

## Pharmacovigilance Plan Review

From: Manette Niu  
To: Marian Major, Chair  
Through: Wei Hua, Acting Branch Chief, AEB  
David Martin, Division Director,  
OBE/DE  
STN No. BLA 125428/00  
Subject: Pharmacovigilance Plan Review, for the  
biologics license application of  
HEPLISAV

Applicant: Dynavax Technologies Corporation

Product: Hepatitis B Vaccine (Recombinant),  
HEPLISAV

Proposed Indication: Immunization against infection caused  
by all known subgroups of hepatitis B  
virus in adults 18 through 70 years of  
age

Current Indication: None

Submission type (original BLA,  
supplement, labeling supplement, etc.) Original BLA  
Submission Date: 26 APR 2012

PVP Submission Date (if applicable): 26 APR 2012

Action Due Date: 24 FEB 2013

## **1. Introduction**

### **A. Product description**

The sponsor seeks licensure of HEPLISAV for active immunization of individuals ages 18 through 70 years of age to prevent infection caused by all known subgroups of hepatitis B virus. The vaccine is comprised of a recombinant, yeast cell-derived hepatitis B virus surface antigen (rHBsAg, adw subtype, 20 mcg) and a proprietary adjuvant sequence (1018 immunostimulatory sequence [ISS, 3000 mcg]). The intended biological activity of HBsAg is to generate antibodies to the alpha determinant of the S protein, and the intended biologic activity of 1018 ISS Adjuvant is to enhance antibody generation by activating the innate immune system via Toll-like receptor 9 (TLR9). This BLA seeks licensure for active immunization by two intramuscular injections (20 mcg HBsAg and 3000 mcg 1018 ISS) at months 0 and 1.

### **B. Pertinent regulatory history**

HEPLISAV is not yet marketed in any country.

### **C. Objectives of the review**

The purpose of this review is to identify safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be licensed.

## **2. Materials reviewed**

Materials reviewed in support of this assessment include: The Pharmacovigilance plan [m1.16.9, 4/26/12], pertinent sections of the licensing application (Risk Management plan [m1.16, 4/26/12], summary of clinical safety [m2.7.4, 4/26/12], sponsor's response to 10/26/2012 Information Request [m1.2, 11/2/2012], sponsor's email response to 11/27/12 FDA/Dynavax discussion dated 11/28/2012, VRBPAC OVRRC Clinical Reviewer overview of safety results, 11/15/12 [Dr. Lorie Smith]; and input from CBER clinical and statistical reviewers (verbal consultation, final written report not available at the time of this report).

## **3. Pharmacovigilance Plan Review (1.16.9)**

(Excerpts from the sponsor's submission are shown *in italics*).

**A. Clinical safety database:** Risk Management Plan (1.16), Summary of Clinical Safety, Integrated Summary of Safety (2.7.4.)

The primary safety data are derived from two pivotal phase 3 trials, Tier 1 Safety Population (T1SP), DV2-HBV-10 and DV2-HBV-16, in which healthy subjects (at least 18 years of age) were exposed to HEPLISAV (n=3777) or ENGERIX-B (n=1087). Additional data for 207 healthy subjects (ages 18-55 years) from one phase 2 trial, DV2-HBV-14 is also available for a total of 3984 HEPLISAV subjects. (Tier 2 Safety Population, T2SP).

The sponsor states: “*No important risks with HEPLISAV have been confirmed... There are 2 important potential safety issues for HEPLISAV...anaphylaxis due to sensitivity to yeast... (and) autoimmune disease, which is a theoretical concern associated with all adjuvants.*” In order to identify autoimmune adverse events (AEs), the sponsor “...adopted a list of adverse events of special interest (AESI) considered appropriate for the assessment of autoimmunity.” These AEs include: Guillain Barre Syndrome, encephalitis, demyelinating disease, systemic lupus erythematosus, scleroderma, psoriatic arthropathy, Crohn’s disease, ulcerative colitis, autoimmune thyroiditis, Grave’s (Basedow’s) disease, diabetes mellitus, psoriasis, vitiligo, Raynaud’s phenomenon, erythema nodosa, idiopathic thrombocytopenic purpura, and Wegener’s granulomatosis. In HBV-16, the sponsor used a questionnaire to solicit signs and symptoms of potential AESI for each subject at each visit, which was referred for expert evaluation, and if diagnosis was confirmed, for independent review (by committee) and adjudication.

