

Summary Basis for Regulatory Action

Date: November 9, 2017

From: Marian Major, Ph.D., Chair of the Review Committee

STN#: 125428/0

Applicant Name: Dynavax Technologies Corporation

Dates of Submission:

Original submission date: April 26, 2012

2nd cycle submission date: March 16, 2016

3rd cycle submission date: February 8, 2017

Goal Date: November 9, 2017

Proprietary Name/ Established Name: HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted]

Indication: For prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

Recommended Action:

Certain disciplines with the Review Committee recommend approval of this product based on the data relevant to their area of expertise. The clinical review group and biostatisticians conclude that the safety data for HEPLISAV-B are not adequate and, therefore, do not recommend approval. OVR and OBE management do not concur with the clinical and statistical reviewers and conclude that the effectiveness and safety data for HEPLISAV-B are adequate for approval in adults 18 years of age and older. This determination is based on management's assessment of the safety and effectiveness data for HEPLISAV-B, taking into consideration VRBPAC discussions and votes in 2012 and 2017 as well as assessments of consultants appointed by OVR.

Review Office Signatory Authority:

Marion F. Gruber, Ph.D., Director, Office of Vaccines Research and Review

- I concur with the summary review.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

Office of Compliance and Biologics Quality Signatory Authority:

Mary A. Malarkey, Director, Office of Compliance and Biologics Quality

- I concur with the summary review for the responsibilities assigned to the Office of Compliance and Biologics Quality.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name, Document date
<p>CMC Reviews</p> <ul style="list-style-type: none"> • <i>CMC Drug Substance/Drug Product (OVRP/DVP)</i> <p><i>Adjuvant (OVRP/DVRPA)</i></p> <ul style="list-style-type: none"> • <i>Facilities review (OCBQ/DMPQ)</i> <ul style="list-style-type: none"> • <i>Establishment Inspection Report (OCBQ/DMPQ)</i> 	<p>Iryna Zubkova, Ph.D. May 22, 2013 November 15, 2016 November 1, 2017</p> <p>Brenda Baldwin, Ph.D. May 13, 2013 November 16, 2016 July 6, 2017</p> <p>Priscilla M. Pastrana February 19, 2013 October 24, 2016 October 25, 2016 June 5, 2017</p> <p>Destry Sillivan February 12, 2013</p> <p>Priscilla M. Pastrana February 24, 2013 August 2, 2017</p> <p>Destry Sillivan February 24, 2013</p> <p>Marian Major February 24, 2013 August 2, 2017</p> <p>Ellen Huang August 2, 2017</p>
<p>Clinical Review(s)</p> <ul style="list-style-type: none"> • <i>Clinical (OVRP/DVRPA)</i> <ul style="list-style-type: none"> • <i>Postmarketing safety epidemiological review (OBE/DE)</i> <ul style="list-style-type: none"> • <i>BIMO (OCBQ/DIS)</i> 	<p>Lorie Smith, M.D. February 26, 2013</p> <p>Alexandra Worobec, M.D. February 26, 2013 April 7, 2017 November 8, 2017</p> <p>Darcie Everett, M.D. April 7, 2017 November 8, 2017</p> <p>Silvia Perez-Vilar, Pharm.D, Ph.D. November 7, 2017</p> <p>Bhanumathi Kannan October 3, 2012 February 22, 2013 November 17, 2016 June 15, 2017</p>
<p>Statistical Review(s)</p> <ul style="list-style-type: none"> • <i>Clinical data Safety (OBE/DB)</i> 	<p>Mridul Chowdhury, Ph.D. January 29, 2013 November 15, 2016 October 24, 2017</p> <p>Ruoxuan Xiang, Ph.D. November 7, 2017</p>

Document title	Reviewer name, Document date
<p><i>Immunogenicity (OBE/DB)</i></p> <ul style="list-style-type: none"> <i>Non-Clinical data Bioassay (OBE/DB)</i> 	<p>Mridul Chowdhury, Ph.D. January 29, 2013 November 15, 2016</p> <p>Ruoxuan Xiang, Ph.D. November 7, 2017</p> <p>Martha Lee, Ph.D. December 31, 2012</p> <p>Lei Huang, Ph.D. November 15, 2016 May 25, 2017</p>
<p>Pharmacology/Toxicology Review(s)</p> <ul style="list-style-type: none"> <i>Toxicology (OVRP/DVRPA)</i> <i>Toxicokinetics (OVRP/DVP)</i> 	<p>Steven Kunder, Ph.D. DABT February 21, 2013</p> <p>Claudia Wrzesinski, Ph.D. January 23, 2013</p> <p>Marian Major, Ph.D. August 14, 2012</p>
<p>Labeling Review(s)</p> <ul style="list-style-type: none"> <i>APLB (OCBQ/APLB)</i> 	<p>Kristine Khuc, Pharm.D. March 20, 2013</p> <p>Daphne Stewart June 16, 2017</p> <p>Sonny Saini, Pharm.D. July 10, 2017</p>
<p>Test Procedures (<i>OCBQ/DBSQC</i>)</p>	<p>Varsha Garnepudi, M.S. November 14, 2016 July 10, 2017</p> <p>Hyesuk Kong, PhD July 19, 2016 May 24, 2017</p> <p>Lokesh Bhattacharyya, PhD January 23, 2013 November 28, 2016 July 10, 2017</p> <p>Anil Choudhary, PhD December 8, 2016</p> <p>Simleen Kauer, PhD November 21, 2012</p> <p>Alfred DeGrosso, PhD October 28, 2016</p> <p>Muhammed Shahabuddin, PhD April 26, 2013</p>
<p>Advisory Committee Meetings</p> <p>November 15, 2012</p> <p>July 28, 2017</p>	<p>https://wayback.archive-it.org/7993/20170111231301/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM333684.pdf</p> <p>https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM582024.pdf</p>

1. INTRODUCTION

Dynavax Technologies Corp (henceforth referred to as Dynavax), the Applicant, submitted Biologics License Application (BLA) 125428 for licensure of Hepatitis B Vaccine (Recombinant), Adjuvanted. The proprietary name of the vaccine is HEPLISAV-B. HEPLISAV-B is proposed by the applicant to be indicated for active immunization against all subtypes of hepatitis B virus (HBV) infection in adults 18 years of age and older. The vaccine is administered intramuscularly (IM) in two doses (0.5 mL each) one month apart.

HEPLISAV-B consists of recombinant hepatitis B surface antigen (HBsAg), subtype adw, produced in yeast cells (*Hansenula polymorpha*) combined with a novel cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate immunostimulatory adjuvant (CpG 1018 adjuvant). The CpG 1018 adjuvant used in HEPLISAV-B is a 22-mer oligodeoxynucleotide with the sequence: 5' TGA CTG TGA ACG TTC GAG ATG A 3'. The HBsAg component of the vaccine is manufactured at Dynavax GmbH (formerly Rhein Biotech GmbH), Dusseldorf, Germany. The CpG 1018 adjuvant is manufactured by Nitto Denko AVECIA, Inc., Milford, MA USA. The Drug Product is formulated and filled at Rentschler Biotechnologie GmbH, Laupheim, Germany and the filled vials are transported to (b) (4) for labeling and packaging.

HEPLISAV-B is supplied as single-use vials of 0.5 mL volume. Each 0.5 mL dose contains:

20 mcg HBsAg
3000 mcg CpG 1018 adjuvant
8 mM sodium phosphate
154 mM sodium chloride
0.01% w/w polysorbate 80
pH 7.0 buffer

The vaccine does not contain preservatives. The proposed shelf-life of the final container product is 36 months at $5\pm 3^{\circ}\text{C}$ from the date of manufacture, which is defined as the date on which the active pharmaceutical ingredient (HBsAg) is added during formulation.

On April 26, 2012, Dynavax submitted a BLA for HEPLISAV-B to CBER, FDA. This BLA was assigned the STN 125428. HEPLISAV-B is not licensed in the United States (U.S.) or any other country and no vaccine containing CpG 1018 adjuvant has been licensed in the U.S. or any other country.

The original PDUFA due date was February 24, 2013. A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held November 15, 2012. At the time of the November 2012 VRBPAC, the BLA submission included two phase 3, randomized, active-controlled, immunogenicity and safety studies (DV2-HBV-10 and -16; 3778 HEPLISAV-B recipients, 1086 recipients of the licensed hepatitis B vaccine ENGERIX-B, manufactured by GlaxoSmithKline; GSK), and seven supportive trials, three of which included immunogenicity assessments. VRBPAC members voted 13:1 that the immunogenicity data submitted in the BLA were adequate to support the effectiveness of HEPLISAV-B for the prevention of HBV infection in adults 18-70 years of age. The Committee voted 8:5, with one abstention, that the available data were not adequate to support the safety of HEPLISAV-B in the same age group. Committee members noted that there were insufficient numbers of subjects studied to detect relatively infrequently occurring adverse events, especially considering the novel adjuvant contained in HEPLISAV-B. CBER issued a 55-item Complete Response (CR) letter on February 22, 2013, which contained comments on clinical safety, bioresearch monitoring, CMC, facilities, and quality control and test procedures.

Dynavax submitted a response to the CR letter on March 16, 2016. This included data from an additional safety study DV2-HBV-23 (N= 8,368 subjects) and revised clinical study reports for phase 3 studies DV2-HBV-10 and -16. While this submission initiated a new 6-month review clock with a Resubmission Action Due date of September 15, 2016, the review clock was extended to December 15, 2016, after Dynavax submitted a Major Amendment to the BLA consisting of a substantial amount of clinical data not previously submitted to the application. A second, 52-item CR letter was issued on November 10, 2016, which contained comments on safety issues that were identified in the new safety study DV2-HBV-23, the revised immunogenicity data for studies DV2-HBV-10 and -16, manufacturing facilities, CMC (adjuvant), quality control and testing procedures and post-marketing pharmacovigilance.

