

MEETING SUMMARY

DEPARTMENT OF HEALTH AND  
HUMAN SERVICES  
PUBLIC HEALTH  
SERVICE  
FOOD AND DRUG ADMINISTRATION  
1401 Rockville Pike  
Rockville, MD 20852-1448

---

TYPE C MEETING SUMMARY FOR  
STN 125428/0 HEPLISAV [Hepatitis B Vaccine (Recombinant)]  
Meeting ID # 8939

MEETING DATE: June 5, 2013  
MEETING FORMAT: Face to face meeting  
MEETING CHAIR: M. Major  
MEETING RECORDER: R. Daemer; K. Berkhausen

**FDA PARTICIPANTS:**

***Review Team:***

|               |                            |            |                    |
|---------------|----------------------------|------------|--------------------|
| M. Major      | Chair, Review Committee    | L. Smith   | Clinical Reviewer  |
| D. Daemer     | Regulatory Project Manager | A. Worobec | Clinical Reviewer  |
| K. Berkhausen | Regulatory Project Manager | A. James   | Clinical Team Lead |
| M. Chowdhury  | Statistical Reviewer       | M. Niu     | PharmacoVigilance  |
| B. Khannan    | BIMO                       | B. Baldwin | Adjuvant Reviewer  |

***Non Review Team:***

|             |                              |           |                          |
|-------------|------------------------------|-----------|--------------------------|
| M. Gruber   | Director, Office of Vaccines | W. Sun    | Director, DVRPA          |
| L. McVittie | Deputy Director, DVRPA       | D. Pratt  | Assist. Dir. DVRPA       |
| R. Pandey   | Branch Chief, Regulatory     | M. Nguyen | Deputy Dir, Epidemiology |
| L. Schrager | Branch Chief, Clinical       | T. Lin    | Statistical Team Lead    |
| C. Noletti  | Clinical Reviewer            | D. Fink   | Clinical Reviewer        |
| N. Miller   | Clinical Reviewer            | P. Agger  | Clinical Reviewer        |

**DYNAVAX PARTICIPANTS:**

|                 |   |
|-----------------|---|
| Eddie Gray      | Chief Executive Officer                   |
| William Heyward | Vice-President (VP), Clinical Development |
| Robert Janssen  | VP, Medical Affairs                       |
| William Turner  | VP, Regulatory Affairs                    |
| Shane Ward      | VP, Corporate Compliance                  |
| Elaine Alambra  | Director, Regulatory Affairs              |

Edie Smith  
(b) (4)

Executive Director, Project Management  
Consultant, Biostatistics

## **BACKGROUND:**

HEPLISAV is a recombinant hepatitis B vaccine for the immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 through 70 years of age. A Complete Response Letter was issued to BLA 125428 on February 22, 2013, outlining 55 deficiencies. FDA considers the size of the safety database for HEPLISAV to be insufficient for approval and requires an additional pre-licensure safety study. Thus, Dynavax has requested a meeting to discuss an amendment to the current BLA proposing a new indication(s) to support a more restricted use of HEPLISAV. Dynavax stated in their meeting packet submitted on April 10, 2013, that they consider the current data in the BLA

sufficient to demonstrate the safety and efficacy of HEPLISAV in adults 40 and older and in individuals who fail to achieve seroprotection with currently licensed vaccines.

Dynavax also states that they would like to discuss the submission of additional data in the CKD population as an amendment to the current BLA. Dynavax submitted three questions in

their meeting packet. Preliminary responses were faxed to Dynavax on June 4, 2013 (see attachment).

## **MEETING DISCUSSION:**

Dr. Marion Gruber opened the discussion by expressing the agency's commitment to finding a path forward for Dynavax's HEPLISAV vaccine. Dr. Gruber explained that the immunogenicity of HEPLISAV has been demonstrated but CBER has concerns with the vaccine's overall safety as well as the size of the currently available safety database.

CBER has held extensive internal meetings to evaluate various ways to proceed towards licensure, taking into consideration the safety concerns expressed by VRBPAC, the risk versus benefits of using the vaccine in particular patient populations, the fact that HEPLISAV is formulated with a novel adjuvant, and the finding of rare and serious AEs in the clinical trial database, which were also evaluated by outside expert consultants.

