Memorandum

Date   November 9, 2017

From   Wellington Sun, M.D.
Director, Division of Vaccines and Related Products Applications (DVRPA)

Subject   BLA STN 125428 Division Director Memorandum

To   Marian Major, Ph.D.
Chair, BLA 125428 Review Committee

Thru   Marion F. Gruber, Ph.D.
Director, Office of Vaccine Research and Review (OVRR)

Background

WHO estimates that about 257 million people are infected by hepatitis B (hepB) with annual death of 887,000 in 2015(1) while in the U.S. the estimated prevalence of chronic hepB is 850,000 to 2.2 million. Since 1980 the annual incidence of hepB in the U.S. had peaked in 1985 at over 25,000 cases and has since decreased to 2,953 cases in 2014(2) with the introduction of universal infant vaccination recommendation in 1991. Acute hepB infection progresses to chronic infection in approximately 5% of healthy adults, but is greater among those with co-morbidities such as diabetes and immunocompromised. The current FDA licensed hepB vaccines include RECOMBIVAX HB (licensed 1983), ENGERIX-B (licensed 1989) and TWINRIX (licensed 2001). These and similar vaccines have an excellent record of safety and effectiveness with over 1 billion doses of hepB vaccine used worldwide, with chronic hepB infected reduced from 8-15% to less than 1% among immunized children(1). Based on the currently available hepB vaccines the CDC developed a comprehensive immunization strategy to eliminate transmission of hepB in the U.S. in 2005-6(3). The adult strategy includes vaccinating at-risk adults, including those with potential sexual , occupational exposures, IV drug abuse, end-stage renal disease, HIV, chronic liver disease, travelers to high endemicity areas, household contacts of high risk individuals and all persons seeking protection from hepB infection(3). In 2011, prompted by several outbreaks of hepB due to assisted blood glucose monitors in long-term care facilities and the increased risk (odds 2.1 95% CI 1.6-2.8) of hepB in adults 23-59

years old the ACIP made the additional recommendation for routine hepB vaccination of unvaccinated adults 19-59 years of age with diabetes mellitus and a permissive recommendation for diabetics ≥ 60 years of age (4).

Regulatory History

Dynavax, the Applicant, submitted Biologics License Application (BLA) STN 125428/0 to the Food and Drug Administration (FDA) on 26 April 2012 intended to support licensure of a recombinant hepB virus vaccine adjuvanted with a novel cytosine phosphoguanine (CPG) enriched oligodeoxynucleotide phosphorothioate immunostimulatory sequence (IS 1018) with the proposed trade name HEPLISAV-B. Each 0.5mL dose of HEPLISAV-B contains 20 mcg rHBsAg and 3000 mcg 1018 ISS adjuvant. The dosing regimen is two 0.5 mL doses administered 4 weeks apart. The licensed comparator used throughout the HEPLISAV-B development program was ENGERIX-B, a hepB vaccine manufactured by GlaxoSmithKline Biologicals in 1-mL dose also containing 20 mcg dose of rHBsAg adsorbed on 0.5 mg aluminum hydroxide as adjuvant. The Applicant seeks the indication is for active immunization against all subtypes of hepB virus infection in adults ≥18 years of age.

HEPLISAV-B was developed under IND first submitted in 2005. Details of the regulatory history of this BLA are well-described in the Clinical Review by Drs. Lorie Smith and Alexandra Worobec dated February 26, 2013(5) and the current Clinical Review by Drs. Darcie Everett and Alexandra Worobec (6). Of note the Applicant originally proposed the indication in healthy adults 18-70 years old (original BLA 2012) and for the current CR response (2016) the indication has been amended to active immunization against hepB in adults 18 and older.

Two Vaccines and Related Biologic Products Advisory Committee (VRBPAC) meetings were held on HEPLISAV-B:

November 15, 2012 – Convened to discuss the original HEPLISAV-B BLA. Committee voted 13:1 that the data in the BLA adequately demonstrated the effectiveness of HEPLISAV-B. Committee voted 8:5, with one abstention, that the safety data available on this vaccine with a new adjuvant was inadequate to recommend approval. The Committee also noted that the studies did not evaluate the vaccine in a racially heterogeneous population of subjects who were most likely to benefit from this vaccine and that concomitant administration studies were not done (7).

