

## **OVRR and OBE Office Directors' MEMORANDUM**

**Date:** November 9, 2017

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**To:** Biologics License Application (BLA) **125428**  
Hepatitis B Vaccine (Recombinant), Adjuvanted (HEPLISAV-B)

**Subject:** Approval of Hepatitis B Vaccine (Recombinant), Adjuvanted (HEPLISAV-B)

### **Summary**

The Director and Deputy Director of OVRR and the Director of OBE (hereafter referred to as OVRR and OBE) have determined that HEPLISAV-B should be approved for prevention of infection caused by all known subtypes of hepatitis B virus in adults age 18 years of age and older based on the effectiveness and safety data derived from pre-licensure clinical trials with HEPLISAV-B. This memo explains the scientific rationale for this determination.

### **Product**

HEPLISAV-B manufactured by Dynavax Technologies Corporation consists of recombinant hepatitis B surface antigen (HBsAg), produced in yeast cells (*Hansenula polymorpha*) combined with a cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate adjuvant (1018). It is administered as a 2-dose schedule, intramuscularly at 0 and 1 month.

### **Clinical studies**

To support licensure of HEPLISAV-B in adults 18 years of age and older Dynavax submitted data from three pivotal, randomized, active controlled, multicenter trials (HBV-10, HBV-16 and HBV-23) that evaluated the immunogenicity and safety of HEPLISAV-B administered at 0 and 1 months compared to that of Engerix-B administered at 0, 1 and 6 months. The primary immunogenicity objective for HBV-10 (2,415 adults 18-55 years of age; HEPLISAV-B: n = 1,810, Engerix-B: n = 605) and HBV-16 (2,449 adults 40-70 years of age; HEPLISAV-B: n = 1,968, Engerix-B: n = 481) was to demonstrate the noninferiority of the seroprotection rate (SPR) of HEPLISAV-B compared to Engerix-B at pre-specified time intervals since the last active dose. The SPR is the proportion of subjects with an anti-HBsAg level  $\geq 10$  mIU/mL, a serum antibody level recognized as conferring protection against hepatitis B virus infection (established from analyses of results from clinical efficacy trials (Szmunes, *et al*, 1981; Francis *et al*, 1882)). The applicant conducted study HBV-23 (8,368 adults 18 - 70 years of age; HEPLISAV-B: n = 5,587, ENGERIX-B:

n = 2,781) to further describe the safety profile of HEPLISAV-B and to demonstrate non-inferiority of the SPR induced by HEPLISAV-B compared with the SPR induced by ENGERIX-B in subjects with type 2 diabetes mellitus. Enrollment was stratified by age group (18 - 39, 40 - 70 years), and type 2 diabetes mellitus status (defined as having a clinical diagnosis of type 2 diabetes and taking at least an oral or non-insulin injectable hypoglycemic agent and/or insulin). Among study HBV-23 participants 14% reported type 2 diabetes mellitus at baseline. In study HBV-10 and study HBV-16 2% and 8% respectively had diabetes.

### **Effectiveness of HEPLISAV-B:**

In studies HBV-10 and HBV-16 the primary immunogenicity objective, i.e., to demonstrate non-inferiority of the SPR induced by HEPLISAV-B compared to ENGERIX-B, was met (clinical review memorandum, sections 6.1.11, Table 4/6.2.11, Table 8; statistical review memorandum, sections 6.1.11, Table 4/6.2.11, Table 9).

In study HBV-23, among subjects with type 2 diabetes; 90% of 640 HEPLISAV-B recipients and 65.1% of 321 ENGERIX-B recipients had seroprotective levels to HBsAg and non-inferiority was demonstrated (clinical review memorandum, section 6.3.11, Table 18, statistical review memorandum section 6.3.11, Table 17).

An age-stratified analysis from study HBV-23 demonstrated that in all age strata assessed, >90% of HEPLISAV-B recipients had a post-vaccination seroprotective level of antibody to HBsAg. In the oldest age group analyzed, adults 60-70 years of age, SPRs were 91.6% among 1,157 HEPLISAV-B recipients compared with 72.6% among 588 Engerix-B recipients (clinical review memorandum, section 6.3.11, Table 20; statistical review memorandum section 6.3.11.2, Table 19). These results are consistent with subpopulation analysis conducted in study HBV-16, demonstrating that the SPR in the HEPLISAV-B vaccinated group was higher than in the Engerix-B vaccinated group for each age stratum (40 - 49 years, 50 - 59 years and 60 - 70 years) (clinical review memorandum, section 6.2.11.3; statistical review memorandum section 6.2.11.3, Table 14).

