

**CBER CMC BLA Review Memorandum**

**BLA STN 125737**

**Hepatitis B Vaccine, Recombinant**

**Lauren Siltz, PhD, CBER/FDA**

**1. BLA#:** STN 125737

**2. APPLICANT NAME AND LICENSE NUMBER**

VBI Vaccines (Delaware), Inc.

**3. PRODUCT NAME/PRODUCT TYPE**

Hepatitis B Vaccine, [Recombinant]

Proprietary Name (Israel): Sci-B-Vac

Proprietary Name (USA): PREHEVBRIO

**4. GENERAL DESCRIPTION OF THE FINAL PRODUCT**

Sci-B-Vac is a recombinant Hepatitis B vaccine produced in Chinese Hamster Ovary (CHO) cells that have been genetically modified to produce the hepatitis B virus (HBV) envelope proteins: the small (S), middle (pre-S2), and large (pre-S1) hepatitis B surface antigens (HBsAg). Currently licensed yeast-derived vaccines contain the small S protein alone. CHO cells secrete HBsAg into the (b) (4)

(b) (4) aluminum hydroxide adjuvant, and filled into single-dose vials. Sci-B-Vac is presented as a sterile suspension for intramuscular (IM) injection as 1.0 ml in single-dose vials, with each vial containing 10 µg/ml HBsAg with 0.5 mg/ml aluminum hydroxide  $[(Al(OH)_3]$ . The immunization regimen consists of three doses administered at 0, 1, and 6 months and is indicated for the prevention of infection caused by all known subtypes of HBV in adults 18 years of age and older.

The proprietary name, PREHEVBRIO, was approved during BLA review. In this memo, the vaccine is referred to as Sci-B-Vac and PREHEVBRIO.

**5. MAJOR MILESTONES**

Filing Meeting: January 14, 2021

Advisory Committee Meetings: Not applicable

PERC Meeting: October 12, 2021

Action Date: November 30, 2021

**6. CMC/QUALITY REVIEW TEAM**

<b>Reviewer/Affiliation</b>	<b>Section/Subject Matter</b>
Lauren Siltz, OVRD/DVP	Module 3 (except for facilities and equipment information) DS Release Assays and Method Validations: (b) (4) DP Release Assays and Method Validations: In vivo potency, (b) (4), Package integrity
Marian Major, OVRD/DVP	Modules 4 (non-clinical) and 5 (assays used to assess clinical endpoints)
Tao Pan, OCBQ/DBSQC	DS Release Assays and Method Validations: (b) (4) DP Release Assays and Method Validations: Physical Inspection, (b) (4), Aluminum content, Volume of injection in containers
Noel Baichoo, OCBQ/DBSQC	DS Release Assays and Method Validations: (b) (4) DP Release Assays and Method Validations: Identification, in vivo potency, (b) (4)
Hyesuk Kong, OCBQ/DBSQC	DS Release Assays and Method Validations: (b) (4) DP Release Assays and Method Validations: Endotoxins, Sterility

**7. INTER-CENTER CONSULTS REQUESTED**

None requested

**8. SUBMISSION(S) REVIEWED**

<b>Date Received</b>	<b>Submission</b>	<b>Comments/ Status</b>
November 30, 2020	STN 125737/0	Original submission
May 7, 2021	STN 125737/0.7 (response to IR dated April 23, 2021)	Removal of in vitro potency assay; submission of revised tables
May 12, 2021	STN 125737/0.8	Records request
May 24, 2021	STN 125737/0.9 (response to IR dated May 10, 2021)	Request for more information on the (b) (4) (DS release)
June 9, 2021	STN 125737/0.11 (response to IR dated May 26, 2021)	Information on DS (b) (4)

<b>Date Received</b>	<b>Submission</b>	<b>Comments/ Status</b>
June 24, 2021	STN 125737/0.13 (response to IR dated March 1, 2021)	Batch record translations; Expected date for submission of (b) (4) shipping validation report
July 27, 2021	STN 125737/0.17	Second records request
October 1, 2021	STN 125737/0.26	Commitment to submit test results for (b) (4)  report
October 27, 2021	STN 125737/0.32 (response to IR dated October 13, 2021)	Request for information on hold times for stability batches and the upper limit for BSA content per dose
November 2, 2021	STN 125737/0.33 (response to IR dated October 26, 2021)	Request for SOPs of analytical procedures for DS and DP release
November 16, 2021	STN 125737/0.38	Response to Remote Interactive Evaluation observations
November 22, 2021	STN 125737/0.39 (Response to IR dated November 17, 2021)	CHO host cell protein data submission commitment; Request for additional FBS CoAs; Clarification on certain steps of the manufacturing process

**9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)**

<b>Submission Type &amp; #</b>	<b>Holder</b>	<b>Referenced Item</b>	<b>Letter of Cross-Reference</b>	<b>Comments/Status</b>
DMF 	(b) (4) 		yes	Information pertinent to container closure was reviewed, assessed, and documented in this memo in Section 3.2.P.2.4 and Section 3.2.P.7

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF [REDACTED]	(b) (4) [REDACTED]	[REDACTED]	yes	Information pertinent to container closure was reviewed, assessed, and documented in this memo in Section 3.2.P.2.4 and Section 3.2.P.7
DMF [REDACTED]	(b) (4) [REDACTED]	[REDACTED]	yes	Information pertinent to excipients was reviewed, assessed, and documented in Section 3.2.P.4
IND 17542	n/a	Investigational New Drug (IND) submission	no	Contains information pertinent to the development of the vaccine.

## 10. REVIEWER SUMMARY AND RECOMMENDATION

### A. EXECUTIVE SUMMARY

SciVac Ltd submitted an original BLA seeking approval of Sci-B-Vac, also referred to by the USA proprietary name PREHEVBRIO, on November 30, 2020. This memo encompasses the review of all quality-related information in Module 3 of BLA 125737, nonclinical studies relevant to evaluating the benefit of aluminum hydroxide [Al(OH)<sub>3</sub>] adjuvant in (b) (4) mice (Module 4) and validation of the clinical diagnostic assay supporting clinical efficacy endpoints (Module 5).

#### ***Chemistry Manufacturing and Controls (CMC)***

Sci-B-Vac is a Hepatitis B virus (HBV) recombinant vaccine produced by expression of three related pre-S1, pre-S2, and S protein components of hepatitis B virus surface antigen (HBsAg) in Chinese Hamster Ovary (CHO) cells. Sci-B-Vac is presented as a sterile suspension for intramuscular (IM) injection as 1.0 ml in single-dose vials, with each vial containing 10 µg/ml HBsAg with 0.5 mg/ml aluminum hydroxide [(Al(OH)<sub>3</sub>]. The immunization regimen consists of three 1 mL doses administered at 0, 1, and 6 months and is indicated for the prevention of infection caused by all known subtypes of HBV in adults 18 years of age and older. Both the drug substance (DS) and drug product (DP) are manufactured at SciVac Ltd. in Rehovot, Israel (FEI: 3012695367).

To produce DS, (b) (4)

The manufacturing of Sci-B-Vac DP consists of formulation, (b) (4), filling, and packaging. During the formulation step, (b) (4) aluminum hydroxide to the desired concentration of 10 µg/ml HBsAg and 0.5 mg/ml aluminum hydroxide adjuvant. After (b) (4) DP is filled into ready-to-fill (RTF) (b) (4) glass vials. Labeled vials are stored at 2-8 °C for up to 36 months. Validation of the manufacturing process included at least three DS and DP PPQ lots and additional validation assessments for specific manufacturing steps or characterization assessments. These include impurity profiles in the DS, hold times, extractables and leachables, media fill/aseptic process simulation studies, filter validation studies, and DP shipping validations.

Testing is performed at multiple stages of the manufacturing process to ensure the product meets specifications. DS release tests consist of: (b) (4)

. DP release tests consist of: physical inspection, identification, (b) (4) aluminum content, volume of injection, *in vivo potency*, (b) (4), endotoxin, sterility and container closure integrity (package integrity).

Several batches of (b) (4)

During the review process, it was concluded that the most likely cause of this finding was the (b) (4)

he sponsor commits to provide data on (b) (4) produced after licensure regardless of the countries where the DP made from those DS batches are distributed. This information will be submitted to the annual report.

Several batches of DS produced from 2019-2021 presented out of specification (OOS) results for (b) (4). This is a release test for the DS, therefore, as these batches did not meet the acceptance criterion (b) (4) they were rejected. The root cause was not identified during the initial investigation of the OOS results. This issue was discussed during the Remote Interactive Evaluation, performed in lieu of an on-site inspection due to the COVID 19 pandemic from October 18-26, 2021, and an observation was issued. In the response to the observation (STN 125737/0.38), SciVac responded with a summary of a follow-up investigation, which determined that the root cause of the OOS (b) (4) results was the (b) (4)

batch was produced that met the specifications for (b) (4) in the DS. The sponsor commits

to submit the (b) (4) results for the (b) (4) batches of DS produced after licensure as a Product Correspondence to the BLA on a quarterly basis.

### ***Non-clinical Studies***

The Sci-B-Vac product has been marketed in countries outside the United States for several years and immunogenicity data from previous clinical studies were provided by the sponsor to demonstrate vaccine effectiveness. Data from one non-clinical pharmacological study (Study 26BC02A) were submitted to demonstrate the benefit of aluminum hydroxide [Al(OH)<sub>3</sub>] adjuvant addition to the 10 µg/mL HBsAg Sci-B-Vac for the induction of humoral immune responses in (b) (4) mice and to compare the potency of Sci-B-Vac adjuvanted vaccine to Engerix-B. Mice were immunized with Sci-B-Vac either with or without Al(OH)<sub>3</sub> adjuvant or with Engerix-B. The data demonstrated that the inclusion of Al(OH)<sub>3</sub> adjuvant with Sci-B-Vac improved antibody responses.