“*In all trials, serious adverse events (SAEs) were collected during the entire study period.*” The period of follow-up ranged from 28 to 52 weeks or longer. In T1SP, two SAEs were considered to be possibly related to study treatment: one case of Wegener’s granulomatosis (HEPLISAV, date of onset approx. 2 months post-vaccination), and one event of bronchial hyperreactivity (ENGERIX-B). In T1SP, there were 2 deaths: one death due to pulmonary embolism which occurred <sup>(b) (6)</sup> days after the last dose of study medication (HEPLISAV), and one death due to myocardial infarction/ heart failure <sup>(b) (6)</sup> days after last study medication (ENGERIX-B). No deaths occurred in other supportive trials.

**Tier 1 Safety Population (T1SP): Pivotal safety trials HBV-10, HBV-16.**

HBV-10: Phase 3, observer-blind, randomized, active-controlled, parallel-group, multicenter trial comparing HEPLISAV to ENGERIX-B in 2428 healthy persons 11 to 55 years of age in Canada and Germany (subjects stratified by age and randomized in a 3:1 ratio to receive either HEPLISAV at weeks 0 and 4 [n=1820], or ENGERIX-B, at weeks 0, 4 and 24 [n=608]).

Serious AEs (SAEs) were reported in 28 (1.5%) in HEPLISAV group, and 13 (2.1%) in ENGERIX-B group. Two cases of antineutrophil cytoplasmic antibodies (ANCA)-vasculitis were reported: Wegener’s granulomatosis (HEPLISAV, date of onset first episode of sinusitis was 84 days post-vaccination; ANCA-positive/diagnosis: 208 days post-vaccination), and an ANCA-positive vasculitis (ENGERIX-B). Two subjects in each treatment group were withdrawn

from the trial due to AE, however only one case of arthritis (ENGERIX-B) was felt to be related to treatment. No deaths were reported.

HBV-16: Phase 3, observer-blind, randomized, parallel-group multi-center study comparing HEPLISAV to ENGERIX-B among 2449 healthy subjects 40 to 70 years of age (subjects randomized in a 4:1 ratio to receive either HEPLISAV [n=1968], or ENGERIX-B [n=481]).

SAEs were relatively infrequent (HEPLISAV, 3.9%; ENGERIX-B 4.8%) and “*reflected the typical medical events requiring hospitalization in the trial population. One SAE was considered by the investigator possibly related with treatment: reactive airway disease (ENGERIX-B). One unrelated SAE resulted in trial withdrawal: hyponatremia (HEPLISAV). Two deaths were reported, one subject in each treatment group: pulmonary embolism (HEPLISAV, day (b) (6)), and myocardial infarction/heart failure (ENGERIX-B, day (b) (6)).*

Seven AESI were referred for adjudication; all occurred in the HEPLISAV group. Five of these 7 events (71%) were confirmed as AESI: hypothyroidism (n=4, 2 with new-onset: days to onset of symptoms: unknown-day 20), vitiligo (n=1, day 1). Two of the four cases of hypothyroidism were found to have laboratory evidence of pre-existing hypothyroidism based on testing of blood samples taken at baseline. The other 2 AEs not deemed AESI were: erythema nodosum (n=1, day 19), VIIth nerve paralysis (n=1, date of onset approx. 4 months post-vaccination). “*Among subjects with pre-existing autoimmune disease who were inadvertently enrolled, there was no difference in AEs between treatment groups.*”

T1SP Elderly patients: HEPLISAV was administered to elderly patients (65 years of age or older, HBV-16)(n=281: 233, HEPLISAV; 48 ENGERIX-B). *There was a slightly higher frequency of SAE in subjects who received HEPLISAV (7.3%) compared with Engerix-B (4.2%, NS). No SAEs considered by the investigator to be related to treatment in either treatment group.*

## **Tier 2 Safety Population, Supportive safety trial HBV-14.**

HBV-14: Phase 2, open-label study following injection with HEPLISAV in subjects 11 to 55 years of age in the US (no comparator arm)(n=207, no subjects under the age of 18 years were enrolled).

Three subjects (1.4%) experience SAEs, none of which were assessed by an investigator to be related to treatment. There were no death reports.

