differential and for which the dermatopathologist makes the following recommendation "Sarcoidosis should be excluded clinically". The narrative states that the subject did not receive a pulmonary consult and chest computed tomography to evaluate for sarcoidosis because the subject's insurance denied the request, leading the subject to decline the studies. Given the events

of granulomatous disease that were identified in previous studies, the primary objective of HBV-23 was to evaluate the safety of HEPLISAV, and a secondary objective was to describe the frequency of specific new-onset granulomatous diseases, please provide your rationale for not pursuing a complete evaluation to rule out a systemic granulomatous disease in subject 131-035.

7. For subject 115-124, who reported the AE of "dry mouth", we note that the event start date is listed as study Day 267, but the action taken with regard to treatment (Engerix-B) is drug withdrawn. Day 267 is well after the subject should have received the third study injection. Please clarify. In addition, as per the narrative, this subject was reporting symptoms of dry mouth prior to Day 267, yet the rheumatologist assessed her as having xerostomia on Day 267. Please explain why Day 267 was chosen as the AE start date.

8. In reviewing subject narratives for AESIs, which may have a prolonged period between symptom onset and diagnosis, we note inconsistencies in the reported AE start dates. For example:

   a. Subject 129-084: Systemic lupus erythematosus is reported with a start date of August 17, 2014, which is when the subject's hand pain worsened. She was evaluated by a rheumatologist and received the diagnosis in January and February 2015. This start date is based upon symptom starting or worsening when an evaluation and diagnosis occurred later.

   b. Subject 115-124: Xerostomia is reported with a start date of April 28, 2015, which is when the subject was evaluated by a rheumatologist who diagnosed xerostomia. She was referred to an otolaryngologist for dry mouth on November 12, 2014 and presumably symptoms preceded this date. This start date is based upon diagnosis when symptoms clearly preceded evaluation and diagnosis.

   c. Subject 130-115: Autoimmune thyroiditis is reported with a start date of June 16, 2014, which is the day the subject received her pre-vaccination blood draw and was first dosed with study vaccine. An abnormal TSH is first reported in the narrative on July 16, 2014. Analysis of a banked serum sample, presumably by Dynavax, collected prior to study vaccine, demonstrated abnormal TSH and "…the investigator changed the event onset date..." This start date is based upon analysis of banked sera.

   d. Subject 125-133: Autoimmune thyroiditis is reported with a start date of July 23, 2014, which is the day that an abnormal TSH is first reported in the narrative. Subsequently, an analysis of a banked serum sample, presumably by Dynavax, collected prior to study vaccine on June 11, 2014, demonstrated an abnormal TSH. This start date is based upon first clinically recognized thyroid abnormality.

   e. Was there a systematic way for reporting AE start dates? Please explain how you instructed investigators to assign the AE start date.

9.   Subject 134-228 reported the potential autoimmune event of "myalgias". Please provide any available additional information on this subject's "intermittent headaches with diminishing vision in his left eye," which was associated with floaters, confusion, and hallucinations, and for which he underwent temporal artery biopsy (negative) and received two courses of steroids. Specifically include the following:

   a.   Were the headache and visual changes further evaluated by a neurologist or ophthalmologist?

   b.   Was any imaging obtained to evaluate these symptoms?

   c.   Did the subject's diminished vision and headaches resolve following steroids?

   d.   To what etiology were the headaches and visual changes attributed?

   e.   Please provide a narrative, admission note, discharge summary, pathology report from the temporal artery biopsy, and the reports of any head imaging performed from his hospital admission for pneumonia, during which the evaluation for temporal arteritis occurred, in September 2014.

10.   We acknowlwedge your analysis of the imbalance in deaths observed between the study groups in HBV-23 presented in your CSR and your Clinical Summary of Safety. Please submit any other analyses you have performed or are performing in order to assess these imbalances.

11.   Please provide the narratives and CRFs for the following subjects who reported the following SAEs:

   a.   Subject 119-279, who reported the SAE of chest pain on Day 7 following Dose 2 of HEPLISAV.

   b.   Subject 130-219, a 34 year-old woman who reported the SAE with investigator term "end stage renal failure" on Day 10 following Dose 2 of HEPLISAV of 7 days duration.

   c.   Subject 131-103, who reported the SAE of cerebrovascular accident the day of Dose 1 of HEPLISAV.

   d.   Subject 129-038, who reported the SAE of transient ischemic attack on Day 24 following Dose 1 of HEPLISAV.

   e.   Subject 132-078, who reported the SAE of cerebrovascular accident on Day 11 following Dose 1 of HEPLISAV.

   f.   Subject 105-314, who reported the SAE of chronic obstructive pulmonary disease on Day 6 following Dose 1 of HEPLISAV.