Dynavax submitted a response to the 2nd CR letter on February 8, 2017, which resulted in a Resubmission Action Due date of August 10, 2017. A second VRBPAC meeting was held on July 28, 2017. CBER considered that effectiveness had been established in the two previous Phase 3 studies. Therefore, the discussions and presentations for this VRBPAC focused on the safety of HEPLISAV-B with attention given to the findings of an imbalance in acute myocardial infarction (AMI) in DV2-HBV-23 where a greater frequency was observed in the HEPLISAV-B group. The VRBPAC members voted 12:1 with 3 abstentions that the available data support the safety of HEPLISAV-B when administered to adults 18 years and older. Further discussions from the committee focused on the proposed post-marketing plan to further evaluate the safety of HEPLISAV-B post-licensure (see Section 8: Advisory Committee Meetings).

On August 9, 2017, Dynavax submitted a high-level draft of a revised post-marketing plan synopsis to address the concerns raised by the VRBPAC. This was considered a Major Amendment to the BLA as it consisted of a substantial amount of clinical data not previously submitted to the application and the review clock was extended to November 9, 2017.

Dynavax originally proposed a proprietary name of HEPLISAV for the vaccine. CBER determined that this could be misleading in that it implied protection against all hepatitis viruses. CBER recommended revising the name to HEPLISAV-B. Dynavax concurred with this revision to the proprietary name.

In the original submission of April 2012, the Indication and Usage section of proposed labeling specified use in adults 18-70 years of age. In the resubmission of March 2016, this was revised by Dynavax to 18 years of age and older. It was determined that this change was acceptable given that age stratified immunogenicity data analyzed from study DV2-HBV-23 support extrapolation of effectiveness to persons >70 years of age and the safety profile is not expected to differ in persons >70 years of age compared with younger adults.

2. BACKGROUND

Hepatitis B virus (HBV) infects the liver and can cause both acute and chronic disease. Worldwide more than 2 billion people have been infected with HBV with approximately 250 million persons chronically infected (1). Acute HBV infection progresses to chronic infection in approximately 5% of healthy adults (2), but is greater among those with co-morbidities; such as those with diabetes and immunocompromised persons (3). Each year chronic HBV causes 0.5 to 1.0 million deaths worldwide from end-stage liver disease and hepatocellular carcinoma (4). In the U.S., universal childhood vaccination has been recommended since 1991 (5). Subsequently, the incidence of acute HBV infection has decreased from over 8.5 per 100,000 (1990) to 1.1 per 100,000 (2015) (6). In the U.S. prevalence remains at 850,000 to 2.2 million, and chronic HBV infection causes ~2,000 deaths annually (6). The CDC estimated that there were up to 47,000 new HBV infections in 2015, with 43% occurring in adults over 40 years of age (6).

Transmission of HBV is by percutaneous and mucosal exposure to infectious blood or body fluids. Nosocomial transmission between patients and from patients to health care workers, including those working in hemodialysis and oncology units, has become rare, declining 95% since implementation of routine vaccination and standard precautions for blood-borne pathogens (3).

Chronic hepatitis B infection can be treated with antiviral therapy. However, in most cases treatment suppresses viral replication but does not cure infection. Therefore, treatment must be continued for life. Two licensed vaccines, both made from yeast-derived recombinant antigen adsorbed to aluminum compounds are currently available for the prevention of HBV in adults in the U.S., ENGERIX-B (GSK) and RECOMBIVAX HB (Merck). There is also one combination vaccine for adults, TWINRIX (GSK), which includes a hepatitis A vaccine component. ENGERIX-B, RECOMBIVAX HB and TWINRIX are approved for use in adults as a three-dose series to be administered at months 0, 1 to 2, and 6 to 12. An accelerated schedule is licensed for TWINRIX as a series of four doses (1 mL each), given on days 0, 7 and days 21 to 30, followed by a booster dose at month 12.

Mechanism of Action

HEPLISAV-B is proposed to act by using an adjuvant that activates TLR9 in plasmacytoid dendritic cells (pDCs) which, combined with HBsAg, leads to production of HBsAg-specific antibodies.

The mode of action of CpG ODNs is based on the concept that, whereas vertebrate (self) DNA is usually methylated when a cytosine is followed by a guanine, bacterial and viral DNA contain unmethylated CpG sequences, which are recognized as foreign by the innate immune system through interaction with toll-like receptor 9 (TLR9) (7).

The CpG 1018 adjuvant in HEPLISAV-B is thought to have the following effects: (1) activation of pDCs through TLR9, (2) conversion of pDCs into activated dendritic cells that present the processed HBsAg component of HEPLISAV-B to CD4+ T cells, and (3) promotion of Th1 T-cell differentiation through the production of IFN- α and IL-12.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

The review of CMC information submitted in the BLA revealed problems that resulted in a number of Information Requests to the Applicant and Complete Response letter comments in 2013 and 2016. These issues were resolved and CBER concluded that there are no significant CMC issues to preclude the BLA from being approved.

a) Product Quality

The information provided in the BLA for HEPLISAV-B demonstrates that the manufacturing process is well-controlled with appropriate validations and in-process control testing. Moreover, adequate quality control testing has been conducted and stability data have been accrued with the drug substance and drug product.

Drug Substance (DS) Hepatitis B Surface Antigen (HBsAg)

Overview

The immunogenic component of HEPLISAV-B, HBsAg, is a 22 nm particle containing the *adw* subtype of the hepatitis B surface (S) protein and lipids. This particle resembles the noninfectious, HBsAg-containing particles that are secreted by human hepatocytes during natural HBV infection. The HBsAg is produced in yeast using recombinant technology. The HBsAg is manufactured at Dynavax GmbH, Dusseldorf, Germany. This is a new manufacturing

facility that is not currently licensed for manufacture of any U.S.-licensed vaccines. The facility is dedicated to the production of HBsAg for HEPLISAV-B.

Manufacture

(b) (4)

Control of Materials

(b) (4)

(b) (4)

Specifications and Methods: The proposed tests, specifications and methods for the release of the HBsAg DS are presented in Table 1.

Table 1. HBsAg DS Release and Stability Specifications

(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

(b) (4)			

(b) (4)

(b) (4)

(b) (4)

CpG 1018 Adjuvant

Overview

The CpG 1018 adjuvant (also referred to as 1018 ISS) is a 22-mer phosphorothioate-linked oligodeoxynucleotide (natural DNA has a phosphodiester linkage) with a molecular mass of (b) (4) (b) (4) that is produced by (b) (4). The sequence of the CpG 1018 adjuvant is 5' TGA CTG TGA ACG TTC GAG ATG A 3'. The molecular formula of the CpG 1018 adjuvant (b) (4). The CpG 1018 adjuvant was selected from a large panel of oligodeoxynucleotides for immunostimulatory activity *in vitro* and *in vivo* and for activity in both human cells and important animal species.

Human DNA sequence databases were searched to evaluate the extent to which CpG 1018 had homology with sequences of known human genes and transcripts. No homologies of concern were identified.

Hybridon Specialty Products was the original site for CpG 1018 manufacturing, and the adjuvant produced was used to make the original reference standard, nonclinical, and clinical materials (b) (4) batches were manufactured in 1998 and 2000). The Hybridon Specialty Products facility changed ownership in 2001 when it was purchased by Avecia Biotechnology (now known as Nitto Denko Avecia, Inc.). (b) (4)

(b) (4)

Manufacture

(b) (4)

Control of Materials

(b) (4)

(b) (4)

Drug Product (DP)

Overview

name-B DP is a sterile, liquid dosage form that is administered as an intramuscular injection. The finished vial (unit) of HEPLISAV-B DP contains 28 mcg of HBsAg and 4200 mcg of CpG 1018 adjuvant formulated in 0.7 mL of 8 mM sodium phosphate, 154 mM sodium chloride, 0.01% w/w polysorbate 80, pH 7.0 buffer.

HEPLISAV-B DP is filled in sterile, single-use, 2 mL, clear borosilicate, Type ^{(b) (4)} glass vials and sealed with a 13 mm gray chlorobutyl rubber stopper with (b) (4) coating on the side in contact with DP. The stopper is capped with a 13 mm flip-off, aluminum seal with a white button. An administered dose of 0.5 mL contains 20 mcg of HBsAg and 3000 mcg of CpG 1018 adjuvant in the buffered solution. HEPLISAV-B is a single-dose unit and is manufactured without the use of preservatives.

During the development process the Applicant developed 3 different formulations of HEPLISAV-B – Formulation 1, 2 and 3. Formulation 3 was used to manufacture the lots used in the clinical trials, which included the lot consistency batches (TDG0008, TDG009 and TDG010).

Manufacture

The manufacturing process consists of the following steps: (b) (4)

(b) (4) aseptic filling and stoppering, capping, visual inspection and bulk unlabeled vial packaging, storage and shipment of vials, vial labeling, finished product packaging.

The current process is performed at a ^{(b) (4)} scale, which results in the manufacture of approximately (b) (4) vials of DP, using (b) (4) mL fill volume per vial.

Control of Materials

Raw materials: All raw materials are of non-human or non-animal origin.

Adventitious Agents Safety Evaluation for the DP: The risk of introducing BSE/TSE contamination into the HEPLISAV-B DP during manufacture was assessed as extremely low.

Specifications and Methods: The proposed tests, specifications and methods for the release of the DP are presented in Table 3. Dynavax also performs the HBsAg identity test on the labeled and packaged product.

Table 3: HEPLISAV-B Drug Product Release and Stability Specifications

Parameter	Test Method	Acceptance Criteria for Release	Acceptance Criteria for Stability
Appearance	(b) (4)	Color: (b) (4) Opalescence: (b) (4) Essentially free of visible particles	Color: (b) (4) Opalescence: (b) (4) Essentially free of visible particles
pH	(b) (4)		
HBsAg identity	(b) (4)	Confirmed	(b) (4)
HBsAg (b) (4)	(b) (4)		
HBsAg concentration	(b) (4)		
HBsAg (b) (4)	(b) (4)		
Potency	(b) (4)		
1018 identity	(b) (4)	Confirmed	(b) (4)
(b) (4)	(b) (4)		
1018 content	(b) (4)		
Particle size	(b) (4)		
Particulate contamination: sub-visible particles/ particulate matter	(b) (4)		
Extractable volume	(b) (4)	≥ 0.5 mL	(b) (4)
Endotoxin	(b) (4)		
Sterility	(b) (4)	Sterile, no growth	(b) (4)
Container closure integrity	(b) (4)	NA	(b) (4)

(b) (4); NA = not applicable, no release or stability specification; NLT = not less than; NMT = not more than; (b) (4)
UCL = upper confidence limit.

