

RECORD OF TELEPHONE 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	05-OCT-2017 01:15 PM
Author	AGNIHOTHARAM, SUDHAKAR
EDR	No
Post to Web	Yes
Outside Phone Number	18777464263
FDA Originated?	Yes
Communication Categories	AD - Advice
Related STNs	None
Related PMCs	None
Telecon Summary	CBER Dynavax Telecon to discuss issues related to Data Quality and Statistics on their updated synopsis of the recent pharmacovigilance plan.
FDA Participants	CBER - Sudhakar Agnihothram, Silvia Perez-Vilar, Deepa Arya, Scott Proestel, Ruoxuan Xiang, Telba Irony, , Marion Gruber, Katherine Berkousen, Mridul Chowdhury and John Scott.
Applicant Participants	Elaine Alambra, Graeme Curie, Rob Janssen, Randy Hyer, Biao Xing.

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Response to
Information Req...

Background:_____

Based on the CBER-DYNAVAX telecons, (09-15-2017 and 09-21-2017), Dynavax submitted the updated Synopses of the Pharmacovigilance Plan for DV-HBV Study 25 on 10/2/2017.

Dynavax also submitted their response to CBER's information request sent on 09-20-2017. This Information Request detailed all of our categorized comments/questions on their Pharmacovigilance Study DV-HBV 25, designed to compare the occurrence of Acute Myocardial Infarction in adults of 18 years and older who receive Heplisav-B or Engerix- B.

OBE reviewed these responses, and this telecon was held to discuss two major issues:

i) Data Quality and ii) Statistical Plans as proposed in the synopses.

Telecon Body:

Study Design/Statistics:

CBER indicated that the non-inferiority study design proposed by Dynavax does not control for Type I error, and would lead to wrong conclusions. CBER explained that the use of power calculations during interim analysis was not to rule out the power to see the signal, and to confirm that the safety signals are not missed during the follow-up. Furthermore, CBER suggested that the Interim analyses should be focused on the demonstration of safety. Dynavax indicated that they are planning to perform one or two interim analyses without adjusting for Type I error. CBER suggested that Dynavax should consider futility analysis, and safety stopping rules during the interim analyses. Dynavax pointed out that they will perform superiority test at the interim with a probability of providing demonstration of safety. CBER clarified that they are not concerned about the alpha being spent in the non-inferiority design, but that Dynavax should really need to follow up on the safety issues. Dynavax acknowledged CBER's concerns and indicated that they will incorporate these suggestions in the final versions of the Risk Management Plan.

Data Quality:

Based on the response to the IR, where Dynavax had indicated that 45% of AMIs are attended outside Kaiser Facilities, CBER stated that this is a relevant concern and asked Dynavax how are they planning to address with this shortcoming given the importance of obtaining good quality data also on these subjects. CBER insisted that VRBPAC's recommendations were prospective follow-up given the need for a comprehensive information on all AMI cases, but Dynavax proposes a retrospective follow-up using health care databases in which 45% of the AMI are attended outside of the KPSC facilities. Dynavax acknowledged CBER's concerns and indicated that ultimately - 28%

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of the 45% will get transferred to Kaiser Permanente, and that they will ensure good quality data for all AMI cases..

CBER asked again for the events that Dynavax was planning to include under the umbrella of AMI. Dynavax said they will obtain that information from Kaiser Permanente and submit it to CBER in the protocol, but that, basically, only includes the ICD-10 code for AMI. Dynavax has indicated that they have no plans for investigating additional cardiac events.

Dialysis Population.

CBER asked why Dynavax planned to exclude dialysis patients from the study post-marketing studies. Dynavax indicated that since the 2-dose regimen is not appropriate for the Dialysis populations, Kaiser Permanente will not be including Dialysis Patients in the Post Marketing Study.

PMR

Finally, CBER indicated that the DV-HBV-25 study will be a Post Marketing Requirement (PMR) as VRBPAC strongly recommended to evaluate the risk of AMIs in subjects who receive HEPLISAV-B. This was the first formal communication from CBER that, if the vaccine were to be approved, DV-HBV-25 would be a PMR.