“*Four subjects (1.9%) were ANA-negative at baseline and ANA-positive at Week 28. A total of 16 subjects (7.7%) were ANA-positive at baseline: 6 (2.9%) who were ANA-negative at Week 28, 6 (2.9%) who had a lower positive titer at Week 28, and 3 (1.4%) whose titer remained unchanged. Two subjects (1%) were*

*anti-dsDNA-positive at baseline, and no subjects were anti-dsDNA-positive at Week 28.”*

#### **Adverse events leading to trial withdrawal:**

*“In T1SP, 5 subjects withdrew due to an AE (HEPLISAV: 3/3777, 0.08%; ENGERIX-B: 2/1087, 0.18%). The 3 AE-withdrawals in the HEPLISAV group were hyponatremia (HBV-16, day 24), GBS (HBV-10, day 110), and pulmonary embolism (HBV-10, day 41) and all were considered not related to vaccination. The 2 AE-withdrawals in the ENGERIX-B group were vision blurred (HBV-10, day 3), and arthritis (HBV-10, day 8). No AE-withdrawals occurred in the Tier 2 trial.”*

#### **Adverse events of special interest (AESIs):**

*AESI occurred in 12 subjects: “8 events in 8/3777 subjects (0.21%) in HEPLISAV group, and 6 events in 4/1087 subjects (0.37%) in the ENGERIX-B group. Only 3 events occurred within 42 days of vaccination: erythema nodosum (HEPLISAV, day 19, HBV-16), vitiligo (HEPLISAV, day 1, HBV-16), Raynaud’s phenomenon (ENGERIX-B, day 32, HBV-10).*

#### **Overview of safety results**

##### **Sponsor’s overview**

*“SAEs in Tier 1 and Tier 2 were infrequent and similar in type and frequency between HEPLISAV (2.8%) and ENGERIX-B (3.3%)... SAEs were more frequent in the 40 and older subgroup (HEPLISAV: 3.2%; ENGERIX-B: 4.1%) compared with the 18 to 39 year old age group (HEPLISAV: 1.2%; ENGERIX-B: 1.1%) consistent with the increasing frequency of medical events requiring hospitalization with increasing age... No cases of anaphylaxis were reported... There were 2 deaths: 1 death in a recipient of HEPLISAV (pulmonary embolism), and 1 death in a recipient of ENGERIX-B (myocardial infarction)...*

*There was no difference between treatment groups in Tier 1 in subjects with AE leading to trial withdrawal (HEPLISAV: 0.08%; ENGERIX-B: 0.18%), or discontinuation of study treatment (HEPLISAV: 0.50%; ENGERIX-B: 0.37%)...*

*There was a total of 2 SAE considered... to be related to treatment: 1 event of Wegener’s granulomatosis (HEPLISAV. approx. 2 months post-vaccination), and 1 event of bronchial hyperreactivity (ENGERIX-B, day 42)...*

*Pregnancy was an exclusion for all clinical trials of HEPLISAV... In T1SP, 13 pregnancies were reported (HEPLISAV: n=10: 6 healthy term deliveries, 1 healthy premature delivery, 2 elective terminations, 1 subject lost to follow-up; ENGERIX-B: n=3: 2 healthy term deliveries, 1 elective termination). In T2SP*

*HEPLISAV group, 3 subjects had healthy term deliveries, and 1 had a stillbirth at 23 weeks gestational age (almost 5 months after vaccination)--maternal factors included chronic hypertension, hypothyroidism, morbid obesity.*

Important missing information includes data in pregnant and lactating women. *“There are no adequate and well controlled clinical trials in pregnant women of HEPLISAV. Animal studies in rats given four intramuscular doses of the components of the vaccine (up to approximately a 200-fold excess relative to the human dose for 1018 ISS Adjuvant and 25-fold excess relative to the human dose for HBsAg on a mg/kg basis), found no adverse effects on maternal reproductive development, fetal development, and the growth and development of the offspring despite the fact that the highest dose level produced an appreciable degree of maternal toxicity.”*

**OVRR Clinical Reviewer overview of safety results (Integrated Safety Summary [ISS] Results, Dr. Lori Smith, MD, VRBPAC, November 15, 2012); November 14-15, 2012 VRBPAC Summary Minutes**

DV2-HBV-10 and DV2-HBV16:

Two deaths were reported in Study DV2-HBV16: one death due to pulmonary embolism in a 46 year old male (b) (6) days after HEPLISAV Lot TDG006 dose #2; one death due to myocardial infarction was reported in a 64 year old male (b) (6) days after ENGERIX-B dose #2; this patient had a history of hypertension.