July 28, 2017 - Convened to discuss the results of DV2-HBV-23. The committee voted 12 yes, 1 no, with 3 abstentions that the available data was adequate to support the safety of HEPLISAV-B when administered to adults 18 years and older. Committee members commented that the differences in frequency of MI between treatment groups was probably due to chance, but strongly emphasized the need for a well-designed post-marketing prospective study that can provide early detection of an AMI signal to evaluate the cardiovascular risk associated with

HEPLISAV-B in a population that should include subjects at risk for cardiovascular disease. Other specific recommendations of the design of such a safety study were also discussed. The Committee was not asked to comment on the overall risk benefit assessment of HEPLISAV-B (7).

BLA Review findings and Discussion

The original BLA contained two phase 3 studies; DV2-HBV-10 (Study 10) and DV2-HBV-16 (Study 16) conducted in hepB-naïve otherwise healthy non-pregnant subjects age 11-55 and 40-70 years old respectively. The pre-specified non-inferiority primary immunogenicity endpoint comparing HEPLISAV-B to ENGERIX-B for both studies were met thereby demonstrating effectiveness of HEPLISAV-B (5). The safety database for the original BLA consisted of 4,425 subjects ≥18 years old exposed to HEPLISAV-B (5, Table 51, p123). While there were no clear safety signals observed, given the novel adjuvant and the 2 cases of rare vasculitides among the HEPLISAV-B arms, one in each of the two phase 3 trials, as well as some numeric imbalances of AE's such as pulmonary embolism (5, Table 52, pg 128), the VRBPAC voted 3 yes, 8 no and 1 abstention that the pre-licensure safety data was sufficient to support approval. The VRBPAC also recommended inclusion of more diverse demographics, e.g. Asians, and questioned whether risk/benefit is more favorable for HEPLISAV-B in a more restricted population. CBER concurred and a Complete Response (CR) letter was issued on February 22, 2013 which informed the Applicant the safety database of 4,425 subjects exposed was insufficient for approval of the proposed indication in 18-70 year olds. CBER also offered discussion of more restricted use of the vaccine for which risk/benefit may be more favorable.

In response to the February 2013 CR the Applicant elected to conduct Study DV2-HBV-23 (Study 23), a phase 3 observer-blinded, randomized active-controlled (ENGERIX-B) safety and immunogenicity clinical trial in adults 18-70 year olds. The data and results from Study 23 were submitted to CBER as the Applicant's response to the February 2013 CR letter.

The primary safety endpoints of Study 23 were descriptive: proportions of new-onset medically attended events (MAE's), serious adverse events (SAE's) including deaths, adverse events of special interest (AESI) which were pre-specified potentially autoimmune or inflammatory disorders and autoimmune adverse events (AIAE's) which were not a defined AESI's but were adverse events considered by the independent study adjudication committee to be autoimmune. Study 23 and 16 were the only trial in the BLA in which AESI and AIAE were prospectively monitored to one year after vaccination and adjudicated by an independent committee while blinded to vaccine assignment. Secondary safety endpoints monitored included new onset granulomatous polyangiitis (GPA), Tolossa-Hunt syndrome (THS), thrombotic events, and abnormal thrombotic and renal laboratory studies (in a subset). All safety endpoints were followed to Week 56, one year after the last vaccination.

The safety population of Study 23 consisted of 5,587 and 2781 adult subjects in the HEPLISAV-B and ENGERIX-B arms respectively (6, Section 6.3.10.1.1) from only sites in the U.S.. The two arms of Study 23 were found to be balanced at baseline with regards to age, sex, race, and cardiovascular disease risk factors such as T2D, hypertension, dyslipidemia, smoking and obesity (6, Section 6.3.10.1.1 and 6.3.10.1.2) which suggested adequate randomization. By design subjects baseline characteristics in Study 23 differed substantially from the previous Studies 10 and 16 with regard to age over 60, 1421(25.4%) vs 403(12.4%), percentage of blacks and African-Americans, 26% vs 9%, diabetics (762)13.6% vs (199)6.1%, hypertensives 36.1% vs 23.8% respectively. Unlike Study 10 and 16 in which healthy subjects were selected the Applicant's intent in Study 23 was to evaluate the vaccine in a subject population that reflects the general U.S. population in this age group of 18-70 (6, Section 6.3.3).

