

RECORD OF EMAIL CONVERSATION

Submission Information

Application Type	BLA
STN	125428/0.0
Review Office	OVRR
Applicant	Dynavax Technologies Corporation / Lic. # 1883
Product	Hepatitis B Vaccine (Recombinant), Adjuvanted
Trans-BLA Group:	No

Telecon Details

Telecon Date/Time	22-NOV-2016 4:54 PM
Author	BERKHOUSEN, KATHERINE
EDR	No
Post to Web	No
Outside Phone Number	
FDA Originated?	No
Communication Categories	AD - Advice
Related STNs	None
Related PMCs	None
Telecon Summary	Dynavax request for advice and clarification of CRL items.
FDA Participants	Katherine Berkhausen
Applicant Participants	Elaine Alambra

Telecon Body: Dynavax sent two emails requesting clarification of CR letter items (CRL item # 40, 43, and 49). Dynavax also proposes various questions to which they seek CBER concurrence. In the email Dynavax acknowledges the extent of their clarification request and suggests a telecom with additional briefing documents to facilitate discussion. I will discuss the requests with the committee chair and DVRPA leadership; and notify Dynavax of our response to their requests. Dynavax was notified that this was under discussion and I would get back with them regarding this request.

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From: Elaine Alambra [mailto:EAlambra@dynavax.com]
Sent: Tuesday, November 22, 2016 4:54 PM
To: Berkhausen, Katherine
Cc: Daemer, Richard J.
Subject: HEPLISAV BLA 125428 / Request for Clarification on IR 10Nov2016, Question 49

Dear Katherine,

Dynavax is preparing our responses to the 10 Nov 2016 CRL and request clarification on a CMC-related question.

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

Dynavax is proposing a telecom with the CMC reviewer(s) to discuss certain aspects of method validation requested by the Agency such as the necessity of using additional impurities to show the accuracy of the method. We can provide a briefing document in advance of the call.

Would the Agency be available next week (wk of 28 Nov) for a telecom? Please let me know and I can provide a call in number.

Happy Thanksgiving!

Sincerely,

Elaine

Elaine Alambra • Regulatory Affairs • Dynavax Technologies Corporation ☎ Tel: 510-665-0474 ✉ email: ealambra@dynavax.com

From: Elaine Alambra [mailto:EAlambra@dynavax.com]
Sent: Tuesday, November 22, 2016 5:37 PM
To: Berkhausen, Katherine
Cc: Daemer, Richard J.
Subject: HEPLISAV BLA 125428 / 10Nov2016 CRL - Request for Clarification: Clinical Questions

Dear Katherine,

Dynavax is preparing our response to the 10 Nov 2016 CRL and requests clarification and guidance on Clinical questions listed below.

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- **CRL 40**

Dynavax proposes that the breakdown by age group of Group 1 (18 to 64) and Group 2 (65 to 70) will be sufficient. **Does the Agency agree?**

- **CRL 43**

- (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 the serious adverse events (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?

- (b) For the summary of safety outcomes by demographic subgroups, Dynavax proposes the following demographic subgroups:
- i. Age (18 to 64, 65 to 70)
 - ii. Gender (Female, Male)
 - iii. Race (White, Black/AA, Asian, Other/Unknown)
 - iv. Ethnicity (Hispanics, Non-Hispanics, Unknown)

Does the agency agree with the proposed demographic subgroups?

- (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?

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

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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)

We acknowledge the extent of our clarification request and would like to propose a telecom in the last week of November or the first full week in December with the Clinical Review Team. This would help ensure that Dynavax's proposed approach is acceptable and that we can promptly respond to any questions the reviewer(s) may have.

I will follow up with you with a phone call mid-next week on our proposed telecom and we will make ourselves available for a telecom at the Agency's convenience.

Sincerely,

Elaine

Elaine Alambra • Regulatory Affairs • Dynavax Technologies Corporation ☎ Tel: 510-665-0474 ✉ email: elambra@dynavax.com