Overall, 2.7% of HEPLISAV recipients and 3.7% ENGERIX-B recipients reported at least one SAE.

There is a numerical imbalance between the incidence of pulmonary embolism in the two groups: HEPLISAV: n=5 (0.1%); ENGERIX-B: n=0. Of the HEPLISAV cases one case was fatal, and the 4 remaining cases occurred in persons with underlying predisposition for thrombosis (obesity/smoker/oral contraceptives/antiphospholipid antibodies-positive; post-operative; prolonged road trip; hospitalization for GBS). The overall incidence of other thrombotic events (e.g., DVT) was similar between HEPLISAV and ENGERIX-B recipients (7 [0.2%] vs. 3 [0.2]).

FDA analysis of SAEs, autoimmune AEs (AIAE)(these reports were referred to the sponsor’s Safety Evaluation and Adjudication Committee [SEAC]), and AEs of Special Interest (AESI)(i.e., neuroinflammatory, musculoskeletal, gastrointestinal, metabolic, skin, autoimmune diseases) treated with immunosuppressive medications showed similar rates of events between the two groups (HEPLISAV, 0.2%; ENGERIX-B, 0.2%). Autoimmune events include (days from vaccination to symptom onset): HEPLISAV: One possible case of Tolosa-Hunt Syndrome/cavernous venous syndrome (165 days); one case of Wegeners granulomatosis (72 days); one report of erythema nodosum (19 days),

two reports of Bell's palsy (15-270 days), one case of uveitis (30 days), vitiligo (1 day, past medical history of another autoimmune disease), and SLE exacerbation (84 days), two cases of RA exacerbation (5-22 days), and one case of microscopic colitis exacerbation (3 days); Engerix-B group: One case of p-ANCA vasculitis (126 days, past history of another autoimmune disease), Bell's palsy (121 days), RA (20, past medical history consistent with RA), and bronchial hyperreactivity (56 days).

FDA analysis found the overall incidence of thyroid disease reported as adverse events was higher in the HEPLISAV group: HEPLISAV: 19 events/16 (0.4%), ENGERIX-B: 2 events/2 subjects (0.1%)(RR=2.6, 95% CI: 0.7, 10.0).

### Safety Summary

1. Review of local and systemic AEs, death and laboratory findings did not reveal any significant differences between recipients of HEPLISAV and ENGEIX-B.
2. Nonfatal SAE occurred with similar incidence between groups.
3. There is a numerical imbalance in the incidence of pulmonary embolism.
4. The overall incidence of thrombotic events is similar between recipients of HEPLISAV and ENGERIX-B.
5. Dynavax analysis found incidence of AESI similar between groups. Three new onset AIAEs were identified (2 cases of hypothyroidism in a 53 year and 55 year old female 26-58 days after vaccination; 1 case of vitiligo in a 77 year old male 1 day after vaccination).
- 6, FDA analysis of other potential autoimmune disease found a higher proportion of HEPLISAV recipients who developed thyroid-related disease (NOTE: Relative Risk Confidence Interval includes 1).
7. Autoimmune AE requiring immunosuppressive therapy occurred with similar incidence in both groups.
8. Four rare serious events were reported. HEPLISAV: A case of cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA)-positive vasculitis Wegener's granulomatosis with symptoms of urticaria (18 days post-vaccination #1), recurrent sinusitis (onset approximately 80 days after dose #1) and pulmonary infiltrates, pleural effusions and glomerulonephritis (approximately 7 months after dose #1); a case of GBS which occurred 105 days after dose #2 and 110 days after inactivated influenza vaccine; and 1 case of amblyopia in a 69 year old male occurring approximately 1 month after dose #3 of HEPLISAV—this subject was initially diagnosed with Tolosa-Hunt Syndrome, the diagnosis was subsequently changed to cavernous venous syndrome. The event occurred 5 months after

vaccination—specialist consultation on this case is in progress; ENGERIX-B group: One case of perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA)-positive vasculitis 3 months after dose #2 in a patient with a past history of mixed connective tissue disease. This patient was ANCA-negative (banked serum), and had a baseline ANA>1:5120.