Dr. Gruber inquired whether Dynavax is still planning to conduct an additional prelicensure safety study as described in the March 2013 meeting request. She noted that the April 2013 Meeting Request no longer includes such a proposal. Dr. Gruber emphasized that CBER would continue to work closely with Dynavax to define a path forward to licensure of HEPLISAV.

Dr. Eddie Gray provided the opening comments for Dynavax. He acknowledged that the HEPLISAV benefit/risk profile will need to be further addressed considering the availability of two safe and effective US licensed vaccines to prevent Hepatitis B disease. He noted that Dynavax will respond collaboratively to CBER's comments in response to Dynavax's questions in the April 10, 2013, meeting request.

Dr. Rob Janssen provided a slide presentation outlining: the HEPLISAV benefit/risk profile indicating that the greatest benefit was in subjects over 40 years of age.

However, an additional prelicensure safety study adequately powered to detect rare AE rates would be challenging when considering the company's resources.

Dr. Janssen proposed alternative options for CBER's consideration, including: 1) restricting the indication to individuals over 40 years of age that were most at risk and would benefit the most; 2) reducing risk by restricting labeling to specific groups and informing consumers in the Precautions, Warnings & Contraindications sections of the package insert about possible side effects and risks; 3) increasing potential benefit and decreasing possible risks by implementing a Risk Evaluation and Mitigation Strategy (REMS) which would include a Communication Plan, Medication Guide, and Elements to Assure Safe Use (ETASU). The ETASU may include certification of prescribers, Dear Doctor letters, and/or dispensing restrictions and; 4) implementing a large post-licensure study not previously discussed.

Dr. Janssen proposed a post-licensure study that would enroll 30,000 subjects receiving HEPLISAV and 30,000 subjects receiving Engerix-B conducted by Northern California Kaiser Permanente (NCKP). NCKP is well recognized for having the EMR and access to a racially and ethnically diverse population (which would address a VRBPAC concern). This would be an independent study conducted by NCKP, designed to include stopping rules and real-time analysis/safety assessments.

Dr. Janssen then discussed a potential indication for HEPLISAV for patients with chronic kidney disease (CKD). Dr. Janssen pointed out that clinical trials in this target population are challenging considering recruitment issues (e.g., it took 18 months to enroll 500 subjects in the CKD trial and it would take Dynavax more than 7 years to enroll the 3,000 people necessary for this study). He asked CBER for clarification as to why the current available CKD database (312 subjects) was insufficient for licensure.

Dr. Lewis Schrager informed the Dynavax team that CBER consulted with four outside experts regarding the possible case of Tolosa-Hunt syndrome (THS). Three of the consults have provided CBER with their expert reviews and all three state that the adverse event classified by Dynavax as cavernous sinus syndrome was likely THS. Dr. Schrager stated that this supported CBER's view that additional prelicensure safety data would be needed for HEPLISAV regardless of the target population considered.

Dr. Schrager noted that the CBER consensus was that Dynavax should focus on the healthy population for a HEPLISAV indication. Dr. Schrager noted that an additional prelicensure safety study could be designed as a one-arm study and according to CBER's calculations, would require 6,000 – 10,000 subjects to address safety concerns such as THS and WG. A component of this larger safety study would be a nested sub-study to address possible effects of HEPLISAV on renal function and the potential for the vaccine to increase the risk of thromboembolic events.

Dr. Schrager noted that if Dynavax chooses to include a comparator arm, the addition of such a comparator group with a sample size of approximately 3,000 subjects would not be unreasonable.

Dynavax inquired what clinical concern would be addressed by an additional pre-licensure safety study with 6,000 subjects. Dr. Wellington Sun replied that two rare autoimmune-mediated events, WG and THS, were observed in a relatively small pre-licensure safety database of 4,000 subjects. CBER views these events as a safety signal and thus, requires additional pre-licensure safety data to reduce concerns of a potential

association between receipt of HEPLISAV and development of rare autoimmune events such as WG and THS. Dr. Sun acknowledged that a sample size of 6,000 would not serve to firmly establish a lack of such association pre-licensure and CBER would therefore also require a post-marketing safety study to obtain a more robust safety profile of this product.