^a Test method adjusted for single-use vials; (b) (4) test.

Exemption from the General Safety Test (GST): In the original BLA submission of 2012 Dynavax included a GST on HEPLISAV-B. In the March 2016 resubmission Dynavax requested exemption from a modified GST for HEPLISAV-B final product based on the amended biologics regulations removing GST requirements for biological products (80 FR 37971). This request was supported by data accumulated from (b) (4) lots of HEPLISAV-B. CBER concurred.

Extractables and Leachables: No risk identified.

Stability of the DP and Proposed Shelf-life: The stability plan includes storage of the DP in vials at 5°C ± 3°C over a period of 36 months with testing at 0, 3, 6, 12, 24 and 36-month time-points using tests and acceptance criteria shown in Table 3. CBER concluded that the stability data provided support this proposed 36-month shelf-life. The Applicant committed to monitor stability of (b) (4) of HEPLISAV-B (b) (4) under long term conditions (5°C ± 3°C).

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. Samples were submitted to CBER in support of the BLA, tested by CBER and found to be acceptable. A Laboratory Quality Product Testing Plan was developed by CBER and will be used for routine lot release.

c) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of HEPLISAV-B are listed in Table 4. The activities performed and inspectional histories are noted in the table and further described in the paragraphs below.

Table 4: Manufacturing Facilities for HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted]

Name/address	FEI number	DUNS number	Inspection /Waiver	Results/ Justification
<i>Drug Substance</i> Manufacturing and Testing: <i>Drug Product</i> Testing: Dynavax GmbH (formerly Rhein Biotech GmbH) Eichsfelder Strasse 11 40595 Düsseldorf, Germany	3010165220	318031242	Pre-License Inspection	CBER June 8-16, 2016 VAI* CBER August 16-23, 2012 VAI*
<i>Drug Product</i> Manufacturing and Testing: Rentschler Biotechnologie GmbH Erwin-Rentschler-Strasse 21 88471 Laupheim, Germany	1000291122	332952766	Waived	ORA/IOG November 28 - December 6, 2016 VAI*
<i>Drug Product</i> Testing: (b) (4)	(b) (4)		Waived	ORA/IOG (b) (4) NAI#
<i>Drug Product</i> Labeling, Packaging and Storage: (b) (4)			Waived	ORA/IOG (b) (4) VAI*
<i>Drug Product</i> Labeling, Packaging and Storage: (b) (4)	(b) (4)		Waived	ORA (b) (4) VAI*

*VAI: Voluntary Action Indicated; #NAI: No Action Indicated

CBER conducted a Pre-License Inspection (PLI) of Dynavax GmbH (formerly Rhein Biotech GmbH) Düsseldorf, Germany from June 8 - 16, 2016. The inspection was classified as Voluntary Action Indicated (VAI) and all inspectional issues were satisfactorily resolved.

ORA/IOG performed a surveillance inspection of Rentschler Biotechnologie GmbH from November 28 - December 06, 2016. The inspection was classified as VAI and all inspectional issues were satisfactorily resolved.

ORA /IOG conducted a surveillance inspection of (b) (4) from (b) (4). The inspection was classified as no action indicated (NAI).

ORA/IOG conducted a surveillance inspection of (b) (4). The inspection was classified as VAI and all inspectional issues were satisfactorily resolved.

ORA conducted a surveillance inspection of (b) (4). The inspection was classified as voluntary action indicated (VAI) and all inspectional issues were satisfactorily resolved.

Container Closure System: The drug product is filled into 2mL clear borosilicate Type^{(b) (4)} glass vials (b) (4). A gray 13-mm chlorobutyl rubber stopper (b) (4) is used to stopper the filled vial. Then the vial and stopper is sealed with a 13-mm flip-off aluminum seal (b) (4) conducted the container closure integrity testing at their (b) (4) facility, employing the (b) (4) test method; all acceptance criteria were met.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Pre-clinical toxicity studies were conducted to identify and evaluate any toxicity findings following the administration of combined HBsAg and CpG 1018 adjuvant and the adjuvant alone. Repeat-dose toxicity and reproductive and developmental toxicity studies were performed with HBsAg plus CpG 1018 and single-dose, repeat-dose and genotoxicity studies were performed with the CpG 1018 adjuvant alone.

Toxicity studies with HBsAg plus CpG 1018 adjuvant. A GLP toxicity study with HBsAg plus CpG 1018 adjuvant was conducted in mice given 3 intramuscular injections (on Days 0, 14, and 28 with a 3-week recovery) with dose levels of 1 to 50 mcg/mouse CpG 1018 adjuvant in combination with a fixed dose of 0.5 mcg/dose/mouse HBsAg (a single human dose is 20 mcg HBsAg and 3000 mcg CpG 1018).

There were mild decreases in the group mean serum albumin, total protein, and triglyceride values for the 50 mcg CpG 1018 + HBsAg dose compared to HBsAg alone. In addition, for the 50 mcg CpG 1018 + HBsAg group the mean red blood cell (RBC) parameters were slightly decreased relative to those for HBsAg alone. The reductions in circulating RBC mass and albumin are class effects of oligonucleotides in rodents, and appear to be treatment-related. Differences in albumin, protein, triglycerides, and RBC parameters were not observed at recovery.

Terminal necropsy findings included increases in spleen weight, and histopathologic changes in the injection sites, plus extramedullary hematopoiesis in the spleen and liver. No severe toxicity was observed, and all effects reflected the expected immunostimulatory properties of the vaccine components.

HBsAg plus CpG 1018 was also tested in rats in a reproductive and developmental toxicity study which assessed the potential effects on mating behavior, fertility, gestation, embryo-fetal development, parturition, lactation and maternal behavior (from implantation through lactation and weaning) and on the development of the offspring (F1 generation) of the treated female rats, including postnatal behavioral/functional and immunological evaluation. The combination of CpG 1018 + HBsAg was administered as 4 IM injections at appropriate intervals before and during gestation. The highest dose level of CpG 1018 was 3000 mcg, while the highest dose level of HBsAg was 2.5 mcg (a single human dose is 3000 mcg CpG 1018 and 20 mcg HBsAg).

There were no adverse effects on maternal reproductive performance, fetal development, the growth and development of the offspring, or any of the other parameters evaluated, even though the highest dose level displayed maternal toxicity. A No-Observable-Adverse-Effect-Level (NOAEL) for reproductive and developmental toxicity and for the growth and development of the F1 generation was observed at the highest dose levels tested.

Toxicity studies with CpG 1018 adjuvant alone. The CpG 1018 adjuvant alone was evaluated in 3 genotoxicity studies, 2 safety escalation studies (rabbit and baboons) and 3 repeated toxicology studies (mice, rats, and cynomolgus monkeys). No significant toxicological findings were found which would prevent the use of this adjuvant at a dose of 0.05 mg/kg for 2 intramuscular (IM) administrations 1 month apart.

Rats or cynomolgus monkeys received subcutaneously (SC) either 0.5, 1.5, 12.5 mg/kg/week of CpG 1018 or PBS weekly for 8 weeks. In general, no mortality or clinical signs of systemic toxicity were observed. Findings were consistent with previously described class effects for oligonucleotides and more pronounced in rats.

Most of the observed changes were reversible, except for accumulation of the CpG 1018 in the kidneys in male rats of all groups as well as female rats receiving 2.5 and 12.5 mg/kg/week which led to minimal to moderate tubular degeneration and minimal to moderate chronic interstitial inflammation in a dose dependent manner. The incidence and severity of these changes were similar after the recovery and terminal sacrifice, indicating that those changes were not reversible. The frequency and the severity of these changes occurred in a dose dependent manner. The lowest given dose to the rats of 0.5 mg/kg/week was 10 times higher than the proposed human dose of 0.05 mg/kg/week. Further the dose was given weekly for 8 weeks, while the anticipated human dose will be given two times with an interval of 1 month in-between. Rats are known to have a relatively long tubular system compared to primates and might be more prone to tubular toxicities than primates. In the submitted non-human primate study doses up to 12.5 mg/kg/week of the CpG 1018 adjuvant were given and no adverse findings in the kidney were observed.

Studies on clearance of CpG 1018. These studies were carried out in cynomolgous monkeys and rats to study the clearance of CpG 1018 from plasma and toxicity following subcutaneous administration. The test article, CpG 1018, was cleared from the plasma within 24 hours at the highest dose tested (12.5 mg/kg) when delivered subcutaneously in monkeys. The latest time point studied in rats was 4 hours post-dosing. The test article was detectable at 4 hours only in the highest dose group (12.5 mg/kg) at 2.1% of the total dose. As indicated above, the final vaccine product contains 3000 mcg CpG 1018 in a 0.5mL volume. For an adult weighing 60 kg this would be equivalent to 0.05 mg/kg. Although the recommended route of administration is intramuscular, it is not expected that the subcutaneous route of

administration used in this toxicology study would significantly impact the rate of clearance of the adjuvant. Similar to the main toxicology studies, modest or minor clinical effects were seen most of which were reflective of the immunostimulatory nature of the test article and most resolved within the 4-week follow-up period.

Overall, the nonclinical toxicity assessments provided in the submission, did not raise significant safety concerns.

5. CLINICAL PHARMACOLOGY

No clinical pharmacology or pharmacokinetic studies were performed in the clinical development program for HEPLISAV-B vaccine. No studies were performed on special populations.

6. CLINICAL/STATISTICAL

a) Clinical Program

Overview of Clinical Trials

A summary of the clinical studies (DV2-HBV-10, DV2-HBV-16 and DV2-HBV-23) submitted to the BLA in support of safety and immunogenicity is presented in Table 5. At the time of initial submission of the BLA (April 2012), Dynavax requested a priority review based on claims of increased effectiveness in adults aged 18 to 70, documented enhancement of patient compliance, and demonstration of safety and effectiveness in a new subpopulation (type 2 diabetes mellitus). This request was denied on May 21, 2012 and Dynavax was notified that the BLA would be reviewed under the standard review timeline.

