# RECORD OF TELEPHONE CONVERSATION

## Submission Information

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| **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

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|---|---|
| **Telecon Date/Time** | 20-SEP-2017 12:26 PM |
| **Author** | AGNIHOTHRAM, SUDHAKAR |
| **EDR** | No |
| **Post to Web** | Yes |
| **Outside Phone Number** | |
| **FDA Originated?** | Yes |
| **Communication Categories** | AD - Advice |
| **Related STNs** | None |
| **Related PMCs** | None |
| **Telecon Summary** | Clarification of CBER`s feedback on the revised synopsis of the Pharmacovigilance plan submitted on 09/11/2017 |
| **FDA Participants** | Sudhakar Agnihothram, Katherine Berkhousen and Richard Daemer DVRPA |
| **Applicant Participants** | Elaine Alambra, Senior Director, Regulatory Affairs |

**Telecon Body:** From: Agnihothram, Sudhakar

Sent: Wednesday, September 20, 2017 5:33 PM

To: Elaine Alambra <EAlambra@dynavax.com>

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Cc: Berkhousen, Katherine <Katherine.Berkhousen@fda.hhs.gov>; Daemer, Richard J. <Richard.Daemer@fda.hhs.gov>

Subject: **STN 125428/0/100 - Request For Further Information**


Dear Elaine,


We have reviewed  the revised synopsis of the pharmacovigilance plan that was submitted on 09/11/201.  Below, please find our request for further information. Please note that some of these points were discussed in the telecon CBER had with Dynavax on 09/15/2017.


1.      Timeliness in obtaining final study results will depend on your capability to recruit (vaccinate) individuals in a timely manner. The current proposal states that "it should take no more than 1 year to achieve the goal of at least 20,000 patients vaccinated with HEPLISAV and approximately 40,000 patients vaccinated with another hepatitis B vaccine". Based in your estimates (page 3), the final report would not be submitted to CBER until November 2021 (3.5 years after study initiation), but only if the proposed accrual is completed within one year (final report submission will occur within 16 months after completion of follow-up of the last HEPLISAV recipient). Please discuss the feasibility of completing recruitment within six months, by inclusion of additional healthcare organizations. Ideally, requests that older age groups of Hepatitis B vaccinees be over represented in the study population. Also, please discuss the feasibility of shortening the time of final data analysis from sixteen months to six months, so that the overall time of the study can be shortened to twenty-five months and the final report can be submitted by July 2020.Please provide specific timelines for start of data collection, recruitment completion, end of data collection, DMC meeting/s, case confirmation activities, and FDA availability of interim and final reports.

a. The post-marketing observational surveillance study will be conducted only by Kaiser Permanente Southern California (KPSC) which serves approximately 4.4 million members. However, all previous versions of the proposed study included Kaiser Permanente Northern California (KPNC). Both HMOs together serve a total of 8.5 million members. Please explain the reasons why KPNC will not participate in the current proposal.


b. The assumptions provided in the power calculations (Table 2, page 9) include: (1) "Total doses given annually during the study period will be ≈30% fewer than the number given in 2015 (≈15% decline seen from 2015 to 2016, lesser decline observed subsequently)", and (2) "Only doses given in Family Practice and Internal Medicine will be included (90% of all doses)". Table 1 shows that 93,730 adults received first hepatitis

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B dose in 2015 in KPSC, so, based in your statement, ≈65,611 adults (30% less) would receive first dose of hepatitis B during the study period (June 2018-June 2019 recruitment period), and among them ≈59,050 individuals (90%) would be vaccinated in Family Practice and Internal Medicine. The current proposal aims to include 60,000 patients within one year (20,000: 40,000), so this is not a conservative estimate. Please justify the feasibility of completing recruitment as described.

2.      You state that to reduce potential selection bias resulting from physician's or patient's decisions based on a patient's risk profile, HEPLISAV will be provided to selected facilities as the sole vaccine for adult use in routine clinical care in "non-randomized clustered design". Thus, "providers and patients will rarely have a choice of hepatitis B vaccines". Nonetheless, providers will still have the option for avoiding hepatitis B vaccination recommendation based on patient risk's profile, and patients could still refuse HEPLISAV vaccination.

a. The best approach to eliminate this potential selection bias would be using individual randomization. Please consider the feasibility of this option in the post-marketing setting.

b. You state on page 1 that "KPSC has over 7,000 physicians, 15 hospitals and 225 medical offices", and in page 2 that "HEPLISAV will be used exclusively at approximately 5 medical centers while another hepatitis B vaccine will be used exclusively at the other 10 medical centers", and in page 9 that "Only doses given in Family Practice and Internal Medicine will be included".

(1) Please confirm the number of Family Practice and Internal Medicine centers and the number of physicians in KPSC. Consider the feasibility of using a larger number of centers/physicians.

(2) Please consider also the feasibility of including a recent historical cohort of hepatitis B vaccinees and/or an additional concurrent cohort as secondary comparison cohort.

3.      We acknowledge that to enrich the study population with particular age groups or at-risk groups for cardiovascular disease is challenging given that the observational study will be conducted in medical center organization/s providing routine clinical care. You provided mean age of hepatitis B vaccinees at the time of first dose in KPSC in 2015 (Table 1).

a. Please provide the number of expected HEPLISAV vaccinees by age groups (based on differences on cardiovascular risk), overall and stratified by medical center.

b. Consider including additional medical care organizations in which older age groups of hepatitis B vaccinees could be overrepresented.