### ***Diagnostic Assay for Clinical Efficacy Endpoint Assessments***

The sponsor used a commercial assay, the VITROS ECi/ECiQ Immunodiagnostic Systems, to assess antibodies to hepatitis B surface antigen (anti-HBs). This is an automated system. The testing was performed by a contract lab, (b) (4). The VITROS Anti-HBs Quantitative assay is performed using the VITROS Anti-HBs Quantitative Reagent Pack and VITROS Immunodiagnostic Products Anti-HBs Calibrators on the VITROS ECi/ECiQ VITROS 5600 Integrated System using Intellicheck Technology.

Information for the VITROS anti-HBs quantitative assay to assess seroconversion and anti-HBs titers was submitted to IND 17542 and the BLA. It was reviewed under the IND prior to testing of clinical samples and found to be appropriately validated for the intended use.

Based on the information submitted in the BLA, I recommend approval of the product.

## **B. RECOMMENDATION**

### **I. APPROVAL**

#### **a. List of DS and DP Manufacturing Facilities**

- SciVac Ltd, 13 Gad Feinsein Rd, PO Box 580, Rehovot, 7610303, Israel

(b) (4)

#### **b. List of Approvable Comparability Protocols**

- Not applicable

**c. List of Post-Marketing Commitments (PMCs)/Post-Marketing Requirements (PMRs)**

- Not applicable

**d. Consideration for Inspectional Follow-up**

Due to the COVID-19 pandemic, an on-site pre-approval inspection was not possible. Thus, a Remote Interaction Evaluation (RIE) was performed from October 18-21, 2021 and October 25-26, 2021. In lieu of an on-site records review, documentation was requested from the sponsor to be reviewed virtually. There were no specific issues that arose during the RIE or records review that require inspectional follow-up.

**e. Lot Release Requirements**

- The Lot Release Protocol was reviewed by the DBSQC team.

**f. Established Conditions (ECs)**

- Not applicable

**II. COMPLETE RESPONSE (CR)**

None

**III. SIGNATURE BLOCK**

<b>Reviewer/Title/Affiliation</b>	<b>Concurrence</b>	<b>Signature and Date</b>
Lauren Siltz, CMC Reviewer/DVP/OVRR	Concur	
Marian Major, CMC Reviewer/DVP/OVRR	Concur	
Robin Levis, Deputy Director/DVP/OVRR	Concur	

**Review of CTD**

**Table of Contents**

3.2.S DRUG SUBSTANCE ..... 3

    3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties ..... 3

    3.2.S.2 Manufacture ..... 4

        3.2.S.2.1 Manufacturer(s) ..... 4

        3.2.S.2.2 Description of Manufacturing Process ..... 5

        3.2.S.2.3 Control of Materials ..... 7

        3.2.S.2.4 Controls of Critical Steps and Intermediates ..... 15

        3.2.S.2.5 Process Validation and/or Evaluation ..... 16

        3.2.S.2.6 Manufacturing Process Development ..... 30

    3.2.S.3 Characterization ..... 33

        3.2.S.3.1 Elucidation of Structure and Other Characteristics ..... 33

        3.2.S.3.2 Impurities ..... 36

    3.2.S.4 Control of Drug Substance ..... 37

        3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s) ..... 37

        3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures ..... 38

        3.2.S.4.4 Batch Analyses ..... 41

    3.2.S.5 Reference Standards or Materials ..... 41

    3.2.S.6 Container Closure System ..... 43

    3.2.S.7 Stability ..... 43

        3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data ..... 43

        3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment ..... 45

3.2.P DRUG PRODUCT ..... 45

    3.2.P.1 Description and Composition of the Drug Product ..... 45

    3.2.P.2 Pharmaceutical Development ..... 46

        3.2.P.2.1 Components of the Drug Product ..... 46

        3.2.P.2.2 Drug Product ..... 47

        3.2.P.2.3 Manufacturing Process Development ..... 48

        3.2.P.2.4 Container Closure System ..... 49

        3.2.P.2.5 Microbiological Attributes ..... 49

        3.2.P.2.6 Compatibility ..... 50

    3.2.P.3 Manufacture ..... 50

        3.2.P.3.1 Manufacturer(s) ..... 50

        3.2.P.3.2 Batch Formula ..... 51

        3.2.P.3.3 Description of Manufacturing Process ..... 52

        3.2.P.3.4 Controls of Critical Steps and Intermediates ..... 55

        3.2.P.3.5 Process Validation and/or Evaluation ..... 55

    3.2.P.4 Control of Excipients ..... 62

        3.2.P.4.1 Specifications ..... 62

        3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures ..... 62

        3.2.P.4.4 Justification of Specifications ..... 63

        3.2.P.4.5 Excipients of Human or Animal Origin ..... 64

        3.2.P.4.6 Novel Excipient ..... 64

3.2.P.5 Control of Drug Product.....	64
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) .....	64
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.....	66
3.2.P.5.4 Batch Analyses .....	68
3.2.P.5.5 Characterization of Impurities .....	69
3.2.P.6 Reference Standards or Materials .....	70
3.2.P.7 Container Closure System.....	72
3.2.P.8 Stability .....	72
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data .....	72
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment.....	74
3.2.A APPENDICES .....	75
3.2.A.1 Facilities and Equipment.....	75
3.2.A.2 Adventitious Agents Safety Evaluation .....	75
3.2.A.3 Novel Excipients.....	80
3.2.R Regional Information (USA) .....	81
MODULE 4 Nonclinical Studies .....	83
MODULE 5 Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints.....	85

**List of Abbreviations**

- AET: Analytical evaluation threshold
- BTG: Biotechnology General
- CFU: Colony forming units
- CHO: Chinese Hamster Ovary
- CMA: Critical material attributes
- (b) (4)
- CPP: Critical process parameters
- CPV: Continuous process verification
- CQA: Critical quality attribute
- DO: Dissolved oxygen
- DP: Drug Product
- DS: Drug Substance
- EoPCB: End of production cell bank
- FBS: Fetal bovine serum
- HBsAg: Hepatitis B surface antigen
- HCP: Host cell protein
- IPC: In-process control
- MCB: Master cell bank
- (b) (4)
- PDL: Population doubling level
- PP: Process parameter
- PPQ: Process performance qualification
- RIE: Remote interactive evaluation

RTF: Ready-to-fill  
TE: Total Error  
USP: United States Pharmacopeia  
WCB: Working cell bank  
WFI: Water for injection

Abbreviations not included in the above list are provided in figure legends and table footnotes or are not used beyond one specific section.

**Module 3**

**3.2.S DRUG SUBSTANCE**

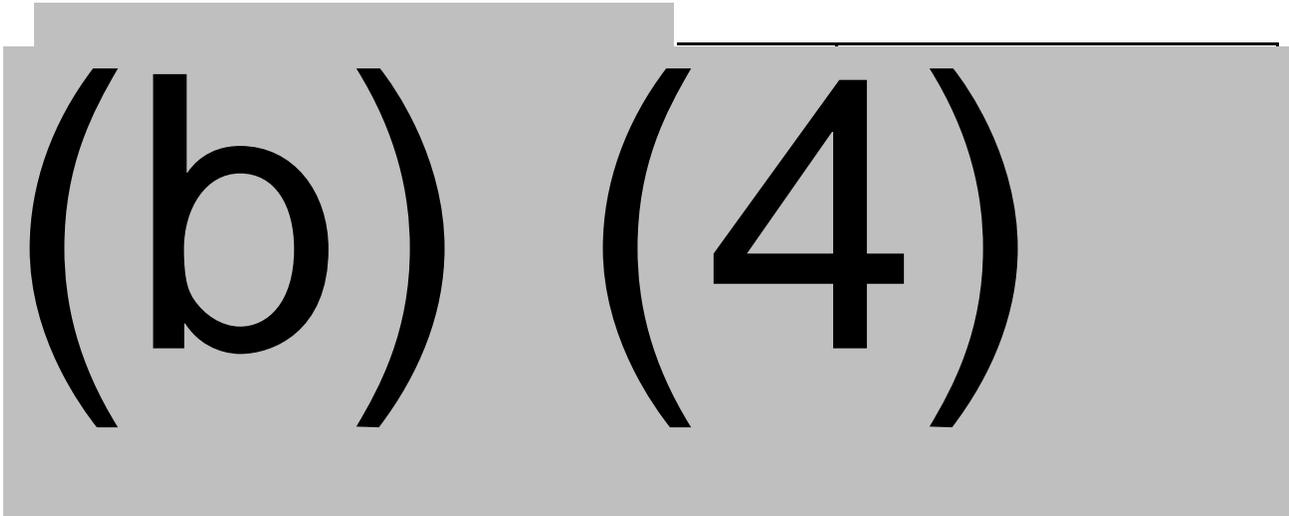
**3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties**

International Name: Vaccinum hepatitis B recombinatum  
European Pharmacopeia Name: Hepatitis B Vaccine (rDNA)  
Proprietary Name (Israel): Sci-B-Vac  
Common name (USA): Hepatitis B Vaccine, [Recombinant]  
Proprietary Name (USA): PREHEVBRIO

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The text "(b) (4)" is visible at the top left of this redacted area.

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The text "(b) (4)" is prominently displayed in the center of this redacted area.

**General Properties:** (b) (4)

**3.2.S.2 Manufacture**

**3.2.S.2.1 Manufacturer(s)**

Sci-B-Vac is manufactured and tested at the sites indicated in Table 2 (derived from Section 3.2.S.2.1 *Manufacturer(s)*).