In support of the BLA submission in April 2012 Dynavax conducted two clinical trials, DV2-HBV-10 and DV2-HBV-16, and submitted immunogenicity, safety and reactogenicity data from a total of 4,877 subjects (3,789 subjects received HEPLISAV-B and 1088 subjects received the comparator ENGERIX-B). However, following review of the safety data from these trials and the discussions at the November 2012 VRBPAC, a Complete Response (CR) letter was issued in February 2013 citing, among other items, the insufficient size of the safety database, as well as the occurrence of two rare granulomatous disease cases following HEPLISAV-B administration. To address the CR item regarding the insufficient size of the safety database, Dynavax conducted Study DV2-HBV-23, an observer-blind, randomized, active controlled trial enrolling subjects 18 to 70 years of age comparing HEPLISAV-B and ENGERIX-B with a randomization ratio of 2:1 (5,587 subjects received HEPLISAV-B and 2,781 subjects received ENGERIX-B).

Table 5. Summary of Completed Pivotal Studies of HEPLISAV-B

	Study Design	HEPLISAV-B Dose/Schedule/ N	Active Comparator Dose/Schedule/ N	Key Endpoint(s)
<u>DV2-HBV-10</u> <u>NCT</u> <u>00435812</u> Study Period: Dec 2006- March 2008	Phase 3, observer-blind, randomized, active-controlled, multi-center study in subjects 11-55 years of age conducted in Canada and Germany	HEPLISAV-B: 20 mcg HBsAg /3000 mcg CpG 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1821 Aged 18 and older n=1810	ENGERIX-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N=607 Aged 18 and older n=605	Primary Endpoint: SPR at Week 12 for HEPLISAV-B and Week 28 for ENGERIX-B Solicited reactions 7 days following each injection AEs/SAEs Study Week 28
<u>DV2-HBV-16</u> <u>NCT</u> <u>01005407</u> Study Period: Feb 15, 2010-May 25, 2011	Phase 3, observer-blind, randomized, active-controlled, multi-center study in subjects 40-70 years of age conducted in Canada and the U.S.	HEPLISAV-B: 20 mcg HBsAg /3000 mcg CpG 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1968	ENGERIX-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N=481	Primary Endpoint: SPR at Week 12 for HEPLISAV-B and Week 32 for ENGERIX-B Lot consistency of HEPLISAV-B measured by GMC at Week 8 Solicited reactions 7 days following each injection AEs Study Week 28, SAEs/AESIs Study Week 52
<u>DV2-HBV-23</u> <u>NCT</u> <u>02117934</u> Study Period: April 18, 2014- March 1, 2015	Phase 3, observer-blind, randomized, active-controlled, multi-center study in subjects 18 to 70 years of age conducted in the U.S.	HEPLISAV-B: 20 mcg HBsAg /3000 mcg CpG 1018 adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=5587	ENGERIX-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM N=2781	Primary Endpoint: MAEs/SAEs/AESIs Study Week 56 SPR at Week 28 in subjects with type 2 diabetes mellitus Secondary Endpoint: SPR at Week 24 for HEPLISAV-B and Week 28 for ENGERIX-B

SPR: Seroprotection Rate: anti-HBsAg level ≥ 10 mIU/mL. AE: Adverse Event; SAE: Serious Adverse Event; AESI: Adverse Event of Special Interest; MAE: Medically Attended Adverse Event. Study Period defined as date of enrollment of first study subject to the date of safety evaluation for the last study subject. Numbers of subjects represent those receiving at least one dose of HEPLISAV-B or ENGERIX-B.

Demographic and Baseline Characteristics

Demographic and baseline characteristics were similar between the two treatment groups for all 3 clinical studies. However, baseline demographics differed between the studies.

DV2-HBV-10: Within each group, almost all subjects were white or non-Hispanic/Latino, the mean age was ~40 years, and the percentage of females was slightly higher than that of males. The breakdown by age was similar between the two treatment groups, with slightly more subjects in the 40 through 55 year subgroup (54.8% and 54.6% subjects, respectively for HEPLISAV-B vs. ENGERIX-B) than the 18 through 39 year subgroup (45.2% and 45.4%, respectively, HEPLISAV-B vs. ENGERIX-B). Subjects were also categorized by weight, height, and body mass index (BMI) as exploratory variables. No significant differences between the two treatment groups were seen for these characteristics. The majority of enrolled study subjects (63-64% for both treatment groups) were non-diabetic (98%), and non-obese (defined as a BMI ≤ 30 kg/m²; 72-75% non-obese for both treatment groups by this definition).

DV2-HBV-16: As for DV2-HBV-10, subjects were categorized by weight, height, and BMI as exploratory variables. No significant differences between the two treatment groups were seen for these characteristics. Age stratification was similar between the two treatment groups, with slightly more subjects in the 50 through 59 year subgroup (39.8% and 39.5% subjects, respectively for HEPLISAV-B vs. ENGERIX-B) than the 40 through 49 year subgroup (32.3% and 33.1%, respectively, HEPLISAV-B vs. ENGERIX-B) and the 60 through 70 year subgroup (27.8% and 27.3%, respectively, HEPLISAV-B vs. ENGERIX-B). The majority of enrolled study subjects (79% for both treatment groups) were non-diabetic (91-92%), and non-obese (BMI ≤ 30 kg/m², 56-57% for both treatment groups).

DV2-HBV-23: Subjects had a mean age of 50.4 years and were 50.6% male. Age stratification for HEPLISAV-B vs. ENGERIX-B subjects, respectively, in each subgroup was as follows: 18 through 29 years - 4.7% and 4.7%; 30 through 39 years - 15.6% vs. 15.5%; 40 through 49 years - 22.7% vs. 22.7%; 50 through 59 years - 31.6% vs. 32.2%; ≥ 60 years - 25.4% vs. 24.9%. Subjects in this study reported more baseline medical conditions and risk factors for coronary artery disease than those enrolled in DV2-HBV-10 and -16 (for example, prior diagnosis of cardiac ischemic disease: 3.7% DV2-HBV-23, 0.6% DV2-HBV-10, 2.7% DV2-HBV-16; type 2 diabetes mellitus: 13.7% DV2-HBV-23, 2.2% DV2-HBV-10, 7.8% DV2-HBV-16; hypertension: 36% DV2-HBV-23, 39% DV2-HBV-10, 29% DV2-HBV-16, smoking: 33% DV2-HBV-23, 36% DV2-HBV-10, 22% DV2-HBV-16). However, medical conditions and cardiac risk factors were balanced between study groups in DV2-HBV-23.

Clinical Efficacy

Efficacy of HEPLISAV-B was assessed by determining the seroprotection rate (SPR): the proportion of subjects with an anti-HBsAg level ≥ 10 mIU/mL, an antibody concentration recognized as conferring protection against HBV infection (8, 9). SPRs following two doses of HEPLISAV-B were compared to SPRs induced by three doses of ENGERIX-B to demonstrate non-inferiority of HEPLISAV-B to ENGERIX-B.

The clinical reviewer and the statistical reviewer agreed that clinical efficacy had been shown in DV2-HBV-10 and DV2-HBV-16. The data submitted to the BLA demonstrated that in all clinical studies, the primary immunogenicity endpoint of seroprotection with HEPLISAV-B met the non-inferiority criterion when compared with ENGERIX-B.

The March 2016 CR letter response from Dynavax included revised clinical study reports (CSRs) for DV2-HBV-10 and DV2-HBV-16. The Applicant determined these revisions were necessary to correct errors in the CSRs submitted in 2012. The errors in the CSRs were primarily concerning subjects erroneously included or excluded from the per protocol (PP) immunogenicity

populations of each study. The safety population for neither study changed as a result of the audit. The revised PP population submitted in the March 2016 Complete Response did not significantly alter the non-inferiority results between HEPLISAV-B and ENGERIX-B and did not change conclusions for the non-inferiority comparison.

DV2-HBV-10

This was a phase 3 observer-blind, randomized, controlled study of approximately 2400 subjects, 11-55 years of age (ages 18-55 in Germany) conducted in Canada and Germany. Subjects were randomized 3:1 to receive either HEPLISAV-B or ENGERIX-B. ENGERIX-B subjects received three 1.0 mL injections (containing 20 mcg of HBsAg) of ENGERIX-B vaccine at Weeks 0, 4 and 24, the FDA-approved ENGERIX-B dose and schedule for adults not on dialysis. HEPLISAV-B subjects received two injections of HEPLISAV-B vaccine at Weeks 0 and 4 and saline placebo at Week 24. The duration of the study was 28 weeks. The study was designed to assess immunogenicity and safety and tolerability of vaccination with HEPLISAV-B when administered to adolescent and adult subjects. The primary immunogenicity analysis determined the difference in SPR between the ENGERIX-B group at Week 28 and HEPLISAV-B group at Week 12 (ENGERIX-B minus HEPLISAV-B). If the upper limit of the 2-sided 95% confidence interval (CI) was below the pre-specified non-inferiority criterion of +10%, HEPLISAV-B was determined to be non-inferior to ENGERIX-B.

Based on the revised immunogenicity data submitted in the March 2016 Complete Response, the estimated difference in SPR between the ENGERIX-B and HEPLISAV-B groups and associated 95% CI was -13.7% (CI: -17.5, -10.4). The upper limit of the CI was -10.4%, which was below the pre-specified non-inferiority criterion of +10%, establishing that the SPR at the Week 12 time point for HEPLISAV-B was non-inferior to that of ENGERIX-B at Week 28. Furthermore, the upper limit of the CI was less than 0, indicating that the immune response, as measured by the SPR at Week 12 following 2 injections of HEPLISAV-B, is higher than that at Week 28 following 3 injections of ENGERIX-B. The numerical change in SPR for the primary immunogenicity analysis was negligible, using the revised PP population numbers and did not change conclusions for Study DV2-HBV-10.

DV2-HBV-16

This was a phase 3 subject- and observer-blind, randomized, controlled study of approximately 2000 adult subjects, 40 to 70 years of age conducted in Canada and the U.S. Subjects were randomized 4:1 to receive either HEPLISAV-B or ENGERIX-B. The dosing regimen and schedule were identical to those of DV2-HBV-10. The duration of the study was 52 weeks.