12.   On page 55 and 56 of the CSR for study HBV-23, you note that 469 subjects (5.6%) were lost to follow-up. You also note that you utilized a vendor to research the status of 271 subjects considered lost to follow-up. Please explain why only 271 of the 469 subjects lost to follow-up were referred to the vendor and how you determined which subjects were referred. Please comment on whether these subjects were selected at random or on what basis subjects were selected to be referred to the vendor.

13.   On page 57 of the CSR for study HBV-23, you note that 48 subjects had a major protocol deviation of "MAE/SAE." Please explain what a major protocol deviation of this category means and how it impacted the disposition of these 48 subjects.

14.   For subject 125-113, who reported the event of "lung cancer metastatic", please identify the histological type of lung cancer.

15.   Please provide a brief narrative of subject 124-171 who reported the MAE of urticaria two days following the first injection with HEPLISAV, which resulted in discontinuation from study treatment, but was assessed as unrelated. Additionally, please identify the alternative cause to which the urticaria was attributed.

16.   Please clarify how Table 12-18, "Study Drug-Related Treatment-Emergent Medically-attended Adverse Events That Were Primary Reason for Early Study Treatment Discontinuation by System Organ Class and Preferred Term (Safety Population)" on page 107 of the CSR was constructed. There appear to be five events that were assessed by the investigator as at least possibly related and have an action taken of "drug withdrawn" that do not appear in the table (deep vein thrombosis in two subjects, one in each of the HEPLISAV and Engerix-B arms, urticaria in the HEPLISAV arm, and rash in two subjects in the Engerix-B arm).

17.   There are several entries in the dataset ADAE that appear to be the same event listed multiple times when an event progressed from non-serious to serious (for example, subject 118-229 chest pain and angina pectoris). Event terms are the same or similar and the stop date for one event is the same as the start date for the other event. Please clarify if this dataset intended to capture the evolution of AEs. If so, which, if any, dataset captures the single event with the greatest severity? This information is critical to be able to reconcile the number of events per subject. Please provide a list of adverse events that appear in the datasets as two separate events but that describe the same actual event. This list should include, at a minimum, subject number, reported term, preferred term, toxicity grade, seriousness, start date, end date, study onset day, and duration of the events. The above information should be provided for each event entry as it is currently listed in the ADAE dataset. If the number of events that are currently listed as more than one entry in the ADAE dataset, but that actually describe the same event, exceeds 15, please provide a revised ADAE dataset with one entry for each adverse event. The severity and seriousness of each event should reflect the greatest values of these variables and the duration and start and stop variables should reflect the total duration of the event.

18.   For subject 126-079, it appears that all eight of the subject's adverse events are listed with an action taken of "drug withdrawn," including the MAE of dysphonia that starts on study day 346 (after all injections should have been administered). For other subjects, additional adverse events reported as occurring after the event(s) that leads to withdrawal

are assessed as "dose not changed." Withdrawal of treatment should be attributed to one event or one group of events and not to every event that is reported subsequent to the decision to withdraw study treatment. Please describe the event(s) subject 126-079 reported that led to the decision to withdraw study treatment.

Regarding the Summary of Clinical Safety:

19.   Page 91 of the Summary of Clinical Safety (BLA 125428 Sequence 0040 Module 2.7.4) states that "The overall rate of myocardial infarction per person-year of follow up in the combined dataset of the large US studies in the TSP, HBV-16 and HBV-23, is consistent with National Heart, Lung, and Blood Institute (NHLBI) population estimates adjusted for age, sex, and race (SCS Table 2.2.1.1)" (Mozaffarian, Benjamin et al. 2015). Please provide a clear comparison of the specific rate used from the paper by Mozaffarian, et al., as well as the specific rate determined from studies HBV-23 and HBV-16 in order to support this statement.