Furthermore, in the following pre-specified secondary analyses the SPR following HEPLISAV-B was statistically significantly higher than following Engerix-B (lower bound of 95% confidence interval of the difference HEPLISAV-B minus Engerix-B greater than 0%): adults 40 through 70 years of age in study HBV-16 (statistical review memorandum, section 6.2.11.1, Table 9); subjects 18 through 70 years of age who reported type 2 diabetes at baseline in study HBV-23 (statistical review memorandum, section 6.3.11.1, Tables 17 and 18); all subjects 18 through 70 years of age in study HBV-23; and subjects from study HBV-23 in the following age groups: 18 through 29 years, 30 through 39 years, 40 through 49 years, 50 through 59 years and 60 through 70 years (statistical review memorandum, section 6.3.11.1, Table 19).

### **Safety of HEPLISAV-B**

At the time of the original BLA submission the safety database included data from 5,845 subjects (HEPLISAV-B: n=4,425; ENGERIX-B: n=1,420) 18 - 70 years of age enrolled in nine clinical trials. Safety data from pivotal studies HBV-10 and HBV-16 demonstrated that the overall rates of solicited and

unsolicited adverse events (AEs) as well as serious adverse events (SAEs) were similar between the treatment arms. In HBV-10 there was one case of c-ANCA-positive GPA (granulomatosis with polyangiitis formerly “Wegener’s granulomatosis”) in a HEPLISAV-B recipient and one case of p-ANCA positive vasculitis in an ENGERIX-B recipient with a history of mixed connective tissue disease. In study HBV-16, there was one case of Tolosa-Hunt syndrome (THS) following HEPLISAV-B administration (clinical review memorandum, section 1 “Executive summary”). Three consultants (one from FDA/CDER and two external to FDA) did not endorse a causal association between the vaccine and this adverse event. Furthermore, these consultants assessed the events of GPA and THS as pathologically distinct.

In 2012, VRBPAC members voted 8:5, with one abstention, that the available data were not adequate to support the safety of HEPLISAV-B. VRBPAC members expressed concern that the size of the safety database was inadequate especially when considering the novel adjuvant contained in HEPLISAV-B (VRBPAC transcripts, 2012). The applicant conducted an additional pre-licensure study, HBV-23. Subjects in study HBV-23 had more chronic medical conditions than subjects in studies HBV-10 and HBV-16. In HBV-23, the overall rates of all medically attended events (MAEs) and SAEs reported were similar between the HEPLISAV-B and ENGERIX-B groups (clinical review memorandum, section 6.3.12.2). Among subjects with type 2 diabetes studied in HBV-23, 1.6% of HEPLISAV-B recipients and 0.8% of ENGERIX-B recipients reported a serious adverse event in the first 28 days post dose 1 or 2. There was no imbalance in any single event between vaccine groups and events occurred in a variety of organ systems and pathogenetic mechanisms (clinical review memorandum, section 6.3.12).

In study HBV-23, imbalances were noted in reports of deaths, myocardial infarctions (MI), and herpes zoster. In the HEPLISAV-B group, 14 subjects (0.25%) reported a treatment emergent acute MI (AMI) compared to 1 subject in the ENGERIX-B group (0.04 %) (clinical review memorandum, section 6.3.12, Table 33). An additional analysis of SAEs possibly representing MI but that may have utilized different preferred terms was conducted using the standard Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for MI. This analysis identified a total of 19 HEPLISAV-B subjects (0.3%) and 3 ENGERIX-B subjects (0.1%) with events included in the SMQ for MI (these events include the 15 reports of AMI). Of note, all subjects reporting an event included in the SMQ for MI reported at least one cardiovascular risk factor at baseline. However, cardiovascular risk factors appeared to be similar between trial arms at baseline. Notably, a discrete risk window for the occurrence of MI following immunization with HEPLISAV-B was not identified. At the request of the FDA, the applicant performed additional analyses to assess the imbalance in AMI. FDA obtained three cardiology consultations (one from FDA/CDER and two external to FDA) for input in evaluating whether these analyses were appropriate and for their assessment of the risk of MI following HEPLISAV-B. All consultants determined that the analyses to assess the imbalance in MI events were generally appropriate. None of the consultants identified a plausible mechanism for the imbalance. Although they commented that the finding could be spurious, all consultants thought that additional monitoring or studies were warranted to further assess the potential risk of MI with the use of HEPLISAV-B. The CDER consultant specifically concluded that based upon the low likelihood that the imbalance represented a true increase in risk, it would be appropriate to monitor the risk in the post-marketing setting.