As one of the primary safety endpoints the overall rates of MAE's were found to be similar between the 2 arms (46.0% vs 46.2%) but imbalances in several Medical Dictionary for Regulatory Activity (MedDRA) Preferred Terms (PT's) with higher rates (at least two-fold) in the HEPLISAV-B arm were observed (6, Section 6.3.12.2). Of these PT's with imbalances, not all of which were clinically significant, most were small and the imbalances were likely due to chance or were not borne out when analyzed by similar terms. Two stood out due to their persistence as HEPLISAV-B safety signals by additional analysis by both the Applicant and CBER: acute myocardial infarction (AMI) and herpes zoster (HZ) (6, Section 6.3.12.2).

There were 32 deaths during the trial; 25 (0.45%) in the HEPLISAV-B arm and 7(0.25%) in the ENGERIX-B arm. None of the deaths were considered related to vaccination by the principal investigators. Death due to cardiovascular causes occurred in subjects 47-70 years of age and the overall rates were 0.14% vs 0.11% in the HEPLISAV-B and ENGERIX-B arms respectively. Among causes other than Injuries and Poisoning there were no safety signals from any particular cause (6, Section 6.3.12.3). The rate of non-fatal SAE's in the HEPLISAV-B arm was slightly higher, 325(5.8%) vs 142(5.1%). Of all new onset SAE Preferred Terms with imbalance seen with HEPLISAV-B the magnitude of the imbalance seen with AMI, 14(0.25%) to 1(0.04%) was of particular concern and resulted in requests by CBER of the Applicant for further detailed analysis. The CBER clinical and statistical reviewers also conducted their own analysis of this safety signal. Because the use of the term major adverse cardiovascular event (MACE) analysis is variably defined in the literature it will not be used here. Because the evaluation of risk of cardiovascular outcomes was not prospectively specified for Study 23 it should be acknowledged at the outset that all these analyses of cardiovascular events are *post-hoc* and are subject to the limitations of *post-hoc* analyses.

The major findings of the investigation into the AMI safety signal during this CR response review are summarized here. Due to the finding of 14:1 imbalance in AMI between the HEPLISAV-B and ENGERIX-B arms of Study 23 CBER requested the Applicant to conduct

further analysis. The Applicant conducted a standard MedDRA query (SMQ) narrow for myocardial infarction (MI) to evaluate all events which were likely to represent AMI or acute cardiac ischemic disease, but may have been reported with a different PT. It showed that there were 19 (0.34%) vs 3(0.11%) cases of new onset acute cardiac ischemic events, including AMI, MI, acute coronary syndrome, coronary artery occlusion and unstable angina, in the HEPLISAV-B and ENGERIX-B arms respectively (6, Section 6.3.12.4) with the SMQ imbalance driven primarily by the AMI signal with a relative risk (RR) = 3.15 (95% Wald CI 0.93, 10.64; 95% Kopman score CI 1.00, 9.98). The Applicant also obtained external consultation to evaluate not only AMI but related cardiovascular outcomes such as cardiovascular deaths, MI's and stroke. All subjects with AMI had at least one known risk factor for cardiovascular disease, most had multiple risk factors; these risk factors included hypertension, hyperlipidemia, diabetes mellitus, smoking, obesity, and history of known ischemic heart disease. All but 1 of the 19 HEPLISAV-B subjects with MI, coronary occlusion, acute coronary syndrome or unstable angina was older than 40 years of age. An event-free analysis of Study 23 by CBER using Kaplan-Meier (K-M) plot showed that the AMI event-free probability diverge between study day 50-100, after the second dose of vaccine (6, Figure 1, Section 6.3.12.4) and continue through the period of follow-up to Week 56. The K-M curve is consistent with prolonged increased risk associated with delay onset after the second dose. The Applicant's corresponding analysis' K-M plot used all major cardiovascular outcomes defined as death from cardiovascular events, MI and stroke from all 3 phase 3 studies and found a HR of 1.66 (95% CI 0.76, 3.61), though including the Study 10 and 16 subjects in the denominator in this case diluted the signal (8, slide CO-106, Applicant July 28, 2017 VRBPAC presentation).   This analysis presented at the July 28, 2017 VRBPAC raised concern by the Committee's cardiologist that between Study day 0 and 100, the period when no difference in rate of major cardiovascular outcomes, a total of 192(2.1%) and 67(1.7%)of HEPLISAV-B and ENGERIX-B safety population subjects dropped out and even a small number of AMI among those lost to follow-up during the 100 days post-vaccination may have significant impact on the measured risk. The lack of accounting for drop-outs due to AMI's within this critical period post-vaccination increases the uncertainty surrounding the true magnitude of the AMI safety signal.

