

**RECORD OF TELEPHONE CONVERSATION**

Submission Type: BLA Submission ID: 125428/0 Office: OVRR

Product: Hepatitis B Vaccine (Recombinant)

Applicant: Dynavax Technologies Corporation

Telecon Date/Time: 12-Sep-2012 11:50 AM Initiated by FDA? Yes

Communication Categorie(s): Information Request

Author: KATHERINE BERKHOUSEN

Summary: IR #9, Request for clinical safety data

FDA Participants: Katherine Berkhausen Non-FDA Participants: Elaine Alambra

Telecon Body:

A request for information was sent via secure email to Elaine Alambra (Dynavax) to request the following information:

Information Requests regarding the Clinical Study Report (CSR) for Study DV2-HBV-10:

1. Table 12-10 on page 90 of the CSR indicates that the unsolicited adverse events experienced by subject 10074 began on study day 19 which is noted as 47 days after the last study injection. Please provide the correct event onset day relative to study start and vaccination for this subject.
2. It appears that all unsolicited adverse events reported by subjects < 18 years of age occurred in the HEPLISAV group. Please clarify if any unsolicited adverse events occurred among Engerix-B recipients in this age group.
3. Page 109 of the CSR states that "clinically important" changes in ANA were reported as AEs. The baseline and Week 28 titers are then reported for 3 subjects. Please provide the rationale for designating these particular events as clinically important. Provide or refer the reviewer to the necessary event narratives.
4. In Table 12-18 on page 110 of the CSR, the percentages listed appear to be based on a denominator of 1809 for the 1018 ISS HBsAg group and 606 for the Engerix-B group. These denominators represent the total N for each study arm. However, not all subjects had data at Week 28. Please clarify or provide a corrected table.

Information Requests Regarding the CSR for Study DV2-HBV-16:

5. On page 40 of the Main Study Report for Study DV2-HBV-16, the reader is referred to the Cancer Therapy Evaluation Program (CTEP) website for the toxicity grading scale (version 4) used for AEs listed in the CTEP Common Terminology Criteria for Adverse Events scale. The link is invalid. Please submit this information or an updated link.
6. Table 12-13 on page 159 of the Main Study Report shows that 4 subjects (0.8%) receiving vaccine from Lot TDG006 experienced severe (Grade 3 or greater) AEs categorized as metabolic disorders. The source table for this table, Table 14.1.4-17 does not report any severe metabolic AEs for subjects receiving this lot. Additionally, the source table includes the following information that is not included in Table 12-13:
  - a. Lot TDG008: 1 (0.2%) severe Gastrointestinal Disorder
  - b. Lot TDG009: 1 (0.2%) severe Ear/Labyrinth Disorder, 1 (0.2%) severe Reproductive/Breast Disorder, 1 (0.2%) severe Skin/Subcutaneous Disorder, 1 (0.2%) severe Renal/Urinary Disorder
  - c. Lot TDG010: 1 (0.2%) severe Hepatobiliary Disorder
  - d. These events are therefore also included in the Consistency Lots totals with the percentages as follows: 1 (0.1%) severe Gastrointestinal Disorder, 1 (0.1%) severe Ear/Labyrinth Disorder, 1 (0.1%) severe Reproductive/Breast Disorder, 1 (0.1%) severe Skin/Subcutaneous Disorder, 1 (0.1%) severe Renal/Urinary Disorder, 1 (0.1%) severe Hepatobiliary Disorder
  - e. Lot TDG006: 5 (0.9%) severe Gastrointestinal Disorders, 1 (0.2%) severe Hepatobiliary disorder
  - f. Engerix-B: 1 (0.2%) severe Renal/Urinary Disorder, 1 (0.2%) severe Gastrointestinal Disorder, 2 (0.4%) severe Ear/Labyrinth Disorders

Please correct Table 12-13 or provide the rationale for excluding the information listed above.

#### Information Requests regarding the Integrated Summary of Safety

7. You state that “one phase 3 pivotal trial (HBV-16) included both an Engerix-B comparator arm and laboratory assessments of serum chemistry and hematology. Therefore, summaries of laboratory assessments from HBV-16 are presented alone, without further pooling or integration with results of other trials.” However, all studies except study DV2-HBV-10 obtained hematology and serum chemistry labs at various time points, albeit by different schedules, throughout the respective trials. Four of these were controlled trials using Engerix-B as the comparator. It is unclear why pooled results were not provided. Please provide such integrated analyses or elaborate on your rationale for not providing them.
8. ESR, C3 and C4 were measured in some studies. However, it does not appear that any integrated summary of these laboratory results has been provided. Please provide such analyses or provide your rationale for not providing them.

9. On page 104 of the Summary of Clinical Safety, you report that 7 potential AIAEs were referred to the SEAC for adjudication: hypothyroidism (n=4), vitiligo (n=1), VIIth nerve paralysis (n=1) and erythema nodosum (n=1). However, on pages 171-174 of the CSR for study DV2-HBV-16, the narratives for these 7 events describe hypothyroidism (n=5 including 2 subjects with evidence of pre-existing subclinical hypothyroidism), vitiligo (n=1), and what appears to be a description of a potential exacerbation of microscopic colitis. Please clarify exactly which 7 events were sent to the SEAC for adjudication and the results of the adjudication process for each event. Please also clarify the clinical reason(s) that the case of hypothyroidism occurring in the TDG006 arm was not thought to be a potential AIAE and therefore not adjudicated by the SEAC.
10. The following requests pertain to statements made on page 23 of the Summary of Clinical Safety.
  - a. You state the following: *In the supportive Tier 3 trials, different grading scales of redness and swelling were used. For the purpose of integration, injection site redness and swelling were regraded according to the FDA's Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Center for Biologics Evaluation and Research 2007). Headache, fatigue, and malaise were analyzed according to their original grading, which used a 3-grade scale (mild/moderate/severe) across trials. Pyrexia was based on the original recorded oral temperature and was categorized by the FDA guidance cited above in 0.5°C increments up to 40°C. Please provide the rationale for re-grading only certain solicited post-injection reactions by the Guidance for Industry scale.*
  - b. You state the following: *In the integrated analysis of post-injection reactions in the T3SP, partial data from HBV-04 were included. Redness and swelling data from HBV-04 were excluded because the original measurement was not captured and a grading scale different from the FDA guidance was used. This exclusion represents 4.7% of the 4425 subjects with redness and swelling data from the T3SP. This analysis does not include data from HBV-02 because of the previous vaccination experience of the trial population (i.e., non-responders to 3 to 6 previous injections of Engerix-B). This exclusion represents 30 subjects who received 1 injection of HEPLISAV (F1), or 0.7% of the 4425 subjects in the HEPLISAV (All) group of the T3SP. This analysis also does not include data from HBV-05, because post-injection reactions during Days 0 to 6 post-injection in HBV-05 were collected as AEs. This exclusion represents 48 subjects who received at least 1 injection of HEPLISAV (F2), or 1.1% of the 4425 subjects in the HEPLISAV (All) group of the T3SP. Please provide an all-encompassing analysis of all post-injection reactions or a more detailed rationale for not doing so.*