

CBER CMC BLA Review Memorandum

BLA STN 125737/0

**PREHEVBRIO
Hepatitis B Vaccine (Recombinant)**

**Priscilla M Pastrana
Consumer Safety Officer
CBER/OCBQ/DMPQ/MRB2**

1. BLA#: STN 125737/0

2. APPLICANT NAME AND LICENSE NUMBER

VBI Vaccines (Delaware) Inc. (US License #2219)

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN: Hepatitis B Vaccine (Recombinant)
 Proprietary Name: PREHEVBRIO

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

PREHEVBRIO [Hepatitis B Vaccine (Recombinant)] is indicated for the prevention of infection caused by all known sub-types of the Hepatitis B in adults. This vaccine is a sterile suspension for injection in a 1.0 mL single-dose vial, which contains 10 µg/mL recombinant Hepatitis B surface antigen (HBsAg) with (b) (4) Aluminum Hydroxide [Al(OH)₃], (b) (4) Adsorption (b) (4) as adjuvant. PREHEVBRIO is administrated via intramuscular (IM) injection into the deltoid muscle in three doses at 0, 1 and 6 months.

5. MAJOR MILESTONES

Application received: 11/30/2020
 First Committee Meeting: 01/07/2021
 Filing Meeting: 01/14/2021
 Filing Action: 01/29/2021
 Proprietary Name Review: 03/03/2021
 Internal Mid-cycle Meeting: 05/10/2021
 Mid-cycle communication: 05/25/2021
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 Labeling: 10/31/2021
 Remote Interactive Evaluation: 10/18 to 10/26/2021
 PMC Study: 10/31/2021
 PDUFA First Action Date: 11/30/2021

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Priscilla M. Pastrana, OCBQ/DMPQ/MRB2	CMC/Facilities

7. INTER-CENTER CONSULTS REQUESTED

Not applicable.

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
November 30, 2020	STN 125737/0	Initial BLA Submission
March 02, 2021	STN 125737/0.2	Responses in Support of DMPQ Information Request (IR) 1
April 12, 2021	STN 125737/0.4	Responses in Support of DMPQ IR 1 Associated to Shipping Validation Study for the Drug Product
October 01, 2021	STN 125737/0.26	Responses in Support of DMPQ IR 2 Associated to the Media Fill Study and the Shipping Validation Study for the Drug Product

Date Received	Submission	Comments/ Status
October 20, 2021	STN 125737/0.30	Responses in Support of DMPQ IR 2 Associated to the Shipping Validation Study for the Drug Product

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 17542	VBI Vaccines (Delaware) Inc.	None	No	No IND review is required. All pertinent information was included in the BLA

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

This BLA from VBI Vaccines (Delaware) Inc. (VBI) in support for their application for licensure of PREHEVBRIO [Hepatitis B Vaccine (Recombinant)] in the US market. PREHEVBRIO is a third-generation hepatitis B recombinant vaccine that is produced by the expression of three proteins of HBsAg in genetically modified mammalian Chinese Hamster Ovary (CHO) cells.

The Hepatitis B Surface Antigen Drug Substance (DS) and Hepatitis B Vaccine (Recombinant) Drug Product (DP) are manufactured at SciVac Ltd., which has been a subsidiary of VBI since 2016. SciVac Ltd. is located at Gad Feinstein Rd POB 580, Rehovot 7610303, Israel.

PREHEVBRIO is produced in genetically modified mammalian CHO cells that produce an envelope of three proteins for the hepatitis B virus (HBV) consisting small (S), middle (pre-S2) and large (pre-S1) HBsAg. The CHO cells (b) (4)

HBsAg is secreted into the (b) (4) DS. This DS (b) (4)

as adjuvant and filled into single-dose vials as the DP. Then vials of the DP are labeled and packaged.

PREHEVBRIO has a shelf-life of three years under storage temperature of 5°C ± 3°C.

Facility and equipment information provided in the BLA was limited to a high-level overview.

The following information was not included in this BLA:

- Qualifications of HVAC, manufacturing equipment and utility (water, clean steam, and compressed gases) systems
- Diagrams of the manufacturing areas, HVAC, and utility systems
- Descriptions of the routine environmental monitoring (EM) and routine monitoring program for the utility systems
- Descriptions of the computerized/automated systems, manual and automated washing processes, sterilization processes, cleaning, and disinfectant agents
- Validations of computerized/automated systems, washing and sterilization processes
- Disinfectant effectiveness study

- Descriptions of the facility capacity increase and modernization project conducted in SciVac Ltd. in 2019
- Description of the (b) (4) used for the downstream process
- Summary from Protocol PRO-0003708, Version No. 1, "Protocol, Hold Time Points During Production Process"
- Summary from Protocol STP-0003840, Version No. 1, "Production Process Holding Time Stability Protocol for (b) (4)"
- Summary from VLR-0004004, Version 2.0, "Process Performance Qualification of Sci-B-Vac"
- Descriptions of the visual inspection, labeling and packaging of DP vials
- Report from the Shipping Validation Study of DP under (b) (4) conditions
- Descriptions of (b) (4), and other testing for the evaluation of the shipping container used for the shipping of DP.

Limited information in support for the following items was provided in this BLA:

- Description of the container closure system for DS
- Media and buffers hold time studies
- Lifetime studies for the (b) (4) and other reusable filters
- Filter Validation Studies for the sterilizing filters used in the manufacture of DP
- Media Fill Study conducted on the filling line used for DP.

Additional clarification was requested regarding the testing facilities for DS.

An Information Request (IR) was sent to VBI on February 02, 2021 to request information regarding the missing and limited items listed above as well as additional clarification in support for the testing facilities for the DS. VBI submitted the responses to this IR on March 02, 2021 and April 12, 2021 under Amendments STN 125737/0.2 (DATS #995570) and STN 125737/0.4 (DATS #1036681), respectively. A second IR was sent to VBI on August 31, 2021 to request additional clarification regarding the media fill studies and the shipping validation of the DP. VBI submitted the responses to the second IR on October 01 and 21, 2021 under Amendments STN 125737/0.26 (DATS # 1450344) and 125737/0.30 (DATS #1492233.)

The responses to the first and second IRs were discussed as part of this memo.

Inspection:

The Pre-License Inspection (PLI) of SciVac Ltd. in Rehovot, Israel could not be conducted due to travel restrictions from the Department of State and the COVID-19 pandemic health emergency.

A records request was conducted according to FD&C Act Section 704(a)(4) and according to DMPQ-MRP-SOP-007, "Records Request Under FD&C 704(a)(4) Authority".

On April 21, 2021 a preliminary record request was sent to Biologics Consulting (VBI US Agent) to request records from SciVac Ltd. VBI submitted the requested records in an amendment to the BLA under STN 125737/0.8 (DATS #1077925) on May 12, 2021.

A follow-up request was submitted to the VBI US Agent on July 08, 2021 to request additional records from SciVac Ltd. in support of the first records request. VBI submitted the requested records in an amendment to the BLA under STN 125737/0.17 (DATS #1224186) on July 27, 2021.

All records were reviewed, no evidence of contrived data or procedures were found. The outcome of the records review was discussed in a separate record review memo. This records review was captured in CMS WA 386996, where the lists of records requests and the review memo have been uploaded.

A Remote Interactive Evaluation (RIE) was conducted for SciVac Ltd. manufacturing facility in Rehovot, Israel on October 18 – 21 and October 25 - 26, 2021 by CBER to evaluate the adequacy of the facility for DS and DP manufacture and to discuss issues identified during the records review. A RIE observation memo was issued to SciVac Ltd. at the end of the RIE on October 26, 2021 with the two following observations.:

- Out of Specification (OOS) results for residual Chinese Hamster Ovary (CHO) host cell protein (HCP) in (b) (4) batches manufactured from April to July 2021 and a (b) (4) batch manufactured in 2019.
- 76% of the deviations initiated from January 01, 2019 to October 24, 2021 were not closed within (b) (4) days as stipulated in SOP-0002536, “*Deviation SOP*,” Revision 3, Effective Date August 03, 2021. Also, this SOP did not provide a procedure for the extension of deviations opened for more than (b) (4) days.

The firm’s responses in support for the RIE observation memo was discussed in a separate memo. The outcome of the RIE was discussed in a separate RIE memo. The RIE of SciVac Ltd. was captured in eNspect Operation ID 209253, where the RIE observation memo, review memo in support of the firm’s responses to the RIE observation memo and the RIE memo have been uploaded. The outcome of the RIE was that the facility appears acceptable and the RIE can be used in lieu of an on-site pre-approval inspection.

(b)(3)



B. RECOMMENDATION

I. APPROVAL

Approval is recommended based on the review of this BLA, amendments in support for responses to Information Requests (IRs), the outcome of the RIE and records review in lieu of PLI.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Priscilla M. Pastrana, Reviewer, OCBQ/DMPQ/MRB2	Concur	
Jie He, Team Lead, OCBQ/DMPQ/MRB2	Concur	
Anthony Lorenzo, Branch Chief OCBQ/DMPQ/MRB2	Concur	
Carolyn Renshaw, Acting Director, OCBQ/DMPQ	Concur	

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE

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

PREHEVBRIO is the name of the Hepatitis B Vaccine (Recombinant.) This vaccine is also named as Sci-B-Vac™. During the development of this vaccine, it was also named as Bio-Hep-B and Hepimmune in the literature. The following nomenclatures are used to name this Hepatitis B Vaccine (Recombinant):

- Vaccinium hepatitis B recombinatum (international nonproprietary name, INN)
- Hepatitis B Vaccine (rDNA) (European Pharmacopeia Name)
- Hepatitis B surface Antigen (HBsAg) (Biochemical Name)
- Sci-B-Vac™ (Company Proprietary Name.)

PREHEVBRIO is a third-generational Hepatitis B Vaccine (Recombinant) produced by the expression of the S, pre-S2 and pre-S1 proteins of the HBV in CHO cells.

The Hepatitis B Surface Antigen DS is the active constituent in the PREHEVBRIO. The DS is composed of (b) (4)

[Redacted]

(b) (4)

(b) (4) (4)

(b) (4)

[Redacted]

(b) (4) (4)

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

(b) (4)

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT

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

The DP is a sterile suspension for injection in a 1.0mL single-dose vial. Each vial contains 10 µg/mL DS absorbed in (b) (4) as adjuvant.

The DP appears turbid when it is mixed and forms a clear-colorless upper solution with white precipitate upon settling. The DP is administrated via intramuscular (IM) injection into the deltoid muscle in three doses at 0, 1 and 6 months.

(b) (4) mL of the DP is filled into ready-to-fill (RTF) (b) (4) vials of 4mL, stoppered with rubber stopper and sealed with aluminum seal with plastic colored flip-off top, to allow withdrawal of the labeled volume of 1.0mL. This container/closure system for the DP is discussed in Section 3.2.P.7 of this review memo. The components or excipients of the DP are discussed in Section 3.2.P.2.1.2 of this review memo.

