

# RECORD OF TELEPHONE CONVERSATION

## Submission Information

<b>Application Type</b>	BLA
<b>STN</b>	125428/0
<b>Review Office</b>	OVRR
<b>Applicant</b>	Dynavax Technologies Corporation / Lic. # 1883
<b>Product</b>	Hepatitis B Vaccine (Recombinant), Adjuvanted
<b>Trans-BLA Group:</b>	No

## Telecon Details

<b>Telecon Date/Time</b>	28-JUN-2016 10:05 AM
<b>Author</b>	Alexandra Worobec; Darcie Everett
<b>EDR</b>	No
<b>Post to Web</b>	No
<b>Outside Phone Number</b>	
<b>FDA Originated?</b>	Yes
<b>Communication Categories</b>	IR - Information Request
<b>Related STNs</b>	None
<b>Related PMCs</b>	None
<b>Telecon Summary</b>	Clinical IR clarifying revisions to Study 10 and 16 data
<b>FDA Participants</b>	Katherine Berkousen
<b>Applicant Participants</b>	Elaine Alambra

### Telecon Body:

**From:** Berkousen, Katherine

**Sent:** Tuesday, June 28, 2016 10:05 AM

**To:** Alambra, Elaine

**Cc:** Daemer, Richard J.; Berkousen, Katherine

**Subject:** 125428.0 Information Request - Clinical

Dear Elaine,

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We continue to review your submission BL 125428/0 and have the following information request. Please respond to this information request no later than two weeks from receipt date.

### HEPLISAV Clinical Information Request (IR) Comment:

1. Please provide:

(a) as a separate table, for Study DV2-HBV-10 and for Study DV2-HBV-16, the following information for each subject originally included in, but now excluded from, the 'per protocol' (PP) population used for the reanalysis of the primary immunogenicity endpoint (i.e. efficacy analysis) for each study.

- Subject ID number
- For Study DV2-HBV-16 only: subject's allocation to the non-inferiority vs. lot-to-lot consistency per protocol population
- Treatment allocation (HEPLISAV vs. Engerix-B)
- Number of doses of test treatment given
- The protocol deviation date
- The date that the subject was determined to be excluded from the PP population with this reanalysis
- The reason(s) for exclusion of the subject from the PP population (e.g. autoimmune disease, pregnancy, major protocol deviation which states the specific protocol deviation(s) incurred)
- The criteria and methodology(ies) used for determining that each respective subject was not suitable for inclusion in the the PP population (for example: tests, procedures, other clinical evaluations performed and their respective results, list of prohibited medications, or major protocol violations)

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(b) a corresponding SAS format file with all the data listed above. Please use in the SAS file the same variable name (LRESULT) used in original analysis for the primary immunogenicity endpoint. The SAS file should show who are the original subjects excluded and who are the new subjects included, using appropriate flags, to facilitate review. The variable name and type in the excluded and included subjects need to be the same as was used in the original BLA, to avoid merging problems.

(c) Please clarify the use of the file named ADGFR (HBV-16 only) when the original Study-16 itself has primary immunogenicity endpoint information along with the lot identification variable. What is the primary immunogenicity endpoint variable's name in ADGFR, in contrast to LRESULT in Study-16? Please clarify if the variable name LRESULT is the same as the variable AVAL in ADLB file and under what value levels of what variable(s).

2. In addition, please provide:

(a) as a separate table, for Study DV2-HBV-10 and for Study DV2-HBV-16, the following information for each subject originally excluded from the 'per protocol' (PP) population and now included in the per protocol population used for the reanalysis of the primary immunogenicity endpoint (i.e. efficacy analysis) for each study.

- Subject ID number
- For Study DV2-HBV-16 only: subject's allocation to the non-inferiority vs. lot-to-lot consistency per protocol population
- Treatment allocation (HEPLISAV vs. Engerix-B)
- Number of doses of test treatment given
- The original protocol deviation date
- The date that it was determined that each respective subject should be included in the PP population with this reanalysis
- The reason(s) for inclusion of the subject in the PP population (e.g. no pregnancy detected)

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- The criteria and methodology(ies) used for determining that each respective subject should be included in the PP population (for example: tests, procedures, other clinical evaluations performed and their respective results)
- (b) a corresponding SAS format file with all the data listed above.

With regard to your ADaM datasets for study HBV-23, we have the following comments:

3. In the ADAE analysis dataset for HBV-23, for rows # 3426 and #7876 (subject 115109, Prostatitis, and subject 134303, Actinic keratosis), the end date of the adverse event (AE) is before the start date ( $ASDTY < AENDY$ ). Please explain and provide the correct start and end dates and study days for these two AEs.
4. You have defined the start date of an AE relative to treatment start date ( $ASTDY$ ) to be the AE start date minus the first treatment date plus 1 ( $ASTDY = ASTDT - TRTSDT + 1$ ). If you refer to the first day of treatment as Study Day 1, and you describe events as occurring on a specific Study Day, this is acceptable. However, in your narratives, you appear to describe an event occurring on the first day a subject received treatment as occurring “one day after having received the first dose.” Please note, when an AE occurs on the day of a subject’s first study treatment, we consider this to have occurred 0 days following treatment. We intend to apply the same principle for events occurring after the first day of study treatment.

With regard to your SDTM datasets for study HBV-23, we have the following comments:

5. In the SUPPEX tabulation dataset (Supplemental qualifiers for Exposure), for row #9 (subject 110108), the value of variable QVAL (data value) is NULL; this variable is required. In other words, for subject 110108, the reason vaccination dose 2 was not administered, is

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not given. Please provide the missing value for row #9, the reason why the subject did not receive vaccine dose 2.

6. On page 54 of the Complete Study Report for HBV-23, you state that 3833 subjects provided informed consent, but were screen failures, and you specify the frequencies for reasons for screen failure. However, subjects who failed screening do not appear to be included in the ADIE analysis dataset (Inclusion/Exclusion Analysis Dataset) or in the IE tabulation dataset (Inclusion/Exclusion Criteria Not Met), which includes 66 subjects. Please provide the following:
  - a. clarify the parameters dictating which subjects were included in the IE dataset.
  - b. the location within the datasets of the reasons for screen failure for these 3833 subjects, if available.

Please provide these data for FDA review no later than two weeks from receipt of this information request.

Kind regards,

Katherine Berkhausen  
CAPT., US Public Health Service

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