Dr. Schrager stated that CBER has considered an indication for use of HEPLISAV in CKD patients and has concluded that this likely would not be a viable licensure pathway for HEPLISAV given that additional immunogenicity and safety data which would be required in this population. Licensure of HEPLISAV in CKD patients would require safety data from a study of 2,000-3,000 CKD subjects. Dr. Lorie Smith sought clarification as to which CKD populations Dynavax would target. Dr. Janssen responded that Dynavax would be targeting CKD patients with a GFR <45. Dr. Smith added that CBER had not yet received complete study reports for this population, making it difficult to define a path forward for HEPLISAV licensure in this population.

Dr. Heyward requested clarification on the following points regarding a potential safety study in 6,000 to 10,000 subjects a) the age range proposed for such a study, b) the required type and duration of subject follow-up, and c) whether CBER would consider licensure based upon an interim analysis. CBER responded that a safety study comprising 6,000-10,000 additional subjects would be sufficient for licensure, that the age range should be 18-70 years old, and that the safety follow-up should be one year. This latter is CBER's standard requirement for safety follow-up of subjects receiving products with novel adjuvants. CBER also noted that licensure could not be considered until the full year follow-up data was submitted to CBER for assessment.

Dynavax asked why CBER requires an additional small prelicensure study when Dynavax is proposing a large post marketing study. Dr. Gruber reiterated that CBER's decision takes into consideration VRBPAC's recommendations, the fact that HEPLISAV contains a novel adjuvant, and the finding of two rare adverse events observed in the relatively small prelicensure safety study. CBER noted that a study of this size would be sufficient to support licensure of HEPLISAV in 18-70 year old subjects if no additional serious safety issues were identified. Dr. Sun added that a robust post-marketing study should also be conducted.

Dr. Janssen asked if Dynavax could obtain copies of the consultations as he did not agree that the case in question represented THS. Dr. Gray thanked CBER reviewers for their time. He noted that Dynavax was not sure of the feasibility of conducting an additional prelicensure safety study. He asked CBER to clarify the regulatory process in this regard. Dr. Sun stated that Dynavax should submit a clinical protocol for CBER's review. Dr. Loris McVittie clarified that this protocol should be submitted to the IND. The final data from this study should be submitted with the CR letter response and would receive a six month review. Dynavax asked if VRBPAC would need to be convened again. Dr. Gruber stated if the data are reassuring it is not likely that CBER would convene another VRBPAC meeting.

This concluded the meeting.

#### **ADDENDUM: CBERPostMeetingComment**

Dr. Janssen asked if Dynavax could obtain copies of the CBER expert consultation reviews.

*CBER Response: CBER does not release review memos in the pre-decisional period and are therefore unable to comply with your request. With regard to your inquiry concerning our expert consultants' diagnosis of the occurrence of a case of THS, extensive and detailed consideration was given to ruling out alternative pathophysiological processes affecting the cavernous sinus, alternate etiologies for the presentation and resolution of symptoms, and application of ICHD-II diagnostic criteria.*

## **ATTACHMENT 1      FAXED TO DYNAVAX ON JUNE 4, 2013**

BLA 125428.0

June 4, 2013

|                    |   |
|--------------------|---|
| Meeting ID         | CRMTS# 8939                                   |
| Applicant:         | Dynavax Technologies, Inc.                    |
| Product Name:      | Hepatitis B Vaccine (Recombinant), Adjuvanted |
| Meeting Type:      | Type C Meeting Meeting                        |
| category:          | General Development                           |
| Meeting date/time: | June 5, 2013 1:00 – 2:30 pm                   |

Dynavax's proposed objectives of this meeting are to develop consensus with CBER on the data necessary to support an amended BLA for more narrow indications. Although we are providing responses to your specific questions below, please note that we continue to have concerns regarding the size of the currently available safety database to support licensure of HEPLISAV as expressed by VRBPAC in November 2012 and the adverse events observed in the pre-licensure studies as stated in our Complete Response letter dated February 22, 2013. Reviews from our expert consultants have not fully addressed these latter concerns. We look forward to discussing with you the scope of additional safety data that will be needed to advance the further clinical development of Heplisav for use in either healthy subjects or subjects with an underlying disease or condition, including any proposal outlines you may have for additional safety studies.

Dynavax's questions are presented in bold font followed by the CBER response.

