

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
(CBER) Division of Epidemiology (DE)**

**ADDENDUM TO PHARMACOVIGILANCE ORIGINAL
BLA MEMORANDUM**

From: Margarita M Gomez Lorenzo, MD

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To: Marion Major, PhD
Chair of the Review Committee

Through: Manette Niu, MD
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Narayan Nair, MD
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Office of Biostatistics and Epidemiology, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Sponsor: VBI Vaccines Inc.

Product: PREHEVBRIO, Hepatitis B vaccine (recombinant, 3-antigen)

**Application Type
/Number:** BLA/ STN 125737/0

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

Submission Date: November 30, 2020

Action Due Date: November 30, 2021

This product was also referred to as *Sci-B-Vac* in the clinical development.

1. Objective

The purpose of this Addendum to Pharmacovigilance Original BLA Memorandum is to document the OBE IR (STN #125737/0/35, sent to VBI on November 2, 2021) and Sponsor's response.

2. Materials reviewed

Table 1b: Additional Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
	VCI Vaccines Inc.	BLA sequence 0036	Modules: Module: 1.11.3 Clinical Information Amendment <ul style="list-style-type: none">• Response to FDA's November 2, 2021 Information Request 1.16.1 Risk management (Non-REMS) <ul style="list-style-type: none">• PREHEVBRIO Pregnancy Outcomes Registry Synopsis (DRAFT / November 5, 2021)

3. DE Assessment of the Sponsor's response to FDA's November 2, 2021 Information Request and the PREHEVBRIO Pregnancy Outcomes Registry Synopsis (DRAFT / November 5, 2021).

An IR was sent to VBI on November 2, 2021 (STN # 125737/0/35) requesting a commitment to conduct a pregnancy registry study, and to revise the protocol to increase the sample size of the pregnancy registry study. In addition, VBI was to provide a justification for the revised sample size. The IR also asked that the sponsor commits to specific milestone dates for conduct of this post-marketing commitment (PMC).

The Sponsor provided a protocol synopsis in which the sample size was increased from 40-50 subjects enrolled over 7 years (June 2, 2021 synopsis) to 120 subjects to be enrolled over 10 years (Nov 5, 2021 synopsis). The Sponsor also clarified that the primary endpoints will include both spontaneous abortion and major congenital malformations and provided the power calculations based on the revised sample size: A sample size of 120 participants (maternal-infant pairs) will provide 80% power to detect a 3-fold increase of Major Congenital Malformations (MCM) from a background MCM rate of 3% based on a one-sided exact test for proportions with significance level of $\alpha = 0.05$, an estimated live birth rate of 67% and a lost to follow up rate of 5%. In addition, the revised sample size of 120 participants, all of whom contribute to the primary adverse pregnancy outcome of spontaneous abortion, would have 80% power to detect a 10% increase in a background rate of spontaneous abortion/miscarriage of 17%, assuming a 5% loss to follow-up.

The revised synopsis includes the following milestone dates:

- Final protocol submission: February 1, 2022
- Study start date: March 1, 2022
- Study/Clinical trial completion: March 1, 2032
- Final Report Submission: December 1, 2032

The sponsor's response to DE's November 2, 2021 (STN # 125737/0/35) IR is acceptable. OBE DE will review the final protocol of the registry study prior to the start of the study. For additional details regarding the PVP please refer to DE's original PVP memo, dated September 8, 2021.