



Our Reference: Application # 125428/0

Date: February 8, 2017

Dynavax Technologies Corporation
ATTENTION: Elaine Alambra
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Dear Ms. Alambra:

Attached is a copy of the memorandum summarizing your January 10, 2017, Type A Meeting via teleconference with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to Submission # 125428/0/72 Sequence #70 in your future submissions related to the subject product.

If you have any questions, please contact CAPT Katherine Berkhausen or Dr. Richard Daemer at (301)796-2640.

Meeting Summary

Meeting ID #: CRMTS #10567
 Application number: 125428/0/72
 Product name: Hepatitis B Vaccine (Recombinant), Adjuvanted [HEPLISAV-B]
 Proposed indication: HEPLISAV–B is indicated for immunization against infection caused by all known subtypes of Hepatitis B Virus in adults 18 through 70 years of age

Applicant: Dynavax Technologies Corporation (Dynavax)
 Meeting type: Type A
 Meeting category: BLA
 Meeting date & time: January 10, 2017 10:00-11:30
 Meeting format: Teleconference
 Meeting Chair/Leader: Marian Major, PhD
 Meeting Recorder: Katherine Berkhausen, CAPT USPHS

Preliminary Responses sent January 9, 2017

FDA Participants:

Marian Major, PhD	Chair, Review Committee	OVRP/DVP
Katherine Berkhausen, RN	Regulatory Project Manager	OVRP/DVRPA
Richard Daemer, PhD	Regulatory Project Manager	OVRP/DVRPA
Sudhakar Agnihothram, PhD	Regulatory Project Manager	OVRP/DVRPA
Timothy Nelle, PhD	Team Lead	OVRP/DVRPA
Rakesh Pandey, PhD	Branch Chief	OVRP/DVRPA
Loris McVittie, PhD	Deputy Division Director	OVRP/DVRPA
Robin Levis, PhD	Deputy Director	OVRP/DVP
Phil Krause, MD, PhD	Deputy Office Director	OVRP
Darcie Everett, MD	Clinical Team	OVRP/DVRPA
Alexandra Worobec, MD	Clinical Team	OVRP/DVRPA
Meghan Ferris, MD	Team Lead	OVRP/DVRPA
Andrea Hulse, MD	Branch Chief	OVRP/DVRPA
Brenda Baldwin, PhD	CMC, Adjuvant	OVRP/DVRPA
Lokesh Bhattacharyya, PhD	Method Validation	OVRP/DBSQ
William McCormick, PhD	Division Director	OVRP/DBSQ
Bhanumathi Kannan	BIMO	OCBQ/DIS
Mridul Chowdhury, PhD	Biostatistics	OBE/DB
Ruoxuan Xiang, PhD	Biostatistics	OBE/DB
Tsai-Lien Lin, PhD	Team Lead	OBE/DB

Maria Said, MD
Deepa Arya, MD

Pharmacovigilance
Team Lead

OBE/DE
OBE/DE

Dynavax Participants:

Elaine Alambra	Senior Director, Regulatory Affairs
Mike Berry, PhD	VP, Process Development and Manufacturing Sciences
Graeme Currie, PhD	VP, Clinical Science and Operations
Martin Gohlke, PhD	Senior Director, Analytical Technologies
Randall Hyer, MD, PhD	VP, Medical Affairs
Robert Janssen, MD	CMO and VP, Clinical Dev & Regulatory Affairs
David Novack	Senior VP, Technical Operations

Background and Objectives:

Dynavax submitted a meeting request on December 13, 2017 to obtain clarification on clinical- and CMC- related items included in the complete response letter issued by CBER on November 10, 2016. The pre-meeting materials were submitted on December 13, 2017.

FDA provided its responses to Dynavax's questions on January 9, 2017. After reviewing the responses, Dynavax notified FDA of their decision to limit the meeting to discussion of question numbers: 1(a)iii, 1(b), 2(a), 2(e), 3(a) i, ii, iii, and 3(b).

The Type A Meeting discussion highlights and agreements are embedded in the appropriate sections in ***bold and italicized*** font.