In study HBV-23, imbalances were noted between study groups in deaths and the medically attended event of herpes zoster. After excluding deaths that were attributable to illicit drug overdose or injury, the imbalance noted was 0.29% in HEPISAV-B recipients and 0.14% in Engerix-B recipients (clinical review memorandum, section 6.3.12.3). Of note, no deaths were assessed as having a known relationship to study vaccine by the investigators or the reviewers. There was a modest imbalance in

reported cases of herpes zoster which occurred without a consistent temporal association with vaccination (HEPLISAV-B: 0.7%, Engerix-B: 0.3%) (clinical review memorandum, section 6.3.12.2, Table 25).

### **Relevant preclinical and clinical studies as well as literature related to MI and inflammation**

CpG motifs have been shown to directly activate plasmacytoid dendritic cells and human B cells through TLR9. The OVRD/DVRPA Division director postulates a possible role for TLR-9 activation contributing to AMI through an effect on systemic inflammation. Scientific literature related to biological plausibility of inflammation as the basis for a causal relationship between CpG adjuvants and AMI is equivocal. Some peer reviewed publications suggest that TLR-9 and CpGs attenuate rather than promote inflammatory cardiac events in animal models (Kim SC, 2014; Cao Z, 2013; Mathur S, 2011). Thus, the statement that there is biological plausibility that TLR9 activation may contribute to AMI is speculative.

Of note, Dynavax has conducted a series of preclinical and clinical studies with the CpG 1018 adjuvant including pharmacokinetic studies evaluating its plasma distribution in rats and cynomolgus monkeys, single-dose toxicity studies in rabbits and baboons using CpG 1018 alone, repeat-dose toxicity studies in mice, rats and cynomolgus monkeys using CpG 1018 alone as well as a repeat-dose toxicity study in mice and a reproductive toxicity study in rats using CpG 1018 plus HBsAg (refer to review memoranda by: Major, 2012; Wrzesinski, 2013; Kunder, 2013). Results from these preclinical studies indicate that more than 95% of the CpG 1018 adjuvant is cleared from the blood within 24 hours post inoculation following subcutaneous administration and that there is no evidence of induction of a systemic, chronic inflammatory response and/or adverse cardiac effects by either HEPLISAV-B or the CpG 1018 adjuvant.

In addition, as part of clinical study HBV-22 interferon regulated gene expression was assessed in subjects receiving HEPLISAV-B. Data showed the expression of interferon-regulated genes peaking at 1 day after injection and returning to pre-injection levels by day 7, indicating that the response induced by CpG 1018 is transient (refer to Dynavax VRBPAC briefing document, 2017). If the CpG 1018 adjuvant induced extensive systemic inflammatory responses, one would have expected increased systemic reactogenicity in subjects vaccinated with HEPLISAV-B. However, in clinical studies HBV-10 and HBV-16, the frequency of systemic post-injection reactions within 7 days of vaccination was similar in subjects who received HEPLISAV-B and ENGERIX-B (see HEPLISAV-B package insert, tables 1 and 2) suggesting that it is unlikely that there is an induction of an enhanced systemic inflammatory response by HEPLISAV-B.