✓ **Reviewer Comments:** *Information provided in Module 3.2.P.1. associated to the description of DP was reviewed from DMPQ standpoint and it was found acceptable.*

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 DS is the active ingredient used in the manufacture of DP. As described in Section 3.2.S.1 from this memo, the DS is composed of (b) (4)

(b) (4) The DS complies with (b) (4)

3.2.P.2.1.2 Excipients

Below is a list of the excipients used in the manufacture of the DP:

Table No. 26: Excipients for the DP

Component	Use	Monograph
Sodium Chloride (NaCl)	(b) (4)	(4)
Potassium Chloride (KCl)		
Disodium Hydrogen Phosphate/Disodium Phosphate Dodecahydrate (Na ₂ HPO ₄)		
(b) (4) /Potassium		
Dihydrogen Phosphate (KH ₂ PO ₄)		
(b) (4)		
(b) (4)		
(b) (4)		
WFI	Solvent	(b) (4)

✓ **Reviewer Comments:** *Information in Module 3.2.P.2.1 associated with the components of the DP was reviewed from DMPQ standpoint and it was found acceptable.*

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The formulation process for the DP was developed in BTG in the 1990's. The initial formulation of the DP contained Aluminum Phosphate (AlPO₄) as adjuvant and Thimerosal as preservative. BTG conducted the following changes in this formulation:

- Implementation of (b) (4) Aluminum Hydroxide (b) (4) adsorption as adjuvant to replace the Aluminum Phosphate in 1994. The (b) (4) Aluminum Hydroxide has a (b) (4) and absorbs HBsAg DS particle forming a suspension that allows the administration of a uniform dose.

- Removal of Thimerosal as preservative in 1998, according to the recommendation of the EMA (EMEA/20962/99 and EMEA/CPMP/1578/00).

After the above changes, BTG did not conduct further changes in the formulation of the DP.

The manufacture of the DP using (b) (4) as adjuvant is currently conducted in SciVac Ltd. after its transfer from BTG in 2005. The formulation process for the DP is discussed in Section 3.2.P.3.3 of this review memo.

3.2.P.2.2.2 Overages

No overage of the DS to compensate for degradation during the DP manufacturing or shelf-life is required.

VBI indicated that SciVac Ltd. overfilled the vials of the DP at a volume of (b) (4) to ensure a 1.0mL withdrawal of DP prior to be injected. This excess of volume is according to (b) (4). The filling process is discussed in Section 3.2.P.3.3 of this review memo.

3.2.P.2.2.3 Physicochemical and Biological Properties

This section is deferred to the PO reviewer.

- ✓ **Reviewer Comments:** *Information in Module 3.2.P.2.2 associated to the DP including formulation development and overages were reviewed from DMPQ standpoint and they were found acceptable. The formulation and filling steps for the DP are discussed in Section 3.2.P.3.3 of this review memo.*

3.2.P.2.3 Manufacturing Process Development

VBI stated that the manufacture of the DP in SciVac Ltd. consisted of (b) (4)(b) (4), formulation, filling, labeling, and packaging steps. They indicated that the manufacturing process development of the DP uses the same process designation (Processes A, B, C and C+) as for the DS.

The manufacture of the DP at a formulation volume of (b) (4) (maximum commercial batch size) was developed in BTG between 1998 to 1999. This manufacturing process was named Process A and the following steps were validated and conducted in the following site:

- Formulation step was conducted in BTG
- (b) (4) (b) (4) filling, labeling and packaging steps were conducted in (b) (4). A maximum of (b) (4) vials of the DP per batch were filled in (b) (4).

As stated in Section 3.2.S.2.6, SciVac Ltd. acquired the rights to manufacture DS and DP in their Rehovot facility in 2005. Then DS and DP manufacturing processes were renamed as Process B. These processes were transferred and validated in SciVac Ltd. in 2007. VBI indicated the batch sizes of formulated HBV DP were validated in SciVac Ltd.:

Table No. 27: DP Batches Validated in SciVac Ltd. Using Process B

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

The firm stated that the manufacture of the DP was renamed from Process C to Process C+. VBI indicated that manufacture of the DP in SciVac Ltd. using Processes C and C+ are similar. They stated that the current manufacturing process for the DP is conducted using Process C+. There are no changes in the quality attributes in support for the DP manufacturing process associated to the changes implemented in Process C+.

(b) (4)

- ✓ **Reviewer Comments:** Information in Module 3.2.P.2.3 associated to the manufacturing process development of DP was reviewed from DMPQ standpoint and it was found acceptable. The discussion of the manufacturing process development for DP is deferred to the OVRP reviewer.

3.2.P.2.4 Container Closure System

The container/closure system of the DP consists of a (b) (4) borosilicate glass vial with a black chlorobutyl (b) (4) rubber stopper and (b) (4) aluminum seal with a light blue plastic flip-off cap. The DP vial is labeled and packed in a carton box with a package insert.

The vial complies with (b) (4) requirements for (b) (4) borosilicate glass container and the stopper complies with (b) (4) requirements for elastomeric closure and non-cytotoxicity.

- ✓ **Reviewer Comments:** Information in Module 3.2.P.2.4 associated to the container/closure system for the DP was reviewed from DMPQ standpoint and it was found acceptable. The description of the container/closure system for the DP and testing conducted to evaluate its integrity are discussed in Section 3.2.P.7 of this review memo.

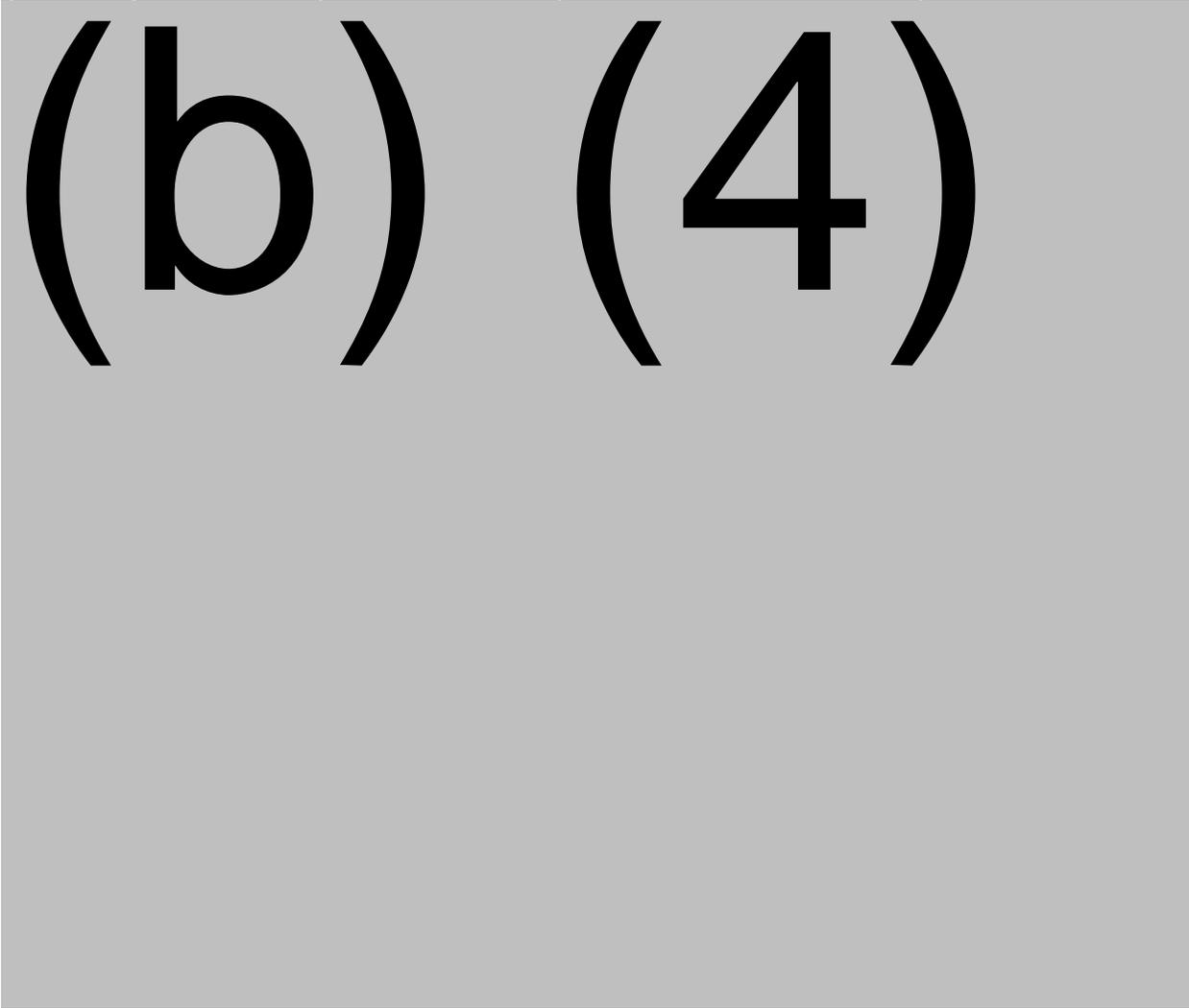
3.2.P.2.5 Microbiological Attributes

The DP is a sterile, single dose product and does not contain preservatives. VBI explained that SciVac Ltd. conducts (b) (4) to the DS and the components (b) (4) used for the formulation of the DP. They stated that the (b) (4) used as adjuvant is purchased (b) (4). The firm indicated that SciVac Ltd. conducted the following (b) (4) testing to the DS excipients, stoppers, vials and release testing for the DP:

Table No. 28: (b) (4) Testing Conducted to the DS, Excipients, Stoppers, Vials and Release Testing for the DP

(b) (4)

DS/Excipient/Container Closure Component/DP	Testing	Test Method	Acceptance Criteria
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DP	Endotoxin	(b) (4)	
DP	Sterility	(b) (4)	Sterile (No Growth)
DP	Package Integrity or Container Closure Integrity Testing (CCIT) at (b) (4)	(b) (4)	

VBI indicated that SciVac Ltd. sterilizes the stoppers with (b) (4) used in the filling of the DP. The sterilization process of the stoppers is discussed in Section 3.2.P.3.5 of this review memo. They stated that the flip-off caps used in the container/closure system of the DP are sterilized by the supplier.

The firm stated that other controls in-place at SciVac Ltd. to prevent microbial contamination of the DP includes the media fill runs and the Packaging Integrity or

CCIT using (b) (4) method is conducted to the DP as part of its release testing and stability program.

- ✓ **Reviewer Comments:** Information in Module 3.2.P.2.5 associated to the microbiological attributes for the DP was reviewed from DMPQ standpoint and it was found acceptable. The media fill runs are discussed in Section 3.2.P.3.5 and the CCIT of container/closure system for the DP is discussed in Section 3.2.P.7 of this review memo.

