



Response to Type A Briefing Package Questions

Our Reference: 125428/0/72; Sequence #070
CRMTS #10567

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SUBJECT: Written Response to questions included in the Type A Briefing Package

PRODUCT: 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

Although we continue to reserve January 10, 2017 /10:00 ET, for a TELECON with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us in writing as soon as possible so that we may clear the meeting time. These responses would then become the official FDA responses to your questions.

Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the Review Committee can provide clarification during the reserved meeting time. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss and/or to reach agreement on such changes at the meeting.

Please include a reference to CRMTS #10567 and STN 125428/0/72 in your future submissions related to the subject product.

Although our template response document indicates that meeting cancellation is possible, we encourage you to proceed with the meeting (telecon) as scheduled. This will provide a full opportunity for clarification together with the best guidance for a complete response to the CRL and confirmation of understanding of positions on both sides.

INTRODUCTION:

Dynavax has requested clarification of three specific CRL items (# 40, 43, and 49). The CRL item is noted in bold and italics font, followed by the specific Dynavax question in bold font. The FDA response follows in a non-bolded font. Please note that the Dynavax proposed questions have been numerically adjusted to begin with the number “1”; and an unnumbered question was given a numerical identifier.

QUESTIONS FROM THE SPONSOR/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 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?

FDA 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.
 - 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 SOC's 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?

FDA 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 SOC's by the demographic characteristics listed. If in preparing your complete response, you have identified differences in frequencies of subjects reporting specific SOC's 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.

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?

FDA 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?

FDA 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.

- (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?

FDA 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?

FDA 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)

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?

FDA 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.

- 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), you may provide accuracy of the method for these (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?

FDA 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). 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). 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.
- (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?

FDA 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) 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)

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.

END