CBER statisticians conducted their own analysis of the relative risk of AMI based on the observation from Study 23 using a Bayesian approach alternatively with or without borrowing from the prior AMI data from Studies 10 and 16. With "full borrowing" (using Study 10 and 16 data as prior) the probability of the RR of AMI being ≥ 1.0 and 2.0 were 94.7% and 65.5% respectively. With no borrowing (using Study 23 data only) the probability of the RR of AMI being ≥ 1.0 and 2.0 were 98.6% and 85.5% respectively (9, Slide 10 and 11). Because the subject populations from Studies 10 and 16 were younger and healthier and the Study 23 subjects were closer to the real-world U.S. population as the Applicant intended, it is likely that the full borrowing approach would under-estimate the RR of AMI and the no-borrowing estimate would

be more accurate for the target population ≥ 18 years old. CBER Statistical reviewers stated the uncertainties surrounding the AMI safety signal from Study 23 do not support approval and recommended further pre-licensure study. Whenever an experimental intervention is associated with increased risk compared to control one should consider the consequences at the intended population level. In the case of HEPLISAV-B and AMI, based on the absolute increase observed in Study 23, the Number Needed to Harm (NNH), calculated as the reciprocal of the absolute increase in risk of AMI, would yields 466 (95% CI 275-1520). This indicates that if the AMI signal were true, for every 466 recipients of HEPLISAV-B over ENGERIX-B there would be one additional case of AMI.

Review of available clinical narratives on the cases of AMI revealed presence of known risk factors in all cases and no uniquely characteristic angiographic findings, therefore the pathogenesis for these AMI's is likely that seen in the population with AMI's. The baseline risk factors, presentation and underlying coronary artery disease of the AMI cases suggest that if the association with HEPLISAV-B is causal it is not by itself sufficient and occurs only in the setting of pre-existing risk factors. This has implications for any risk benefit analysis and potential risk mitigation strategies.

While there is no clearly established causal mechanism between the CPG adjuvant and AMI there is biological plausibility that TLR9 activation may contribute to AMI through its effects on systemic inflammation, a potential mechanism for AMI (10). For example, repeated injection of TLR9 agonist is known to induce a macrophage activation syndrome (11) and TLR9 activation induces foam cells that promote atherosclerosis (12). CPG has been shown to enhance TLR9(+) human tumor cell invasiveness mediated by matrix metalloproteinase 13 (MMP-13) activity causing breakdown of collagen (13). The destabilization of the fibrous cap of the atherosclerotic plaque by MMP-13 is one proposed mechanism of AMI (14). It is thought that MMP's may be involved in atherosclerotic plaque erosion or rupture resulting in thrombus formation leading to AMI (13). TLR9 in not only activated by foreign DNA; activation can occur by endogenous mitochondrial DNA and such activation has been found to mediate autoimmunity in the heart (15). Our incomplete understanding of the mechanism of action of CPG as vaccine adjuvant, the natural TLR9-mediated processes of the immune system, as well as the pathophysiologic mechanism of AMI should be cause for caution in discounting any connection between CPG and AMI given our current knowledge.

The observed imbalance of herpes zoster with 38(0.68%) and 9(0.32%) cases (RR = 2.102, 95% CI 1.02, 4.03) in the HEPLISAV-B and ENGERIX-B arms was also unexpected (6, Section 6.3.12.2). According to the Applicant the incidence of herpes zoster in Study 23 was 4.8 (8/1655) and 1.2 (1/814) per 1,000 person year in the 25-44 yo age group, and 7.8 (25/3221) and 3.1 (5/1636) per 1,000 person years in the 45-64 yo age group for HEPLISAV-B and ENGERIX-B respectively. CBER Division of Epidemiology reviewer found that of zoster cases in the

HEPLISAV-B and ENGERIX-B group, 13 (34.2%) and 1 (11.1%), respectively, occurred in of individuals aged ≤49 years (16). Not only was the incidence of zoster 2 fold higher in the HEPLISAV-B arm than the ENGERIX-B arm, the relatively higher risk of zoster in the younger age group is unusual especially since the incidence of zoster in the ENGERIX-B arm is consistent with the expected incidence by age in the subject population(17), The occurrence of zoster has been described as sequalae from certain vaccines, but not hepB. Post-vaccination zoster has been postulated to be due to vaccine-induced immunomodulation (18, 19). The mechanism or protection against zoster reactivation is thought to be mediated by T-cells and NK cells and involve interferon gamma (20, 21). An epidemiologic link has also been found between the occurrence of zoster and AMI (22) though only one of the zoster cases developed AMI in Study 23. The co-occurrence of the AMI and zoster signals in the same trial may be due to chance but also raises the question whether they may be due to related yet poorly understood immunomodulating effects from HEPLISAV-B.