**Table 2. Sci-B-Vac DS and DP Manufacturing and Testing Sites and Other Relevant Facilities**

Site Name	Address	FDA Establishment Identifier (FEI/DUNS)	Manufacturing Responsibilities or Type of Testing
SciVac Ltd	13 Gad Feinsein Road POB 580, Rehovot, 7610303 Israel	3012695367	HBsAg bulk DS manufacturing, DS testing (characterization, in-process control (IPC), release and stability), and storage (DS, (b) (4) release testing of raw materials

(b) (4)

Site Name	Address	FDA Establishment Identifier (FEI/DUNS)	Manufacturing Responsibilities or Type of Testing
-----------	---------	---	---

(b) (4)

Note: (b) (4) was listed as a manufacturing facility, however all tests performed at this location were characterization tests (b) (4)

### 3.2.S.2.2 Description of Manufacturing Process

(b) (4)

□ **Manufacturing process steps**

(b) (4)

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

(b) (4)



**Drug Substance Quality Release Tests**

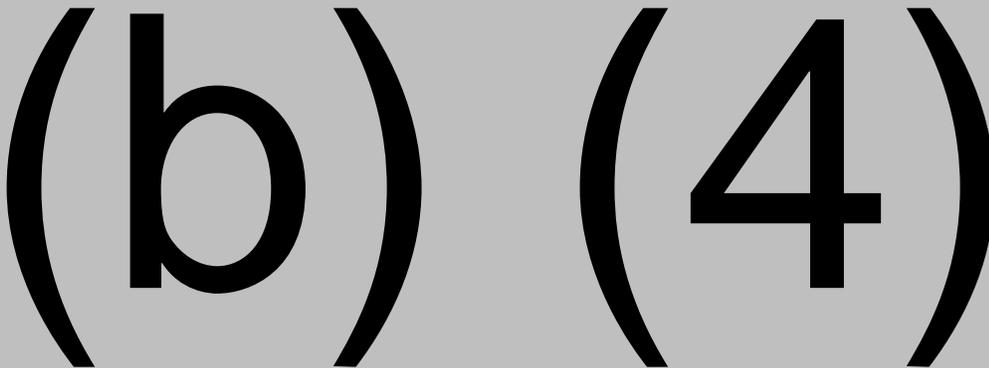
DS release test data for the (b) (4) batches listed in Table 10 in this memo were included in the BLA in Table 10, *Section 3.2.S.2.5 Process Validation*. All results met the pre-defined acceptance criteria in place at the time of testing.

**Drug Product Potency Test**

Potency test results of (b) (4) DP batches produced from the above DS batches were presented in Table 11, *Section 3.2.S.2.5 Process Validation*. DS batches (b) (4) were used for stability and R&D testing, so were not used to manufacture DP. All reported batches met the acceptance criteria for the in vivo potency assay (release test) and for the in vitro potency assay (see Table 11, derived from Table 11, *Section 3.2.S.2.5 Process Validation*).

***Reviewer Note: Although the in vitro potency assay was not included as a release test for DP, the data are included in the BLA for completion and to demonstrate consistency between batches.***

**Table 11. Potency Results of (b) (4) DP Batches**



(b) (4)

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

(b) (4)

(b) (4)

[Redacted]

[Redacted]

### 3.2.P DRUG PRODUCT

#### 3.2.P.1 Description and Composition of the Drug Product

Sci-B-Vac drug product (DP) is a sterile, aqueous suspension delivered in single-dose vials intended for intramuscular injection. Each vial contains a dose of 10 µg/ml of HBsAg adsorbed on 0.5 mg/ml of aluminum hydroxide [Al(OH)<sub>3</sub>]. The vials are over-filled with a filling volume of (b) (4) to ensure a withdrawal volume of 1.0 ml. The composition of DP is described in Table 22 (derived from Table 1, *Section 3.2.P.1 Description and Composition of the Drug Product*). Sci-B-Vac is supplied in 4 ml glass

vials fitted with a rubber injection stopper, sealed with an aluminum seal with a plastic, colored flip-off top.

**Table 22. Drug Product Composition**

Constituent	Function	Nominal Quantity (µg/1 ml dose)	Reference to Quality Standards
HBsAg Bulk DS	Active Ingredient	10 µg	(b) (4)
Sodium chloride (NaCl)	(b) (4)		
Potassium chloride (KCl)	(b) (4)	20 µg	
Sodium chloride (NaCl)	(b) (4)		
Disodium hydrogen phosphate dodecahydrate (Na <sub>2</sub> HPO <sub>4</sub> 12H <sub>2</sub> O)	(b) (4)	380 µg	
Potassium di-hydrogen phosphate anhydrous (KH <sub>2</sub> PO <sub>4</sub> )	(b) (4)	20 µg	
(b) (4)			
(b) (4)			
(b) (4) Aluminum hydroxide (Al(OH) <sub>3</sub> ) (b) (4)	Adjuvant		
Water for injection (WFI)	Solvent	(b) (4)	

**3.2.P.2 Pharmaceutical Development**

**3.2.P.2.1 Components of the Drug Product**

**3.2.P.2.1.1 Drug Substance**

The active drug substance (DS) consists of (b) (4)

(b) (4)

. The adjuvant, aluminum hydroxide, has been used in hepatitis B and other vaccines for decades. Its purpose is to adsorb the HBsAg bulk DS (b) (4) to prevent (b) (4) so a uniform dose can be administered and to increase the immune response to the antigens.

**3.2.P.2.1.2 Excipients**

No incompatibilities between HBsAg bulk DS and the excipients have been reported in the literature.

### 3.2.P.2.2 Drug Product

#### 3.2.P.2.2.1 Formulation Development

The initial composition of the DP developed by BTG and used in the first legacy clinical studies was similar to the current DP, except the adjuvant was Aluminum phosphate (AlPO<sub>4</sub>) and contained Thimerosal as a preservative. Early comparative studies reported a higher frequency of pain at the injection site, likely caused by the (b) (4) of Aluminum phosphate. Thus, in 1994, BTG replaced Aluminum phosphate with Aluminum hydroxide. Clinical efficacy studies showed that immunogenicity was similar (Study 38-92-001, Section 5.3.5.2 in the BLA).

In 1998, following the recommendation of the EMA (EMEA/20962/99 and EMEA/CPMP/1578/00), BTG removed Thimerosal from the DP composition. The removal had no adverse effect on DP quality and stability studies demonstrated the product was stable for over (b) (4) months when stored at 5 ± 3 °C.

The final composition of DP remains unchanged since 1998 and since the technology transfer from BTG to SciVac Ltd in 2005. All clinical batches manufactured by SciVac Ltd are presented in Table 23 (derived from Table 4, Section 3.2.P.2.2 *Pharmaceutical Development*).

**Table 23. Clinical Lots Manufactured by SciVac Ltd**

Batch	Manufacturing Date	Study No.	Study Type and Target Population	Section in Module 5
B0041V1	(b) (4)	SG005-05	Phase 3 in healthy adults	5.3.5.1
B0641V1		38-13-040	Phase 3 in healthy adults	5.3.5.1
B1201V1		SciB018	Phase 4 in healthy adults	5.3.5.2
B1291V1		Sci-B-Vac-001 Sci-B-Vac-002	Phase 3 in healthy adults; pivotal	5.3.5.1
B1301V1		Sci-B-Vac-002	Phase 3 in healthy adults; pivotal	5.3.5.1
B1331V1		Sci-B-Vac-002	Phase 3 in healthy adults; pivotal	5.3.5.1

#### 3.2.P.2.2.2 Overages

No overages are required. The vials are over-filled with a filling volume of (b) (4) to ensure a withdrawal volume of 1.0 ml.

#### 3.2.P.2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties relevant to the safety and performance of the DP are (b) (4). The (b) (4) of DP is controlled at release and on stability. (b) (4) is assessed as an in-process control during DP manufacture. (b) (4) is tested at release and on stability. In addition,

each batch of DS is tested for (b) (4) DP manufacturing process.

### 3.2.P.2.3 Manufacturing Process Development

The manufacturing of Sci-B-Vac DP consists of formulation, (b) (4), filling and packaging. The process designations (process A, B, C, C+) are the same between DS and DP. In summary, the original manufacturing process development (Process A) was carried out by BTG Ltd, while the filling and formulation was performed by (b) (4) (b) (4). These sites were both reported as “Facility I”. In 2005, SciVac Ltd acquired the rights for the manufacturing and marketing of Sci-B-Vac DP, and the technology was transferred to the SciVac Ltd facility, referred to as Facility II, in 2007. The initial manufacturing runs at SciVac Ltd were designated as Process B, and the DS and DP manufacturing processes were shown to be reproducible and comparable to DP obtained from the BTG manufacturing process. In addition, a bridging clinical trial (SG-005-05) demonstrated equivalent efficacy between Process A and Process B. In 2015, the DS manufacturing process changed to Process C to incorporate a (b) (4) step. This change had no impact on the DP manufacturing process. In 2019, the SciVac Ltd facility (b) (4) for use in Sci-B-Vac manufacturing, which included (b) (4) (b) (4). In addition, the (b) (4) system was changed (b) (4). These changes were designated as Process C+. As no process changes were implemented as part of Process C+, a comparability study was deemed not necessary, and the Process C batches are considered to be representative of the commercial process. Table 24 (derived from Table 1, *Section 3.2.P.2.3 Manufacturing Process Development*) contains a summary of key DP batches.

**Table 24. Drug Product Batches**

(b) (4)

<sup>a</sup> Manufacturing information not available

### **3.2.P.2.4 Container Closure System**

For information on the container closure system, refer to Section 3.2.P.7 of this memo.

### **3.2.P.2.5 Microbiological Attributes**

Sci-B-Vac is manufactured as a sterile, single dose product, which is confirmed by results of sterility, bacterial endotoxins, and package integrity testing. (b) (4)

(b) (4) and all formulation components are either purchased (b) (4) from the manufacturer or are (b) (4). The aseptic filling process has been qualified through three consecutive media fill runs, and routine re-validation is performed every (b) (4) months. Package integrity testing is performed at DP release and is monitored as part of the stability program.

