

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	15-AUG-2017 04:00PM
Author	AGNIHOTHAM, SUDHAKAR
EDR	No
Post to Web	Yes
Outside Phone Number	
FDA Originated?	Yes
Communication Categories	IR - Information Request
Related STNs	None
Related PMCs	None
Telecon Summary	To inform Dynavax about the inadequacy of their pharmacovigilance plan that was submitted as an major amendment on 8/9/17
FDA Participants	Sudhakar Agnihothram, Richard Daemer, Marian Major, Wellington Sun, Steven Anderson, Deepa Arya and Silvia Perezvilar.
Applicant Participants	Rob Janssen, Graeme Currie, Randy Hyer , and Elaine Alambra

RECORD OF TELEPHONE CONVERSATION

Telecon Body:

CBER provided a brief recap of key regulatory actions since the last telephone call with Dynavax on August 1, 2017. During this call CBER emphasized the need of a revised Pharmacovigilance Plan (PVP) to address concerns raised by VRBPAC. An Information Request was sent to Dynavax on August 2, 2017 which identified the main elements to be included in the revised PVP. Submission of the synopsis of the revised PVP by Dynavax on 8/9/17 resulted in a Major Amendment letter issued by CBER on 8/9/17.

CBER continued that we have noted the following deficiencies in the synopsis of the revised PVP that was submitted by Dynavax on August 9, 2017 in the amendment STN 125428/0096.

- Deficiency 1: The synopsis did not include recent historical data on vaccine uptake, population demographics, and co-morbidities by age group of adults aged 18 years and older who have been vaccinated with at least one dose of hepatitis B vaccine through Kaiser Permanente of Northern California (KPNC) and Kaiser Permanente of Southern California (KPSC). CBER further indicated that no information was submitted in the synopsis on how Dynavax plans to enrich for higher risk groups, including diabetics, and populations at risk for cardiac diseases.
- Dynavax responded that they were working with Kaiser Permanente on seeking these details and they plan to include them in the detailed synopsis of the PVP which they plan to submit by the end of August.
- Deficiency 2: Duration and length of the proposed studies included in the PVP are too long (i.e. 4 years). Dynavax responded that they will be analyzing data from earlier time points including 12 months and 18 months, and will provide results of interim analyses to CBER in addition to providing the results of final analyses. Dynavax further added that Kaiser Permanente (KP) has (b) (4) [REDACTED] In response, CBER suggested Dynavax consider more frequent interim analyses (i.e. quarterly or monthly). Dynavax acknowledged this as a consideration. Dynavax emphasized that they would be adjudicating all MI events although it was currently unclear on how this would be performed.
- Deficiency 3: CBER requested that Dynavax include additional details on their propensity score methods, and suggested that Dynavax include plans for statistical analysis. Dynavax acknowledged that they will provide these details.
- Deficiency 4: CBER indicated that Dynavax should provide further information on how they plan to address the potential for selection bias. In particular, Dynavax should address issues such as patients choosing to get vaccinated at a different site that offers another hepatitis B vaccine and physicians choosing to postpone vaccination or send patients to another KP clinic to receive a different hepatitis B vaccine. CBER suggested that cluster randomization might offer a good way of controlling selection bias, and should be taken into consideration by Dynavax. Dynavax acknowledged that they will work with KP on the design of the PVP and provide the requested details.
- Deficiency 5: CBER indicated that Dynavax should provide more information on the randomization approach. Dynavax acknowledged this request.

RECORD OF TELEPHONE CONVERSATION

- Deficiency 6: CBER requested that Dynavax provide more clarification on the stopping rules with emphasis on the potential actions that will be taken if the proposed hazard ratio of 3 or 4 is met. CBER also advised Dynavax that such actions should include consideration about stopping the commercial distribution of the vaccine. Dynavax indicated that they intend to gather and analyze data and the details will be communicated to FDA as well as to the Biomonitoring committee. Dynavax acknowledged that they will provide the required information in the updated synopsis.
- Deficiency 7: CBER indicated that the following details were missing in the synopsis of the PVP: i) the number of clinics participating in the KP Northern and Southern California systems and ii) how similar or dissimilar these clinics were in terms of patient population including at-risk patients. Dynavax acknowledged that they will provide these details in the updated synopsis.

Dynavax asked whether CBER had any comments on the latest version of the Package Insert that was submitted by Dynavax on 7/21/17. CBER responded that they will contact Dynavax if they have any questions or comments.

CBER indicated that they look forward to receiving the detailed synopsis that addresses all of the above mentioned deficiencies.