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4.      Outcome

a. Potential for outcome misclassification. You state in page 4 that "Across both cohorts, approximately 45% of persons with AMI were identified through claims submitted for care delivered outside of KPSC

    facilities". Please indicate if the quality and completeness of the information obtained from claims originating outside of KPSC is similar to that from AIM episodes attended in KPSC facilities.

b.  Have you considered including any cardiac event/s other than AMI as secondary outcomes?


5.      Interim analyses

a.      You indicate that "vaccine accrual and number of unconfirmed AMIs will be reported monthly beginning 6 months after the first HEPLISAV dose is administered to monitor assumptions used to determine study duration (vaccine uptake and AMI event rates)"

(1). One of the assumptions for the power calculations (Table 2, page 9) is "Accrual of both HEPLISAV and comparison vaccine is roughly evenly distributed through the year". Thus, could you consider

    start monitoring vaccine accrual beginning 1 month after the first HEPLISAV dose to follow the accrual rates in a timely manner?

(2). "These reports will be aggregated across all medical centers and not by cluster". Would these reports include vaccine accrual by vaccine group to confirm whether the accrual of HEPLISAV vaccinees

    goes as planned? Would these reports include vaccine accrual by age groups (based on differences on cardiovascular risk)?

(3). Do you have a contingency plan to ensure recruitment as planned if the accrual rate, particularly for HEPLISAV is lower than expected?

(4). Would these monthly reports be available until the end of data collection (13 months after last HEPLISAV recipient is vaccinated) to monitor AMI event rates?

(5). Please specify who would receive these monthly reports and when.


b. You state that "Quarterly vaccine accrual and aggregated number of unconfirmed AMIs, and results of the pre-specified interim analysis will be reviewed by an independent DMC"

        (1). Please clarify when the DMC will receive these quarterly reports?

(2). Would the DMC receive these quarterly reports until the end of data collection (13 months after last HEPLISAV recipient is vaccinated) to monitor AMI event rates? If so, please clarify the DMC would be allowed to request additional interim analyses?

b.     You indicate that "if the hazard ratio is 3 or greater, a formal comparison of confirmed AMIs will be conducted. If the hazard ratio of the formal analysis is 3 or greater, Dynavax will suspend administration of HEPLISAV in this study, if applicable. Regardless, the determinations of the DMC and underlying data will be provided to FDA for discussion of next steps. Commercial use of HEPLISAV will be determined by discussions with FDA".

 (1). Please consider performing the formal analysis if the point estimate of the hazard ratio is 2 or higher.

(2). Please indicate specific timelines for the formal comparison of confirmed AMIs.

c.     Given that (1) the interim analysis would be conducted at approximately 12 months following the first HEPLISAV recipient's vaccination, (2) the recruitment would be completed within one year, and (3) second dose of HEPLISAV is administered one month following first dose administration, all study participants may have already received the two doses of HEPLISAV by the time the results are available. Do you mean that you will propose to suspend HEPLISAV administration in KPSC? Please clarify.

(1). Please specify when this information would be communicated to the FDA (no more than 60   days after initiation of the analyses)

d.     Please consider conducting additional interim analyses (unconfirmed cases) besides the one you have proposed (immediately after):

(1). When number of events needed to discard a hazard ratio of 2.0 or greater when $\geq$ 80% power has been reached.

    (2). 30 days after follow-up for the last HEPLISAV recipient ends.

    Please specify when this information would be communicated to the FDA (no more than 60 days after initiation of the analyses).

6.     Sample Size, Power and Data Analysis

a.     We note that you plan to use a standard covariate adjusted Cox proportional hazards model in your primary analysis, with a propensity score adjusted Cox model and inverse probability of treatment weighted (IPTW) Cox model included as sensitivity

analyses. Since the trial is not randomized, covariate distributions in the Heplisav and control groups may still be different due to selection bias. Moreover, physicians may avoid certain hepatitis B vaccinations based on the patient risk profile, and patients may choose medical centers offering specific hepatitis B vaccinations. Therefore, we recommend the IPTW Cox model for the primary analysis, although we would consider results from the other models as well, as additional analyses. Please also note that propensity score matching is preferable to adjustment using propensity score as a covariate (Austin, Peter C. "The performance of different propensity score methods for estimating marginal hazard ratios" (2012)).

b.      Your power calculation and planned analyses are based on the anticipated event rate in the overall study population. Please conduct additional power calculations and subgroup analyses based on age group (e.g., above 50 and below 50 years), which have different cardiovascular risks.

c.      Your sample size (power) calculation does not appear to account for the cluster design. In a cluster design in which analysis and inference will be at the individual level, the sample size should be calculated accounting for the clustering, specifically the potential similarities among subjects within a cluster (intracluster correlation). Not accounting for the intracluster correlation can lead to loss of power (inflation of Type 2 error probability) due to insufficient effective sample size. Especially when the number of clusters is small and the cluster sizes are large, the standard sample size calculation should be adjusted even if the intracluster correlation is small. This impact applies as well to the statistical analysis, where failure to account for intracluster correlation can inflate the Type 1 error probability, thereby constituting an invalid analysis. Therefore, we strongly encourage you to consider the intracluster correlation in the sample size calculation, as well as in the statistical analysis.

d.      Please consider also incorporating dose as a covariate in the Cox model in order to provide analyses by dose.

e.    Please clarify whether you plan to analyze only first AMI event, any AMI event, or both.

f.    Please consider performing a secondary analysis by month post-vaccination

Please let us know if you have any questions.

Thanks,

Sudhakar