**3.2.P.2.6 Compatibility**

Compatibility of Sci-B-Vac with the primary packaging components has been assessed across the product shelf life in multiple stability studies (b) (4). In addition, a study was performed to assess the Sci-B-Vac compatibility in the syringe and any effects on product quality (b) (4) in the syringe. Two needle types were used in this study to represent the minimum and maximum allowed range for IM injection: 22 G 1½” and 25 G 1”. The volume in container and (b) (4) ability, in vitro potency, and (b) (4) were tested and all results met the acceptance criteria.

<b>Overall Reviewer’s Assessment of Section 3.2.P.2:</b>	
<input type="checkbox"/>	The information provided is acceptable.
<input type="checkbox"/>	The (b) (4) is not included in the package insert.

**3.2.P.3 Manufacture**

**3.2.P.3.1 Manufacturer(s)**

Sci-B-Vac is manufactured, filled, packaged, inspected, and tested at the sites indicated in Table 25 (derived from Table 1, Section 3.2.P.3.1 Manufacturer(s)).

**Table 25. Sci-B-Vac DP Manufacturing and Testing Sites and Other Relevant Facilities**

Site Name	Address	FDA Establishment Identifier (FEI/DUNS)	Manufacturing Responsibilities or Type of Testing
SciVac Ltd	13 Gad Feinsein Rd. PO Box 580, Rehovot, 76100303 Israel	FEI: 3012695367 DUNS# 51- 447-7301	- Manufacturing, filling, labeling, and packaging of DP - In-process control testing - Release testing of DP (all except specified below) - Stability testing of DP (all except specified below) - Storage of DP

(b) (4)

Site Name	Address	FDA Establishment Identifier (FEI/DUNS)	Manufacturing Responsibilities or Type of Testing
	(b) (4)		

**3.2.P.3.2 Batch Formula**

The formulated bulk DP batch size intended for commercial use is between (b) (4) to prepare a single formulated DP batch. The quantities of each component are presented in Table 26 (derived from Table 1, *Section 3.2.P.3 Manufacture*). No overages are required. The vials (b) (4) to ensure a withdrawal volume of 1.0 ml.

**Table 26. Formulated Bulk DP HBsAg Theoretical Batch Formula**

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

The lot number format for finished Sci-B-Vac vaccine is BxxxDNO.

(b) (4)

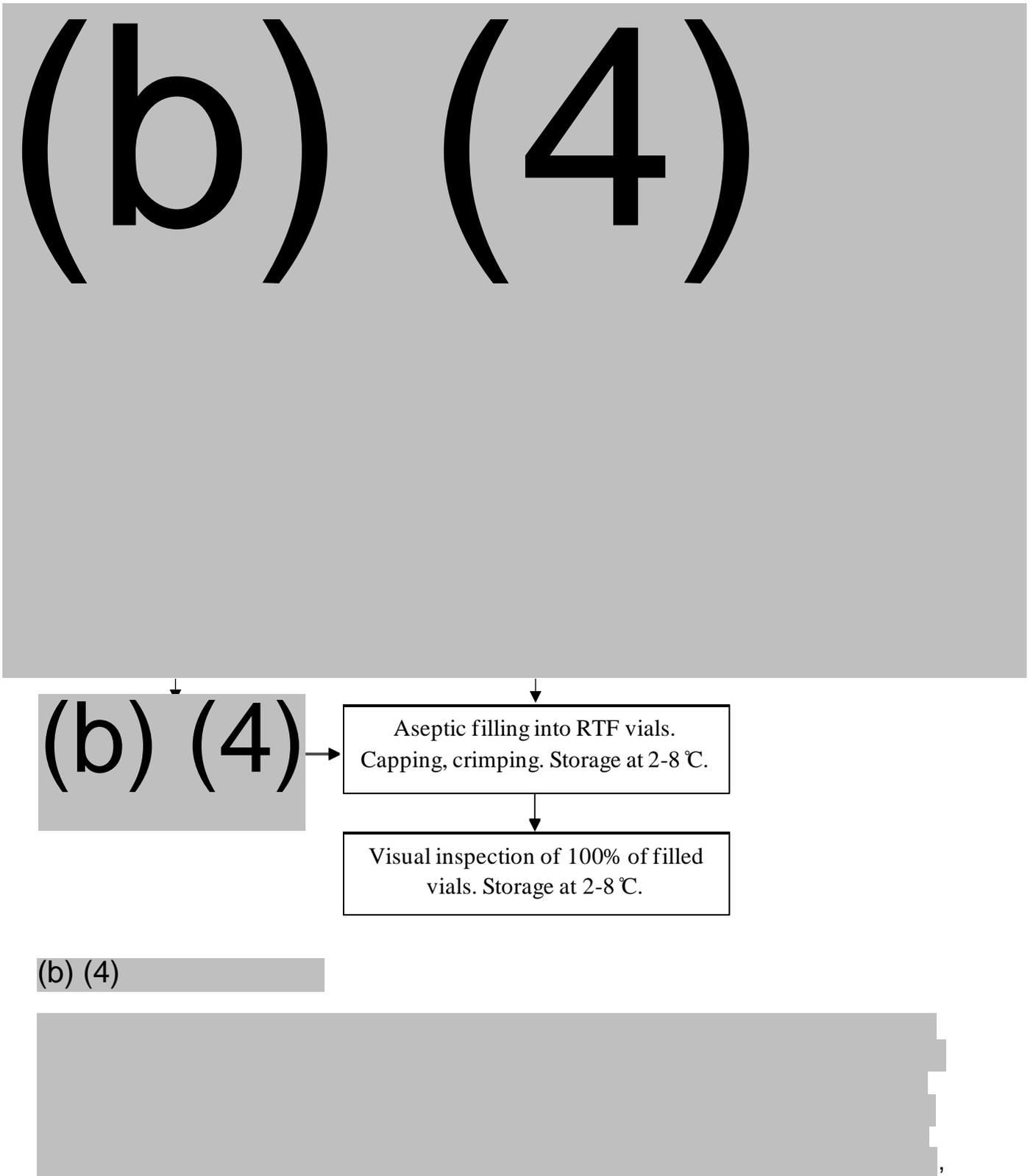


<b>Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:</b> <input type="checkbox"/> The information provided is acceptable.
---

**3.2.P.3.3 Description of Manufacturing Process**

Manufacture of Sci-B-Vac is performed at the SciVac Ltd facility in Rehovot, Israel in compliance with cGMP. The process begins with the DS and consists of (b) (4), formulation, aseptic filling, and packing. The duration of the DP manufacturing process is approximately (b) (4); no hold steps during DP formulation are described in the BLA. A flow diagram of the DP manufacturing process is provided below (derived from Figure 1, *Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls* in the BLA):

Figure 1. Flow Diagram of DP Manufacturing Process



(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**Filling of Formulated Bulk DP**

Sci-B-Vac DP is filled into 4 ml (b) (4) nominal capacity) ready-to-fill (RTF) (b) (4) glass vials at a concentration of 10 µg/ml, with a fill volume of (b) (4) ml to allow withdrawal of the labeled 1.0 ml volume. The filling process is performed using (b) (4)

[Redacted]

[Redacted] are cleaned according to relevant SOPs. Environmental monitoring is performed prior to initiation and during the filling process. Filling is performed at (b) (4). The filled, stamped, and labeled vials are stored at 2-8 °C. Visual inspection of 100% of the vials in each batch is performed by qualified personnel at (b) (4). The vials are visually inspected against a (b) (4) background and a (b) (4) background. If more than (b) (4) of the vials are rejected for any reason, a deviation procedure will be initiated. After visual inspection, vials are sampled at the (b) (4) of filling, and lot release tests are performed.

### Labeling and Packaging

Labeling is performed using a labeling machine located in a controlled room at the SciVac Ltd facility dedicated to the labeling and packaging of the DP. Labeling is performed at (b) (4) and vials must not be kept at (b) (4). Labeled vials are (b) (4) secondary packaging is performed. Secondary packaging boxes consist of 10 vials per unit.

#### Overall Reviewer's Assessment of Section 3.2.P.3.3:

- In the formulation of DP, (b) (4) This process was observed during the remote interactive evaluation, and it was shown that (b) (4).
- The information provided is acceptable.

### 3.2.P.3.4 Controls of Critical Steps and Intermediates

Critical process parameters of the Sci-B-Vac DP manufacturing process are shown together with the results obtained during the process validation in Section 3.2.P.3.5 of this memo. No information on stability of intermediates was provided, as the DP formulation and filling are continuous processes.

#### Overall Reviewer's Assessment of Section 3.2.P.3.4:

- The information provided is acceptable.

### 3.2.P.3.5 Process Validation and/or Evaluation

The process validation of Sci-B-Vac DP includes the following, in addition to manufacturing in process studies: (i) media fill studies, (ii) filter validation studies, (iii) an extractables and leachables assessment, (iv) autoclave validation, (v) equipment cleaning validation, and (vi) DP shipping validation studies. Three (3) consecutive formulated bulk (b) (4) were produced from the DS batches (b) (4). These batches were used to manufacture (b) (4) DP batches, as described in Table 27 (derived from Table 1, *Section 3.2.P.3.5 Process Validation*).

**Table 27. PPQ DP Batch Numbers and Filling Dates**

(b) (4)

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

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

[Redacted]

[Redacted]

[Redacted]

### Extractables and Leachables Assessment

Key material attributes considered in the Extractables and Leachables Risk Assessment include: (b) (4)

Three product contact items were rated as Medium risk and required extractables and/or leachables studies: (i) (b) (4) (see above section for filter validation studies), (ii) the DP vials, and (iii) the DP stoppers. Extractables and leachables tests were performed on the vial and stopper, and no risks were identified. Controlled extraction tests performed on the vials included (b) (4) analysis.