### **Vaccine and Related Biological Products Advisory Committee meetings of 2012 and 2017**

The Vaccines and Related Biological Products Advisory committee (VRBPAC) convened November 15, 2012, to discuss the safety and effectiveness data for HEPLISAV-B available at that time, i.e., data from studies HBV-10 and HBV-16 (3,778 HEPLISAV-B recipients, 1,086 recipients of licensed hepatitis B vaccine, Engerix B) and seven supportive trials. VRBPAC members voted 13:1 that the immunogenicity data were adequate to support the effectiveness of HEPLISAV-B. As mentioned in the above section on safety of HEPLISAV-B VRBPAC 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. VRBPAC members expressed concern that the size of the safety database was inadequate especially when considering the novel adjuvant contained in HEPLISAV-B. A second VRBPAC meeting was held July 28, 2017, to discuss whether data that now included safety data derived from study HBV-23 would support the safety of HEPLISAV-B for use in persons  $\geq 18$  years (VRBPAC transcripts, 2017). The committee's deliberations focused primarily on the cardiac findings. Several committee members commented that the imbalance in MI was likely a spurious finding. Some committee members opined that although the imbalance was an issue of concern that it should not preclude licensure. Because of the concerns expressed regarding the observed imbalance in MI VRBPAC members strongly recommended that the applicant conduct a post-market pharmacovigilance study to specifically address the potential risk of MI. The committee voted 12:1, with 3 abstentions, that the safety data support use of HEPLISAV-B in persons  $\geq 18$  years.

While the 2017 VRBPAC meeting on HEPLISAV-B focused on safety, the Committee also considered data presented by the applicant on the effectiveness of HEPLISAV-B, including data not previously presented to the VRBPAC in 2012, i.e., the new immunogenicity analysis from Study HBV-23 showing non-inferiority in SPR among adults with type 2 diabetes mellitus. Because of the potentially improved compliance with completing the two-dose series, as well as the shorter time to seroprotection compared to currently licensed hepatitis B vaccines, and its ability to induce seroprotective levels of HBsAg antibodies in groups that tend to respond relatively poorly to currently approved hepatitis B vaccines (e.g., persons with diabetes mellitus and older adults) several committee members noted that HEPLISAV-B fills an unmet medical need.

#### **OVRR's and OBE's assessment of effectiveness of HEPLISAV-B**

The immunogenicity data submitted to the BLA demonstrate the effectiveness of HEPLISAV-B. Data derived from studies HBV-10 and HBV-16 demonstrate that HEPLISAV-B induces a rapid and robust immune response when administered as a 2-dose schedule as determined by the proportion of subjects with an anti-hepatitis B antibody concentration  $\geq 10$  mIU/ml. Notably, the immune response induced by HEPLISAV-B after the second dose was non-inferior to the immune response induced after the administration of the third dose of the licensed comparator vaccine, Engerix B. In addition, in studies HBV-16 and HBV-23, it was demonstrated that the SPR in subjects in the HEPLISAV-B group were statistically significantly higher than in the Engerix-B group in the overall study populations and in study HBV-23 in all age strata analyzed. Furthermore, in study HBV-23 in subjects with type 2 diabetes mellitus, the difference between SPRs (HEPLISAV-B minus Engerix-B) met the prospectively defined criterion for the primary endpoint of non-inferiority. In this population, HEPLISAV-B also induced a statistically significant higher SPR. Older adults and persons with diabetes mellitus tend to respond relatively poorly to currently licensed hepatitis B vaccines. Therefore, HEPLISAV-B has the potential to fill an unmet medical need through increased compliance with completing the vaccination series (i.e., 2 doses versus 3 doses), a shorter time to seroprotection, and by protecting adult subpopulations that have a less robust immune response to currently licensed vaccines.

HEPLISAV-B will be approved for use in the general adult population 18 years of age and older, which includes diabetics. The effectiveness data in diabetics is important for the HEPLISAV-B prescribing information considering their relatively poor immune response to currently approved hepatitis B vaccines. HEPLISAV-B has not been evaluated in persons older than 70 years of age. However, based on the age stratified immunogenicity analyses and the magnitude of the difference in SPRs between

HEPLISAV-B and ENGERIX-B which increased with increasing age (see above and the clinical review memorandum, section 6.3.11.3, table 20) it is expected that the demonstrated benefit of HEPLISAV-B relative to ENGERIX-B would persist in persons older than 70 years of age.

