
NON REGULATORY FACE-TO-FACE MEETING SUMMARY FOR
STN 125428/0 HEPLISAV [Hepatitis B Vaccine (Recombinant)]

MEETING DATE: December 19, 2012, 1:30 – 3:00 EST

Committee Members Present:

Marian Major
Richard Daemer*
Katherine Berkousen
Lori Smith
Alexandra Worobec
Mridul Chowdhury
Manette Niu
*meeting recorder`

Other Attendees:

Marian Gruber
Phil Krause
Wellington Sun
Douglas Pratt
Lew Schrager
Rakesh Pandey
Andrea James
David Martin

Dynavax Attendees:

Tyler Martin
William Turner

CBER agreed to a (non-regulatory) face to face meeting, at the request of Dynavax, to discuss the path forward status post the November 15, 2012 VRBPAC discussions and vote. Dynavax provided the questions for the discussion which are noted in **bold** font, followed by the CBER response.

Discussion Topics:

1. **As presented to VRBPAC, both FDA and Dynavax have concluded that HEPLISAV met pre-specified non-inferiority criteria for immunogenicity, as compared to ENGERIX B. At this time, does the FDA review team have any concerns regarding the immunogenicity of HEPLISAV?**

CBER stated that there were no concerns regarding immunogenicity.

2. As presented to VRBPAC, both FDA and Dynavax concluded that there were no clinically significant safety differences between recipients of HEPLISAV and ENGERIX-B. At this time, does the FDA review team have any concerns regarding the safety of HEPLISAV?

CBER noted that their role is to present data at VRBPAC meetings. At the time of the VRBPAC, the review was still ongoing and at this time CBER does have some safety concerns. Regarding potential auto-immune events and the adjuvant mechanism of action there did not appear to be any glaring concerns with respect to numbers. However, shortly before VRBPAC a concern arose regarding a suspected case of Tolosa Hunt syndrome (T-H). The documents which Dynavax sent were reviewed by CBER and they are seeking a consult review by outside experts. CBER is continuing the review while awaiting the expert review before they can provide feedback.

CBER noted that the VRBPAC committee had expressed concerns about numbers in the safety data base. Dynavax stated that the safety data base is being expanded but they do not believe that the suspected case of T-H meets the clinical diagnostic criteria and that no signal was detected. CBER stated they were not addressing the T-H simply as a number and that other potential autoimmune cases are of concern. CBER stated that although the VRBPAC did not specifically cite the Wegener's granulomatosis or T-H cases, they did weigh in to express their larger concern regarding the lack of a robust safety data base. If the safety data base had been clean, the numbers may otherwise have been acceptable. Dynavax stated there was no suggestion of a connection between the Wegener's and that the T-H was not the final diagnosis for the suspected case, although a biological connection would be reason for concern. CBER stated that although the final disposition of the T-H was not certain, CBER was regarding it seriously.

Dynavax stated that CBER had provided input regarding the numbers required for their safety data base for Study #10 and that they believed that based upon mistaken input from the FDA there was confusion among the VRBPAC committee members. CBER noted that these numbers followed CBER historical recommendations and that the database necessary would be different depending on AE's. In addition, CBER noted that the committee made their own decisions and that Study #10 was conducted off IND.

Dynavax stated that the VRBAC committee was confused by discussion of the proposed pharmacovigilance plan. CBER noted that they routinely ask for a minimum of 1 year follow-up with novel adjuvants.

CBER asked if Dynavax had requested an outside consult to review the SAEs in light of the fact that the vaccine would likely be intended for use in millions of people and why they believed the safety data base is adequate. Dynavax responded that they do not believe the number of cases of SAES observed with HEPLISAV is in disequilibrium with other hepatitis B vaccines.

Dynavax suggested that the CBER review committee use the Engerix-B label as a guide for their review. They stated that their vaccine was intended for use in high risk populations and was not intended as a general use vaccine as defined by ACIP; given that this is intended for use in high risk populations it is a better vaccine. Dynavax noted their use of "naïve" language at the pre-BLA

meeting and stated that they were not really expecting use of HEPLISAV in the general population, but rather in high risk populations.

CBER attempted to clarify the roles of the ACIP and FDA and stated that FDA performs their evaluations based on what the applicant provides in their submissions. Dynavax stated that hepatitis B vaccine labeling is all over the map. CBER stated that they are working on updating labeling. CBER noted that regarding Dynavax's statement, they intend to use the vaccine in high risk populations, yet they did not perform their studies that way. CBER stated that at risk populations were not prospectively defined in Dynavax's studies. CBER stated that they cannot tell sponsors what structures they should work on for their intended groups. Dynavax stated that this is a question of balance and they were not certain of what the numbers should be for their safety data base. CBER asked if Dynavax has a specific indication and stated that CBER can only consider data that is provided by applicants in their submissions.

CBER again stated that sponsors are required to show vaccine safety in whatever populations they study. CBER also noted that this was presented as a general use vaccine in the BLA and at VRBPAC. CBER stated that even if a vaccine is targeted to high-risk groups or if the indication is changed to emphasize high-risk groups safety data still needs to be adequate.

CBER asked if Dynavax had any additional ongoing studies and Dynavax responded that there were several. Dynavax indicated that they would like to submit these studies performed in high risk groups as an amendment to the BLA to extend the review. CBER stated that their role was to review studies in healthy individuals 18-70 years of age as indicated in the current BLA and anything else would require internal discussion. CBER once again reiterated the safety data base size concerns.

Dynavax agreed to submit additional clinical data related to their evaluation/consult of the adverse event (possible T-H Syndrome) that previously was not submitted to CBER.

3. As discussed at the VRBPAC meeting, Dynavax proposes to do a post approval concomitant use study. Does the FDA agree?

CBER stated that it was premature to discuss this item.

4. As presented at the VRBPAC meeting, the immunogenicity data of HEPLISAV across all racial ethnicities is consistent. Dynavax believes that a post approval study conducted through Kaiser Permanente Northern California and Kaiser Permanente Southern California provides the best opportunity to gather additional information on ethnic and socioeconomic diversity. Does the FDA agree?

CBER stated that it was premature to discuss this item.

5. As with other hepatitis B vaccines the indication proposed by Dynavax is based on the age range studied throughout the clinical development program. The specific recommendations for the use of Hepatitis B vaccines in various at risk populations has historically been provided by ACIP. Does the FDA agree?

See discussion under Question #2 regarding FDA and ACIP roles.

6. **Dynavax proposes that a post approval pharmacovigilance study be conducted at Kaiser Permanente Northern California and Kaiser Permanente Southern California. Kaiser estimates they could enroll 30,000 HEPLISAV recipients without chronic kidney disease, between the age of 18 and 70, in 18 months. Dynavax proposes 2 methods of signal detection. First, a risk interval analysis within the HEPLISAV control and cross cohort analysis with 3 matched vaccinated controls for each HEPLISAV recipient – A postmarketing evaluation of the safety of Ann Arbor strain of live attenuated influenza vaccine in adults 18-49 years of age is attached for reference. Secondly, an expert review of pre-defined autoimmune events of special interest (AESI) would be conducted to further refine the safety assessment – Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine is attached for reference. Dynavax proposes the analysis takes place when 5,000, 15,000 and 30,000 HEPLISAV recipients are available. Does the FDA agree with this proposal?**

CBER stated that it was premature to discuss a pharmacovigilance plan.

This concludes the meeting.