Questions from the applicant:

1. Regarding CRL Item #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.*

Dynavax Questions:

- (a). For the summary of safety outcomes by demographic subgroups, Dynavax proposes the following:
 - i. Age: (18-39, 40-70, 65-70 years)
 - ii. Sex: (Female, Male)
 - iii. Race: (White, Black/African American). We propose not discussing Asian or Other race. In HBV-23, there were small numbers of subjects who were Asian (N = 95) or of Other race (N = 139). Among Asians there were 0 AESIs, 2 SAEs (HEPLISAV: 1.8% [n = 1]; Engerix-B: 2.6% [n = 1]), and 1 death, and among those of Other

- iv. races, there were 0 AESIs, 7 SAEs (HEPLISAV: 4.0% [n = 4];
Engerix-B: 7.5% [n = 3]), and 0 deaths.
iv. Ethnicity: (Hispanic or Latino).

Does the Agency agree?

CBER Response to Question 1 (a):

- i. We prefer that you also include the age subgroup 18 – 64 years to describe safety in non-elderly adults.
- ii. We agree that the subgroup analysis for sex should include the subgroups of male and female.
- iii. While CBER understands that it will be difficult to draw conclusions regarding safety by subject demographics, particularly in groups with low numbers of subject enrollment, please be sure to provide the number and frequency, with confidence intervals, of subjects reporting specific safety events for all races differentiated during the data collection process, including “Asian” and “Other race.” Presentation of results for all subgroups, such as in tabular form, should be displayed together and as prominently for smaller subgroups as for larger subgroups. Discussion of the results should address notable differences between subgroups in the context of the total number of subjects in a particular subgroup included in an analysis.

Type A Meeting Discussion:

Dynavax clarified the race subgroups that were collected from subjects during the trial and stated that they will present data by each race subgroup as collected during the trial, instead of including an “Other race” category made up of several race subgroups with small numbers.

CBER Response: The way Dynavax proposes to present the data tables is acceptable.

- iv. Please include the following two subgroups for ethnicity: 1) Hispanic or Latino and 2) Not Hispanic or Latino
- (b). Dynavax proposes using a minimum event rate $\geq 1/1000$ in SOCs or preferred terms in either treatment group for discussion of numerical imbalances. Events discussed in the response to CRL #29 will not be discussed in the response to CRL #40.

Does the Agency agree?

CBER Response to Question 1 (b):

We understand that this question refers to the minimum event rate of system organ class terms or preferred terms in either treatment group to warrant discussion of numerical imbalances in the analysis of safety outcomes by demographic subgroups. If this is what you intended to ask, please be aware that it is not necessary to provide us with the frequencies or to discuss all individual PTs or SOCs by the demographic characteristics listed. If in preparing your complete response, you have identified differences in frequencies of subjects reporting specific SOCs or PTs between the treatment groups, which are notable due to size of the imbalance, potential relationship to the study vaccine, or other factors (for example, as identified for acute myocardial infarction and the cardiac SOC), an analysis of the event reports by demographic subgroups should be included in a thorough assessment of the imbalance in event frequency. If this is not your intended question, please clarify your question.

Type A Meeting Discussion:

Dynavax asked for clarification on CBER's process of identifying notable imbalances and whether there was a standard criterion for the minimum size of an imbalance.

CBER Response:

CBER clarified that the question and discussion referred to the analysis and discussion of safety by demographic subgroups, to which Dynavax agreed.

CBER responded that data would need to be displayed for all demographic subgroups, that there is no set threshold to identify imbalances that would require further investigation or discussion, and that the threshold proposed is reasonable. CBER asked Dynavax to state any criterion that they used to determine further discussion of imbalances. If CBER requires further information about any events that fall below the threshold, CBER will request this information.

2. Regarding CRL Item #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. CBERs 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.

Dynavax Questions:

Dynavax proposes presenting the data for the modified TSP in tables but not discussing the results. The rationale for this approach is that HBV-14 and HBV-22 contribute only 232 of the 13,464 subjects in the modified TSP and there were no AESIs or deaths in HBV-14 or HBV-22. In HBV-14, 1 subject (03032) reported 6 SAEs unrelated to study treatment and 1 subject (05024) reported an SAE of cholelithiasis. No SAEs were reported by the subjects in HBV-22.

Does the Agency agree?

CBER Response to Question 2:

Your proposal is acceptable. However, please note within the discussion that you will not be discussing the modified TSP, the reason why, and the subject numbers and preferred terms of the events listed above. Please also include the data for the modified TSP in any tables presented in the addendum to the Clinical Summary of Safety.