3.2.P.2.6 Compatibility

This section is deferred to the PO reviewer.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The following facilities are used for the manufacture, storage and testing of the DP:

Table No. 29: DP Manufacturing and Testing Facilities

Manufacturing/Testing/Storage Facilities	Activities
SciVac Ltd. 13 Gad Feinsein Rd POB 580 Rehovot 7610303, Israel FEI: 3012695367	<ul style="list-style-type: none"> • Manufacture, Filling, Labeling, Packaging and Storage of the HBV DP • In-process, Release and Stability Testing of the HBV DP
(b) (4)	

- ✓ **Reviewer Comments:** The above facilities listed for the manufacture, testing and storage of the DP in Module 3.2.P.3.1 were also listed in the FDA form 356h, Module 1.2 from this BLA. During the review of the mentioned modules and the FDA form 356h, additional clarification is required regarding the FIE # for (b) (4) **See IR Question #2.c. – 02/02/2021 (See Below.)**

2. Regarding Module 1.2 – Cover Letters “CMC Sites Summary List”:

- c. It was noted that the FEI number of (b) (4) is missing in this table. However, it was noted in our database that the FEI number of this facility is (b) (4). Please review and update this table to include the correct FEI number for (b) (4)

Firm Responses: VBI reviewed and updated the Modules 1.2, 2.3.P.3.1 and 3.2.P.3.1 to include the FEI number (b) (4)

- ✓ **Reviewer Comments:** Modules 1.2, 2.3.P.3.1 and 3.2.P.3.1 were reviewed to include the above FEI number for (b) (4)

3.2.P.3.2 Batch Formula

The formulated bulk DP batch size between (b) (4) . This amount of formulated bulk DP is used to fill (b) (4) vials to (b) (4) vials of 1mL. Below is the batch formula of the formulated bulk DP batch sizes (b) (4) ; in addition, to the 1mL single-dose vial:

Table No. 30: Amounts of DS and Excipients in 1mL Single-Dose Vial and Formulated DP Batches of (b) (4)

Component	(b) (4)	(4)
DS		
Sodium Chloride		
Potassium Chloride		
Sodium Chloride		
Disodium Hydrogen Phosphate/Disodium Phosphate Dodecahydrate		
(b) (4)		
Potassium Dihydrogen Phosphate		
(b) (4)		
(b) (4)		
(b) (4)		
WFI		

As stated in Section 3.2.P.2.2.2 of this memo, the vials of DP are overfilled at a volume of (b) (4) to ensure a withdrawal of 1.0mL DP prior to be injected.

- ✓ **Reviewer Comments:** Information in Module 3.2.P.3.2 associated to the batch formula for the DP in 1mL single-dose vial and formulated bulk product batches of (b) (4) was reviewed from DMPQ standpoint and it was found acceptable.

3.2.P.3.3 Description of Manufacturing Process

The DP manufacturing process consists of Formulation, Filling, Visual Inspection, Storage, Labeling, and Packaging Process Steps. The following chart illustrates the DP manufacturing steps with their IPCs:

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

The Labeling and Packaging Process Steps were not included in the above chart. The DP manufacturing process has a duration of (b) (4) from the beginning of the Formulation Process until the end of the Filling Process. The Filling Process has a duration of (b) (4). A maximum of (b) (4) DS batches are (b) (4) formulated bulk DP batch of a volume between (b) (4). The size of the filling DP batch is between (b) (4) 1mL vials.

Information in support of the rooms, LAF hood and equipment used for the manufacture of the DP is discussed in Section 3.2.A.1 of this review memo.

The CPPs and IPCs associated with the manufacture of the DP are discussed in Section 3.2.P.2.4 of this review memo.

Non-critical process parameters (PPs) associated with the manufacture of the DP are discussed in the respective manufacturing process step of this section.

□ **Manufacturing Process Steps**

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

- Filling Step: The Filling Step consists of the filling of (b) (4) DP into 4mL Ready to Fill (RTF) (b) (4) glass vials to allow withdrawal of a labeled volume of 1.0mL with a HBsAg concentration of 10µg/mL according to (b) (4). Between (b) (4) vials are filled with DP per run with a filling yield of (b) (4). The Filling Step has a maximum duration of (b) (4).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted text block]

Vials sampled from the (b) (4) of the filling process are tested for visual inspection and CCIT as follows:

Table No. 33: Testing Conducted to the DP Vials

Testing	Number of Vials Tested Per Sampling (b) (4) of Filling)	Acceptance Criteria
Visual Inspection	(b) (4) Vials	Turbid When Mixed, Clear Colorless Upper Solution and White Precipitate Upon Settling
CCIT	(b) (4) Vials	(b) (4)
(b) (4)	(b) (4) Vials	(b) (4)

(b) (4)

[Redacted text block]

(b) (4)

- Vial Inspection Step: This step consists of the 100% visual inspection of the DP vials filled, stoppered and capped in the Filling Step. This step is conducted by qualified personnel at a temperature of (b) (4) for a maximum of (b) (4) of DP is inspected at a time. This step starts with (b) (4)

. At the end of the visual inspection for the (b) (4) the amount of rejected and accepted vials are counted. The accepted vials are stored at 2°C to 8°C and their time out of storage is calculated.

The percent of total number of inspected vials rejected for each category of defect is calculated and trend analysis conducted. If more than (b) (4) of vials were rejected for any reason, the manufacturing department and QA is to be notified. If more than (b) (4) of vials were rejected for any reason, a deviation is initiated.

An Acceptance Quality Limit (AQL) testing is conducted by a (b) (4) person on a subset of vials from the (b) (4) of the filling run, as defined must pass to determine the quality of the batch. The number of vials for the AQL testing is determined according to ISO2859, "General Inspection Level II."

- DP Storage Step: After visual inspection, DP vials from the (b) (4) of the Filling Step are sampled for release testing. The rest of the DP vials are stored at 2°C to 8°C, until labeling and packaging.
- Labeling and Packaging Steps: The Labeling Step is conducted at (b) (4) using a labeling machine and in a controlled room dedicated for these steps. The Labeling Step has a maximum duration of (b) (4) of DP is labeled at a time. The Labeling Step consists of (b) (4)

After labeling, 100% visual inspection is conducted for the detection of mislabeled, double labeled and damaged vials. Rejected vials are destroyed. Unused and rejected labels are returned to QA for destruction. At the end of the Labeling Step, the DP vials are returned to the 2°C to 8°C storage area, until secondary packaging.

✓ **Reviewer Comments:** Information in Modules 3.2.P.3.1, 3.2.P.3.2 and 3.2.P.3.3 associated to the manufacturer, description of the DP manufacturing process and batch numbering were reviewed from DMPQ standpoint. The manufacturer information and the batch numbering were found acceptable. Additional information is required regarding the visual inspection, labeling and packaging steps. See IR Questions #7.a., #7.b. and #7.c. – 02/02/2021 (See Below.)

7. Please provide the following information in support of Modules 2.3.P.3.3 and 3.2.P.3.3 associated to the Manufacture of Sci-B-Vac Drug Product (HBV DP):
- Summary that describes the visual inspection of the vials of Sci-B-Vac Drug Product. Ensure to include a description of the critical, major and minor defects to be detected during visual inspection and their acceptance/rejection limits. Ensure to include a description of the re-inspections allowed to conduct if the first visual inspection failed or additional re-inspection required to be conducted with their acceptance/rejection limits. Also, ensure to describe the handling of the rejected vials.

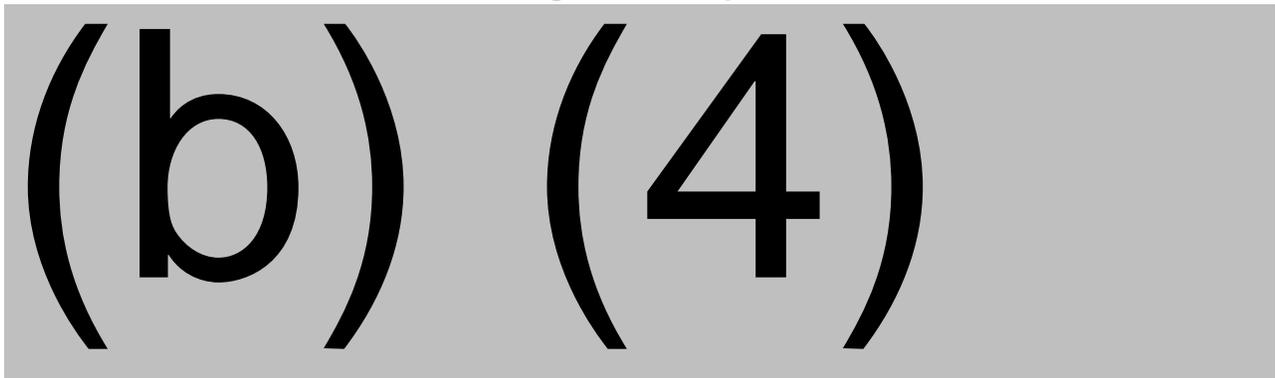
Firm Responses: VBI indicated that visual inspection is conducted on (b) (4) at a time and the room used for visual inspection is labeled with the batch number. They stated that the visual inspection is documented in the visual inspection room logbook and in the batch record. The firm explained that line clearance and change-over is conducted prior to initiate the visual inspection process and (b) (4). The line clearance and change-over processes are described in the firm's response to the IR Question #7.c.

The visual inspection of the DP batch is conducted at a temperature of (b) (4) for a maximum of (b) (4). Qualified personnel conduct the visual inspection of the DP vials using a (b) (4).

(b) (4). At the end of each vials (b) (4) inspected, the personnel document the number of vials accepted and rejected in the batch record. Vial dropped during the visual inspection process is considered as rejected.

Below is a description of critical, major, and minor defects to be detected during visual inspection and their acceptance/rejection limits:

Table No. 34: Description of Critical, Major and Minor Defects to be Detected During Visual Inspection



(b) (4)

VBI explained that an investigation is initiated, and re-inspection is conducted in the following cases:

- If one or more of the above defects exceed their alert limit in the inspected vials
- If critical or major defect is detected during the AQL verification.

The firm indicated that the rejected vials are segregated according to their defect and they are stored in a segregated area of the 2°C to 8°C storage area. This area is labeled with the HBV DP batch number and the number of rejected vials. Then these vials are discarded in a container dedicated for medicine destruction after the reconciliation of vials at the end of the packaging process. An outsourced company is in charge for the disposal of this container.