In addition, (b) (4) DP that had been stored beyond its expiration date was screened for organic leachables and elemental impurities. The test article, batch (b) (4), which was stored (b) (4) at  $5 \pm 3^\circ\text{C}$  for <sup>(b) (4)</sup> months, was compared to a (b) (4) prepared lot of DP, batch (b) (4), which was stored (b) (4). Both batches were stored in the (b) (4) vials. Tests included screening of (b) (4)

(b) (4) No leachables were present in the test article at levels equal or greater than the (b) (4)

### Shipping Validation Studies

The DP is stored and shipped at 2-8°C. DP vials will be packed in carton vial packs containing 10 vials. (b) (4)

(b) (4)

(b) (4)

The results of the shipping validation studies will be reviewed by a member of DMPQ.

**Overall Reviewer's Assessment of Section 3.2.P.3.5:**  
 The information provided is acceptable.

### 3.2.P.4 Control of Excipients

#### 3.2.P.4.1 Specifications

The excipients used in the manufacture of Sci-B-Vac DP are listed previously in this memo in Section 3.2.P.3.2. The excipients comply with the current versions of the relevant Pharmacopoeia monographs. All materials are tested by SciVac and/or by qualified laboratories as part of SciVac's release process.

#### 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

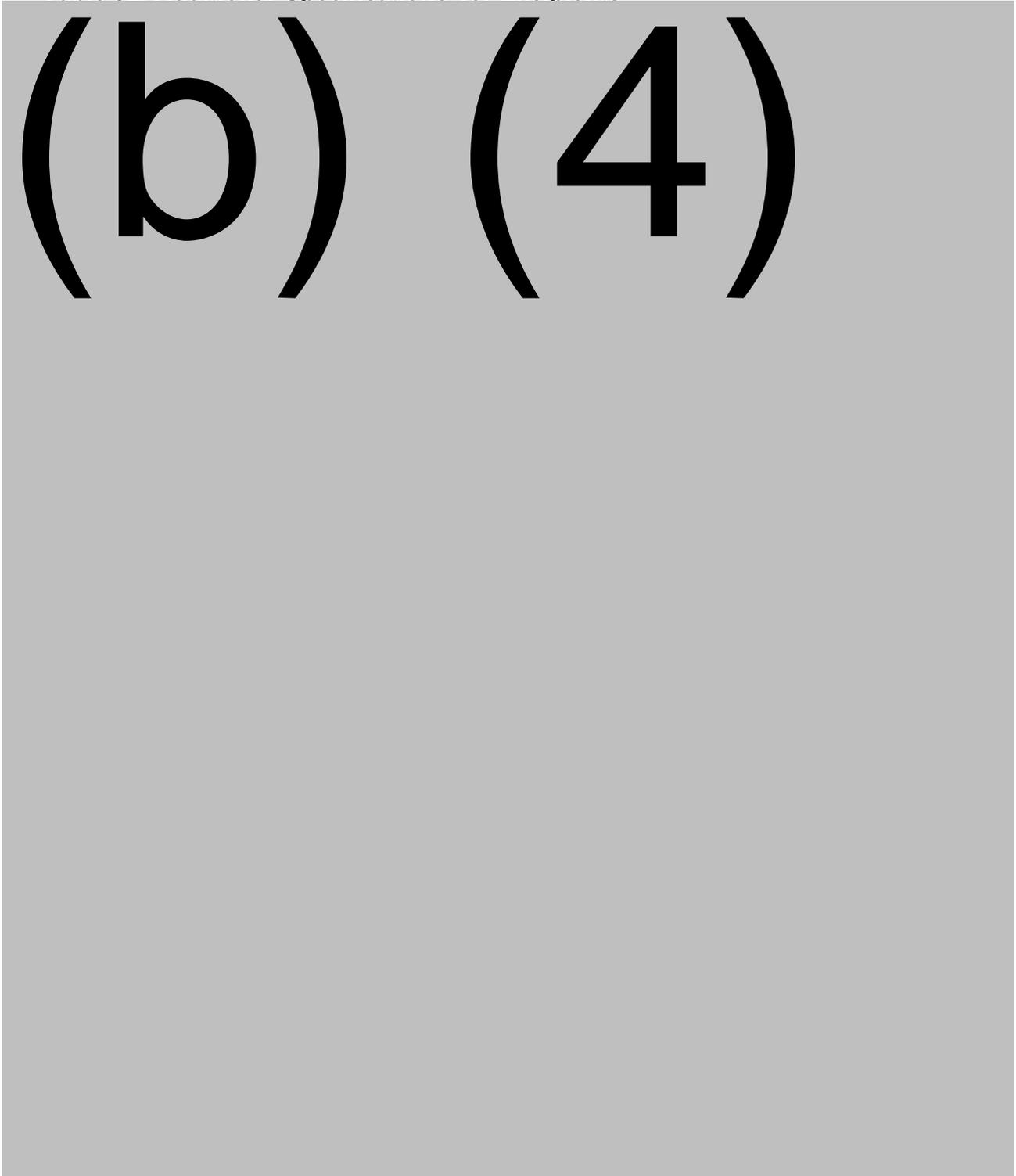
All excipients used in the formulation of Sci-B-Vac DP are tested using the respective compendial analytical procedures. Additional in-house tests used for the release of Aluminum hydroxide include (b) (4)

(b) (4) The specifications for these tests are listed in Table 32.

**3.2.P.4.4 Justification of Specifications**

All excipients are tested in compliance with the current (b) (4) monographs. Justifications for additional specifications are presented in Table 32 (derived from Tables 1-5, *Section 3.2.P.4.4 Justification of Specifications*).

**Table 32. Additional Specifications for Excipients**



(b) (4)

(b) (4)

### 3.2.P.4.5 Excipients of Human or Animal Origin

Sci-B-Vac DP does not contain excipients of human or animal origin.

### 3.2.P.4.6 Novel Excipient

Sci-B-Vac DP does not contain novel excipients.

#### Overall Reviewer's Assessment of Section 3.2.P.4:

- The information provided was acceptable.
- No deficiencies identified.

### 3.2.P.5 Control of Drug Product

#### 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The DP specifications for Sci-B-Vac are summarized in Table 34, Section 3.2.P.5.4 of this memo.). The specifications are based on the late-stage clinical specifications. The major changes between the clinical specifications and the proposed commercial specifications were the implementation of (b) (4) test. An in vitro potency assay was initially included as a release test, but it was removed at the request of CBER due to insufficient data collected during development and limited quantities of important reagents for re-validation of the assay (see IR below in Reviewer's Assessment section). The sponsor notes that a test for formaldehyde is performed specifically at the (b) (4). This is because the formaldehyde levels (b) (4).

#### Justification of Specifications

Specifications were based on historical data, clinical data or comply with USP or Ph. Eur. All specifications were justified and found to be acceptable.

**Overall Reviewer’s Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:**

- On April 23, 2021, the following IR was sent to the sponsor:

“1.7) In section 3.2.P.5 of the BLA you have included the SOP and validation of an in vitro potency assay and included the in vitro potency assay as a release test for Drug Product together with the in vivo potency assay. However, in Section 1.2 Reviewer’s Guide (page 6) you state that you are unable to provide all the information requested by the Agency during pre-BLA meetings regarding this assay due to limited availability of data collected during development and limited quantities of critical reagents. You indicate that you will qualify new lots of critical reagents and will supplement the validation of the assay with these new lots. Due to these issues, the in vitro potency assay is not currently considered sufficiently developed and validated to be included as a potency assay for Drug Product release after licensure. Please withdraw the assay information from the BLA, Drug Product release specifications, and stability plans, and update all relevant BLA sections as appropriate. We acknowledge that during the pre-BLA consultations the Agency offered to engage in discussion and correspondence to support further development of the in vitro potency assay. However, such correspondence for development of the assay should take place through IND communications, not as part of the BLA review process. If you would like to request Agency input on the assay development and validation, please submit any developmental information for the assay to your IND for Sci-B-Vac. Alternatively, the assay change may be submitted as a prior approval supplement post licensure.”

On May 7, 2021, the sponsor responded (Amendment 125737/0.7) that they had withdrawn or relocated all information related to the in vitro potency assay from the BLA and removed the in vitro potency assay as a release test for drug product and removed it from the post-approval stability commitment. The response was acceptable.

- With the removal of the in vitro potency assay as a DP release test, DVP discussed the possibility of requesting that the sponsor add an antigen content test for DP release to confirm the concentration of the antigen (b) (4) . After an internal discussion, we decided that an antigen content test was not necessary based on decisions made for other approved products. For Vaxelis (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate and Hepatitis B Vaccine, STN 125563), (b) (4) . However, the in vivo potency test will continue to be performed for release and stability monitoring of DP lots.
- The information provided is acceptable. Deficiencies were identified and were resolved.