The co-primary immunogenicity objectives of this phase 3 study were: 1) to demonstrate lot consistency through clinical evaluation of three consecutively manufactured lots of HEPLISAV-B, and 2) to demonstrate non-inferiority of the immune response to HEPLISAV-B as measured by the SPR at 8 weeks after the last active dose (Week 12), compared to the SPR for ENGERIX-B vaccination at 8 weeks after the last active dose (Week 32). Immunogenicity criteria for demonstration of lot consistency were met when measured 8 weeks after the last vaccination of HEPLISAV-B (Week 12).

Clinical consistency of the 3 consecutively manufactured lots of HEPLISAV-B was established at Week 12 (8 weeks after the last dose of HEPLISAV-B). Following demonstration of lot consistency, results from the 3 HEPLISAV-B consistency lots were pooled for comparison to ENGERIX-B. For the comparison of SPRs noninferiority was demonstrated between the two treatment arms. The SPR in the HEPLISAV-B group was 90.1% and that of the ENGERIX-B group was 70.5%; the estimated difference between these rates (HEPLISAV-B minus ENGERIX-B) was 19.6% (95% CI: 14.7%, 24.8%). The SPR for the HEPLISAV-B group at Week 12 was non-inferior to the SPR for the ENGERIX-B group at Week 32 because the lower limit of the 95% CI

(14.7%) was greater than the pre-specified value of -10%. A secondary objective was to assess the statistical difference between the SPRs in each group if the non-inferiority criterion was met. The lower limit of the 95% CI was greater than 0, therefore, the SPR in the HEPLISAV-B group was found to be statistically higher than the SPR in the ENGERIX-B group.

DV2-HBV-23

This was a phase 3 subject and observer-blind, randomized, active-controlled study of approximately 8250 subjects, 18 - 70 years of age conducted at 40 sites in the U.S. Subjects were randomized 2:1 to receive either HEPLISAV-B or ENGERIX-B.

The dosing regimen and schedule were identical to those of the previous studies. The duration of the study was 56 weeks.

Although CBER did not request additional data on immunogenicity in the February 2013 CR letter, immunogenicity was included by Dynavax as an endpoint in DV2-HBV-23. Review of the data showed that the SPR response in HEPLISAV-B recipients at Week 24 was non-inferior to the SPR response in ENGERIX-B recipients at Week 28 for all PP subjects, consistent with the results of studies DV2-HBV-10 and -16.

CBER initially decided in 2016 that it would not review the immunogenicity data derived from the subpopulations in DV2-HBV-23. However, this issue was further discussed within CBER after the July 2017 VRBPAC meeting. It was then determined that diabetic and other subgroup immunogenicity data in DV2-HBV-23 should be reviewed under the current BLA.

Dynavax included as a primary immunogenicity endpoint a comparison of SPRs between HEPLISAV-B and ENGERIX-B at Week 28 in type 2 diabetic subjects. The difference between SPRs (HEPLISAV-B minus ENGERIX-B) was 24.9% (95% CI: 19.3%, 30.7%), which met the prospectively-defined criterion for the primary assessment of noninferiority (lower limit of the 95% CI greater than -10%) as well as the secondary objective showing that the SPR in the HEPLISAV-B group at Week 28 was statistically significantly higher than in the ENGERIX-B group at Week 28 (lower limit of the 95% CI greater than 0).

In a secondary subgroup analysis SPRs at Week 24 for HEPLISAV-B recipients were compared with SPRs at Week 28 in ENGERIX-B recipients by age group (18-29, 30-39, 40-49, 50-59, 60-70 years). HEPLISAV-B met the pre-specified criterion demonstrating immunological non-inferiority to ENGERIX-B for each age group and the SPRs at Week 24 for each of the HEPLISAV-B age groups were significantly higher than in the ENGERIX-B age groups at Week 28 (lower limit of the 95% CI greater than 0).

Bioresearch Monitoring Review

Bioresearch Monitoring Branch were conducted following the initial submission of the BLA in April 2012 and again following the resubmission of the BLA in March 2016.

2012 Inspections. For the initial submission two clinical investigators conducting investigations at sites #22, #23, #24, #25, #26 and #38 (Table 6) were inspected. The inspections assignment included clinical study DV2-HBV-16 titled *An Observer-Blinded, Randomized, Parallel-Group, Multi-Center Study Comparing the Safety and Immunogenicity of HEPLISAV™ to Licensed Vaccine (ENGERIX-B®) Among Healthy Subjects 40 to 70 Years of Age.*

Table 6: Inspections of Clinical Sites and Outcome

Study site /Site #	Location	Number of subjects enrolled	Issue of Form FDA 483	Final classification
Radiant Research, Inc. / Site # 38	Chicago, IL	242	No	VAI
Primary Physician's Research (PPR) / Sites # 22, 23, 24, 25, and 26	Pittsburgh, PA*	169	No	VAI

VAI- Voluntary Action Indicated

*The primary study site was disbanded in August 2011 and was no longer active for the FDA to conduct an inspection at the study sites. FDA inspected the records at the sponsor's location.

2016 Inspections. Five clinical investigator inspections were conducted in support of the BLA (Table 7). The inspections included clinical study DV2-HBV-23 titled *A Phase 3, Observer-Blinded, Randomized, Active-Controlled (ENGERIX-B), Multicenter Trial of the Safety and Immunogenicity of HEPLISAV in Adults 18 to 70 years of Age.*

Table 7: Inspections of Clinical Sites and Outcome

Site number	Study site	Location	Issue of Form FDA 483	Final classification*
122 and 222	Radiant Research, Inc.	Chicago, Illinois	Yes	VAI
119	Clinical Research Advantage, Inc.	Birmingham, Alabama	No	NAI
124	Clinical Research Advantage, Inc.	Las Vegas, Nevada	No	NAI
132	Radiant Research, Inc.	Columbus, Ohio	No	NAI
138	Radiant Research, Inc.	Atlanta, Georgia	No	NAI

* VAI-Voluntary Action Indicated NAI-No Action Indicated

The Bioresearch Monitoring inspection results from the aforementioned study sites revealed problems that resulted in Complete Response letter comments in 2013 and 2016. These issues were resolved and CBER concluded that there are no significant bioresearch monitoring issues to preclude the BLA from being approved.

b) Pediatrics

The Pediatric Research Committee (PeRC) convened on October 3, 2012 to consider the proposal for a full waiver of pediatric studies in the HEPLISAV-B developmental program.

The PeRC ultimately agreed to a full pediatric waiver for all pediatric subgroups due to no meaningful therapeutic benefit over existing therapies and considered that the product is not likely to be used in a substantial number of pediatric patients. Some of the discussion points included:

- There are 4 vaccines currently licensed for vaccination against hepatitis B in children. Two of these are combination vaccines (COMVAX, PEDIARIX). Combination vaccines are the preferred method of vaccine administration in children per the ACIP. The current hepatitis B vaccines are very effective in this population with efficacy rates of 96-100%.

NOTE: Subsequent to this meeting COMVAX was discontinued by the manufacturer and is no longer available for purchase. Therefore, currently there are 3 vaccines licensed for vaccination against hepatitis B in children, one of which is a combination vaccine (PEDIARIX).

- A potential unmet medical need filled by HEPLISAV-B primarily involves hyporesponders, those needing accelerated protection and improving compliance. OVRB outlined how these issues do not apply to the pediatric population as they do adults.
- The PeRC expressed concerns regarding the possibility that providers caring for adults and children may try to substitute this adult vaccine for one of the ACIP recommended vaccines in the pediatric vaccination schedule. It was determined that the vial or carton should clearly indicate that this vaccine is for vaccination of adults only.

NOTE: This was included on the carton submitted for review and approved by CBER.

c) Other Special Populations

Pregnancy was an exclusion criterion for all clinical trials of HEPLISAV-B. No trials were conducted specifically to assess the safety of HEPLISAV-B in pregnancy. No clinical data are available to address the use of HEPLISAV-B during lactation. No data have been submitted regarding the safety and immunogenicity of this product in immunocompromised patients. Individuals aged 18-70 were enrolled in Studies DV2-HBV-16 and -23.

7. SAFETY

Overview

There were concerns regarding the occurrence of two rare granulomatosis events in two HEPLISAV-B recipients. The first case, granulomatosis with polyangiitis (GPA) (previously “Wegener’s granulomatosis” and diagnosed as such at the time the study was conducted), occurred in DV2-HBV-10. The second case, Tolosa-Hunt syndrome (THS), occurred in DV2-HBV-16. As a result of these events a secondary, unpowered endpoint of DV2-HBV-23 was the proportion of subjects diagnosed with GPA and THS. Neither of these events occurred in DV2-HBV-23.

In DV2-HBV-23 there were observed imbalances between trial arms in the frequency of deaths, myocardial infarctions (MI), and herpes zoster. Rates of cardiac serious adverse events were more frequent in the HEPLISAV-B group compared to the ENGERIX-B group (HEPLISAV-B 0.9%, ENGERIX-B 0.5%). This difference in frequency was most notable in the Medical Dictionary for Regulatory Activities (MedDRA) preferred term of acute myocardial infarction (AMI), which was reported in 14 subjects in the HEPLISAV-B group (0.25%) and one subject in the ENGERIX-B group (0.04%). Additional analyses by Dynavax on cardiac events in DV2-HBV-23 corroborated the imbalance.

Following are summaries of safety reviews of the three safety studies.

DV2-HBV-10

The primary safety objective of this study was to compare safety and tolerability of vaccination with HEPLISAV-B when administered to adolescent and adult subjects (11 to 55 years of age) with the safety and tolerability of ENGERIX-B.

Safety and tolerability were evaluated until Week 28 on the basis of the following parameters: solicited post-injection local and systemic adverse events (AEs), unsolicited AEs, serious adverse events (SAEs), clinical laboratory results, including anti-nuclear antibody (ANA) and anti-dsDNA, and oral temperature. The safety population included 2415 subjects aged 18 to 55 years (3:1 randomization; HEPLISAV-B: n=1810; ENGERIX-B: n=605).