20.   Page 91 of the Summary of Clinical Safety notes that "While the NHLBI dataset describes events rather than subjects and is limited to events of myocardial infarction, the number of subjects in the pooled safety populations of HBV-16 and HBV-23 reporting events identified by the Myocardial infarction SMQ (22 in the HEPLISAV treatment group and 5 in the Engerix-B group) is similar to the expected number of events based on the NHLBI data." Please provide a comparison of the number of events in the pooled safety population of HBV-16 and HBV-23 to the expected number of events based on the NHLBI data. Also, please describe how the expected number of events was calculated.

21.   Please provide the same comparisons, as described above in Questions #19 and #20 between those population estimates described in Mozaffarian, et al., and the specific rate and number of events determined from study HBV-23 alone.

22.   Please provide the specific rate determined from a combination of studies HBV-10, HBV-16, and HBV-23.

Regarding the Immunogenicity of Studies HBV -10 and HBV-16 :

In your Complete Response dated March 15, 2016 (CR dated February 22, 2013), you submitted revised Complete Study Reports (CSRs) for studies DV2-HBV-10 and DV2-HBV-16. You state that you determined the revisions were necessary following audits you performed after another regulatory agency identified concerns with a study not included in your U.S. licensing application. Following review of your revised data and responses to our information requests seeking further clarification, we have identified the following issues:

23.   There remain inconsistencies between the new datasets, the old datasets, and the tabular summaries of the data that you have provided. In order to perform a complete review of the data from studies DV2-HBV-016 and DV2-HBV-010, CBER requires submission of accurate datasets and summaries, along with clear explanations for inconsistencies and differences among versions of these files that have already been submitted. Specifically, we have noted the following inconsistencies that need to be addressed:

    a.   In study DV2-HBV-016 subject 35020 is identified in the original 2012 ADSL16 dataset (submitted with the original BLA, amendment 0 4/28/12) as included in

the lot consistency per protocol population (LCPPFLG = 1). Revised April and May ADSL datasets (submitted in amendments 45 and 49) and the May tabular response to the FDA April 27, 2016 IR (amendment 49) indicate that the subject is newly excluded (LCPPFLG=0). However, in the response to the FDA June 28, 2016 IR (amendment 54), the July ADSL dataset and the July tabular presentation of data indicate that the subject is *not* newly excluded (ELCPP = N). Please explain how the original 2012 ADSL16 dataset, the April and May ADSL datasets and the May tabular presentation and the July HBV-16-EX dataset and tabular presentation were generated such that the fields LCPPFLG and ELCPP were populated with the current results, how generating those data resulted in conflicting results and which results are accurate.

b. In the original DV2-HBV-16 2012 ADSL16 dataset the NIPPFLG for all subjects = ".". Please explain by what flag and in what dataset the non-inferiority per protocol population was identified.

c. In DV2-HBV-16 the following subjects are identified as newly excluded (identified as NIPPFLG = 0) from the non-inferiority per protocol population in the revised ADSL datasets submitted April 8, 2016 and May 27, 2016 (amendments 45 and 49) and in the hbv-16-ex dataset submitted July 7, 2016 (identified as ELCPP = Y, amendment 54) : subjects 37002, 37003, 37004, 37005, 37006, 37007, 37009, 37011, 37013, 37014, 37015, 37016, 37020, 37021, 37024, 37025, 37301, 37302, 37304, 37305, 37308, 37310, 37312, 37313, 37314, 37317, 37320, 37601, 37602, 37603, 37604, 37605, 37606, 37607, 37611, 37612. However in your May 27, 2016 response to FDA's April 27, 2016 IR, a tabular presentation of original data from 2012 and revised data from 2016 indicate that the subjects were originally *included* in the NIPPFLG and remain *included* in the NIPPFLG in the revised 2016 datasets. Please explain in which 2012 dataset subjects were designated as being included or excluded from the non-inferiority population (NIPPFLG = 0 or 1; see question #2). Please explain how the tables presented in the response to the April 27, 2016 IR were generated, i.e., what dataset(s) were used. Please explain the apparent discrepancy between the April, May and July datasets and the May tabular presentation of the data.