There were no clear safety signals from the prospective evaluations of AESI and AIAE's. CBER clinical reviewer disagreed with some of the Applicant's adjudications of AESI on whether some of the diagnoses should be considered autoimmune but many of the diagnoses were usually in the setting of insufficient clinical information and varying clinical judgment. The Applicant identified nine new-onset immune-mediated conditions in the HEPLISAV-B group (Bell's palsy in five subjects, alopecia areata, hypothyroidism, polymyalgia rheumatica, and ulcerative colitis) and one new-onset immune-mediated condition in the ENGERIX-B group (Bell's palsy)., while the CBER reviewer counted 18 new-onset AESIs in 17 subjects in the HEPLISAV-B group – Bell's palsy in five subjects, hypothyroidism in two subjects, ulcerative colitis in two subjects, VIth cranial nerve paralysis in two subjects (one was actually insufficiently evaluated for MS), and alopecia areata, polymyalgia rheumatica, IIIrd cranial nerve paralysis, Raynaud's phenomenon, Graves' disease, systemic lupus erythematosus, and granulomatous dermatitis in one subject each – and 5 new-onset AESI in 5 subjects in the ENGERIX-B group (hypothyroidism in two subjects, and Bell's palsy, lichen planus, and lichenoid drug eruption in one subject each).These disagreements on whether the AE's were autoimmune or that they were new onset did not impact the overall safety conclusion that there was no new potential safety signal from any particular diagnosis of autoimmune disorder from Study 23.

Of the Study 23 secondary safety endpoints for further investigation of the potential signals from Studies 10 and 16, there were no new cases of the two rare vasculitides of GPA and THS observed in Study 10 and 16 respectively. Their background incidences are estimated to be 1/100,000 and 0.1/100,000 respectively (6, Section 6.3.9). Thus, with the safety sample size of 5,587 one can conclude with 95% confidence that the true incidence would be no higher than 1/1862 or 54/100,000. There is clearly a role for post-licensure pharmacovigilance to continue to

monitor this risk with wider use of the vaccine. There were no safety signals with regards to the other secondary endpoints of venous thrombotic or renal adverse events.

The benefit of HEPLISAV-B is based on the demonstration that it elicited rates of protective levels of anti-HBsAg antibody (≥ 10 mIU/mL), the seroprotection rate (SPR), which was non-inferior to the SPR of the licensed hepB vaccine ENGERIX-B. The immunogenicity data from Study 16 showed the SPR's of HEPLISAV-B to be higher than ENGERIX-B after the first and second dose and higher at Week 52, after 2 doses of HEPLISAV-B and 3 doses of ENGERIX-B (5, Table 32, 34). Because the effectiveness of HEPLISAV-B had already been demonstrated by Studies 10 and 16 CBER did not require evaluation of immunogenicity in Study 23 and considered Study 23 as primarily a safety trial with the primary objective to evaluate the overall safety of HEPLISAV-B with respect to clinically significant adverse events. Nonetheless the Applicant added a primary immunogenicity objective to demonstrate its non-inferiority in subjects with type 2 diabetes mellitus (T2D). The SPR in diabetics given HEPLISAV-B was non-inferior to that in diabetics given ENGERIX-B. While the Applicant claimed the demonstration of effectiveness in T2D as a primary endpoint the diagnosis of diabetes was not an inclusion criteria, nor was non-T2D status an exclusion criteria. Thus, the Applicant, other than collecting the information on baseline diabetes status, did not enrich the Study 23 subject population for diabetics. This is borne out by the percentage of HEPLISAV-B subjects withT2D in Study 23 of 13.6% (6, Section 6.3.10.1.2) which is similar to the 11.5% seen in this age group in the general U.S. population (23). CBER notified the Applicant during discussion of the protocol that the data on diabetics as per the Applicant's design would not be sufficient to support a diabetic indication nor inclusion in the package insert and informed the Applicant that should it desire an indication in diabetic's further discussion with CBER on the appropriate study design would be necessary. This is also emphasized by CBER during the 2012 VRBPAC discussion (7)   The Applicant did not pursue further discussion on the study design necessary for a diabetic indication. Study 23 protocol also did not include any pre-specified safety analysis of the subpopulation of diabetics. Nonetheless, the Applicant did not change its stated primary immunogenicity objective in T2D subjects in the protocol. The Applicant did not include a safety endpoint for diabetics. The Applicant submitted results from DV2-HBV-02, a phase 2, observer-blinded, parallel-group study of 18-65 years old hypo-and non-responders to a licensed hepB vaccine who were randomly assigned to receive either a single dose of ENGERIX-B or HEPLISAV-B and then followed for 52 weeks after vaccination. Nineteen subjects received HEPLISAV-B and 16 ENGERIX-B. This was a descriptive study with no formal hypothesis testing. The results were indicative of a trend showing higher SPR with HEPLISAV-B than ENGERIX-B in these non and hypo-responders. Unfortunately, the results are difficult to interpret given the dropout rates were 47% and 63% in the HEPLISAV-B and ENGERIX-B arms respectively. -Study 23 included as pre-specified secondary endpoints the demonstration of non-inferiority of SPR's and then statistically higher SPR's in subpopulations based on age, sex, race,