## **B. Safety concerns**

This is the first time the 1018 ISS adjuvant has been used in the US. The adjuvant’s intended biological activity is “*to enhance antibody generation by activating the innate immune system via Toll-like receptor.*” The safety database for the phase 3 trials (n=HEPLISAV: 3,777, ENGERIX-B: 1087 recipients) is insufficient to exclude the possibility of rare side effects. Nevertheless, two relatively rare autoimmune diseases (background rate 1-12.2/million) with similar histopathology were observed in the HEPLISAV group. We are concerned about the possibility of a biologically plausible association between HEPLISAV vaccination and autoimmune disorders. We recommend further studies to: 1) expand the safety database, and 2) quantify and characterize the incidence of autoimmune and other adverse events after HEPLISAV.

The efficacy and safety of HEPLISAV was presented to the Vaccine and Related Biological Products Advisory Committee on November 15, 2012 (VRBPAC). The majority of committee members “considered the pre-licensure safety database inadequate to support the safety of HEPLISAV for use in adults 18-70 years of age. The Committee members stated “there were insufficient numbers of subjects studied to detect relatively infrequently occurring adverse events, especially considering that the adjuvant contained in HEPLISAV is not contained in any other US-licensed vaccine...(and)...that the safety database should be increased prior to licensure for the proposed indication and usage, and that the study populations should be more ethnically diverse, to reflect the US population...”

## **C. Sponsor’s proposed actions**

The sponsor proposes to use routine pharmacovigilance activities to monitor safety.

Safety data in pregnant women is considered “*important missing information for HEPLISAV.*” As part of routine pharmacovigilance activities, the sponsor proposes that “*all reports of exposure to HEPLISAV during pregnancy will be followed up to the outcome.*”

The sponsor’s proposed US prescribing information includes:

### **“4 CONTRAINDICATIONS**

*Severe allergic reaction such as anaphylaxis, after a previous dose of any hepatitis B vaccine or to yeast (a vaccine component), is a contraindication to administration of HEPLISAV*

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Managing Allergic Vaccine Reactions**

*Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.”*

The sponsor has not proposed enhanced pharmacovigilance activities.

The sponsor initially proposed a Phase IV prospective, observational cohort study in a total of 10,000 subjects aged 18 years and older enrolled in a US HMO who received at least one HEPLISAV (N=5000) or ENGERIX-B (N=5000) vaccination, as “*one possible approach to further define the safety profile of HEPLISAV. The study will assess the incidence of medically significant adverse events, including autoimmune disease, during the 12 months following first vaccination with HEPLISAV compared with ENGERIX-B...The study will enable an assessment of the RR of medically significant adverse events (AEs)... Data collection will begin 1 year after approval of HEPLISAV in the US...The study report is anticipated to be available 4 years after the start of the data collection.*”

On November 2, 2012, the sponsor responded to FDA’s Information Request dated October 26, 2012 regarding study design and analysis and proposed to conduct a cohort study that will “*include recipients of HEPLISAV (N=5000) matched to controls (N=15000) in a 1:3 ratio on the basis of potential confounding factors such as age and sex and other co-existing conditions such as pre-existing autoimmune disease, diabetes mellitus, and pregnancy.*”

#### **4. Review of information from the Managed Review process**

Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical, and product reviews.

#### **5. Postlicensure Safety Review**

Product not previously licensed.

#### **6. Integrated Risk Assessment**

The safety database for the phase 3 trials (n=HEPLISAV: 3,777, ENGERIX-B: 1087 recipients) is insufficient to exclude the possibility of very rare side effects. Nevertheless, two relatively rare autoimmune diseases (background rates 1-12.2/million) with similar histopathology were observed in the HEPLISAV group. We are concerned about the possibility of a biologically plausible association between HEPLISAV vaccination and autoimmune diseases.

Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical and product reviews.

#### **7. Recommendations**

A. Recommend further studies to: 1) expand the safety database, and 2) quantify and characterize the incidence of autoimmune and other adverse events after HEPLISAV.

B. Specialist consultation on cases of Wegener's granulomatosis and possible Tolosa-Hunt Syndrome/cavernous sinus syndrome to ascertain diagnosis, and evaluate the biologic plausibility of an association between HEPLISAV vaccination and autoimmune disease.

C. Decision as to the adequacy of the PVP is deferred pending the sponsor's response addressing the concerns of the Clinical Reviewer.