## **OVRR's and OBE's assessment of safety of HEPLISAV--B**

### **Auto-immune events**

Three inflammatory vascular conditions were identified following vaccination with HEPLISAV-B: GPA in study HBV-10 and THS in study HBV-16, and granulomatous dermatitis in study HBV-23. The clinical reviewers state that because these are very rare disorders, the likelihood of them occurring by chance in a safety database of <10,000 HEPLISAV-B recipients is very low (clinical review memorandum, section 1 "Executive summary"). Of note, three expert consultants did not endorse a definitive causal association between HEPLISAV-B and THS and furthermore, these consultants assessed the events of GPA and THS as pathologically distinct. The granulomatous dermatitis is discussed below.

In study HBV-16 and HBV-23 any potential immune-mediated adverse events were referred to a blinded Safety Evaluation and Adjudication Committee's (SEAC) for assessment of whether they were autoimmune and relationship to vaccination. In study HBV-16 the SEAC adjudicated 3 events as new onset autoimmune events (hypothyroidism: n = 2; vitiligo: n = 1) and concluded that none of these events were related to receipt of HEPLISAV-B. In study HBV-23 the SEAC adjudicated 4 events as new onset autoimmune events (alopecia areata, polymyalgia rheumatic, ulcerative colitis and autoimmune thyroiditis (with concurrent diagnosis of papillary carcinoma)), and concluded that none of these events were related to receipt of HEPLISAV-B and that one event was due to an alternative cause. The SEAC did not consider the granulomatous dermatitis noted above as autoimmune. This case as well as 5 cases of Bell's Palsy considered non-autoimmune by the SEAC were considered autoimmune by the clinical reviewers (clinical review memorandum, section 1 "Executive summary"). OVRR and OBE conclude that there were no safety signals from the prospective evaluation of auto-immune adverse events and that these do not impact the overall safety conclusion for HEPLISAV-B. Of note, the applicant has committed to conduct an observational post-market surveillance study to assess new onset immune-mediated diseases following HEPLISAV-B.

### **Imbalance in MI**

OVRR and OBE determined that the imbalance in MI merits further evaluation in the post-market phase. In addition, as also recommended by VRBPAC in 2017, reports of AMI are described in Section 6 "ADVERSE REACTIONS" of the package insert for HEPLISAV-B. However, based on the overall number of adverse events examined in Study HBV-23 (> 1000), the imbalance in AMI could have occurred by chance. OVRR and OBE agree with members of the VRBPAC who expressed the view that the finding is likely spurious and not reflective of a causal relationship with HEPLISAV-B, and who voted 12-1 with 3 abstentions that safety of HEPLISAV-B had been demonstrated.

OVRR's and OBE's assessment of the imbalance in AMI in Study HBV-23 also takes into account the following scientific and clinical considerations:

- lack of a consistent temporal association between AMI and vaccination, with 57% of cases occurring 6 months or more after a dose of HEPLISAV-B;
- presence of underlying risk factors for cardiovascular disease in all persons with reported AMI (including cases in persons with advanced co-morbidities and multiple risk factors);
- presence of advanced multi-vessel obstructive coronary artery disease in most cases, based on blinded review of cardiac catheterization reports performed by an outside cardiologist appointed by the applicant;
- lack of evidence for inflammatory or immune-mediated etiology, based on the blinded review of clinical annotations and cardiac catheterization reports by an outside cardiologist appointed by the applicant;
- the likelihood of spurious findings in studies of this size with many safety outcomes evaluated and the increased likelihood of spurious findings particular for serious adverse events when the study population has significant pre-existing health conditions, as was the case in HBV-23;
- lack of a consistent finding across clinical studies;
- lack of evidence for inflammation in the systemic reactogenicity data collected in the one week post-vaccination period in studies HBV-10 and HBV-16;
- available data on CpG oligonucleotides are generally not supportive of the biological plausibility of a causal relationship with the adjuvant contained in HEPLISAV-B; and
- lack of evidence of cardiac toxicity in preclinical toxicology studies.

The analyses of confidence intervals, the Bayesian statistical analysis, and the calculation of “number needed to harm” presented by the statistical reviewers and cited by the OVRP/DVRPA Division Director are based on the assumption that the AMI/MI finding is *not* due to chance. Of note, these statistical analyses were also presented in open session to the VRBPAC in 2017, which included an expert in statistics, and thus, were considered in the VRBPAC vote that supported the safety of HEPLISAV-B. Although the statistical reviewer’s summary conclusion is that the “...data do not support safety...,” this conclusion is outweighed when evaluated with the totality of the scientific and clinical considerations listed above. Furthermore, it should be recognized that the statistical reviewer’s recommendation that vaccine trial safety outcomes be evaluated based on the upper bound of the 95% confidence interval does not reflect current or past CBER thinking about how non-prespecified clinical trial outcomes should appropriately be evaluated.