BMI, and smoking status which were met in all subpopulations with the exception for Asians. The Applicant's criterion for delta in the analysis for statistically significant higher SPR was not agreed upon by CBER as adequate for demonstration of statistical superiority. In any case, statistical superiority in SPR should not be necessarily equated with superiority of the vaccine given the safety concerns.

HEPLISAV-B may potentially increase hepB vaccine coverage due to its 2-dose regimen compared to the 3-dose regimen of currently U.S. licensed hepB vaccines in the proposed target population of ≥ 18-year-old. Presumably this will be due to increased compliance rate as well as increased immunogenicity. The overall benefit of HEPLISAV-B based on this BLA would be only incrementally additive to the accumulated benefit of hepB vaccinations using currently licensed vaccines, which have already significantly lowered the incidence of hepB in the U.S.. These licensed vaccines have an extensive record of safety and effectiveness and have made significant impact on lowering hepatitis B disease rates in the U.S. (2).

Risk Benefit and Regulatory Options

The framework for making a decision on the HEPLISAV-B BLA is based on a structured risk benefit analysis that includes several key decision factors: the nature of the disease including its epidemiology, its benefits, risks and risk management.

Disease: Hepatitis-B disease burden in the U.S. has dramatically decreased in the last 3 decades due to introduction of the universal infant vaccination program in 1991 using the currently licensed vaccines. The total reported new cases of hepB in the U.S. declined from a peak of 25,000 in the mid-1980's to 3,300 in 2015, currently adults over age 25 accounted for 93% of those cases(8). On a population level the current hepB vaccines have been remarkably effective and there have been no significant safety issues. Most of the current adult cases have risk factors such as HIV, sex partners of hepatitis B carriers, men who have sex with men, hemodialysis, iv drug use and healthcare occupation, among others. About 5-10% of adults are hypo-responders to the 3-dose hepB series with male sex, age >40, high BMI, smoking and immunosuppression as predisposing factors.

Benefit: The benefit based on the SPR was demonstrated by the first two phase 3 studies. In Study 23 the Applicant has further characterized the vaccine's benefit by again demonstrating immunogenicity non-inferiority and then demonstrating the SPR was statistically significantly higher than ENGERIX-B in adults over 18 years of age. The 2-dose series may potentially improve coverage rate due to the one less clinic visit. The immunogenicity data also demonstrated statistically significantly higher SPR compared to ENGERIX-B by age, race, except Asians, and by subpopulations defined by BMI, smoking status and presence of T2D. Thus there is a need for a vaccine which is more immunogenic in these special populations and HEPLISAV-B's increased immunogenicity may address this need.

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Risks: The licensure decision on preventive vaccine applications has far reaching impact on public health due to the size of the intended population which can number in the millions. Even rare serious adverse events caused by the vaccine will result in harm to large number of individuals if the vaccine is administered to the population at large. Analysis of the risks must consider the nature of the risks, the relative certainty it is caused by the vaccine, the magnitude of the risk, and the severity of the consequences. The ascertainment of the risks is followed by considerations of available measures to minimize the risks (risk management). Finally analysis of the balance of risks and benefits by FDA then determines whether the product should be approved.