✓ **Reviewer Comments:** *The description of, the critical, major, and minor defects to be detected during visual inspection for DP vials and their acceptance/rejection limits, re-inspection of vials and disposal of rejected vials were reviewed and found acceptable.*

b. *Summary that describes the labeling and packaging procedures for Sci-B-Vac Drug Product. Ensure to describe the equipment used for these processes.*

Firm Responses: The description of the labeling and packaging processes for the DP is the same as described in Module 3.2.P.3.3. The equipment used for the labeling process is described in the firm's response to the IR Question #12.i.

✓ **Reviewer Comments:** *The firm's response is acceptable.*

c. *Summary that describes the segregation, line-clearance, change-over, reconciliation controls in place to prevent mix-up during visual inspection, labeling and packaging processes.*

Firm Responses: VBI provided a description of the segregation, line-clearance, change-over, reconciliation controls in place to prevent mix-up during visual inspection, labeling and packaging processes in SciVac Ltd. as follows:

(b) (4)

[Redacted]

[Redacted]

(b) (4)

- ✓ **Reviewer Comments:** *The description of the segregation, line-clearance, change-over, reconciliation controls in place to prevent mix-up during visual inspection, labeling and packaging processes in SciVac Ltd appear acceptable.*

3.2.P.3.4 Controls of Critical Steps and Intermediates

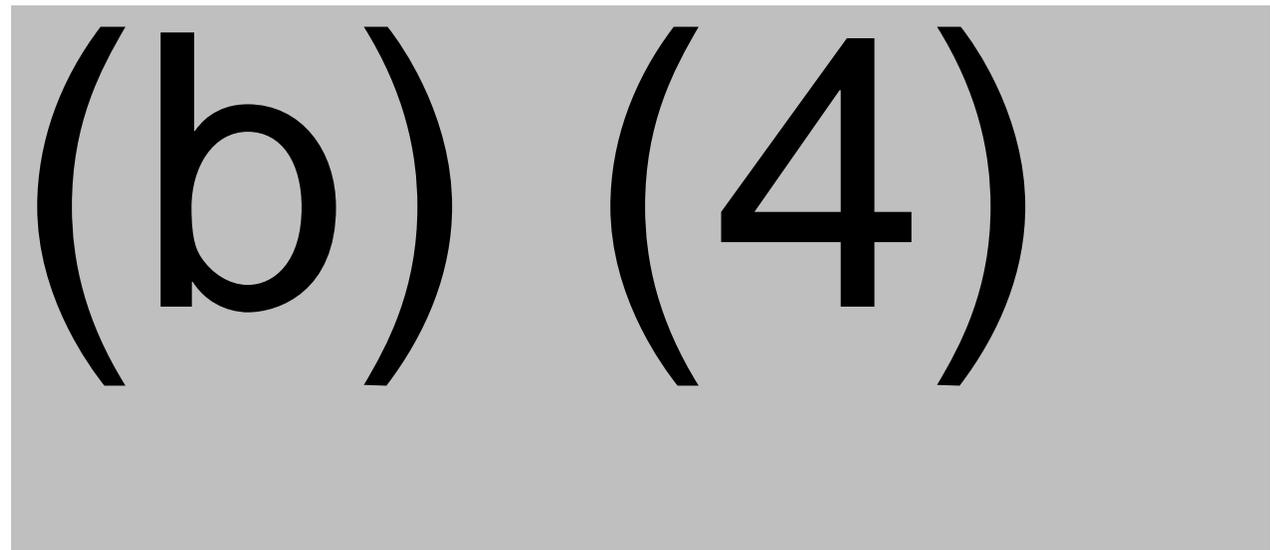
The CPPs associated to the DP manufacturing are the following:

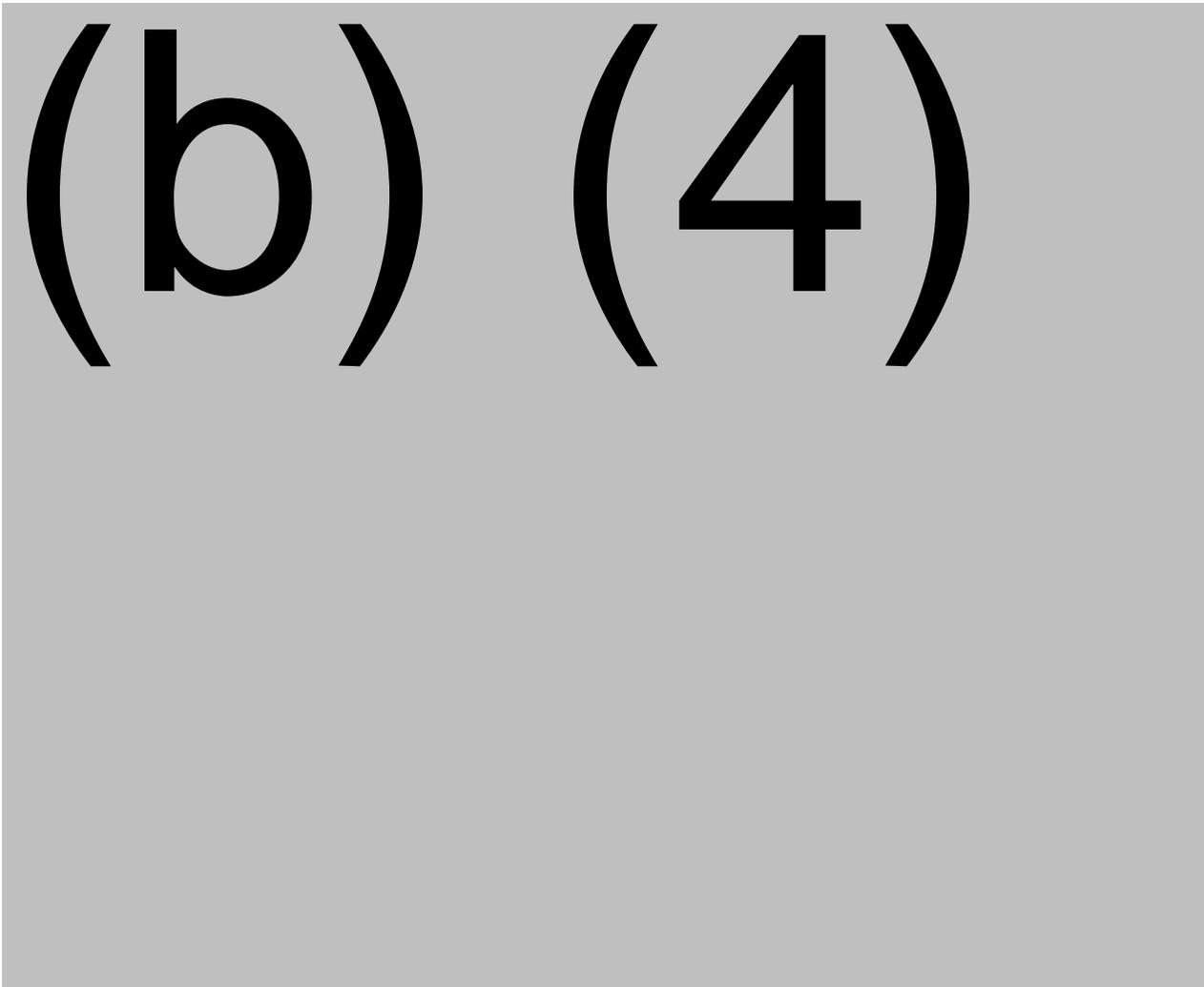
Table No. 35: CPPs Associated to the DP Manufacturing

A large grey rectangular area redacting the content of Table No. 35. The redaction consists of two large, bold, black characters: a lowercase letter 'b' and the number '4', each enclosed in large parentheses. This is a common way to indicate that the content is withheld under FOIA exemption (b)(4).

The IPCs associated to the DP manufacturing are the following:

Table No. 36: IPCs Associated to the DP Manufacturing

A large grey rectangular area redacting the content of Table No. 36. The redaction consists of two large, bold, black characters: a lowercase letter 'b' and the number '4', each enclosed in large parentheses. This is a common way to indicate that the content is withheld under FOIA exemption (b)(4).



✓ **Reviewer Comments:** Information provided in Module 3.2.P.3.4 associated to the Controls of Critical Steps and Intermediates for the DP was reviewed from the DMPQ standpoint and it was found acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

Note: The Qualification Studies and Cleaning Validation Studies of the equipment used for the DP manufacture are discussed in Section 3.2.A.1 of this review memo.

Validation of the DP Manufacture Process:

(b) (4) [Redacted]

[Redacted]

[Redacted]

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

(b) (4)

[Redacted]

✓ **Reviewer Comments:** *Information provided in Module 3.2.P.3.5 associated to the Process Validation and/or Evaluation for the DP was reviewed from the DMPQ standpoint. SciVac Ltd. demonstrated in the three DP batches manufactured in the PPQ Study that they complied with endotoxin and sterility criteria of (b) (4) and No Growth. Also, they demonstrated that these PPQ DP batches did not exceed the alert and action limits for visual inspection.*

Media Fill or Aseptic Process Simulation (APS) Study:

VBI stated that SciVac Ltd. conducted a Media Fill study after the implementation of the (b) (4) filling line with the ready-to-use vials for the filling of the DP. This study was conducted in June 2020. This study consisted of three media fill runs using (b) (4) to simulate the Formulation and Filling Steps of DP, including the addition of the adjuvant to the (b) (4)

A minimum of (b) (4) vials of 4mL (b) (4)

(b) (4)

The firm indicated that the simulation of the (b) (4)

The acceptance criteria for this Media Fill study and requalification of the APS are the following:

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

(b) (4)

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

(b) (4)

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

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

✓ **Reviewer Comments:** Information of the Media Fill Study provided in Module 3.2.P.3.5 in support for the Process Validation and/or Evaluation for the DP was reviewed from the DMPQ standpoint. However additional information is required regarding this study. See IR Question #8 – 02/02/2021 (See Below.)