Recommendations in the 2008 FDA Guidance: “Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” cited by the OVRP/DVRPA Division Director are focused specifically on new antidiabetic therapies to treat type 2 diabetes, because of specific concerns about cardiovascular risks associated with drugs in that class. These recommendations do not apply to drugs or vaccines in other classes, whether or not they are intended for use in diabetics.

OVRP and OBE conclude that the scientific and clinical considerations listed above together with the possibility that the imbalance in AMI reports could have arisen solely by chance, provide assurance that HEPLISAV-B does not cause acute myocardial infarction.

### **Imbalance in cases of herpes zoster**

The modest imbalance in zoster cases among HEPLISAV-B recipients and controls is not germane to an assessment of AMI/MI risk. While some previous studies reported an increased risk of MI in individuals who experience zoster, in one such study the reported increased risk was only immediately after a clinically significant case of zoster (Minassian *et al*, 2015), and in another the reported increased risk became apparent only years after the zoster episode (Breuer *et al*, 2014). It is as yet unclear if either of these findings is correct (and it is possible that neither finding will be borne out on further investigation), but it is difficult to reconcile either report with the observed timing of zoster and MI cases in study HBV-23 after HEPLISAV-B immunization, with only one subject reporting both acute zoster and subsequent acute MI. Of note, Dynavax has agreed to a post-market study to evaluate the incidence of Herpes Zoster.

### **Proposed postmarket studies and OVRr's and OBE's view of same**

OVRr and OBE have determined that a post-market study is required to assess the signal of a serious risk of AMI observed in Study HBV-23. FDA's authority to require a post-market study for HEPLISAV-B is derived from Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, which authorizes FDA to require certain post-market studies (post-market requirement or PMR) and clinical trials for any or all of three specified purposes, including to assess signals of serious risk related to the use of a drug. The applicant's proposed post-market safety study evaluates potential AMI risk and is generally consistent with other post-market studies required by FDA based on factors such as study design, sample size, involvement of multiple study sites, timeliness and others. As proposed, the study is a pseudo-cluster design and will enroll 25,000 HEPLISAV-B recipients and 25,000 recipients of another hepatitis B vaccine in 15 clinical centers at Kaiser Permanente Southern California (KPSC). FDA will begin receiving monthly numbers for vaccine accrual and unconfirmed AMI events in a timely manner, starting three months after initiation of the study, as well as receiving the results of three interim analyses. At its conclusion, the study will have approximately 87% statistical power to exclude an upper bound of a hazard ratio of >2.0. The pharmacovigilance review memo makes note in several places of a requested cardiology consult (that has not occurred yet), which is intended to provide additional information on possible cardiac outcomes that may be considered for the post-market studies. However, OVRr and OBE agree with the OBE/DE Division director that considerations of other potential endpoints are not critical to the PMR study.

The applicant has committed to conduct an additional observational post-market surveillance study (post market commitment or PMC) which will include assessment of the incidence of new onset immune-mediated diseases, herpes zoster, and anaphylaxis. The proposed study will provide important vaccine-specific safety information on these conditions and is consistent with other FDA post-market safety studies in its timeliness.

In summary, OVRr and OBE have determined that the sponsor's proposed PMR study for potential AMI risk and the proposed PMC study are adequate to evaluate the identified potential risks.



**OVRR's and OBE's summary conclusions on risk benefit of HEPLISAV-B**

Based on the totality of the data and taking into consideration the VRBPAC discussions and votes in 2012 and 2017, the assessments of the consultants appointed by OVRR to evaluate the cardiac and auto-immune findings and the assessments of the SEAC appointed by the applicant, OVRR and OBE conclude that the benefits of HEPLISAV-B outweigh any risks and that the effectiveness and safety data are adequate for approval in adults 18 years of age and older. Furthermore, given the 2-dose schedule and favorable seroresponse rate in populations which do not respond well to currently available hepatitis B vaccines HEPLISAV-B has the potential to address an unmet medical need.

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