Based on a risk assessment by the Division of Vaccines and Related Products Applications clinical reviewers, The clinical Team Leader and Branch Chief do not favor approval for the proposed indication due to their conclusion that the potential benefit does not outweigh the risks(7, Section 11.3 and 11.4).

The following regulatory options are available for this BLA:

1. Approval of indication in individuals 18 years and older as proposed by the Applicant with labeling of the risk of AMI in the package insert and a pharmacovigilance plan that includes post-marketing requirement to further assess cardiovascular risks.

2. Complete Response and requirement for additional pre-licensure safety study, ideally a prospective, randomized controlled study to evaluate cardiac risks.

3. Approval for a population with low risk for AMI (e.ge. 18-39 years old) with labeling of the risk of AMI in the package inserts and a pharmacovigilance plan that includes post-marketing requirement to further assess cardiovascular risks.

4. Deny application approval per 21 CFR 601.4(b)

The following discussion of these options is my analysis of the risks and benefits, followed by my recommendation for the regulatory decision. Implicit in these options is that the risks can be managed through primarily the use of the package insert.

Option 1 would allow the vaccine to be marketed and used in all adults older than 18 including those with AMI risk factors. These risk factors for AMI in the population are, in rank order of adjusted odds ratios, current smoking 2.87, diabetes 2.37, hypertension 1.91, abdominal obesity 1.62(24). This regulatory option would allow for the vaccine to be approved for use in the adult population despite the presence of these risk factors because FDA considers the AMI imbalance to be unexpected and indicates only *a potential* serious risk and is likely due to chance, which is the Applicant's position. The role of the postmarketing study and not clinical trial in this instance is focused primarily to identify and *characterize* the unexpected serious risk but still a requirement under Section 505(o)(3) .

I have concerns with this option. The AMI imbalance should be considered at least a *signal* of serious risk. The annual incidence rate of hepB in adults in the U.S. is 0.8/100,000 (25). This suggests that one would need to vaccinate 125,000 adults to prevent a single case of hepB. If the AMI signal is not due to chance and based on the absolute increase in risk of AMI seen in Study 23 the NNH is indeed 466, this means that for every case of hepB prevented there will be 268 additional cases of AMI in this scenario!

Another concern with Option 1 is the Applicant's interest in an indication in diabetics; it was included as a primary endpoint in Study 23. Diabetes is a significant risk factor for AMI. It is estimated there are 30 million diabetics among those ≥ 18 years old in the U.S. in 2015 (23) and they are recommended to receive hepB vaccination based on current ACIP recommendations. Another FDA Center, the Center for Drug Evaluation and Research (CDER) has extensive experience with evaluating cardiovascular risk in diabetics and has a current Guidance on this topic (26). The Guidance was prompted by a published meta-analysis in which an anti-diabetic drug was unexpectedly found to have an odds ratio of myocardial infarction of 1.43(95% CI 1.03-1.98) (27). This Guidance for therapeutic drug is relevant to this preventive vaccine application because diabetics are recommended to receive hepB vaccination. The CDER Guidance uses the upper bound of the 2-sided 95% CI of the cardiovascular risk ratio between the investigational drug and control of 1.8 as a threshold for acceptable risk for anti-diabetic drugs. Whereas "if the data from all the studies that are part of the meta-analysis will not by itself be able to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8, then an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound *before* (emphasis mine) NDA/BLA submission."(26) The upper bound of the 95% CI of the relative risk of AMI in the subject population over 18 in this application exceeded the acceptable threshold for diabetics, who would be at higher risk at baseline. Furthermore, as pointed out above the Applicant did not pre-specify nor provide sufficient number of diabetics in Study 23 to adequately evaluate cardiovascular risk. There were only 762 and 381 diabetics in the HEPLISAV-B and ENGERIX-B arms respectively. Despite the Applicant's inclusion of an immunogenicity comparison in diabetics as a primary endpoint, the BLA does not provide an adequate number of T2D patients to inform safety of this vaccine in diabetics, especially given the AMI signal in the overall study subjects. Thus any reference in the package insert (PI) to immunogenicity in diabetics would constitute an implied indication inconsistent with 21 CFR 201.57(c)(2)(v). There are 20 million known diabetics over the age of 44 and there are 1.1 million individuals with annual new diagnosis of diabetes mellitus, many with the other underlying conditions that put them at already increased risk of AMI (12). CBER should not accept a *higher* upper bound of 95% CI of the relative risk of AMI or other composite cardiovascular risk in licensure of a preventive vaccine than what is acceptable for a therapeutic drug, which is what Option 1 would do. This ostensible inconsistency in risk tolerance within