Overall, more subjects receiving HEPLISAV-B reported local pain (dose 1: 38.5% vs. 33.6%, dose 2: 34.8% vs. 24.7%), redness (dose 1: 4.1% vs. 0.5%, dose 2: 2.9% vs. 1%), and swelling (dose 1: 2.3% vs. 0.7%, dose 2: 1.5% vs. 0.5%) after the first or second dose than subjects receiving ENGERIX-B. The majority of events were reported as mild in intensity. The incidence and severity of systemic solicited AEs (fever $\geq 38^{\circ}\text{C}$, fatigue, headache, and malaise) were similar between treatment groups.

Overall, unsolicited AEs occurred with similar incidence among subjects in each treatment group. A larger proportion of subjects in the ENGERIX-B arm experienced a severe unsolicited AE (14.4%) compared to the HEPLISAV-B arm (10.6%).

SAEs. Overall, the incidence of SAEs was similar between treatment groups (1.5% in the HEPLISAV-B group and 2.1% in the ENGERIX-B group) and did not raise safety concerns.

Autoimmune AEs. Potentially immune-mediated adverse events that occurred within 7 months of the first dose of vaccine were reported in 0.2% (n = 4) of HEPLISAV-B recipients and 0.7% (n = 4) of ENGERIX-B recipients. The following events were reported in the HEPLISAV-B group in one subject each: granulomatosis with polyangiitis [GPA] (formerly Wegener's granulomatosis), lichen planus, Guillain-Barré syndrome, and Grave's disease. The following events were reported in the ENGERIX-B group in one subject each: Bell's palsy, Raynaud's phenomenon, and Grave's disease. One additional ENGERIX-B recipient with a history of mixed connective tissue disease had p-ANCA-positive vasculitis.

In addition, an event of rheumatoid arthritis and an event of systemic lupus erythematosus in two subjects in the HEPLISAV-B group were reported as exacerbations of pre-existing disease.

Autoimmune laboratory assessments. Antinuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid (dsDNA) were assessed in subjects at baseline and Week 28. No clinically significant differences were identified between treatment groups.

Study Safety Conclusions

- No clear safety signals arose from the review of the safety data submitted for Study DV2-HBV-10.
- Similar rates of AEs were observed in both study groups.

The reviewer noted the following: One case of c-ANCA-positive GPA (Wegener's granulomatosis) occurred in a HEPLISAV-B recipient and one case of p-ANCA positive vasculitis occurred in an ENGERIX-B recipient who had pre-existing autoimmune disease. On its own, the development of granulomatosis with polyangiitis in temporal association with the receipt of HEPLISAV-B is notable. The two cases of vasculitis in this study may not be comparable given that the subject in the ENGERIX-B arm had a history of autoimmune disease (see review memorandum prepared by Dr. Lorie Smith).

DV2-HBV-16

The primary safety objective of this study was to compare safety and tolerability of vaccination with HEPLISAV-B when administered to subjects 40 to 70 years of age with the safety and tolerability of ENGERIX-B.

Safety monitoring for Study DV2-HBV-16 was conducted in a similar manner as in Study DV2-HBV-10, with the exception that an algorithm was prospectively designed to capture potentially autoimmune AEs and SAE's and AESI's were monitored for 52 weeks. The safety population included 2449 subjects (4:1 randomization; HEPLISAV-B: n=1968; ENGERIX-B: n=481).

Overall, the proportions of subjects experiencing any AE were similar among treatment groups. AEs rated as grade 3 or higher occurred with a slightly lower incidence in the HEPLISAV-B consistency lots (4.5%) than in the ENGERIX-B arm (5.8%).

The majority of unsolicited AEs were deemed unrelated to the study vaccine by the investigator. More AEs led to discontinuation of treatment in the HEPLISAV-B lots (consistency lots total: 0.9%) than in the ENGERIX-B arm (0.4%).

SAEs. Two deaths were reported in study DV2-HBV-16, one in a HEPLISAV-B recipient and one in an ENGERIX-B recipient both of which were assessed as not related to study treatment. Non-fatal SAEs occurred with similar frequency in the HEPLISAV-B group (3.9%) and the ENGERIX-B group (4.8%).

Autoimmune AEs. A list of autoimmune and potentially immune-mediated conditions was pre-specified and events considered to be possibly autoimmune were reviewed and evaluated by a Safety Evaluation and Adjudication Committee (SEAC). The SEAC adjudicated 3 events as new-onset autoimmune AEs, all occurring in the HEPLISAV-B group: hypothyroidism (n=2), vitiligo (n=1).

Review of the initial BLA submission in 2012 identified one additional subject with a potentially immune-mediated AE that was not initially referred to the SEAC for adjudication. The subject was diagnosed with cavernous sinus syndrome, which was considered by treating physicians to possibly be Tolosa-Hunt syndrome (THS). Additional information was requested in the February 2013 CR letter and was submitted to the FDA in March 2013.

Four expert consultations were obtained by FDA to determine the diagnosis and to aid in the evaluation of the relationship of the THS case to the vaccine. Of the three consultants that commented, two did not believe that there was evidence of overlap between THS and GPA, which was identified in DV2-HBV-10. One consultant noted that there can be overlap, but that the case of THS reported in DV2-HBV-16 did not display features the consultant would expect if it were GPA. Of the three consultants that commented, none endorsed a causal association between the vaccine and the AE.

Autoimmune laboratory assessments. ANA and anti-dsDNA were assessed in subjects at baseline and Week 56 or at the time of early discontinuation. No clinically significant differences were identified between treatment groups.

Study Safety Conclusions

- The overall rates of solicited and unsolicited AEs, SAEs and AEs of special interest (immune mediated) were similar among the treatment arms.

The clinical reviewer noted that while the incidence of autoimmune events was low, all autoimmune AEs occurred in HEPLISAV-B recipients.

Five cases of pulmonary embolus were reported among HEPLISAV-B recipients and none were reported among ENGERIX-B recipients. Four of these cases occurred in individuals with some degree of underlying predisposition to thrombosis. Given the other clinical factors potentially contributing to the occurrence of these thrombotic and embolic events, the reviewer noted that it is difficult to discern the clinical significance of the numerical imbalance in the incidence of these events observed in this study (see review memorandum prepared by Dr. Lorie Smith).

DV2-HBV-23

The primary safety objective of this study was to evaluate the overall safety of HEPLISAV-B with respect to clinically significant AEs. The primary safety endpoints were proportion of subjects

with the following: new-onset medically-attended AEs (MAEs), SAEs or deaths, AEs of special interest (AESIs), and autoimmune AEs (AIAEs) not pre-specified as AESIs. Secondary safety endpoints were to describe the frequency of the following: new-onset GPA or THS, new-onset thrombotic events, new-onset abnormal thrombotic screens in the laboratory sub-study, and new-onset abnormal renal blood or urine tests in the laboratory sub-study.

The safety population included 8368 subjects (2:1 randomization; HEPLISAV-B: n=5587; ENGERIX-B: n=2781).

MAEs. The rate of MAEs reported from vaccination through the Week 56 study visit was approximately 46% in both study groups. The following MAEs occurred in at least 0.5% of either one of the treatment groups and at a rate of at least twice the other treatment group: Herpes zoster (38 HEPLISAV-B subjects, 0.7%; 9 ENGERIX-B subjects, 0.3%), Tooth infection (17 HEPLISAV-B subjects, 0.3%; 17 ENGERIX-B subjects, 0.6%), and Exostosis (6 HEPLISAV-B subjects, 0.1%; 14 ENGERIX-B subjects, 0.5%). Events of venous thromboembolism, including pulmonary embolus and deep vein thrombosis occurred with similar frequency between treatment groups (0.21% HEPLISAV-B, 0.25% ENGERIX-B).

Deaths. There were 32 deaths in study DV2-HBV-23, 25 in the HEPLISAV-B group (0.4%) and 7 in the ENGERIX-B group (0.3%). These were classified as follows:

Cardiac: 8 HEPLISAV-B, 3 ENGERIX-B
General: 2 HEPLISAV-B, 0 ENGERIX-B
Hepatobiliary: 1 HEPLISAV-B, 0 ENGERIX-B
Infectious: 1 HEPLISAV-B, 0 ENGERIX-B
Injury and Poisoning: 8 HEPLISAV-B, 3 ENGERIX-B
Neoplasm: 2 HEPLISAV-B, 1 ENGERIX-B
Nervous System: 1 HEPLISAV-B, 0 ENGERIX-B
Respiratory: 2 HEPLISAV-B, 0 ENGERIX-B

Nine deaths in the HEPLISAV-B group and 3 deaths in the ENGERIX-B group (under Injury and Poisoning and Nervous System) were determined by the Applicant and the clinical reviewer to be due to illicit drug overdose or injury based upon the narratives provided. Excluding these deaths, 16 subjects in the HEPLISAV-B group (0.29%) and 4 subjects in the ENGERIX-B group (0.14%) experienced a fatal AE.

Within 1 month of vaccination, there was 1 non-injury, non-poisoning death in the HEPLISAV-B group, due to acute coronary syndrome, and 2 in the ENGERIX-B group, due to MI and hypertensive heart disease. There were 5 non-injury, non-poisoning deaths within 90 days in the HEPLISAV-B group and 3 in the ENGERIX-B group.

SAEs. Overall, SAEs were reported in 345 HEPLISAV-B subjects (6.2%) and 148 ENGERIX-B subjects (5.3%). The relative risk (RR) point estimate was 1.16 (95% CI: 0.96,1.40; 90% CI: 0.99,1.36). Overall, the most common organ systems represented by SAEs were infections and infestations (HEPLISAV-B 1.3%, ENGERIX-B 1.2%), cardiac disorders (HEPLISAV-B 0.9%, ENGERIX-B 0.5%), gastrointestinal disorders (HEPLISAV-B 0.7%, ENGERIX-B 0.5%), nervous system disorders (HEPLISAV-B 0.7%, ENGERIX-B 0.6%), respiratory, thoracic, and mediastinal disorders (HEPLISAV-B 0.6%, ENGERIX-B 0.4%), and neoplasms (HEPLISAV-B 0.6%, ENGERIX-B 0.5%).