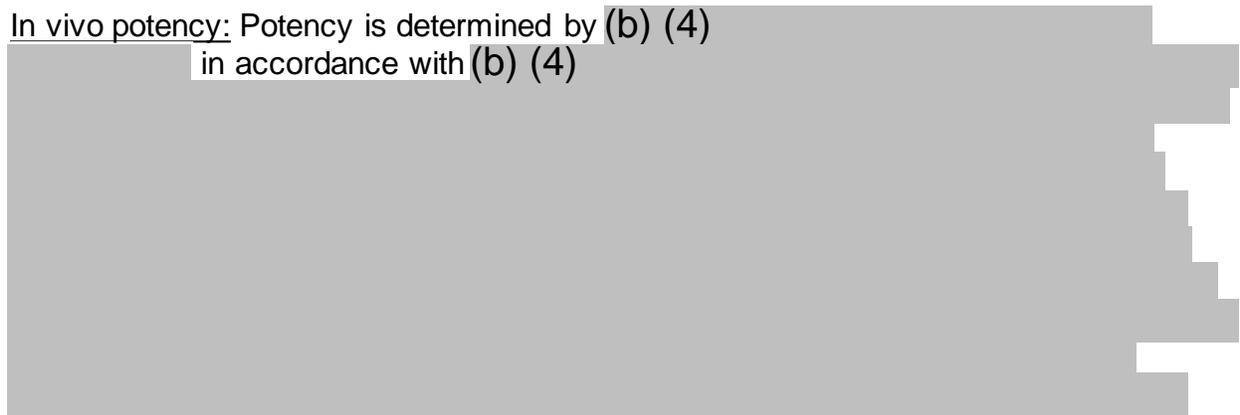
**3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures**

The DP release methods are listed in the Batch Analysis Section 3.2.P.5.4 in this memo (see Table 34). DVP was responsible for reviewing the following DP release tests: in vivo potency, (b) (4), and package integrity. See Table 33 below for a summary of DVP and DBSQC responsibilities.

**Table 33. DVP and DBSQC Review Responsibilities**

<b>Test</b>	<b>Analytical Method</b>	<b>Reviewer(s)</b>
Physical Description	Visual Inspection	Tao Pan, DBSQC
Identification	(b) (4)	Noel Baichoo, DBSQC
(b) (4)	(b) (4)	Tao Pan, DBSQC
Aluminum Content	(b) (4)	Tao Pan, DBSQC
Determination of Volume of Injection in Containers	Container content for injections, (b) (4)	Tao Pan, DBSQC
In Vivo Potency	By (b) (4)	Noel Baichoo, DBSQC; Lauren Siltz, DVP; Jennifer Kirk, OBE, Statistical Reviewer
(b) (4)	(b) (4)	Noel Baichoo, DBSQC; Lauren Siltz, DVP
Endotoxin	(b) (4)	Hyesuk Kong, DBSQC
Sterility	(b) (4)	Hyesuk Kong, DBSQC
Container Closure Integrity	(b) (4)	Lauren Siltz, DVP

In vivo potency: Potency is determined by (b) (4) in accordance with (b) (4)



1 page has been determined to be not releasable: (b)(4)

Container closure integrity: Container closure integrity (identified as package integrity by the sponsor) is determined by (b) (4)

[Redacted]

All results met the predefined acceptance criteria.

**Overall Reviewer’s Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:**

- ❑ After correspondence with Jennifer Kirk (CMC Statistical Reviewer), the sponsor decided to conduct the in vivo potency assay with (b) (4)

[Redacted]

- ❑ The sponsor submitted SOPs for DP analytical procedures under STN 125737/0.33 on November 2, 2021 in response to an IR sent by the Agency on October 26, 2021.
- ❑ The information provided is acceptable.

**3.2.P.5.4 Batch Analyses**

Batch analyses data from the PPQ campaign is summarized in Table 34 (derived from Table 2, *Section 3.2.P.5.4 Batch Analysis*). Note that Table 34 includes results from the in vitro potency assay, which was removed as a release test, but the results were retained in the PPQ review for information purposes. Historical batches that were not a part of the PPQ campaign are described in Section 3.2.P.5.4 of the BLA, and all batches met the acceptance criteria that were in place at the time of batch production.

**Table 34. Batch Analysis Data for Sci-B-Vac Validation Lots**

(b) (4)

(b) (4)

### 3.2.P.5.5 Characterization of Impurities

Process-related impurities and DS-related impurities have been described in Section 3.2.S.3.2 Impurities. Potential DP-specific impurities are (b) (4) and leachables from the DP container closure system. (b) (4) is monitored as part of the release testing and stability testing. Data across the stability testing have shown essentially no change in adsorption across the shelf life of the DP, where the levels of (b) (4). An assessment of the potential impurities (b) (4)

Aluminum hydroxide was performed by the supplier, and no risks were identified. The extractables and leachables from the container closure system is summarized in Section 3.2.P.2.4.

**Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:**

- The information provided is acceptable.

**3.2.P.6 Reference Standards or Materials**

Reference standards used in the production and testing of DS are described in Section 3.2.S.5 Reference Standards or Materials. (b) (4)

As such, the DP primary reference material is reflective of the clinical material, and both the primary and secondary reference materials are fully characterized using release and extended characterization assays. The current primary reference standard for DP is summarized in Table 35 (derived from Table 1, *Section 3.2.P.6 Reference Standard*) and Table 36 (derived from Table 2, *Section 3.2.P.6 Reference Standard*). The following release tests utilize the IHRS: Identity/Identification, in vivo potency (results are reported as relative potency of the test sample in comparison with the IHRS), and (b) (4).

**Table 35. Current DP Primary Reference Standard (b) (4) .**

DP Date of Manufacture	(b) (4)
DP Manufacturing Process	
DP Lot Size	
Clinical Immunogenicity (seroprotection rate after <sup>(b) (4)</sup> injections)	
Storage Conditions	
DS Batch Number used to Manufacture (b) (4)	
DS Manufacturing Process	

**Table 36. Release Tests of (b) (4)**

(b) (4)

The safety test refers to the General Safety Test conducted according to the procedure described in 21 CFR 610.11. This test was removed from DP release following revocation by FDA.

Release tests and characterization of DS batch (b) (4) that was used to produce DP (b) (4) are as follows: (b) (4)

[Redacted]

[Redacted]. All results met pre-defined acceptance criteria.

For the secondary reference standard, the DS batch (b) (4) to produce DP lot (b) (4). The secondary reference standard is (b) (4)

[Redacted]

[Redacted] All results met pre-defined acceptance criteria.

Stability monitoring of the primary and secondary reference standards up to (b) (4) has been performed in compliance with (b) (4). After the (b) (4) timepoint, the parameters will be tested every (b) (4) months. The in-house standards shelf life can be (b) (4) if the acceptance criteria are met. See Table 37 (derived from Table 14, Section 3.2.P.6 *Reference Standards or Materials*) for a summary of the stability program for the primary and secondary DP reference standards. Results from stability studies of (b) (4) are summarized in Section 3.2.P.8.3 Stability Data.

**Table 37. Stability Program for Primary and Secondary DP Reference Standards**

(b) (4)

(b) (4)

### 3.2.P.7 Container Closure System

The Sci-B-Vac DP is filled into clear (b) (4) borosilicate glass vials, which are closed with a black, chlorobutyl (b) (4) rubber injection stopper. The glass vial complies with (b) (4). The vials are manufactured by (b) (4). Release specifications for the vials are the following: visual inspection, physical inspection (measurement), bacterial endotoxins, sterility, (b) (4). The stopper complies with (b) (4). Release specifications for the stoppers are the following: Appearance and dimensions, bacterial endotoxins, (b) (4).

(b) (4) aluminum seal with a light blue plastic flip-off top is used to secure the stopper. Release specifications for the flip-off seals are the following: appearance and dimensions (physical measurement).

For the clinical studies and (b) (4) borosilicate (b) (4) clear class vials manufactured by (b) (4) were used as the container closure system. The current vials are manufactured by (b) (4).

Letters of authorization were included for the container closure system in Module 1. A risk assessment demonstrated that the switch in the container closure system has no impact on DP quality or safety. Extractables and leachables testing is described in this memo in Section 3.2.P.3.5 Extractables and Leachables Assessment.

**Overall Reviewer’s Assessment of Section 3.2.P.7:**

- The information provided is acceptable.

### 3.2.P.8 Stability

#### 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The stability program in support of the DP shelf life was established according to ICH Q5C guidelines. The proposed shelf life of 36 months at  $5 \pm 3^\circ\text{C}$  is supported by (b) (4) primary stability DP lots that were placed on stability for (b) (4) months (see Table 38, derived from Table 1, *Section 3.2.P.8.1 Stability Summary and Conclusion*). The drug substance used to manufacture these DP lots followed manufacturing process (b) (4). The lots were filled in the (b) (4) “ready-to-fill” vials instead of the currently used (b) (4).

vials, which were shown to have no impact on DP quality (Section 3.2.P.2.3 and REP-0003685). The rubber stopper and seal remain the same. A confirmatory stability study of DP filled in the (b) (4) vials is ongoing at the time of writing this memo.

**Table 38. Primary Stability Studies in Support of DP Shelf Life at  $5 \pm 3^\circ\text{C}$  (b) (4)**

Batch Number	Purpose of stability study	Manufacturing date	Storage condition	Storage position	Study duration
(b) (4)	(b) (4)	(b) (4)	$5 \pm 3^\circ\text{C}$	(b) (4)	(b) (4) months
			$5 \pm 3^\circ\text{C}$		months
			$5 \pm 3^\circ\text{C}$		months
			$5 \pm 3^\circ\text{C}$		months
			$5 \pm 3^\circ\text{C}$		months
			$5 \pm 3^\circ\text{C}$		months

Four stability studies were implemented: (i) real time storage at  $5 \pm 3^\circ\text{C}$ , (ii) accelerated storage at (b) (4) (iii) thermal stress study (b) (4) (iv) light exposure study at (b) (4) Forced degradation studies (b) (4) ) determined that the stability-indicating method is (b) (4).

Stability Results at  $5 \pm 3^\circ\text{C}$ : For this study, the following characteristics were determined at regular intervals over the course of (b) (4) months: physical inspection, (b) (4) HBsAg S protein (b) (4) (identification), (b) (4) in vivo potency, aluminum content, endotoxins, sterility, and package integrity (container closure integrity). All results met the pre-defined acceptance criteria in place at the time of testing, supporting the proposed shelf life of 36 months at  $5 \pm 3^\circ\text{C}$ . Although relative potency trended downwards over 36 months, the values were within the acceptance criteria (the estimated relative potency of the upper confidence interval is not less than (b) (4)).