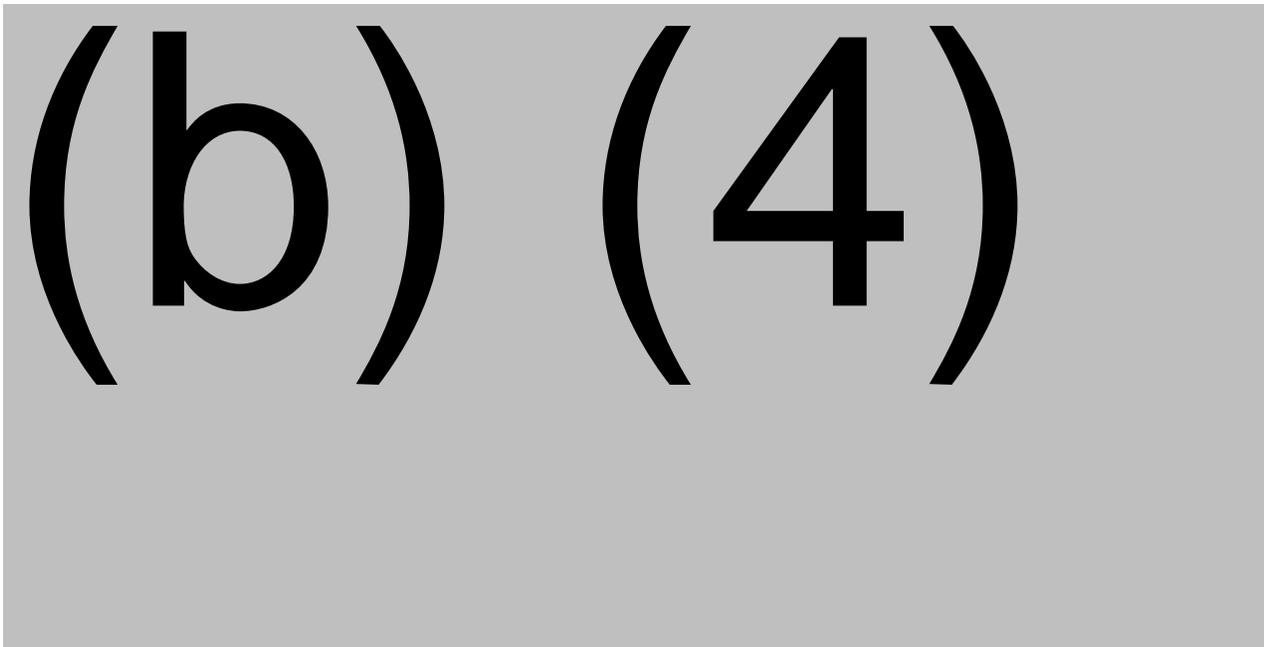
8. Please provide the following information in support of the Media Fill Study in Modules 2.3.P.3.5 and 3.2.P.3.5 associated to the Process Validation of Sci-B-Vac Drug Product:

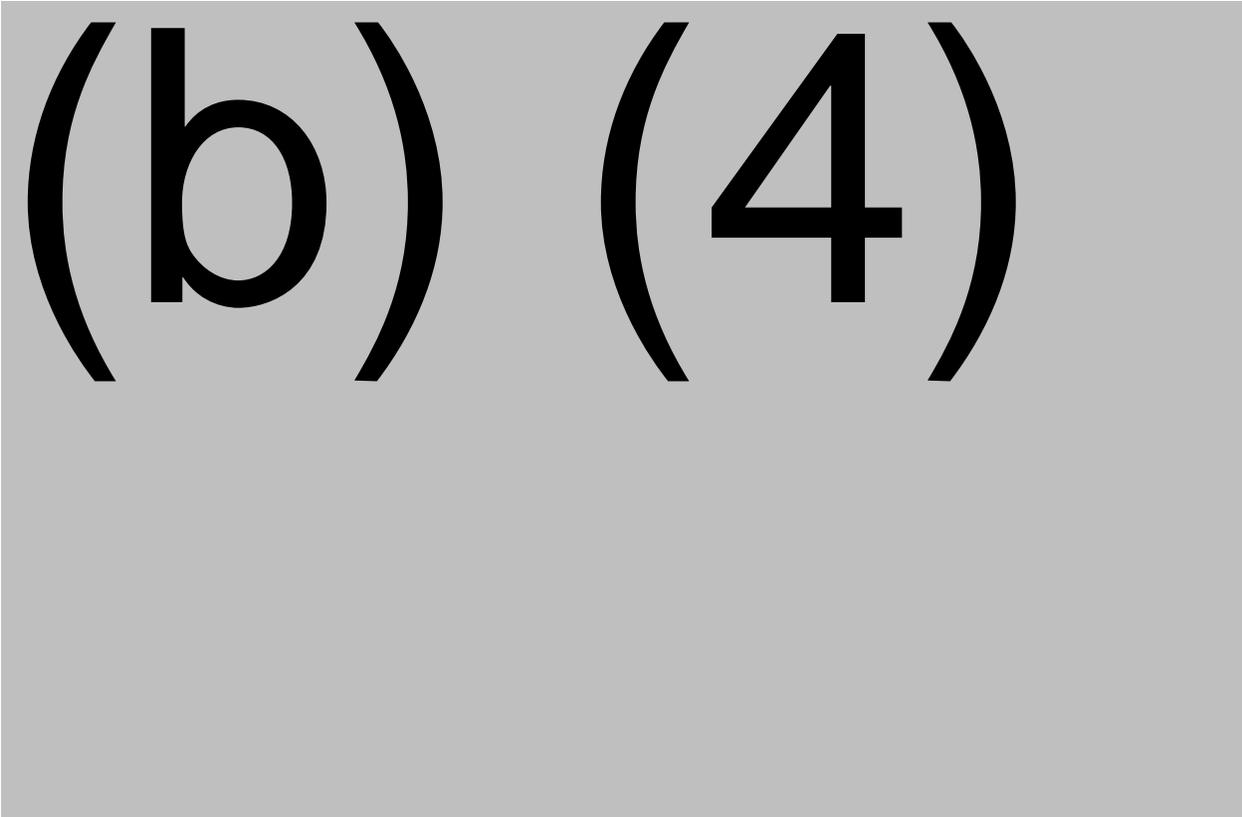
Summary that describes the Media Fill Study conducted on the filling line used for the Sci-B-Vac Drug Product. Ensure to provide a summary of the testing conducted with their results and acceptance criteria. Ensure to include a list of the planned and unplanned interventions conducted. Also, ensure to include a summary of the Environmental Monitoring (EM) and personnel monitoring conducted in this study, including sampling locations, alert and action limits, and results. Ensure to include a summary that describes the actions to be taken in the case of an excursion during the Media Fill Study. Ensure to include a summary that describes the deviations initiated in this study with their root causes and actions taken for resolution and closure, if applicable.

Firm Responses: VBI explained the summary describes the Media Fill Study on the (b) (4) filling line used for the DP in SicVac Ltd. was provided in Section 3.2.P.3.5.4 from Module 3.2.P.3.5 of this BLA. This summary provides the results and acceptance criteria in support for the testing conducted in this study. Also, this summary provided the result, alert and action limits for the EM and personnel monitoring conducted in the Grade (b) (4) and (b) (4) areas from the formulation and filling rooms during this study.

The firm provided a list of the planned and unplanned interventions conducted in this Media Fill study as follows:

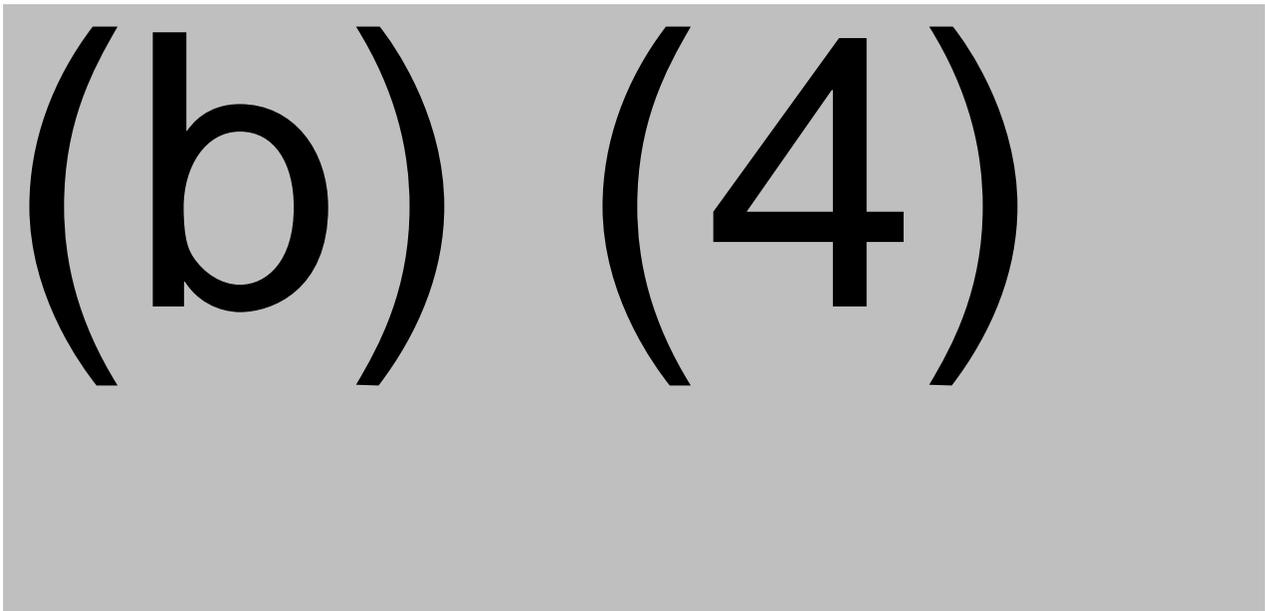
Table No. 46: List of Planned and Unplanned Interventions





VBI explained that the acceptance criteria in support for the Media Fill Study in SciVac Ltd. was updated recently to comply with the FDA Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing (September 2004) as follows:

Table No. 47: Media Fill Study Acceptance Criteria



The firm indicated that a deviation was initiated in the Media Fill batch (b) (4) due to three personnel monitoring excursions as follows:

(b) (4)

VBI stated that SciVac Ltd. implemented the following actions for the correction, mitigation, and resolution of this deviation:

- Training of aseptic techniques to the filling personnel including the hand sanitization and change of (b) (4) pair of gloves frequently
- Training in the handling of empty vials (b) (4)

The firm explained that the above deviation does not affect this Media Fill batch.

✓ **Reviewer Comments:** *The Media Fill Study in support for the (b) (4) filling line in SciVac Ltd. was discussed in Section 3.2.P.3.5 of this review memo. However, the firm did not provide a summary that describes the deviations initiated in support for the EM and personnel monitoring excursions in page 11 of 70 on Section 5.4 from Module 3.2.P.3.5. See IR Question #1 – 08/31/2021. (See Below).*

1. *Regarding the EM and personnel monitoring excursions described in page 11 of 70 on Section 5.4 from Module 3.2.P.3.5.*

Please provide a summary that describes the deviations initiated in this Media Fill Study in support for EM and personnel monitoring excursions. Ensure to include their root causes and actions taken for resolution and closure.

Firm Responses: VBI provided a summary that describes three deviations initiated in this Media Fill Study at SciVac Ltd. with their root cause and actions taken for resolution and closure as follows:

- Dev-0000185-2019: Two personnel monitoring excursions during the media fill batch (b) (4) as follows:
 - (b) (4)

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

(b) (4) [Redacted]

The firm indicated that these deviations did not impact the media fill batches (b) (4) [Redacted] filled in this Media Fill Study.

✓ **Reviewer Comments:** *The firm's response is acceptable.*

Filter Validation Study:

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4) [Redacted]

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

(b) (4)

(b) (4)

The firm indicated that this study complied with the same criteria as the (b) (4) Bacterial Retention Study.