As noted above, rates of cardiac SAEs were more frequent in the HEPLISAV-B group compared to the ENGERIX-B group (HEPLISAV-B 0.9%, ENGERIX-B 0.5%). The RR point estimate and CIs based on the asymptotic method were 1.73 (95% CI: 0.98, 3.04; 90% CI: 1.07, 2.78). This difference in frequency of cardiac SAEs was most notable in the preferred term of AMI, which was reported in 14 subjects in the HEPLISAV-B group (0.25%) and 1 subject in the ENGERIX-B group (0.04%). This gave rise to a RR of 6.97 (95% Koopmans score CI 1.17, 41.44). When

additional SAEs that may represent myocardial infarctions mapped to different preferred terms were considered, based upon the standard Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for myocardial infarction (MI) (includes the preferred terms acute myocardial infarction, myocardial infarction, coronary artery occlusion, acute coronary syndrome, and angina unstable), 19 HEPLISAV-B subjects (0.3%) and 3 ENGERIX-B subjects (0.1%) reported an SAE of MI (these events included the 15 reports of AMI). The RR of MI, based on the SMQ was 3.15 (95% Koopman score CI 1.00, 9.98). All subjects reporting events identified as MI had at least one risk factor for cardiovascular disease and/or prior known cardiovascular disease.

The clinical and statistical reviewers concluded that both methods and analyses showed excess risk of MI in the HEPLISAV-B arm compared to ENGERIX-B. Rates of non-serious MAEs in the organ system of cardiac disorders were similar between treatment groups (HEPLISAV-B 1.22%, ENGERIX-B 1.19%).

Timing of MI in the 22 subjects relative to vaccination is outlined below:

- Within 1 week of the last active vaccination, 1 subject in the HEPLISAV-B group and none in the ENGERIX-B group reported an MI.
- From 1 week to 1 month, 2 subjects in the HEPLISAV-B group and 1 in the ENGERIX-B group reported an MI.
- From 1 month to 3 months, 6 subjects in the HEPLISAV-B group and none in the ENGERIX-B group reported an MI.
- The remaining MI events (10 in the HEPLISAV-B group and 2 in the ENGERIX-B group) were reported more than 3 months after the last active injection.

FDA obtained three cardiology consults to aid in the evaluation of the differences in cardiovascular events between treatment groups. All consultants determined that the tools used to analyze the imbalance in cardiac events were appropriate. However, they also commented on the difficulty of analyzing the data thoroughly as MI events were not prospectively studied and as a result, some events may have been missed. All consultants opined that additional monitoring or studies were needed. One consultant indicated that, for multiple reasons, this was not likely to be a reliable safety signal and that the risk should be monitored through a passive surveillance system post-marketing. The other two consultants could not exclude the hypothesis that there is increased cardiovascular risk associated with HEPLISAV-B. They indicated that further investigations were warranted.

AESIs. These were pre-specified by a list of conditions FDA considers potentially immune-mediated. AEs that were potentially AESIs were referred to a specialist and to the SEAC for review and adjudication. The SEAC adjudicated cases as autoimmune or not autoimmune, and if autoimmune, adjudicated whether the event was new in onset and the relationship to vaccination.

Sixty-one subjects reported at least 1 potential AESI that was referred to the SEAC for adjudication. Thirty-nine HEPLISAV-B subjects (0.7%) reported 41 potential AESIs and 22 ENGERIX-B (0.8%) subjects reported 24 potential AESIs.

The SEAC determined new-onset autoimmune adverse events were reported in 0.1% (n=4) of HEPLISAV-B recipients [1 each of: alopecia areata, polymyalgia rheumatica, ulcerative colitis, and autoimmune thyroiditis (with concurrent diagnosis of papillary thyroid carcinoma)]. None of these events was considered to be related to vaccination by the SEAC. No new-onset autoimmune adverse events were reported in the ENGERIX-B group.

Five events of VIIth nerve paralysis (Bell's palsy) in the HEPLISAV-B group and one in the ENGERIX-B group were not assessed as autoimmune events by the SEAC, but were new in onset and were counted as immune-mediated.

Five additional events in 4 subjects who received HEPLISAV-B were adjudicated as new-onset events, but the diagnosis was not confirmed by the SEAC, and thus, they are not included in the counts of AESIs (rheumatoid arthritis, Takayasu's arteritis, Vith nerve palsy, and Sjogren's syndrome and Raynaud's phenomenon in the same subject).

FDA obtained two expert consultations regarding the subject who reported Takayasu's arteritis. Both consultants agreed the event was likely Takayasu's arteritis, but that it was a chronic, pre-existing condition.

In summary, 9 new-onset immune-mediated conditions in the HEPLISAV-B group (Bell's palsy in 5 subjects, alopecia areata, hypothyroidism, polymyalgia rheumatica, and ulcerative colitis) and 1 new-onset immune-mediated condition in the ENGERIX-B group (Bell's palsy) were identified.

In an assessment by the clinical reviewer, there were 18 new-onset AESIs in 17 subjects in the HEPLISAV-B group and 5 new-onset AESI in 5 subjects in the ENGERIX-B group. Of these events, 16 events in 16 subjects in the HEPLISAV -B group and 5 events in 5 subjects the ENGERIX -B group did not have an alternative plausible cause. The reviewer noted one subject with a history of recurrent bilateral ankle cellulitis prior to vaccination who received HEPLISAV-B and reported a rash 69 days following the second vaccination, which was diagnosed as granulomatous dermatitis by biopsy of the forearms. The subject's dermatopathologist recommended evaluation for sarcoidosis; a systemic granulomatous disease; this evaluation was not performed. The SEAC adjudicated this event as not autoimmune, also noting the possibility of symptoms occurring prior to vaccination and the limited response to steroids.

Study Safety Conclusions

- The rate of all MAEs and SAEs reported in the 56-week study period were similar between the HEPLISAV-B and ENGERIX-B groups.
- Imbalances unfavorable to HEPLISAV-B in the frequency of deaths, MI, and herpes zoster were observed.
- After excluding deaths that were due to overdose or injury, 0.29% of HEPLISAV-B and 0.14% of ENGERIX-B recipients experienced fatal SAEs.
- Nineteen HEPLISAV-B subjects (0.3%) and 3 ENGERIX-B subjects (0.1%) reported events in the standard MedDRA query (SMQ) narrow for MI. These included 14 events of AMI in HEPLISAV-B subjects (0.25%) and 1 event of AMI in ENGERIX-B subjects (0.04%).
- All subjects who reported SAEs of MI had cardiovascular risk factors such as cardiac ischemia, type 2 diabetes, hypertension, hyperlipidemia, smoking within the last year, obesity (BMI \geq 30).
- Proportionally more subjects in the HEPLISAV-B group reported events of MI within 3 months after the last active injection.
- The relative risk for cardiovascular events (based upon the MedDRA query for MI including the preferred terms acute myocardial infarction, myocardial infarction, coronary artery occlusion, acute coronary syndrome, and angina unstable) in the HEPLISAV-B group was calculated as approximately 3 times that of the ENGERIX-B group.
- Venous thromboembolic AEs occurred with similar frequency between the two treatment groups.
- Nine subjects in the HEPLISAV-B group and 1 subject in the ENGERIX-B group reported new onset immune-mediated conditions.

The clinical reviewer noted that given the randomization ratio and the low background rate of autoimmune events, the clinical significance of the difference in the frequency of potentially immune-mediated AEs within this study is not clear (see review memorandum prepared by Dr. Darcie Everett).

8. ADVISORY COMMITTEE MEETINGS

Due to the presence of a novel adjuvant in the vaccine a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held on November 15, 2012 to discuss efficacy and safety data. At the time of the November 2012 VRBPAC, the BLA submission included two phase 3, randomized, active-controlled, immunogenicity and safety studies (DV2-HBV-10 and -16; 3778 HEPLISAV-B recipients, 1086 recipients of the licensed hepatitis B vaccine ENGERIX-B, manufactured by GSK), and seven supportive trials, three of which included immunogenicity assessments. VRBPAC members voted 13:1 that the immunogenicity data submitted in the BLA were adequate to support the effectiveness of HEPLISAV-B for the prevention of hepatitis B virus infection in adults 18-70 years of age. The Committee voted 8:5, with one abstention, that the available data were not adequate to support the safety of HEPLISAV-B in the same age group. Committee members noted that there were insufficient numbers of subjects studied to detect relatively infrequently occurring adverse events, especially considering the novel adjuvant contained in HEPLISAV-B (10).

A second VRBPAC meeting was held on July 28, 2017 to discuss the safety of HEPLISAV-B, with attention given to the imbalance in AMI in DV2-HBV-23. The VRBPAC members voted 12: 1 with 3 abstentions that the available data support the safety of HEPLISAV-B when administered to adults 18 years and older. Further discussions from the committee focused on the requirements of the proposed pharmacovigilance plan (PVP) to further evaluate the safety of HEPLISAV-B post-licensure. The VRBPAC members identified a number of deficiencies and limitations in the PVP proposed by Dynavax including the need to assess potential acute myocardial events in recipients of HEPLISAV-B in a timely manner, address selection bias in recruitment of subjects and the development of an event driven analysis (11).

9. OTHER RELEVANT REGULATORY ISSUES

At the completion of the review of the BLA, there were differences of opinion regarding licensure of HEPLISAV-B. The Division of Vaccines and Related Product Applications (DVRPA) clinical reviewers did not recommend approval of the HEPLISAV-B citing concerns with imbalances in autoimmune and cardiac events observed in the clinical trials (see Risk/Benefit Assessment in Section 11b). The DVRPA Division Director did not concur with the clinical reviewer recommendation not to approve, but instead recommended approval only for individuals 18 to 39 years of age in order to mitigate the potential risk of AMI. Approval in older age individuals would be based on additional prospective safety trial(s) to evaluate cardiovascular outcomes associated with HEPLISAV-B (see DVRPA Division Director memorandum).