- 1. Dynavax considers that the current data in the BLA are sufficient to demonstrate the safety and efficacy of HEPLISAV in adults 40 years of age**

and older. Of the 2 pivotal trials presented in the BLA, Study DV2-HBV-16 consisted entirely of persons in this age group and approximately half of study DV2-HBV-10 was in this age group. Both studies demonstrated similar safety profiles between HEPLISAV and Engerix-B and the immunogenicity results of study DV2-HBV-16 demonstrate the superiority of HEPLISAV when compared to Engerix-B. Dynavax proposes to submit any required additional analyses for persons over 40 years of age and amend the current BLA with the following revised indication: *HEPLISAV is indicated for immunization against infection caused by all known subtypes of hepatitis B virus in adults age 40 and over.* Does the Agency agree?

**CBER response:** We do not agree that the current BLA contains the data needed to support licensure of HEPLISAV for the more restricted age indication that you have proposed. We consider the size of the safety database in your license application to be insufficient to support the proposed indication and use of your Hepatitis B Vaccine (Recombinant), Adjuvanted, in adults age 40 years and older. The safety concerns expressed previously by CBER and those cited by VRBPAC still apply to adults age 40 years and older.

2. At this time, Dynavax has prepared the standard BLA documents for a HEPLISAV indication in persons 18 years and older with CKD. This includes data from the pivotal trial DV2-HBV-17 and several smaller trials. The results from pivotal trial DV2-HBV-17 establish that HEPLISAV demonstrated a similar safety profile, induced earlier seroprotection, induced superior seroprotection at the primary endpoint, and demonstrated more persistent seroprotection when compared to Engerix-B. Dynavax proposes to submit our final data on the CKD population to the current BLA and amend the BLA to include an appropriate dosing schedule for persons with CKD: *HEPLISAV can be used for immunization against infection caused by all known subtypes of hepatitis B virus in adults with CKD using a schedule of 3 intramuscular (IM) injections, the first given at elected date; the second 1 month later; and the third, 6 months after the first dose (3 doses total; 1 dose each given at 0, 1, 6 months).* Does the Agency agree?

**CBER response:** Data for the CKD population were not submitted to the BLA. CBER recently received limited summary data for two studies, Study DV2-HBV-17 and Study DV2-HBV-18, conducted in this population. Based on our assessment of these summary data, which included only 312 subjects at various stages of disease progression, we do not agree that submission of the final data on the CKD population to the current BLA would support an indication restricted to this population.

3. The current recommendation for persons who fail to achieve seroprotection with currently licensed vaccines is to repeat a course of the currently licensed vaccines. Dynavax considers that the current data in the BLA, including the demonstration of superior immunogenicity to Engerix-B following primary immunization in DV2-HBV-10 and DV2-HBV-16 as well as a trend toward increased seroprotection in nonresponders (DV2-HBV-02) strongly suggest that HEPLISAV may be useful in this population. Dynavax proposes that

**the current HEPLISAV data are sufficient for an indication in persons who failed to achieve seroprotection following vaccination with currently licensed vaccines: *HEPLISAV is indicated for immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 and over who have been unresponsive to the currently licensed alum adjuvanted hepatitis B vaccines.* Does the Agency agree?**

***CBER response:*** Study HBV-DV2-02, which was submitted to BLA STN 125428, was not sufficient to support a labeling indication for hyporesponders. This was a Phase 2 study of hypo- and non-responders to hepatitis B vaccine, in which 35 total subjects, 18-65 years of age, were evaluated. Because the number of individuals in this study was so small and given that the formulation of hepatitis B vaccine plus 1018 ISS adjuvant evaluated in this trial is different than the final proposed formulation, we do not agree that the available data support an indication for use in hyporesponders.

- 4. In response to the Information Request of 24 January 2013, Dynavax requested proprietary name review and proposed a new name, HEPLISAV-B. For consistency, Dynavax will need to change the name of the product in our European Marketing Authorization Application that is currently under review. Can the Agency confirm that the name HEPLISAV-B is acceptable?**

***CBER response:*** CBER confirmed that the name HEPLISAV-B is acceptable in an email communication (telecon) dated April 10, 2013. Dynavax has acknowledged in an email communication that this question can be removed from the meeting agenda.