Stability Results at (b) (4)

(b) (4)

Thermal Stress Study: The thermal stress study (b) (4)

Photostability Study: The photostability study was conducted on (b) (4) . Conditions consisted of samples (b) (4)

showing that the samples are sensitive to light exposure.

### 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The stability study designs comply with the current ICH Q1A (R2) and Q5C standards. The analytical methods and acceptance criteria are identical to DP release specifications. (b) (4) will be placed on long-term stability at  $5 \pm 3^\circ\text{C}$ , with vials (b) (4) to represent the worst-case scenario, (b) (4) to represent all batches produced during that (b) (4). The post-approval stability protocol is summarized in Table 39 (derived from Table 5, Section 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment).

**Table 39. DP Stability Post-approval Testing**

Test	Time Point (months)				
	0	3	6	12	24
Physical Inspection	X	X	X	X	X
(b) (4)	X	X	X	X	X
Identity Test (HBsAg S protein) (b) (4)	X	X	X	X	X
In vivo potency	X	NT	NT	X	X
(b) (4)	X	X	X	X	X
Aluminum content	X	NT	NT	NT	NT
Endotoxin	X	NT	NT	NT	NT
Sterility	X	NT	NT	NT	NT
Package integrity	X	NT	NT	NT	NT

Transcriptions available upon request: Contact the Division of Viral Products, 240-402-7302.

NT = not tested

**Overall Reviewer’s Assessment of Section 3.2.P.8:**

□ The sponsor provided in vitro potency results throughout this section; however, this assay was removed from the post-approval stability program and from release testing by request of the Agency via an IR sent on April 23, 2021. Thus, this memo disregarded in vitro potency data that was presented in this section, as the assay has not been reviewed or validated by the Agency.

□ On October 13, 2021, the Agency submitted the following IR to obtain more information on the DS batches used to formulate the DP stability batches:

“1. Please provide information on the storage conditions and length of hold time for each of the DS batches, prior to formulation, that were used to formulate DP for the DP stability studies presented in Sections 3.2.P.8.1 and 3.2.P.8.3 of the BLA.”

The sponsor responded on October 27, 2021. The storage condition of DS batches was (b) (4), while the hold times of the DS batches that were used to formulate DP used in stability studies ranged from (b) (4)

[Redacted]

The information provided is acceptable.

□ The stability data support the proposed shelf life of 36 months at 5 ± 3°C. The post-approval stability protocol is acceptable.

**3.2.A APPENDICES**

**3.2.A.1 Facilities and Equipment**

Facilities and Equipment was reviewed by DMPQ.

**Overall Reviewer’s Assessment of Section 3.2.A.1:**

□ Facilities and Equipment was reviewed by DMPQ.

**3.2.A.2 Adventitious Agents Safety Evaluation**

See Section 3.2.S.2.3 in this memo for assessment of materials of biological origin in DS and for the adventitious agents safety evaluation of the cell lines used to produce the HBsAg bulk DS. No excipients of human or animal origin are used in the formulation of DP.

An overview of the historical virus testing performed on (b) (4) is provided in Table 40 (derived from Table 11, *Section 3.2.A.2 Adventitious Agents*). The presence of (b) (4)

[Redacted]

1 page has been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

An IR was sent to the sponsor regarding these batches on May 26, 2021 and are further discussed in the Reviewer's Assessment below.

□ **Viral Clearance Studies**

Sci-B-Vac does not contain live or inactivated viruses. Therefore, viral clearance studies were performed to demonstrate the removal and/or inactivation of potential adventitious viral agents at the following stages of production: (b) (4)

Viral clearance studies were performed from 2003-2019. BTG performed initial studies in 2003 to support the vaccine approval in Israel. After transfer to SciVac Ltd in 2007, viral clearance studies were deemed not necessary, as the manufacturing process remained the same. After the (b) (4)

(b) (4) (Manufacturing Process B to Process C), new viral clearance studies were performed in 2013 and 2015. Viral clearance was not significantly affected by this change. An additional viral clearance study was performed in 2019, with the (b) (4)

(b) (4)

Tables 41 and 42 (derived from Table 17 and 18, *Section 3.2.A.2 Adventitious Agents*) present the LRFs of enveloped and non-enveloped viruses, respectively, from studies performed from 2003-2019. The 2003 study used the previously used (b) (4) (Process B) and are presented for information only. The study performed in 2013 examined viral clearance using (b) (4)

(b) (4)

(b) (4) (4)

(b) (4)

(b) (4) (4)

(b) (4)

(b) (4)

**Overall Reviewer's Assessment of Section 3.2.A.2:**

□ In Section 3.2.A.2.6.1.1.6 Adventitious Agents, the sponsor noted that several batches of (b) (4) . On May 26, 2021, the following IR was sent to the sponsor for more information:

1. Please provide a full list of drug substance (DS) batches (b) (4) from the start of manufacturing to the present, with batch numbers and manufacturing dates.
2. Please provide a table to show all differences in the manufacturing process that were applied to the DS batches (b) (4) compared to the current manufacturing process.
3. Please provide all investigation reports and root cause analyses for all DS batches that have (b) (4) .”

The sponsor responded on June 9, 2021. Table 43 (derived from Tables 1 and 2 from Section 1.11.1 Quality Information Amendment, 125737/0.11) provides a summary of all batches (b) (4) .

Table 43. DS Batches (b) (4) and Differences in the Manufacturing Process Compared to the Current Commercial Process.

(b) (4)

The sponsor provided the following investigation reports: DR032-13 (b) (4), DEV-0000231-2019 (b) (4) and DEV-0000271-2020 (b) (4). Dev-0000231-2019 concluded that the most likely cause of (b) (4)

Based on the provided information, we believe the most likely cause of the (b) (4)

The response to the IR was acceptable.

□ On September 27, 2021, the following request was sent to the sponsor:

“Regarding the detection of (b) (4) in certain drug substance (DS) batches, the Agency requests that SciVac Ltd. submits test results for (b) (4) that are produced after the licensure of PREHEVBRIO, regardless of the countries where the DP batches made from those (b) (4) DS batches are distributed. Please submit this information as a part of the annual report(s) that span(s) the production of the (b) (4) DS batches. Please acknowledge the receipt of this request and your commitment to fulfilling this request”.

In the cover letter submitted in STN 125737/0.26 on October 1, 2021, the sponsor committed to submit test results in the BLA annual report for (b) (4) that are produced after the licensure of PREHEVBRIO, regardless of the countries where the DP batches made from those (b) (4) DS batches are distributed. The response is acceptable.

□ Viral clearance studies demonstrate the ability to remove and/or inactivate all tested enveloped and non-enveloped viruses.

### 3.2.A.3 Novel Excipients

No novel excipients are used for formulation of the vaccine.

### 3.2.R Regional Information (USA)

#### Executed Batch Records

Executed batch records were provided for batch (b) (4). In the original BLA, separate English translations were provided along with the original batch records in Hebrew. The following information request was sent on March 1, 2021:

“The completed batch records included in Section 3.2.R (b) (4) Sci-B-Vac Vial Inspection, (b) (4) HBsAg) are in Hebrew. While we acknowledge that English translations of blank batch records are included in Section 3.2.R (SOP-0000045, SOP-0000046, SOP-0000076, SOP-0000237, SOP-0002550, and SOP-000238), please submit certified translations of the executed batch records, (b) (4) Sci-B-Vac Vial Inspection, (b) (4) HBsAg for (b) (4) of Sci-B-Vac.”

The sponsor provided the following documents on June 24, 2021, after email correspondence with the Agency: (i) the blank translation from Hebrew to English, (ii) the certificate of translation performed by (b) (4), and (iii) the English batch records filled by a Quality Assurance (QA) referent and checked by a second QA referent.

The provided batch records were deemed acceptable, and no objectionable findings were noted.

#### Method Validation Package

Method validation protocols are summarized and discussed in Sections 3.2.S.4.2 and 3.2.S.4.3 for drug substance (b) (4) and Sections 3.2.P.5.2 and 3.2.P.5.3 for drug product (in vivo potency, (b) (4), and package integrity). Other method validations were reviewed by OCBQ/DBSQC. For the statistical review of the in vivo potency assay, see the memo by Jennifer Kirk.

#### Combination Products

Not applicable.

<b>Overall Reviewer’s Assessment of Combination Products Section:</b>
---

<input type="checkbox"/> Not applicable.
--

#### Comparability Protocols

There are no comparability protocols for this BLA.

## Other eCTD Modules

### Module 1

#### A. Environmental Assessment or Claim of Categorical Exclusion

VBI Vaccines (Delaware) Inc. claimed a categorical exclusion from the requirement to prepare an environmental assessment based on 21 CFR 25.31(a). The sponsor claimed that use of this product does not increase the active moiety. The claim for categorical exclusion is acceptable.

#### B. Labeling Review

##### Full Prescribing Information (PI):

Section 3: The description of the dosage (in µg/ml) and volume in each vial is acceptable.

Section 11: The description of Sci-B-Vac is accurate, describing that the vaccine contains the full antigenic structure of the Hepatitis B surface antigen, including the small (S), middle (pre-S2), and large (pre-S1) surface antigens. The dose of the HBsAg antigen is provided, as well as the concentration of the aluminum hydroxide adjuvant. The excipients are provided and include: sodium chloride, potassium chloride, disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate anhydrous, and water for injection. The vaccine does not contain preservatives, excipients derived from humans or animals, or novel excipients.