✓ **Reviewer Comments:** *Information of the Bacterial Retention Study provided in Module 3.2.P.3.5 in support for the Process Validation and/or Evaluation for the DP was reviewed from the DMPQ standpoint. However additional information is required regarding this study. See IR Question #9 – 02/02/2021 (See Below.)*

9. Please provide the following information in support of the Bacterial Retention Study in Modules 2.3.P.3.5 and 3.2.P.3.5 associated to the Process Validation of Sci-B-Vac Drug Product:

Summary that describes the Filter Validation Studies for the sterilizing filters used in the manufacture of the Sic-B-Vac Drug Product. Ensure to provide a summary of the testing conducted with their results and acceptance criteria. Ensure to include a summary that describes the deviations initiated in these studies with their root causes and actions taken for resolution and closure, if applicable.

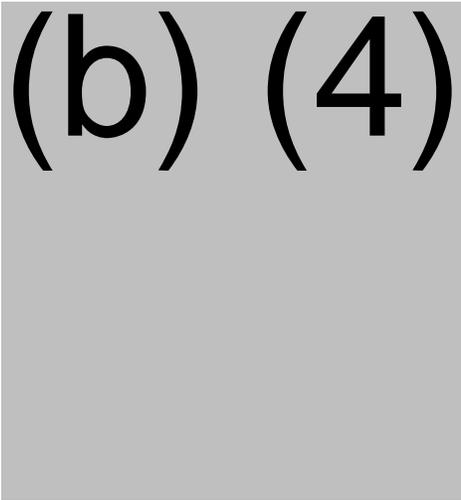
Firm Responses: VBI explained that the summary that describes the bacterial retention studies as the Filter Validation Studies for the sterilizing filters used in the manufacture of the DP in SicVac Ltd. was provided in Section 3.2.P.3.5.5 from Module 3.2.P.3.5 of this BLA. This summary provides the results and acceptance criteria in support for these bacterial retention studies. The firm indicated that no deviation was initiated in these bacterial retention studies.

✓ **Reviewer Comments:** *The bacterial retention studies for the sterilizing filters used in the manufacture of the DP were discussed in Section 3.2.P.3.5 of this review memo and they were found acceptable.*

Shipping or Transportation Validation Study of the DP:

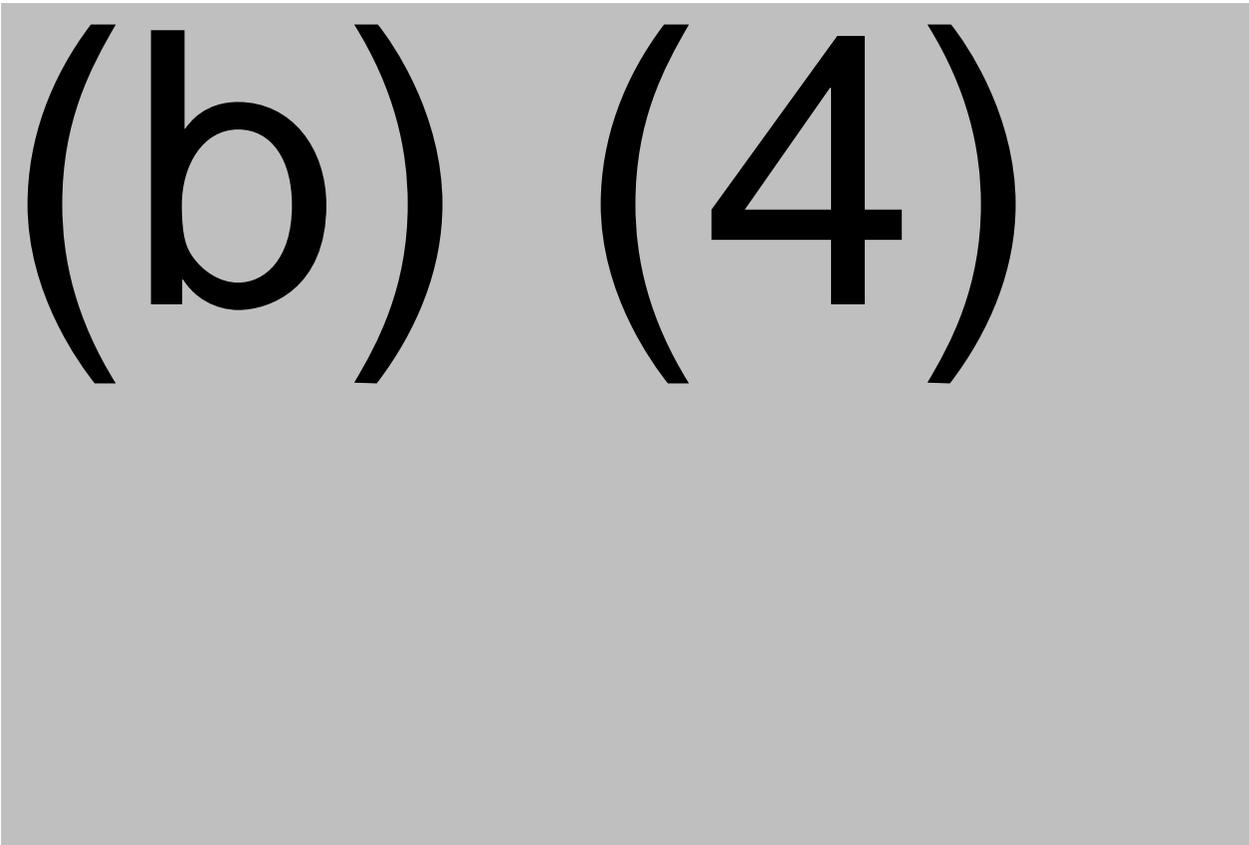
The DP is shipped at 2°C to 8°C to distribution centers using a Master Shipper. (b) (4) (b) (4) 10-unit carton packs of the DP (b) (4) 10-unit carton packs are packed in the Master Shipper. The dimensions of the Master Shipper are (b) (4) Below is the illustration of the Master Shipper:

Figure No. 3: Master Shipper



The Master Shipper is packed into two different types of shipping containers as follows:

Table No. 50: Description of the Shipping Containers for the DP



Below are the illustrations for the above shipping containers:

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

(b) (4)

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

As discussed in Section 3.2.S.2.3 of this review memo, the materials or excipients used for the manufacture of the DP are tested according to the applicable Pharmacopoeia specification. Full monograph (b) (4) testing is conducted every (b) (4) batches or in (b) (4) basis. Additional testing is conducted according to SciVac Ltd. internal policy for the reduced testing program of qualified suppliers. The acceptance criteria of these additional testing are according to the respective Pharmacopoeia specification. The Certificate of Analysis (CoA) from the excipients are reviewed as part of their incoming process according to SciVac Ltd. internal policy.

- ✓ **Reviewer Comments:** *Information provided in Module 3.2.P.4.1 associated to the Specification of materials for the DP manufacture was discussed in the review memo of requested manufacturing site records under Section 704(a)(4) (FDASIA Sec. 706.) The review of this information is deferred to the OVRP reviewer.*

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

This section is deferred to OVRP and DBSQC reviewers.

3.2.P.4.4 Justification of Specifications

The justification of microbiological (b) (4) specifications for (b) (4) NaOH, KCl, Na₂HPO₄ and KH₂PO₄ was discussed in Section 3.2.P.2.5 of this review memo.

3.2.P.4.6 Novel Excipient

This section is not applicable to this BLA.

- ✓ **Reviewer Comments:** *Information provided in Module 3.2.P.4 associated with the specification of excipients and their justification used for the manufacture of the DP were reviewed from the DMPQ standpoint and found acceptable. The reviews of the specifications, analytical procedures, validation of these procedures and justification of specification(s) are deferred to the OVRP and DBSQC reviewers. The materials*

used for the DP manufacture were discussed in the review memo of requested manufacturing site records under Section 704(a)(4) (FDASIA Sec. 706.)

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 CCIT, endotoxin and sterility release specifications of the DP are the following:

Table No. 57: DP Release Specifications

Test	Method	Monograph / Historical Data	Acceptance Criteria
Endotoxin	(b) (4)	(b) (4)	(b) (4)
Sterility	(b) (4)	(b) (4)	No Growth
Package Integrity (Container Closure Integrity Testing or CCIT)	(b) (4)	(b) (4)	(b) (4)

✓ **Reviewer Comments:** The endotoxin and sterility release specifications for the DP provided in Modules 3.2.P.5.1 and 3.2.P.5.6 were reviewed and found acceptable from the DMPQ standpoint. The CCIT, endotoxin and sterility release testing for the DP are conducted according to (b) (4). The reviews of the specifications and justification of specification(s) are deferred to the OVRR and DBSQC reviewers.

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

This section is deferred to Product Office and DBSQC reviewer.

3.2.P.5.4 Batch Analyses

The following PPQ DP batches were manufactured using Process C+ in support for this BLA:

Table No. 58: PPQ DP Batches Manufactured After the Implementation of Process C+

(b) (4)

These batches were manufactured in a PPQ Study in support for this BLA and reported in VLR-0004004. The manufacture of these PPQ batches is discussed in Section 3.2.P.3.5 of this review memo.

The Certificate of Analysis (CoA) from the above PPQ DP batches were provided in this BLA. Endotoxin and sterility release testing were conducted the above DP batches. The sterility release testing complied with a criterion of sterile (no growth.) The endotoxin release testing complied with a criterion of (b) (4) and the CCIT complied with a criterion of (b) (4).

- ✓ **Reviewer Comments:** Information provided in Module 3.2.P.5.4 associated to the DP batch analyses was reviewed from DMPQ standpoint and found acceptable. The review of the other batch analyses for the DP is deferred to the OVRP reviewer.

3.2.P.5.5 Characterization of Impurities

This section is deferred to the PO reviewer.

3.2.P.6 Reference Standards or Materials

This section is deferred to DBSQC reviewer.

3.2.P.7 Container/Closure System

The DP is filled into a clear (b) (4) borosilicate glass vial of 4mL, closed with a black chlorobutyl (b) (4) rubber injection stopper and (b) (4) aluminum seal with a light blue plastic flip-off top. Then the filled, stoppered, and capped vial is labeled with relevant information and packaged in a carton box with package insert. The components of the container/closure system for the DP are discussed below.

Vials

RTF (b) (4) or RTU vials of 4mL are supplied by (b) (4). These vials are made of clear (b) (4) borosilicate glass that comply with (b) (4). Also, these vials are (b) (4). These vials are (b) (4) prior being shipped to SciVac Ltd. Upon their receiving in SciVac Ltd., (b) (4) testing are conducted with selected samples from these vials. Also, full monograph testing is conducted to the vials, for every (b) (4) batches or (b) (4).