- (a) Per our understanding of FDA's request, Dynavax proposes the following summary tables of the listed safety outcomes for each of the 3 analysis populations requested. We understand that the main interest of integrated

analyses that the Agency requested are SAEs; therefore, the proposed summary tables will include only SAEs except for:

- i. the summary of deaths, which will include all deaths; and
- ii. the summary of AESIs, which will include all reported events including both SAEs and non-SAEs.

Does the Agency agree?

CBER Response to Question 2 (a):

In general we agree and have the following request for your presentation of AESIs. It is our understanding that in your Clinical Summary of Safety submitted March 16, 2016, you present two analyses of AESIs, both of which include AESIs that have a PT or LLT that is on the AESI list. They do not necessarily include subjects with PTs that are not on the list, even if they were adjudicated by the SEAC as new-onset AESIs. In your analysis of AESIs, please include an additional analysis of AESIs that presents the following: 1) in studies that utilized a SEAC, subjects who reported events that were determined to be AESIs, whether the PT or LLT for that event is on the list of AESIs or not, and 2) in studies that didn't utilize a SEAC, all AESIs that were identified through your retrospective search of the datasets.

Type A Meeting Discussion:

Dynavax clarified that the events that were not included in the Clinical Summary of Safety's AESI presentation referenced above were several events of hypothyroidism. These events were either reported in studies that utilized a SEAC and were adjudicated as autoimmune, or were reported in studies that did not utilize a SEAC (for example, DV2-HBV-10). Dynavax noted that these events were discussed separately in a section on thyroid disorders.

CBER responded that they prefer to see an analysis of all events adjudicated by the SEAC as AESIs, including hypothyroidism AESIs, in an AESI presentation described above. The events of hypothyroidism from studies that did not utilize a SEAC can be discussed separately in the section on thyroid disorders.

- (b) For the summary of safety outcomes by demographic subgroups, Dynavax proposes the following:
- i. Age (18-39, 40-70, 65-70 years)
 - ii. Gender (Female, Male)
 - iii. Race: (White, Black/African American). We propose not discussing Asian or Other race. In the 6 month PSP, there were small numbers of subjects who were Asian (N = 190) or of Other race (N = 219).

Among Asians, there were 1 AESI, 2 SAEs (HEPLISAV: 0.8% [n = 1]; Engerix-B: 1.6% [n = 1]), and 1 death, and among those of Other race, there were 0 AESIs, 9 SAEs (HEPLISAV: 3.7% [n = 6]; Engerix-B: 5.3% [n = 3]), and 0 deaths.

- iv. Ethnicity (Hispanics or Latino)

Does the Agency agree with the proposed demographic subgroups?

CBER Response to Question 2 (b):

Please see the response to Question 1a above. The same demographic subgroups may be used for the integrated summary.

- (c) In addition, considering the potential high number of tables with sparse cells, we propose to perform the demographic subgroup analyses only for:
 - i. deaths;
 - ii. all SAEs; and
 - iii. AESIs.

Does the Agency agree with the scope of the subgroup analyses?

CBER Response to Question 2 (c):

We agree. Please see comment in response to question 2a above and include a subgroup analysis of AESIs as outlined in our comment.

- (d) See table and question on the next page.

Table 1: Planned Analyses of Safety Outcomes by System Organ Class / Preferred Term

Safety Outcomes	Analysis Populations			Events Included	Analysis by Demographic Subgroups (Age, Gender, Race, Ethnicity)
	6-mo PSP ^[a]	1-yr PSP ^[b]	mTSP ^[c]		
Deaths	Yes	Yes	Yes	All deaths	Yes
All SAEs	Yes	Yes	Yes	SAE	Yes
Cardiac SAEs	Yes	Yes	Yes	SAE	No
Myocardial infarction	Yes	Yes	Yes	SAE	No
Cerebrovascular disease	Yes	Yes	Yes	SAE	No
Venous thromboembolism	Yes	Yes	Yes	SAE	No
Acute and chronic renal failure	Yes	Yes	Yes	SAE	No
AESIs	Yes	Yes	Yes	MAE	Yes

[a] 6-Month Primary Safety Population: HBV-10, 16 and 23, with 6 months safety data (through Week 28)

[b] 1-Year Primary Safety Population: HBV-16 and 23, with 1 year safety data (through Week 56)

[c] Modified Total Safety Population: HBV-10, 14, 16, 22 and 23, with 6 months safety data (through Week 28)

Does the Agency agree with the scope of the subgroup analyses?