different Centers of FDA would be difficult to reconcile. The July 2017 VRBPAC seems to have voted in favor of Option 1 but it was unequivocal in insisting that there must be a robust post-marketing pharmacovigilance plan to address the AMI safety signal. It stipulated that the study must be prospective, focused, with collection of baseline cardiovascular risk factors, capable of early real-time detection of pre-specified adverse cardiovascular event with built-in interim analyses. It did not explicitly advise a clinical trial but the parameters best fit a prospective clinical trial to assess the risk of AMI. It felt strongly that the study must be a requirement and should be conducted in the at-risk population to increase the sensitivity to detect the adverse events. Lastly, it again reiterated there should be more Asian subjects studied. Notably the only cardiologist on the Committee abstained from the vote. In this instance the VRBPAC may not have fully appreciated the various regulatory options available to the CBER to require studies and clinical trials and to mitigate and minimize risk. Any observational post-marketing study of the AMI signal has major challenges with the potential biases as with any observational study without true randomization. There are also logistical challenges that may delay detection of true AMI events. The Applicant did not submit a pharmacovigilance plan that is adequate to address the AMI signal as determined by the CBER DE reviewer (16). Importantly even a robust post-marketing study or clinical trial does not minimize an as-yet unproven true risk in recipients of the licensed vaccine who are receiving the vaccine outside the study in the course of the study. For all the reasons above I concur with the clinical review team that the benefit does not outweigh the potential risk to justify approval of HEPLISAV-B for individuals ≥ 18 years old and therefore this option should be rejected.

Both Option 2 and 3 start from the same conclusion that there is indeed a safety signal of an association between HEPLISAV-B and AMI and that it is not likely to be due simply to chance. Option 2 is the more traditional approach taken when the strength of an identified safety signal is of concern, for example when the upper bound of the 95% CI of the relative risk is between 1.3 and 1.8 for cardiovascular risks of anti-diabetic drugs in diabetics per the CDER Guidance. The issuance of a CR per Option 2 would most likely require for response to the CR a prospective randomized controlled safety trial to confirm safety *before* licensure. Option 3 departs from Option 2 in the belief that the risk for AMI can be mitigated by restricting the indication to a subpopulation of the ≥ 18 year olds with low risk of AMI. In Study 23 it was observed that all but one AMI's occurred in subjects over the age of 40 with known cardiovascular risk factors and underlying coronary artery disease. This age dependency of AMI is also true for the general population. In the INTERHEART study of 12,461 cases of AMI only 6% occurred in patients <40 years of age (28). Given the demonstrated benefit of the vaccine, by lowering the potential population risk with the restriction of the indication and usage to individuals less than 40 years old who have low risk of AMI would shift the overall risk benefit balance to favorable for approval. There likely would be benefit in this younger age group since the 3-dose completion

rate is lower in this age group. Under this option there would still be a post-marketing requirement to demonstrate the safety of the vaccine in the indicated population of 18-39. Should the Applicant want to pursue licensure of the vaccine in those over the age of 40 it can work with CBER on the design of a prospective randomized study in a population over 40 years old for which there is sufficient clinical equipoise to evaluate the safety and immunogenicity as part of a future biologics license application supplement submission. This option would allow availability of HEPLISAV-B to provide benefit to the population at low risk for AMI while accumulating real-world use safety data and allow further rigorous investigation of the AMI safety signal in an at-risk population in those ≥ 40 years old using a pre-licensure randomized prospective controlled design.

Option 4 is appropriate only if one considers HEPLISAV-B to be unsafe due to a *known* risk that would clearly outweigh any benefit from the vaccine. This option should be reserved for when there is high level of certainty of the lack of safety from the data in the BLA. In the case of this application the level of evidence and the degree of uncertainty on the major safety finding of AMI does not rise to that level of certainty. This option would preclude further studies of the safety signals found in this BLA. For this reason, I do not concur with the clinical review team's recommendation of this option.

Recommendation; HEPLISAV-B should be approved for the active immunization against all subtypes of hepB virus infection only in adults 18-39 years of age. This course of action best achieves a favorable balance of the benefit and the serious risk of AMI potentially caused by HEPLISAV-B in the adult population. This strategy would provide benefit of the vaccine to adults at low risk of AMI while discouraging the use of the vaccine in the age group at risk for AMI until the risk can be further evaluated.

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