24. In your response, we request that you clearly describe which database contains accurate final study information for studies DV2-HBV-10 and DV2-HBV-16. We also request that you provide documentation of all differences between your final databases, other databases you have sent us and the original 2012 databases for these studies, and explanations and documentation for those differences, to include an accurate accounting of all <u>newly</u> excluded and <u>newly</u> included subjects, for the non-inferiority and lot consistency per protocol populations for Studies DV2-HBV-10 and DV2-HBV-16. We also request accurate summaries based on the final datasets. Provision of the following information would satisfy this request for documentation of these changes:

a. One new master ADSL dataset each for study DV2-HBV-10 and study DV2-HBV-16 in which the master ADSL dataset merges the original ADSL dataset used to generate the CSRs for DV2-HBV-10 and -16 in 2012 with the respective revised ADSL dataset used to generate the revised CSRs for DV2-HBV-10 and -16 in 2016. Each subject would have two rows in this master dataset: one

representing 2012 data and one representing 2016 data. Each row must clearly designate which is the 2012 data row and which is the 2016 data row. Each dataset would have the following additional columns: a column indicating if the LCPPFLG changed from 2012 to 2016 (y or n), a column indicating if the NIPPFLG changed from 2012 to 2016 (y or n). Please make sure that all columns in submitted datasets include the definition for each variable within the column info description box.

b.   A separate excel file that replicates each dataset and provides additional information to describe changes between 2012 and 2016, including highlighting of all fields that changed from 2012 to 2016 and inclusion of a 2016 outcome column in the excel file containing a comment that explains why the change took place. The comment in this column should link to the source data that identifies the protocol violation/deviation or correction that warrants the change in population assignment.

c.   A document for each dataset that lists the changes between 2012 and 2016 and why the change was made. Please include in the document a summary of the total number of subjects with changes from 2012 to 2016 (i.e. In DV2-HBV-16 a total of X subjects were newly excluded from the NIPP, a total of X subjects were newly included in the NIPP, a total of X subjects were newly excluded from the LCPP, a total of X subjects were newly included in the LCPP.)

25.   Please confirm that the revised CSRs for study DV2-HBV-10 and DV2-HBV-16 are accurate and that no other datasets were affected by the inconsistencies observed in the DV2-HBV-16 ADSL datasets.

The following concerns were identified during our continued review of the application following our September 9, 2016 IR communication. Additional information is needed for a complete safety assessment of the vaccine as the current submission contains insufficient information to make such an assessment possible.

Regarding Study HBV-23:

26.   Subject 128-042 reported an MAE of MI 112 days following the first injection of HEPLISAV of one day duration. In the CSR, on page 106, you report that this was a history of MI and not an acute treatment-emergent event. However, this event was coded as treatment-emergent in the ADAE datasets. Please explain this discrepancy. Please describe for this event, and in general, how you reconcile discrepant reporting and provide any other information you have regarding this event.

27.   In the CSR, on page 106, you note that two subjects, 122-308 and 122-448, received Engerix-B and reported a medically attended adverse event (MAE) of troponin increased, and that these events "were non-serious MAEs without myocardial infarction." Both subjects reported serious adverse events coincident with the MAEs of troponin increased, "diabetes mellitus inadequate control" and urosepsis. Please provide the narratives of these events, CRFs, lab results, and any other information available relevant to determining the diagnosis and severity of the MAEs of troponin increased for these subjects.

28.   Please provide the CRFs and the narratives for any subjects reporting the following:

      a.   an SAE of chest pain or non-cardiac chest pain

      b.   an SAE of cerebrovascular accident, transient ischemic attack, or other preferred term indicative of one of these events.

29.   In our analysis of your ADAE dataset, we note the following events for which the rate in the HEPLISAV group exceeded that in the Engerix-B group. Please provide your assessment of these imbalances, including any explanation for the differences noted between study groups, an exploration of the potential relationship between HEPLISAV and the events, and a discussion of any biologically plausible mechanism.

      a.   MAEs of herpes zoster

      b.   MAEs of atrial fibrillation

      c.   MAEs and SAEs of bipolar and bipolar 1 and SAEs of depression and depression suicidal

      d.   MAEs of drug hypersensitivity

      e.   SAEs of sepsis

      f.   SAEs of diabetic ketoacidosis

30.   We note in section 16.1.4 of the complete study report, *List and Description of Investigators and Sites*, it appears that 24 subjects transferred from one study site to another. However, we cannot locate the reason subjects transferred from one site to another. Please specify where in the submission the explanation is located or provide an explanation for why subjects transferred from one site to another and how you ensured seamless follow-up and capture of safety information.