FDA Response to Question 2 (d):

We agree. However, this table of proposed analyses for the integrated safety analysis should not preclude a thorough assessment of events with an observed imbalance in frequency between treatment groups, such as cardiac SAEs and myocardial infarction, for which descriptive analyses by demographic subgroups may be informative.

- (e) Dynavax plans to include terms used in our MACE analysis to address cerebrovascular disease: stroke including ischemic stroke and hemorrhagic stroke.

Does the Agency agree?

CBER Response to Question 2 (e):

We understand your analysis will include adverse events with the following terms: Basal Ganglia Stroke, Brain Stem Stroke, Cerebrovascular Accident, Haemorrhagic Stroke, Haemorrhagic Transformation Stroke, Stroke in Evolution, Basal Ganglia Infarction, Basal Ganglia Stroke, Brain Stem Embolism, Brain Stem Infarction, Brain Stem Stroke, Cerebellar Embolism, Cerebellar Infarction, Cerebral Artery Embolism, Cerebral Infarction, Cerebrovascular Accident, Embolic Cerebral Stroke, Embolic Stroke, Ischaemic Cerebral infarction, Ischaemic Stroke, Lacunar Infarction, Lacunar Stroke, Thalamic

Infarction, Thrombotic Cerebral Infarction, or Thrombotic Stroke. It is acceptable to submit an analysis using these terms. Please perform an additional analysis that includes Transient Ischaemic Attack in addition to the terms above.

Type A Meeting Discussion:

Dynavax clarified the process for selecting terms used in the MACE analysis.

CBER stated that the comment was in reference to performing an analysis for the integrated safety analysis. For the integrated analysis of stroke, an additional analysis including events with the preferred term Transient Ischaemic Attack was requested.

Dynavax also noted that the process for selecting terms used in the MACE analysis for myocardial infarction was the same as the process for selecting terms for stroke.

CBER stated that the responses submitted in September and October 2016 will be reviewed as part of the next review cycle. Internal discussion, including discussion with experts in cardiology, is anticipated regarding the most appropriate terms to consider for assessment of cardiac risk.

3. Regarding CRL Item #49: 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)-d) ...

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

f)-h) ...

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) (b) (4) you may provide accuracy of the method for these (b) (4) (b) (4)

j)-k) ...

Dynavax Questions:

- (a) In item 49e, the agency requests LOD/LOQ data for other impurities present in HEPLISAV drug product. As the method is supposed to determine the (b) (4) but not individual impurities, Dynavax's understanding for validation of such a method is that LOD/LOQ of other impurities does not need to be assessed. However, Dynavax provided LOD/LOQ data of a representative impurity (b) (4) to show method capability to detect impurities.

Does the Agency agree that after clarification of the intended use of the method, the provided validation data that include LOD/LOQ data for a representative impurity (b) (4) are acceptable?

CBER Response to Question 3 (a):

We need further clarification before we can address your question.

- (i) In the Type A briefing package, you indicate that the (b) (4) may include (b) (4) impurity. If that is the case, then this (b) (4) should also include the impurity (b) (4) which is (b) (4) between the (b) (4) (see, for example Figure 4 in your method validation report # VAL-Q234B-R). Thus, your (b) (4) result includes percent of (b) (4) (b) (4). This is not consistent with how (b) (4) is defined in your SOP for this assay (DUS-SOP-QC-0110). Please clarify.
- (ii) We note in your Type A briefing package that you propose to determine (b) (4) (b) (4). But, you did not validate the method for this intended application. You validated the method for absolute contents of (b) (4) and each impurity (method validation report # VAL-Q234B-R). We felt that your approach was acceptable because the main component and the impurities (b) (4) constituted the total. Hence, we asked you to evaluate LOQ and LOD of the impurities. Alternatively, you may validate your assay for (b) (4) with respect to the total evaluating linearity, precision and accuracy for (b) (4) as the reportable result. However, this assumes that the issue discussed

under (i) above is resolved. Please clarify how you wish to perform your method validation.

