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Division / Office	DVRPA/OVRR
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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	VBI Vaccines, Inc.
Established Name	Hepatitis B Vaccine (Recombinant)
(Proposed) Trade Name	Prehevbrio
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc	10 µg/mL HBsAG with 0.5 mg/mL aluminum hydroxide
Dosage Form(s) and Route(s) of Administration	1.0mL suspension for intramuscular injection
Dosing Regimen	0, 1, and 6 months
Indication(s) and Intended Population(s)	Prevention of infection caused by all known subtypes of hepatitis B virus in adults

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1. EXECUTIVE SUMMARY

The VITROS assay used to assess immunogenicity in the pivotal clinical studies (Sci-B-Vac-001 and Sci-B-Vac-002) was reviewed and found acceptable under IND 17542/9 and was not reviewed in this memo. Therefore, this review focuses on the validation of the drug product potency assay, an in vivo assay based on the (b) (4) anti-Hepatitis B surface antigen assay system. (b) (4)

(b) (4) from the negative control group and the assay's limit of quantitation (LOQ). The current assay procedure, using assay kit (b) (4), was validated in 2018. The validation included the establishment of the limits of detection (LOD) and quantification, as well as a study comparing kit (b) (4) to the previous kit (b) (4). In 2019, VBI revised the assay to use (b) (4) concentrations instead of (b) (4) based on a statistical analysis to demonstrate the comparability of the assay using (b) (4) concentrations. This review focuses on the 2018 validation study, including the kit comparability study. VBI also proposed the change from (b) (4) concentrations for the assay, but VBI abandoned this change while the current BLA, STN 125737/0, was under review. VBI established the LOQ as (b) (4) mIU/mL and the LOD as (b) (4) mIU/mL for the in vivo potency assay. VBI also assessed the comparability of the current assay kit (b) (4) and the previous assay kit (b) (4), based on the agreement of the (b) (4). While comparability was demonstrated based on pre-specified success criteria for all 3 parameters, the current kit appears to result in slightly lower relative potencies (percent difference in relative potencies [old – new]: (b) (4) compared to the previous assay kit. I defer to the product reviewer to assess the impact of this difference.

2. REGULATORY BACKGROUND

The VITROS assay used to assess immunogenicity in the pivotal clinical studies (Sci-B-Vac-001 and Sci-B-Vac-002) was reviewed under IND 17542/9 and found acceptable. Therefore, the VIRTOS assay is not reviewed in this memo.

Drug product potency is assessed using an in vivo assay based on the (b) (4) anti-Hepatitis B surface antigen (HBsAg) assay system. For this assay, (b) (4)

(b) (4)

VBI states that their relative potency specification is based on (b) (4). However, (b) (4) recommends an upper 95% confidence limit that is not less than (b) (4). Furthermore, this specification may not adequately control the product's potency if the potency assay is insufficiently precise, as an imprecise assay may result in extremely wide confidence limits for subpotent lots that easily meet this specification. An IR was sent to VBI on November 17, 2021 asking VBI to revise their specification to be that the upper 95% confidence limit is not less than (b) (4). In their response received on November 22, 2021 (BLA 125737/0.39), VBI revised their specification as requested.

The current assay procedure, using assay kit (b) (4), was validated in 2018. The validation included establishment of the limits of detection and quantification, as well as a study comparing kit (b) (4) to the previous kit (b) (4). In 2019, VBI revised the assay to use (b) (4) concentrations instead of (b) (4) based on a statistical analysis to demonstrate the comparability of the assay using (b) (4) concentrations. This review focuses on the 2018 validation study, including the kit comparability study, and the assessment of comparability of (b) (4) concentrations.

Multiple versions of the relevant Module 3 documents were submitted to this BLA in both the original submission and the responses to two information requests (BLA 125737/0.7, response to 23 April 2021 information request and BLA 125737/0.23, response to 11 August 2021 information request). This review refers to:

- “Qualification Report of the (b) (4) Anti-HBs Kit (b) (4) (Document Number: VLR-0000897) from BLA 125737/0.7
- “In-Vivo Potency Assay Revision Justification Report” (REP-0003286) from BLA 125737/0.23
- “Performance Evaluation of the Effect of Moving from (b) (4) Concentrations to (b) (4) Concentration Levels on Seroconversion in In-Vivo Assay” from BLA 125737/0.23 (REP-003286 Appendix).

3. DISCUSSION OF BIOASSAY STUDIES

3.1 In Vivo Potency Assay: Validation

3.1.1 Validation

(b) (4)

5 pages have been determined to be not releasable: (b)(4)

(b) (4)



4. CONCLUSIONS

VBI has established the in vivo potency assay LOQ as ^{(b) (4)} mIU/mL and the LOD as ^{(b) (4)} mIU/mL. VBI also assessed the comparability of the current assay kit (b) (4) and the previous assay kit (b) (4), based on the agreement of the (b) (4). While comparability was demonstrated based on pre-specified success criteria for all 3 parameters, it appears that the current kit results in somewhat higher relative potencies (b) (4) compared to the previous assay kit. I defer to the product reviewer to assess the impact of this difference.