31.   As per the Safety Evaluation and Adjudication Committee (SEAC) Charter, Version 5, dated May 21, 2015, section 6.0 g, subjects with newly discovered potentially autoimmune hypothyroid disease entered the SEAC adjudication process but had baseline laboratory specimens examined. "Subjects with a documented diagnosis of hypothyroidism prior to enrollment in the study, or by laboratory examination of specimens obtained at baseline prior to the first administration of study vaccine [did] not require expert consultation or SEAC evaluation." We note that this was added in version 4 in November 18, 2014. Given that this represents a change in the procedures for adjudicating thyroid disease, and in order to assess all events of hypothyroidism similarly, please provide a list of all subjects, and their treatment assignment, who had thyroid assessments performed on their pre-vaccination laboratory draw, the results of that assessment, and whether those subjects were referred to the SEAC for evaluation.

32.   As per the HBV-23 CSR, page 87, you report 61 subjects with 65 diagnoses of potential new-onset AESIs or AIAEs evaluated by the SEAC. The datasets and the Adverse Events Listings Table 16.12.6.1 show 61 subjects with 68 events evaluated by the SEAC; thirty-nine subjects who received HEPLISAV reporting 41 events and 22 subjects who received Engerix-B reporting 27 events. Please clarify this apparent discrepancy.

33.   Subject 136-149 received HEPLISAV and was diagnosed with new-onset Hashimoto's thyroiditis and papillary thyroid cancer. In regard to the Week 28 elevated anti-thyroglobulin (anti-TG) level, the narrative notes that "the panel [SEAC] noted that this result was written in the case narrative as being taken from serum collected at baseline; however the date of the sample was 28 weeks after the subject received the first dose of blinded study vaccine." Please describe the events that led to erroneous information in the narrative prepared for the SEAC, other subjects and laboratory results that may have been erroneously reported, and the procedures that were put in place following this event in order to prevent other similar events from occurring.

34.   Incomplete or inconsistent information was provided for several subjects who reported potential adverse events of special interest. Please provide the following information:

   a.   Subject 103-108 received HEPLISAV and was diagnosed with hypothyroidism, by her primary care physician, based on one slightly elevated thyroid stimulating hormone (TSH). Analysis of the subject's banked study baseline serum demonstrated a normal TSH. The investigator and the SEAC questioned the diagnosis. The subject declined further laboratory testing for hypothyroidism and evaluation by a specialist. As the diagnosis of this potential autoimmune event appears to be in question, please provide the results of testing of the banked Week 28 (approximately two months prior to diagnosis) serum for TSH and thyroid autoantibodies and the banked study baseline serum for thyroid autoantibodies, if autoantibodies are found at Week 28.

   b.   Subject 112-326, who received HEPLISAV and was diagnosed with hypothyroidism with negative testing for anti-thyroperoxidase (anti-TPO) and anti-TG antibodies. The subject was evaluated by an endocrinologist but the results of the endocrinologist's assessment of the subject, following the negative thyroid autoantibody testing, were not provided in the narrative. Please provide the endocrinologist's assessment of the etiology of the subject's hypothyroidism.

   c.   Regarding subject 118-111, who was diagnosed with hypothyroidism following vaccination with Engerix-B, the narrative states the subject had a history of "inflammatory bowel disease (IBS)." Please clarify if this subject had a history of inflammatory bowel disease or irritable bowel syndrome and if inflammatory bowel disease, please comment on the subject's eligibility prior to study enrollment.

   d.   Subject 114-027 was diagnosed with Graves' disease following vaccination with HEPLISAV based upon low TSH and elevated thyroid stimulating immunoglobulin (TSI). This event was assessed by the SEAC as a pre-existing autoimmune event based upon the endocrinologist's assessment of low-normal TSHs over the eight years prior to study enrollment. As the subject had clear evidence of persistent abnormal TSH and elevated TSI following, but not prior to, vaccination, based upon the information available, CBER considers this a new-onset adverse event of special interest (AESI). A pre-vaccination elevated TSI would likely provide evidence that the AESI was pre-existing.

e. Subject 133-107 received HEPLISAV and was initially diagnosed with hypothyroidism by their primary care physician. The subject was also evaluated by an endocrinologist for hypothyroidism and further testing was performed. The investigator and the SEAC later determined that this diagnosis was an error. Please provide the endocrinologist's ultimate assessment of the subject following the laboratory and ultrasound evaluations. The subject had laboratory results that were consistent with subclinical hyperthyroidism, yet this does not appear to be reported as an adverse event. Please clarify if the subject's subclinical hyperthyroidism was evaluated by an endocrinologist or considered as a potential immune-mediated condition.