Following the VRBPAC meeting held on July 28, 2017, Dynavax submitted a PVP that included a study to assess AMI in recipients of HEPLISAV-B compared to another hepatitis B vaccine. Initially, this PVP was not found to be adequate to address the concerns of the VRBPAC and Dynavax was asked to revise the plan and provide substantial additional information. Several study limitations were identified by the Office of Biostatistics (OBE)/Division of Epidemiology (DE) reviewer, including potential for selection bias, potential differential outcome misclassification, timeliness in gathering data based on recruitment capability, and lack of representation of individuals with risk factors for cardiovascular disease other than diabetes, particularly those of an older age. The final PVP submitted by the applicant was considered

inadequate by the DE reviewer to address the AMI safety signal (see review memorandum prepared by Dr. Silvia Perez-Vilar). The DE Director did not agree with this assessment. Although limitations of the study were noted it was determined that the proposed study design was consistent with post-market safety studies typically approved by the FDA, and more importantly, FDA is required to use the least burdensome approach to obtaining clinical information. The critical issue under consideration was not whether superior study designs exist, but rather whether the proposed study is sufficient to address the safety issue. Therefore, the DE Director found that the PVP study designs agreed to by the FDA and the Applicant were acceptable (see Addendum to review memorandum prepared by Dr. Silvia Perez-Vilar).

OVR and OBE management and members of the CBER Safety Working Group reviewed the safety concern and the proposed PVP. They expressed the opinion that the study limitations could be reasonably mitigated through the planned interim analyses, which would provide an early indication of an increased incidence of AMI in HEPLISAV-B recipients. In addition, CBER will perform its own safety surveillance in collaboration with the Centers for Disease Control and Prevention after product approval. With these factors in mind and given the clinical benefit of HEPLISAV-B in certain populations, OVR management determined that the clinical benefit outweighed any risk from administration of the vaccine. Please refer to the supervisory memorandum prepared by Drs. Marion Gruber, Steven Anderson and Philip Krause for an explanation regarding OVR management's decision to license HEPLISAV-B in adults 18 years of age and older.

10. LABELING

The proposed proprietary name, HEPLISAV-B, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on March 20, 2013, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on April 10, 2013.

Dynavax submitted revised versions of the package insert (PI) as well as carton and container labels as a result of comments provided by CBER. Appropriate sections of the revised PI and carton/container labels were reviewed for accuracy and recommendations were provided by the clinical, statistical, product, pharmacovigilance, and Advertising and Promotional Labeling Branch (APLB) reviewers. The APLB found the prescribing information and carton/container labels to be acceptable from a promotional and comprehension perspective. All issues with the PI were acceptably resolved after exchange of information and discussions with the applicant. Issues identified with the carton and container labeling were acceptably resolved.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The clinical reviewers did not recommend approval of HEPLISAV-B (see Risk/Benefit Assessment in Section 11b).

There were no issues identified in other disciplines (CMC, toxicology, BIMO, facilities) that would preclude licensure. HEPLISAV-B has the potential to provide a clinical benefit due to the immunogenic properties of the vaccine. Based on the immunogenicity data submitted in this BLA, HEPLISAV-B induces a rapid and robust immune response in all populations tested. This vaccine has the potential to address an unmet medical need in hypo-responders to currently licensed vaccines, or in those seeking or needing rapid protection. The main safety concern is associated with the higher frequency of AMI events in people receiving HEPLISAV-B in the third Phase 3 clinical trial (DV2-HBV-23) compared to those receiving ENGERIX-B. This

imbalance was not seen in the other two clinical trials (DV2-HBV-10 and -16) where fewer at-risk subjects were enrolled. Despite this imbalance the VRBPAC voted 12 to 1 with 3 abstentions on July 28, 2017, that the available data support the safety of HEPLISAV-B when administered to adults 18 years and older. There was extensive VRBPAC discussion regarding the imbalance in AMI events in DV2-HBV-23. A number of committee members expressed the view that the observed imbalance was a spurious finding and the discussions focused on the need for a thorough post-marketing pharmacovigilance plan to assess whether there is a real association between AMI and administration of HEPLISAV-B. During the VRBPAC meeting of July 28, 2017 there was strong support for this hepatitis B vaccine that consists of 2 doses 1 month apart. It was noted that such a vaccine could provide faster protection for many at-risk groups and provide protection in individuals that either do not respond to the current 3 dose vaccines or choose not to receive the 3 dose vaccines due to the 6-month immunization schedule. During review of the BLA, three consult reviews were obtained from cardiologists regarding the cardiac events observed in DV2-HBV-23. Although all the consultants expressed some level of concern for the observed imbalance, none found a clear association between HEPLISAV-B treatment and the cardiac events, one consultant indicated that, for multiple reasons, this was not likely to be a reliable safety signal. Taking into consideration all of these factors the Chair of the review committee concurs with OVR's decision to license HEPLISAV-B. This decision also takes into account the fact that the post-marketing pharmacovigilance plan proposed by Dynavax to assess the risk of AMI was found to be adequate by OVR, OBE and the CBER Safety Working Group.

b) Risk/ Benefit Assessment

The clinical team expressed the opinion that with a decline in the incidence of acute hepatitis B in the U.S. as a result of universal childhood vaccination and the existence of two licensed 3-dose hepatitis B vaccines in the U.S., a vaccine that improves immunogenicity in certain populations (e.g., hypo-responders) or that utilizes a shorter immunization schedule must be assessed in the context of the safety risk. The clinical reviewers maintained that potential increased risk for serious cardiovascular events and for autoimmune disease outweighs the potential benefit in any segment of the population receiving HEPLISAV-B. DVRPA management advocated for a restricted age indication (e.g. 18 to 39 years of age) to mitigate the risk with the recommendation that Dynavax perform additional studies in individuals 40 years of age and older to assess cardiovascular events. The clinical reviewer concluded that based on subgroup analysis of age, sex, race, and diabetic status, no specific group has been identified to not have an increased risk of MI with HEPLISAV-B compared to ENGERIX-B. This may reflect the multi-factorial nature of cardiovascular risk. Consequently, the reviewer did not recognize any populations to which this vaccine could attempt to be limited. Based on the available information, and the risks of immune-mediated disorders, particularly granulomatous diseases, and cardiovascular disease, in the judgement of the clinical reviewer, the overall risk benefit of HEPLISAV-B is not favorable to support licensure for the proposed indication and use. The clinical reviewer does not accept there are any feasible methods of mitigating risk, or that further evaluation of these risks should be done. The DVRPA Division Director concurred with the clinical reviewer against approval for 18 years and above, instead recommending approval for the age group 18-39, a population in which risk of AMI is low.

OVR management determined that the imbalance in AMI is likely spurious and unrelated to vaccination with HEPLISAV-B. In view of the demonstrated effectiveness of HEPLISAV-B discussed in this document and the potential of the vaccine to fulfill an unmet need it was concluded that the benefit of this vaccine outweighed any risk. Dynavax is required to conduct a post-marketing study to address the question of the incidence of AMI in HEPLISAV-B recipients. This includes interim analyses which will rapidly indicate if there is an imbalance in incidence for this event in this group of vaccinees.

c) Recommendation for Postmarketing Activities

As discussed above Dynavax is required to conduct a post-marketing study under Section 505(o) of the Food, Drug, and Cosmetic Act (FDCA). These post-marketing activities which Dynavax has agreed to and are to be included in the approval letter are shown below:

AGREED UPON POSTMARKETING REQUIREMENT

POSTMARKETING STUDIES SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR § 601.70

1. Post-marketing study to evaluate the occurrence of acute myocardial infarction in adults 18 years of age and older who receive HEPLISAV-B compared with another hepatitis B vaccine. The study will use a non-randomized clustered design and will evaluate approximately 25,000 patients who receive HEPLISAV-B and approximately 25,000 patients who receive another hepatitis B vaccine. Two interim and one final comparison between vaccine groups of unconfirmed acute myocardial infarctions will be conducted and reviewed.

Final Protocol Submission:	December 31, 2017
First Interim Analysis Report Submission:	August 31, 2019.
Second Interim Analysis Report Submission:	February 29, 2020.
Study Completion Date:	May 31, 2020
Final Analysis of Unconfirmed Events Report Submission:	September 30, 2020.
Final Report Submission:	June 30, 2021.

AGREED UPON POSTMARKETING COMMITMENTS

2. Post-marketing observational study of the safety of HEPLISAV-B in adults 18 years of age and older to evaluate the incidence of new-onset immune-mediated diseases, Herpes Zoster, and anaphylaxis.

Final Protocol Submission:	May 31, 2018
Study/Clinical Trial Completion:	August 31, 2020
Final Report Submission:	February 28, 2022

3. To establish a pregnancy registry for providing information on outcomes following pregnancy exposure to HEPLISAV-B. Data in this registry will be used to assess risks relevant to pregnancy, including pregnancy outcomes of pre-term births, major congenital malformations, spontaneous abortions, and still births. The registry will collect information on 250-300 pregnant women as soon as possible after conception.

Final Protocol Submission:	February 9, 2018
Study/Clinical Trial Completion:	August 9, 2023
Final Report Submission:	December 31, 2023

12. REFERENCES

1. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, & Ott JJ (2015) Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 386(10003):1546-1555.
2. Hyams KC (1995) Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis* 20(4):992-1000.
3. Mast EE, *et al.* (2006) A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep* 55(RR-16):1-33; quiz CE31-34.
4. WHO (2017) World Health Organization: Hepatitis B Factsheet. Available at: <http://www.who.int/mediacentre/factsheets/fs204/en> Accessed November 9, 2017.
5. CDC (1991) Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep* 40(RR-13):1-25.
6. CDC (2015) Centers for Disease Control and Prevention. Viral Hepatitis - Statistics & Surveillance. <https://www.cdc.gov/hepatitis/statistics/2015surveillance/index.htm> Accessed November 9, 2017.
7. Shirota H, Tross D, & Klinman DM (2015) CpG Oligonucleotides as Cancer Vaccine Adjuvants. *Vaccines (Basel)* 3(2):390-407.
8. Szmunes W, Stevens CE, Zang EA, Harley EJ, & Kellner A (1981) A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): a final report. *Hepatology* 1(5):377-385.
9. Wainwright RB, Bulkow LR, Parkinson AJ, Zanis C, & McMahon BJ (1997) Protection provided by hepatitis B vaccine in a Yupik Eskimo population--results of a 10-year study. *J Infect Dis* 175(3):674-677.
10. VRBPAC (November 15, 2012) Vaccines and Related Biological Products Advisory Committee Meeting <https://wayback.archive-it.org/7993/20170111231301/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM333684.pdf> Accessed November 9, 2017.
11. VRBPAC (July 28, 2017) Vaccines and Related Biological Products Advisory Committee Meeting <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM582024.pdf> Accessed November 9, 2017.