Below are the specifications for the testing conducted to these vials:

Table No. 59: Vials Release Specifications

Test	Method	Acceptance Criteria
(b)	(b)	(4)

(b) (4)

VBI indicated that SciVac Ltd. used clear (b) (4) borosilicate glass vials of 4mL supplied by (b) (4) for the manufacture of the clinical batches and batches used in the Stability Studies in support for this BLA. These vials were (b) (4) when they were received in SciVac Ltd.

As part of the facility upgrades in the manufacturing areas at SciVac Ltd. in 2019, it was decided to implement RTU clear (b) (4) borosilicate glass vials of 4mL from (b) (4). As discussed previously, the vials from (b) (4) are (b) (4) and sterilized using (b) (4) in their facility prior to be shipped to SciVac Ltd.

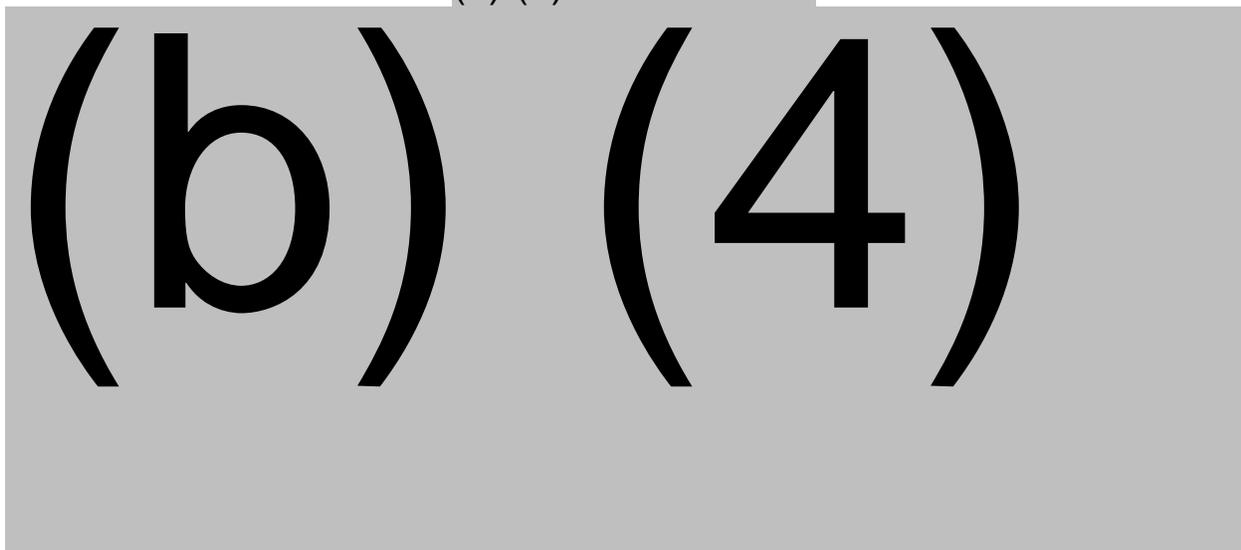
The firm explained that the 4mL vials from (b) (4) have the same dimensions, made of the same material and the material used for the manufacture of the vials are bought from the same manufacturer (b) (4). The firm clarified that there are not changes in the stopper and the aluminum flip-off cap used in the container closure system for the DP.

The 4mL vials from (b) (4) were used in the DP batches manufactured for the PPQ Study in support for this BLA to demonstrate that there are no changes in the Filling Step, container/closure system and CCIT. These PPQ DP batches were placed on stability under long term, accelerated (b) (4) conditions to demonstrate that there are no changes in the quality and purity of the DP filled in the 4mL vials from (b) (4).

VBI stated that there are no changes in the Filling Step, container/closure system, CCIT and stability of the DP in SciVac Ltd. with the implementation of the 4mL vials from (b) (4) to replace the ones from (b) (4).

VBI provided copy of REP-00003685, "Quality Assessment: Change from (b) (4) Glass Vials for Sci-B-Vac," Version 1.0, Effective Date May 13, 2020 to demonstrate that the vials from (b) (4) did not impact the filling of the DP in SciVac Ltd. A comparison of the clear (b) (4) borosilicate glass vials of 4mL from (b) (4) was provided in this assessment as follows:

Table No. 60: Comparison of Clear (b) (4) Borosilicate Glass Vials of 4mL from (b) (4)



The comparison of the chemical composition for the 4mL vials from (b) (4) are the following:

Table No. 61: Chemical Composition Comparison of Clear (b) (4) Borosilicate Glass Vials of 4mL from (b) (4)



VBI stated that SciVac Ltd. concluded the following in this assessment:

- The 4mL vials from (b) (4) have identical dimensions and volume
- The 4mL vials from (b) (4) are made of the same material of construction with same chemical composition. Also, both vials are manufactured using the same process.
- The 4mL vials from (b) (4) comply with the same (b) (4) requirements for glass pharmaceutical containers.
- The DP is compatible with the 4mL vials from (b) (4)
- The 4mL vials from (b) (4) are appropriated for the filling of the DP
- The filling of the DP and the CCIT will not be affected with the implementation of the 4mL vial from (b) (4)

The firm indicated that the (b) (4) for the 4mL vials from (b) (4) was validated to comply with a (b) (4). They stated that this (b) (4) was validated according to (b) (4)

Stoppers

Black chlorobutyl (b) (4) rubber injection stoppers are manufactured and supplied by (b) (4). These stoppers comply with (b) (4) for elastomeric closures and (b) (4) for non-cytotoxicity. The stopper formulation is (b) (4). These stoppers are not made with Natural Rubber Latex or Dry Natural Rubber. The (b) (4) used for coating the stoppers are Grade (b) (4)

These stoppers are (b) (4) and packaged (b) (4) in their manufacturing facility. At their receiving in SciVac Ltd., (b) (4) testing are conducted on these stoppers. Also, full monograph testing is conducted on the stoppers, every (b) (4) batches or (b) (4).

Below are the specifications for the testing conducted to these stoppers.

Table No. 62: Stoppers Release Specifications

(b) (4)

After releasing these stoppers, (b) (4)

(b) (4) [redacted] prior to the filling of the HBV DP. The sterilization of the stoppers is discussed in Section 3.2.A.1 of this review memo.

Aluminum Flip-off Seal

Clear aluminum seals with a light blue plastic flip-off are manufactured and supplied by (b) (4). These seals are (b) (4). They are sterilized by the manufacturer prior to be shipped to SciVac Ltd. (b) (4) are the incoming tests for these aluminum flip-off seals when received in SciVac Ltd. Below are the specifications for the testing conducted on these aluminum flip-off seals.

Table No. 63: Aluminum Flip-Off Seals Release Specifications



Released seals are (b) (4), prior the filling of the DP.

Container/Closure Integrity Testing (CCIT)

CCIT is conducted as part of the release testing and stability studies for the DP according to VOP-0002580, "Container Closure Integrity Testing (CCIT)," Version 3.0, Effective Date April 22, 2020. This CCIT is conducted using (b) (4) method with (b) (4). The firm indicated the number of DP vials used in this CCIT are as follows:

Table No. 64: Number of DP Vials Used for the CCIT

Tested Samples	Number of Tested Vials per Batch	Negative Control per Batch	Positive Control per Batch	Total Number of Vials per Batch
Release Testing	(b) (4)	[redacted]	[redacted]	[redacted]
Stability Testing				

(b) (4) [redacted]

[redacted]

[redacted]

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

(b) (4)



|



|



|



|



(b) (4)



✓ **Reviewer Comments:** Information provided in Module 3.2.P.5.7 associated with the container/closure system for the DP and VLR-0002578 was reviewed from DMPQ standpoint and it was found acceptable.

3.2.P.8 Stability

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

The proposed shelf life of HBV DP is 36 months at a storage temperature of 5°C ± 3°C is according to the stability data from the following DP batches that were stored at the mentioned storage temperature for ^{(b) (4)} months:

Table No. 66: Stability Duration and Conditions of the DP Batches

HBV DP Batch No	Manufacturing Date	Stability	Duration	Storage Position	Conditions - Temperature and Relative Humidity (RH)
(b) (4)	(4)	Long Term	(b) (4) months	Upright	5°C ± 3°C
		Accelerated	(b) (4)		
		Long Term	(b) (4) months	Upright (b) (4)	5°C ± 3°C
		Accelerated	(b) (4)		
		(b) (4) Forced Degradation)	(b) (4)		
		Long Term	(b) (4) months	Upright	5°C ± 3°C
		Accelerated	(b) (4)		
		Long Term	(b) (4) months	Upright	5°C ± 3°C
		Accelerated	(b) (4)		
		Forced Degradation	(b) (4)		
		Long Term	(b) (4) months	Upright (b) (4)	5°C ± 3°C
		Accelerated	(b) (4)		
		(b) (4)	(b) (4)		
		Long Term	(b) (4) months	Upright (b) (4)	5°C ± 3°C
		Accelerated	(b) (4)		
		Forced Degradation	(b) (4)		

VBI stated that SciVac Ltd. manufactured these batches using Process C. They explained that these batches were filled using the (b) (4) filling and capping machine and (b) (4) machine. The firm indicated that the (b) (4) borosilicate glass vials from (b) (4) were used for the filling of these batches. They stated that batch (b) (4) is the first in-house reference standard.

The firm explained that the quality attributes from these DP batches were not affected during the mentioned storage period at 5°C ± 3°C, which supports the proposed shelf-life of 36 months for DP stored at 5°C ± 3°C.

Endotoxin, sterility and CCIT were conducted to these DP batches at the following time points:

Table No. 67: CCIT, Endotoxin, Sterility Testing and Time Points

Temperature and RH	Endotoxin	Endotoxin Criterion	Sterility	Sterility Criterion	CCIT	CCIT Criterion
5°C ± 3°C	0, 9, 12, 24, 36 and (b) (4) months	(b) (4)	0, 9, 12, 24, 36 and (b) (4) months	Sterile	0, 9, 12, 24, 36 and (b) (4) months	(b) (4)

(b) (4)

VBI provided the CCIT, endotoxin, and sterility testing results for the DP batches (b) (4) at the above time points. They also provided endotoxin, sterility and CCIT results for the DP batches (b) (4) at time points 0, 9, 12, 24 and 36 months. The endotoxin, sterility and CCIT for the HBV DP batches complied with the above criteria for endotoxin, sterility and CCIT.

No CCIT, endotoxin, and sterility testing was conducted to the DP batches stored at (b) (4).