35. Subject 105-238 received HEPLISAV and reported an MAE with a preferred term of phlebitis superficial 245 days following the second dose. This event was not flagged as a VTE in the datasets, nor does it appear to be reported as such in the CSR. Please explain. Please provide the narrative and CRFs for this subject. Did this subject have thrombophilia testing performed? If so, please provide the results.

36. In study HBV-23, subjects who reported MAEs of VTE were to return to the study site to have laboratory evaluations for thrombophilia. Please provide a summary of these evaluations and your interpretation of any abnormalities, or provide the location within the submission that contains this information.

37. In the CSR on page 82, you report that "all subjects in both vaccine treatment groups who had a new-onset thrombotic/thromboembolic event had at least one pre-disposing risk factor for thrombosis with the exception of "one Engerix-B subject". Please clarify the pre-disposing risk factor for subject 140-099.

38. Incomplete information was provided for several subjects who experienced adverse events. Please provide the following information:

a. For subject 108-065, who reported granuloma annulare, please provide any other information available regarding the event, evaluation of the subject, and whether the event may be potentially immune-mediated.

b. For subject 113-016, who reported pyoderma gangrenosum, please provide any other information available regarding the event, its assessment, associated symptoms or diagnoses, an update on the subject's condition and new diagnoses, and whether the event may be potentially immune-medicated.

c. For subject 123-049, who reported "anaphylaxis reaction secondary to allergy serum" on the same day the subject received dose 2 of HEPLISAV, please provide further information describing this event and why it was not attributed to vaccination.

d. For subject 117-125, who reported abnormal serum protein electrophoresis, please provide the laboratory records as there appear to be inconsistencies in the narrative in describing laboratory evaluation dates. Please provide an update for this subject, as the narrative states he was to be evaluated January 2016.

    e.   For subjects 102-063 and 112-237, who reported multiple myeloma, please provide narratives and CRFs for these events and subjects, respectively.

    f.   Subject 102-046, received HEPLISAV and had one reported MAE, diaphragmatic paralysis, 226 days after the second dose that was also serious. Please provide a brief narrative which includes the investigator's assessment of the etiology of the event (for example trauma, cardiac surgery, ALS, myopathy, MS, Guillain Barre syndrome).

39.   For subjects who reported a pregnancy that was ongoing at the conclusion of the study, please submit updated information regarding the outcome of those pregnancies, or identify the location within previously submitted material.

40.   Please provide an analysis of safety events, including deaths, MAEs, SAEs, and AESIs, reported in study HBV-23 by age, gender, race, and ethnicity.

41.   Please provide a complete list of all subjects in study HBV-23 who were lost to follow-up (LTFU) and who were subsequently reengaged. This request is based on the incomplete information obtained during the BIMO inspections. The inspections noted that sites did not accurately capture the LTFU subjects and those who were subsequently reengaged. For example, two subjects whose records were reviewed during the inspection were LTFU and reengaged but neither were identified on a site list of LTFU and reengaged subjects. With an incomplete list of potentially affected subjects we are unable to determine the full scope of number of LTFU subjects and reengaged in study HBV-23.

42.   A BIMO inspection in study HBV-23 identified a Protocol Deviation guidance document instructing sites to maintain a protocol deviations log as an Excel spreadsheet. These documents could potentially be changed at any time by any individual without the ability to track who made changes and when they were made. Because the study populations were based upon protocol deviations, please explain how you verified that the information in the logs was complete and accurate.

Regarding your Integrated Safety Analysis:

43.   In your Summary of Clinical Safety, you present integrated analyses of safety endpoints based upon a Primary Safety Population (PSP) and a Total Safety Population (TSP). The PSP includes study HBV-10, which monitored SAEs for 28 weeks following dose 1, and studies HBV-16 and -23, which monitored SAEs for one year or more following dose 1. The TSP includes studies which did not employ the final formulation of HEPLISAV. CBER's integrated safety analysis will focus on deaths, SAEs, and AESIs because these events were collected in studies HBV-23 and -22, the studies submitted since the initial BLA review; we will not analyze MAEs and AEs in an integrated fashion. In order to address concerns that studies monitoring AEs for varying lengths of time and studies using distinct formulations of study product are not integratable, CBER plans to analyze an integrated summary of safety using the following populations:

    a.   Primary Safety Population (PSP)

        i.   6 month PSP: HBV-10, HBV-16, HBV-23

SAEs reported from vaccination through Week 28

    ii.   1 year PSP: HBV-16, HBV-23

SAEs reported from vaccination through study end (Week 52-56)

    b.   Modified Total Safety Population (mTSP):