**Reviewer Comment: On October 13, 2021, the Agency submitted the following IR:**

***“We make reference to the package insert for PREHEVBRIO. The Description section of the package insert will need to cite the content of the residual fetal bovine serum (FBS) per vaccine dose; therefore, please estimate the final amount of FBS in each vaccine dose based on your bovine serum albumin (BSA) clearance studies. Please provide these calculations or results of tests and propose an upper limit for FBS content per vaccine dose to be included in the package insert.”***

***The sponsor submitted their response on October 27, 2021 as a part of amendment STN 125737/0.32. According to their calculations, the proposed upper limit for residual bovine serum albumin (BSA) per vaccine dose is estimated to be less than 2.5 ng/ml, which is equivalent to 0.0025 ppm. They argued that the major protein in FBS is BSA, therefore, this estimate can be applied to FBS. We did not agree with their proposed statement. Based on the CoAs submitted for FBS, the BSA level is around (b) (4) . FBS is used at (b) (4) in the manufacturing process, therefore BSA is at (b) (4) . If the amount of BSA per vaccine dose is 2.5 ng/mL, this is a (b) (4) . Applying this to FBS in cell culture, the percentage would be (b) (4) . 21 CFR 610.15(b) states that, if serum is used at any stage, it’s concentration in the final medium should not exceed 1 ppm. Therefore, the level of FBS in per vaccine dose is acceptable.***

Section 16: The information provided on supply and storage conditions is acceptable.

**Carton and Container Label:**

The labeling items are reviewed by DVRPA and OCBQ.

The CMC information provided on the primary and secondary labels is acceptable.

**Modules 4 and 5**

**Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints**

Modules 4 and 5 were reviewed by Dr. Marian Major/DVP.

**MODULE 4 Nonclinical Studies**

**Study 26BC02A - Demonstration of the Aluminum Hydroxide Al(OH)<sub>3</sub> Adjuvant benefit in Sci-B-Vac vaccine formulations in (b) (4) mice.**

Report REP-FORM-047 contains a summary of the non-clinical study (26BC02A) performed by VBI to demonstrate the benefit of aluminum hydroxide Al(OH)<sub>3</sub> adjuvant addition to the 10 µg/mL HBsAg Sci-B-Vac for the induction of humoral immune responses in (b) (4) mice and to compare (b) (4) of Sci-B adjuvanted vaccine to Engerix-B. The study was performed at the (b) (4)

This is the only non-clinical pharmacological study submitted to the BLA. The Sci-B-Vac product has been marketed in countries outside the United States for several years and immunogenicity data from previous clinical studies were provided by the sponsor to demonstrate vaccine effectiveness.

Table 44 shows the study design. Mice (6-8 weeks old) were immunized via the intraperitoneal route at 0 and 3 weeks and bled at day (d) 0, d10, d20, d34, d49, and d63. Sera were tested for anti-HBsAg antibody titers by SciVac QC at the Rehovot site in Israel using the (b) (4)

**Table 44. Study Design for 26BC02A**

Group n=8	Description	Lot#	HBsAg ug/mL	Dose volume (ul)	HBsAg ug/dose	Al(OH) <sub>3</sub> ug/mL [Al+++]	Al+++ ug/dose
1	Sci-B-Vac	B2016V2	10	50	0.5	(b) (4)	(b) (4)
2	Sci-B-Vac	B2016V1	10	50	0.5	NA	NA
3	Engerix-B	AHBVC551BF	20	50	1.0	(b) (4)	(b) (4)

The vaccine materials used for immunization were produced, formulated and released at SciVac Ltd. (Rehovot, Israel) between (b) (4) and were delivered to VBI Vaccines Inc. (Ottawa, Canada) on January 3rd, 2017.

### **Analysis of Serum Samples**

An (b) (4) was used to determine anti-HBsAg antibody titers in mouse sera. Collected (b) (4) serum samples were shipped at a maintained temperature of (b) (4) to SciVac Ltd (Rehovot, Israel) for the determination of anti-HBsAg titers according to SOP-B-HB-272-*Determination of Hepatitis Vaccine Potency by (b) (4)*. The level of anti-HBsAg antibody titers was expressed in IU/mL.

### **Results**

#### **Safety**

All mice on the study progressively gained weight. There were no significant body weight differences between groups and no adverse reactions.

#### **Seroconversion rates**

At d10 post-1st immunization, 100% of animals in group 1 (received adjuvanted Sci-B-Vac vaccine), seroconverted (mean titer ~ 100 IU/mL), 12.5% of animals in group 2 (received unadjuvanted Sci-B-Vac vaccine), seroconverted (mean titer ~1 IU/mL) and 75% of animals in group 3 (received Engerix-B (GSK)) seroconverted (mean titer ~5 IU/mL).

At d34, 13 days after the 2<sup>nd</sup> immunization, 100% of animals in groups 1 and group 3 seroconverted (mean titer for group 1 = ~750 IU/mL, mean titer for group 3 = ~900 IU/mL). For group 2, 37.5% of animals seroconverted with little or no increase in antibody titers.

#### **Overall Reviewer's Assessment of Relevant Sections of Module 4:**

The data submitted under Module 4 are acceptable.

#### **Module 4 – Nonclinical studies**

- ❑ Aluminum hydroxide adjuvanted Sci-B-Vac vaccine induced a higher immune response in immunized mice than the unadjuvanted vaccine.
- ❑ A single dose of adjuvanted Sci-B-Vac induced seroconversion in 100% of immunized mice after 10 days, compared to 75% of animals dosed with Engerix-B.
- ❑ After 2 doses of vaccine there appeared to be no difference in the seroconversion rates or antibody titers of the mice dosed with adjuvanted Sci-B-Vac compared with mice dosed with Engerix-B.
- ❑ The Sci-B-Vac vaccine was shown to be immunogenic in mice and appeared to induce comparable levels of anti-HBs antibodies as Engerix-B after two doses.

## **MODULE 5 Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints**

The sponsor used the VITROS anti-HBs quantitative assay to assess seroconversion and anti-HBs titers.

The original VITROS validation protocol was submitted on Jul 26, 2017, as part of the original IND (IND 17542) and revised in Am 4 (Nov 20, 2017) in response to FDA's September 26, 2017 non-hold comments. FDA returned comments on the revised protocol on Jan 3, 2018 and the requested changes were implemented in the final report. In addition to the assay validation, the results of a (b) (4) serum stability study were provided in the VITROS validation report. An updated validation report was submitted to the BLA, which included results of the (b) (4) serum stability study. These results had been previously submitted to IND 17542.

### **Summary of the VITROS assay**

The sponsor used a commercial assay, the VITROS ECi/ECiQ Immunodiagnostic Systems, to assess antibodies to hepatitis B surface antigen (anti-HBs). This is an automated system. The testing was performed by a contract lab, (b) (4)

The VITROS Anti-HBs Quantitative assay is performed using the VITROS Anti-HBs Quantitative Reagent Pack and VITROS Immunodiagnostic Products Anti-HBs Calibrators on the VITROS ECi/ECiQ VITROS 5600 Integrated System using Intellicheck Technology.

The method involves the reaction of anti-HBs in the sample with HBsAg (ad and ay subtypes) coated onto wells. A horseradish peroxidase (HRP)-labeled HBsAg conjugate (ad and ay subtypes) then complexes with the bound anti-HBs forming an "antigen sandwich." Unbound materials are removed by washing. The bound HRP conjugate is measured by a luminescent reaction. A reagent containing luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent, is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent increases the level and duration of the light produced. The light signals are read by the VITROS ECi/ECiQ Immunodiagnostic System. The amount of HRP conjugate bound is directly proportional to the concentration of anti-HBs present in the sample.

The conjugate reagent and coated wells provided as part of the VITROS Anti-HBs Quantitative Reagent Pack contain purified native hepatitis B surface antigen (HBsAg) obtained from donors who were tested individually and found to be negative for antibodies to human immunodeficiency virus (HIV 1+2) and hepatitis C virus (HCV).

The reagent pack (supplied ready to use) includes 100 human HBsAg (ad and ay subtypes) coated wells; 13.3 mL conjugate reagent (human HBsAg (ad and ay subtypes)-HRP conjugate in phosphate buffered saline with human plasma), bovine

serum albumin, protein stabilizers and antimicrobial agent (Kathon, 2% w/v) and 6.2 mL assay reagent (EDTA phosphate buffered saline with antimicrobial agent (Kathon, 1 %, w/v)). Reagents do not require mixing prior to loading onto the system.

One set of calibrators is supplied with each kit which includes human plasma with nominal values of 0, 30 and 250 mIU/mL anti-HBs. In addition, a lot calibration card, a protocol card and 24 calibrator barcode labels (8 for each calibrator) are included.

**Validation of the Assay**

***Manufacturer Validation***

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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

**Module 4 – Nonclinical studies**

- ❑ Aluminum hydroxide adjuvanted Sci-B-Vac vaccine induced a higher immune response in immunized mice than the unadjuvanted vaccine.
- ❑ A single dose of adjuvanted Sci-B-Vac induced seroconversion in 100% of immunized mice after 10 days, compared to 75% of animals dosed with Engerix-B.
- ❑ After 2 doses of vaccine there appeared to be no difference in the seroconversion rates or antibody titers of the mice dosed with adjuvanted Sci-B-Vac compared with mice dosed with Engerix-B.
- ❑ The Sci-B-Vac vaccine was shown to be immunogenic in mice and appeared to induce comparable levels of anti-HBs antibodies as Engerix-B after two doses.

**Module 5 - Validation of Analytical Procedures for Assessment of Clinical Endpoints**

- ❑ The anti-HBs VITROS method met pre-determined acceptance criteria and is suitable for the quantitative determination of anti-HBs antibodies as performed by the testing lab, (b) (4).
- ❑ The stability study demonstrated that sera are stable between the range of (b) (4) and suitable for anti-HBs antibody testing on the Ortho VITROS 5600 platform.