- (iii) Please note that in the Type A briefing package, you indicate, “Product-related impurities of 1018 are determined during the release testing of 1018 using an (b) (4) method.” However, we found that the specification you proposed in Amendment 57 (August 19, 2016) for the drug product, did not include any specification for the impurities derived from the adjuvant (product-related impurities). Please clarify how you are controlling impurities in the drug product.

Type A Meeting Discussion:

Dynavax clarified that the (b) (4) method measures (b) (4) in the drug product (b) (4). This method is not meant to measure concentration of (b) (4) (b) (4). Dynavax also clarified that (b) (4) impurity was different from (b) (4) impurity. CBER pointed out that confusion was created because neither the assay SOP (DUS-SOP-QC-0110) nor the validation report (VAL-Q234B-R) provided this information. This is new information from Dynavax to CBER.

Dynavax clarified during the meeting and in an email communication received on January 10, 2017 that the (b) (4) (b) (4) impurity is a (b) (4) that is missing the (b) (4) (b) (4) (b) (4) is controlled by (b) (4) and is measured as one of the unspecified impurities in 1018 drug substance. The acceptance criterion is not more than (b) (4) is not a degradation product and as such, cannot increase with storage of 1018 or HEPLISAV. The (b) (4) (b) (4) impurity has a different structure than the (b) (4) impurity, which (b) (4) earlier than the main compound. (b) (4) (b) (4)

Dynavax agreed to perform a study to show that there is no change in content of the impurities of 1018, including (b) (4) (b) (4) in the formulated final product under normal conditions and under forced degradation conditions.

CBER agreed that the plan for this study could be submitted with the response to the CR letter and that the final data from the studies could be submitted during the review cycle.

Dynavax agreed to provide data on specificity with (b) (4) as the reportable result.

- (b) In item 49i, the agency requests accuracy data for different impurities present in HEPLISAV drug product. As the method is intended to determine the (b) (4) and not the proportion of individual impurities, Dynavax's understanding for validation of such a method is that accuracy of other impurities does not need to be assessed. However, Dynavax provided accuracy data of a representative impurity (b) (4) to show method capability to determine impurities.

Does the Agency agree that after clarification of the intended use of the method, the provided validation data that included accuracy data for a representative impurity (b) (4) are acceptable?

CBER Response to Question 3 (b):

We do not agree that determination of accuracy for one component necessarily demonstrates accuracy for other components, more so because the (b) (4) (b) (4) from the assay are (b) (4) (see, for example Figures 4, 10, 16, and 18 in your method validation report # VAL-Q234B-R). Accuracy of the main component (b) (4) and other impurities need to be determined (b) (4)

Type A Meeting Discussion:

Dynavax agreed to provide results on method accuracy however they would be limited by the fact that the maximum purity they could obtain for the target is about (b) (4) Dynavax suggested performing a study by spiking the product with different levels of impurities to address the issue of accuracy. CBER agreed that the data from such a study would not need to be submitted with the CR letter response and could be submitted during the review cycle.

4. Does the Agency have any additional guidance that Dynavax should address within the response to the CRL?

Please confine your responses to the CRL questions. We encourage you to not resubmit the BLA with *additional* changes. We recommend that you include the original CRL comment with the original numbering and follow each with your response.

We also encourage you to provide a comprehensive yet focused response to each of our questions. We emphasize our concern with the numerical imbalance in cardiac events observed in Study DV2-HBV23. Complete information and analyses will assist us in evaluating the clinical significance of the imbalance and overall risk/benefit profile of your candidate vaccine. This will also assist us in obtaining an effective and efficient review from an expert cardiac consultant. We will inform you if additional questions or concerns arise.

Type A Meeting Discussion:

- ***Dynavax asked if CBER would request a VRBPAC during the next review cycle.***

CBER responded that VRBPAC was a possibility and could not be ruled out at this time.

- ***Dynavax asked if there were any additional requests regarding the assessment of cardiac risk.***

CBER responded that their previous response in September 2016 will be reviewed as part of the next review cycle. Any additional information needed after their response to the CRL will be requested at that time.

- ***Dynavax asked if there were any additional concerns and if there were any items from the CRL that were considered resolved.***

CBER responded that the issues were laid out in the CRL and advised Dynavax to respond to each of the items in the CRL.