HBV-10, HBV-14, HBV-16, HBV-22, HBV-23

SAEs reported from vaccination through Week 28

Please provide an addendum to the Summary of Clinical Safety, analyzing important safety outcomes based upon these populations. At a minimum, this should include deaths, SAEs, cardiac SAEs, myocardial infarction, cerebrovascular disease, venous thromboembolism, acute and chronic renal failure, and AESIs, Please also include an analysis of safety outcomes by age, gender, race, and ethnicity based on these populations.

Regarding the overall submission:

44.   Multiple hyperlinks to clinical sections of your submissions are not functional. Please ensure that all hyperlinks are working appropriately.

MANUFACTURING FACILITIES

45.   Regarding the Shipping Study of the drug product from Rentschler Biotechnologie GmbH to your labeling and packaging contract manufacturers (**(b) (4)**):

    a.   Please provide a copy of the summary report for the shipping study and include a description and results including a description of the shipping configuration, target maximum shipping duration, target shipping temperatures, and acceptance criteria. Please also compare this with your routine shipping conditions.

    b.   Please clarify if you conducted any Performance Qualification runs for the shipping of HEPLISAV Drug Product from Rentschler Biotechnologie GmbH to **(b) (4)**. If no shipping validation studies were performed, please provide the rationale why none were conducted for shipments from Rentschler Biotechnologie GmbH to **(b) (4)**.

CHEMISTRY, MANUFACTURING, AND CONTROL

46.   In your response to item #51 in our Complete Response letter dated February 22, 2013, you indicated that the **(b) (4)** method was implemented to determine the purity and product-related impurities of the **(b) (4)**. We were unable to find the **(b) (4)** results for the **(b) (4)** reference standard; please provide these results.

QUALITY CONTROL AND TESTING PROCEDURES

Lot Release and In-support Testing

47.   Please provide your endotoxin test results for lot numbers   (b) (4)
        , to include their sample testing dilution and the percent PPC recoveries for all
        dilutions tested.

48.   Regarding in–vivo potency determination:

   a.   The DUS-SOP-QC-0204   (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.

   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.

Quality Control Tests and Method Validations

49.   Regarding the (b) (4) assay for adjuvant (1018 ISS) in HEPLISAV Drug Product by
        (b) (4) :

        In your submission dated August 19, 2016 (Amendment 56) you agreed to include the
        (b) (4) assay for adjuvant (1018 ISS) in the HEPLISAV Drug Product by (b) (4) as
        a release test. We have reviewed your method SOP (DUS-SOP-QC-0110) and the
        method validation report (VAL-Q234B-R) and have the following requests for
        information.

   a.   Please provide appropriate data to show that the   (b) (4)   shows all
          impurities present in 1018 ISS (adjuvant) and that none of them are   (b) (4)

   b.   In your method validation report it is stated that the validation applies to Dynavax
          Berkeley and Dynavax Europe laboratories. Please identify your originating and
          receiving laboratories for this assay. In which laboratory(ies) were all of the
          validation characteristics, other than Reproducibility, evaluated?

   c.   You have determined linearity by   (b) (4)
          (section 7.3 of your validation report). Please explain
          how this mixture compared with the actual drug product by providing detailed
          compositions of both.

d. You have assessed LOQ and LOD for the (b) (4) only by (b) (4) HBsAg (section 7.4 of your validation report).

    i. Please explain how this mixture compared with the actual drug product by providing detailed compositions of both.

    ii. As per your assay method (DUS-SOP-QC-0110) you do not measure (b) (4) impurity (b) (4) You measure (b) (4) . Please provide data for LOQ and LOD for (b) (4) or show by your data that LOQ and LOD for (b) (4) are essentially the same as those of (b) (4) in the drug product.

e. Please provide data to demonstrate LOQ and LOD for other impurities present in 1018 ISS in the drug product.

f. Regarding intermediate precision:

    i. In attachment K of your validation report, you have identified results for (b) (4) but not for the other impurities. Please identify which table corresponds to which impurity in this attachment.

    ii. Please provide overall RSD from three experiments for (b) (4) (b) (4) and that for each of the other impurities.

g. Although not clearly stated, it appears from your report that all of the validation data, except those for Reproducibility, were obtained in one laboratory. However, you indicated that the validation applies to both of your laboratories, located at Berkeley and in Europe, implying that you plan to carry out this test at both laboratories to obtain data for lot release. Please provide comparability data from both laboratories with sufficient number of the drug product lots to indicate that the results from the two laboratories are comparable. We suggest that you assess at least 6 lots.

h. In attachment (b) (4 of your validation report, you have identified results for (b) (4) and (b) (4) but not for the other impurities. Please identify which table corresponds to which impurity in this attachment.

i. You indicated that you inferred accuracy based on the results of the linearity, precision and specificity (section 7.7 of your validation report) but have not shown any data or data analysis to indicate how you concluded accuracy of the method for the (b) (4) and different impurities, except (b) (4). We do not agree that accuracy can be inferred automatically from the results of the specificity, linearity and precision. Please provide details of your data/data analysis to show how you inferred accuracy of your method from the results of the specificity, linearity and precision. Alternatively, please provide data to demonstrate accuracy of the (b) (4) and of different impurities from spike-recovery studies or by comparing with results obtained using an orthogonal method. Since you decided to measure (b) (4) impurities (b) (4) you may provide accuracy of the method for these two impurities (b) (4)

j.   You assessed accuracy of the method for ^{(b) (4)} on the basis of (b) (4) . We do not agree with your approach because the percent measurement may be affected due to variation in the area of the (b) (4) and other impurities. Please provide data in which assessment of accuracy is based on (b) (4) of each impurity.

k.   You have not conducted robustness studies for your method. Please provide the data and the statistical evaluation of your results from adequate studies to demonstrate your method robustness.

PHARMACOVIGILANCE POST MARKETING

Items 50-51 are a reiteration of our information request dated September 28, 2016, to which you submitted a response on October 5, 2016. Full evaluation and assessment of these responses require a more complete understanding of the potential safety concerns. Clarification of safety issues as described in the clinical review section of this letter is required to determine which concerns should be included as identified or potential risks in a pharmacovigilance plan as well as to help formulate a potential post-marketing study.

50.   The Phase 4 Post-Marketing Study Concept (Appendix 1 of the Risk Management Plan, STN 125428/0.42, module 1.16) states that "it is estimated that the study duration will be approximately 8 years in duration including protocol development and study preparation, subject accrual and collection of safety events, data analysis, and report writing." Please provide the number of years that will be needed specifically for subject accrual as well as an explanation and justification for this time estimate. What rate of vaccination uptake are you expecting?

51.   The Phase 4 Post-Marketing Study Concept (Appendix 1 of the Risk Management Plan, STN 125428/0.42, module 1.16) states that a sample size of 20,000 subjects per group will achieve 90% power to detect a 2.5 fold increase in the incidence of most immune-mediated diseases. Please describe:

   - what is meant by "most immune-mediated diseases".

   - the calculation used to determine this sample size, including the background incidence rate and the rationale for using this background incidence rate.

52.   Please submit a revised Pharmacovigilance Plan/Risk Management Plan (submitted with Track Changes) that incorporates any new or changed findings or analyses and is reflective of the most updated safety information. Your responses to items in this CR letter will be incorporated into considerations around a potential post-marketing study. We anticipate that additional discussion and development of a potential post-marketing study will be needed.

We reserve further comment on the proposed pharmacovigilance plan and the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

For PDUFA products, please submit your meeting request as described in our guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants,* dated May 2009. This document is available on the internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf, and CBER's *SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*. This document is available on the internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm. Both documents may be requested from the Office of Communication, Outreach, and Development, at (240) 402-8020.

We acknowledge receipt of your amendments dated September 23, 2016, October 2, 2016, October 5, 2016, October 7, 2016, October 8, 2016, and October 12, 2016. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of these amendments, in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Katherine Berkhousen, CAPT., USPHS or Richard Daemer, Ph.D., at 301-796-2640.

Sincerely yours,

Wellington Sun, M.D.
Director
Division of Vaccines and
    Related Products Applications
Office of Vaccines
    Research and Review
Center for Biologics
    Evaluation and Research