The firm also provided the stability data from the DP batch (b) (4) manufactured in January 2018 and it is used as (b) (4) In-house Reference Standard. This batch was manufactured using Process C, same filling line, same crimping machine and same vials as the (b) (4) HBV DP batches described in Table 89. This batch was stored at the following conditions:

Table No. 68: Stability Duration and Conditions of DP Batch (b) (4)

Stability	Duration	Storage Position	Conditions - Temperature and Relative Humidity (RH)
Long Term	(b) (4) months	(b) (4)	5°C ± 3°C
Accelerated	(b) (4)	(b) (4)	(b) (4)
Forced Degradation			

Endotoxin, sterility and CCIT were conducted to this batch at the following time points:

Table No. 69: CCIT, Endotoxin, Sterility Testing and Time Points

Temperature and RH	Endotoxin	Endotoxin Criterion	Sterility	Sterility Criterion	CCIT	CCIT Criterion
5°C ± 3°C	0, 9, 12 and 24, months	(b) (4)	0, 9, 12 and 24, months	Sterile	00, 9, 12 and 24, months	(b) (4)

(b) (4)

The long-term stability of this batch is still on-going and the CCIT, endotoxin and sterility testing will be conducted at 36 (b) (4) months.

VBI explained that SciVac Ltd. changed the endotoxin testing criterion from (b) (4) to (b) (4) according to the historical data from this testing.

No CCIT, endotoxin, and sterility testing was conducted to this DP batch stored at (b) (4)

VBI stated that SciVac Ltd. conducted photostability (light exposure) study to the PPQ DP batch (b) (4). They indicated that this study has a duration of (b) (4) and the purpose of this study is to demonstrate that the HBV DP is not prone to degradation by light. No CCIT, endotoxin, and sterility testing was conducted to this DP batch as part of the photostability study.

- ✓ **Reviewer Comments:** The endotoxin and sterility testing results from stability data in support for the DP batches provided in Modules 3.2.P.8.1 and 3.2.P.8.3 were reviewed from DMPQ standpoint and they were found acceptable. The review of the stability data from the DP batches are deferred to the OVRP reviewer.

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

VBI explained that SciVac Ltd. placed the PPQ DP batches (b) (4) in long term stability at temperature of 5°C ± 3°C for (b) (4) months and accelerated stability at temperature of (b) (4). They indicated that the vials were stored (b) (4) position, since it is considered the worst-case condition for long term and accelerated stability.

The firm stated that CCIT, endotoxin and sterility testing will be conducted at the following time points:

Table No. 70: CCIT, Endotoxin, Sterility Testing and Time Points

Temperature and RH	Endotoxin	Endotoxin Criterion	Sterility	Sterility Criterion	CCIT	CCIT Criterion
5°C ± 3°C	0, 36 and (b) (4) months	(b) (4)	0, 36 and (b) (4) months	Sterile	0, 36 and (b) (4) months	(b) (4)

(b) (4)

VBI stated that these PPQ DP batches have to comply with the above criteria for CCIT, endotoxin and sterility testing.

VBI indicated that SciVac Ltd. will place (b) (4) per year in stability at 5°C ± 3°C for (b) (4) months to demonstrate the shelf-life of 36 months for the DP. CCIT, endotoxin and sterility testing will be conducted at time points 0 and (b) (4) months. These testing has to complied with the above criteria as stated in Table 91. Also, the stability data from the DP batch will be compared with the historical stability data from other DP batches stored at 5°C ± 3°C for (b) (4) months.

The firm stated that SciVac Ltd. will report and investigate any stability confirmed failure as OOS to determine the root cause. The investigation will include the evaluation of the release data from the DS and the DP batches manufactured in the relevant year and additional testing to be conducted to the DP batch impacted.

- ✓ **Reviewer Comments:** The CCIT, endotoxin and sterility testing criteria and frequency in support for the post-approval stability protocol and stability commitment for the DP in Module 3.2.P.8.2 were reviewed from DMPQ standpoint and they were found acceptable. The review of the post-approval stability protocol and stability commitment are deferred to the OVRP reviewer.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Note: Facilities, Utilities, Equipment, Automated and Computerized Systems, Cleaning and Sterilization Processes in support for the Manufacture of DS and DP are discussed in this section of the review memo.

Facilities

VBI stated that SciVac Ltd. manufacturing facility in Rehovot, Israel was built in 2006. SciVac Ltd. manufactures DS and DP. This manufacturing facility is approximately (b) (4) and consists of (b) (4) buildings as follows:

(b) (4)

(b) (4)

The manufacturing area in the (b) (4) building is segregated into (b) (4) dedicated areas for the manufacture of DS and DP.

The DS manufacturing area consists of the following rooms:

Table No. 71: DS Manufacturing Rooms

(b) (4)

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



The above rooms are used for the following processes in support for the DP:

- PAL and MAL to enter and exit the facility
- Solution preparation
- Aseptic core area for the formulation and filling processes

The surfaces in the DS and the DP manufacturing areas are made of durable, non-shedding and non-absorbing materials with cleanable finishes. The rooms used for the (b) (4) and rooms used for the DP manufacturing have large windows to allow the observation of these processes. Also, the (b) (4) can be observed from one of the windows in the DP manufacturing area. A technical corridor is located (b) (4) of the DS and the DP manufacturing areas to allow access to the AHUs and the HEPA filters for maintenance and without breaching the cleanroom integrity.

The firm provided the following diagrams in support for SciVac Ltd. manufacturing facility:

Table No. 73: Facilities Diagrams

Diagram Title	Diagram No., Version and Approval Date	Diagram Description
SciVac Site Map	116-30-2330, Ver. 0 October 30, 2019	This diagram illustrates the (b) (4) buildings in SciVac Ltd. with their respective areas
General Layout	116-00-0590, Ver. 26 October 31, 2019	This diagram illustrates each room in the (b) (4) building, at SciVac Ltd. with their room size, room classification, temperature, relative humidity, and differential pressure parameters

In Sections 3.2.S.2.5 and 3.2.P.3.5 from this review memo was discussed that a PPQ study was conducted in 2019 in support for the following:

- Changes in the HBs Ag manufacturing in support for the implementation of the Process C+
- Implementation of the (b) (4)
- Changes in the (b) (4) areas to segregate as dedicated areas for HBsAg DS and HBV DP manufacturing
- Implementation of a (b) (4) filling line
- Implementation of RTU vials for the filling of the DP.

These changes were conducted to increase the manufacturing capacity in SciVac Ltd., reduce the exposure of vials to the environment during filling process and improve material flow pattern. The results from this study were reported in VLR-00004004, *Version 2.0, "Process Performance Qualification of Sci-B-Vac."*

Note: Information in support of VLR-00004004 are discussed in the following sections of this review memo:

Table No. 74: Information in Support of VLR-00004004 Discussed in the Following Sections of this Review Memo

Information	Sections of this Review Memo
DS batches manufactured using the (b) (4) and Process C+	3.2.S.2.5
DP batches filled in the (b) (4) filling line	3.2.P.3.5
Implementation of the "RTU" vials	3.2.P.7
(b) (4)	Equipment Part of Section 3.2.A.1

Flow Patterns

VBI provided the personnel, material, and waste flow patterns diagrams in support for the DS and the DP manufacturing areas as follows:

Table No 75: Flow Patterns Diagrams

Diagram Title	Diagram No., Version and Approval Date	Diagram Description
Personnel Flow	116-30-2311, Ver. 3 September 11, 2019	This diagram illustrates a (b) (4) flow of personnel in the DS and the DP manufacturing areas.
Material Flow	116-30-2309, Ver. 3 September 11, 2019	This diagram illustrates the (b) (4) flow of material (including raw material, QC raw material, (b) (4) DS, in-process DP, final DP and packaging material) in the DS and the DP manufacturing areas.
Waste Flow	116-31-2312, Ver. 3 September 11, 2019	This diagram illustrates the (b) (4) flow of waste from the DS and the DP manufacturing areas.

Contamination Controls

VBI explained that in addition to PREHEVBRIO, SciVac Ltd. manufactures Hepatitis B vaccine DS and DP at pediatric doses of 2.5 µg/mL and 5.0 µg/mL. Other products

manufactured in their facility includes clinical batches for the (b) (4) (b) (4) Program No. (b) (4) for VBI and (b) (4)

VBI stated that the following controls are in-place for the prevention of contamination in the DS and the DP manufacturing areas at SciVac Ltd.:

- Manufacturing in campaign basis
- Use of dedicated equipment
- Segregation of manufacturing areas
- Personnel, materials, and waste flow patterns
- Gowning procedures
- Validated SOPs for the cleaning of manufacturing areas
- Disinfectant effectiveness study conducted to the cleaning and disinfectant agents used for the cleaning and sanitization of manufacturing areas
- Dedicated SOPs for each DS and DP manufacturing step
- Aseptic techniques for bioburden-controlled and aseptic operations during DS and DP manufacturing
- Microbial trend analysis of solutions prior (b) (4)
- Filling step conducted in a filling line with (b) (4)
- EM and personnel monitoring conducted during aseptic operations
- Media fill runs conducted every (b) (4) months

Heating, Ventilating, Air Conditioning (HVAC) System

VBI indicated that the HVAC system in SciVac Ltd. consists of the following Air Handling Units (AHUs) and Fan Coils (FCs):

Table No. 76: HVAC System in SciVac Ltd.

Area	AHU	Room No. and Name
DP Manufacturing Area	(b)	(4)
DP Manufacturing Area	(b)	(4)

Area	AHU	Room No. and Name
DP Manufacturing Area	<div style="font-size: 48px; font-weight: bold;">(b) (4)</div>	
DP Manufacturing Area		
DS Manufacturing Area		
General		
Sterility Testing Laboratory		
Raw Material Sampling Area		

The firm indicated that Outside Air (OSA) supply units provide fresh air to the AHUs that serve the following areas:

Table No. 77: OSA Supply Units in SciVac Ltd.

OSA	AHU	Area
<div style="font-size: 48px; font-weight: bold;">(b) (4)</div>		

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

The HVAC system in SciVac Ltd. is connected to a control and monitoring system that monitors the operation and alarms of the AHUs, FCs and OSA supply units. This monitoring system also monitors the differential pressure, temperature, and humidity parameters from the environmental controlled rooms.

VBI provided the following diagrams in support of the HVAC system in SciVac Ltd.:

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

The firm indicated that Performance Qualification (PQ) study has been conducted in support for the HVAC system in SciVac Ltd. They stated that this PQ study complied with the following criteria:

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

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

(b) (4)

Water for Injection (WFI) System

The WFI System is located in the (b) (4) and produce WFI that complies with (b) (4). The WFI System consists of the following systems:

- Pre-Treatment System
- WFI Generation System
- WFI Distribution System

Below is a description of the above systems in support for the WFI system.

Pre-Treatment System:

Potable water from the (b) (4) Water System supplies the pre-treatment system. This water is treated with (b) (4) to reduce the (b) (4). Then this treated water (b) (4)

The (b) (4) water is used for the following purposes:

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

The (b) (4) water to be used for the WFI generation system has (b) (4). After, the (b) (4) step, the water (b) (4)

The action and alert levels for the Pre-Treatment System are the following:

Table No. 81: Pre-Treatment System Alert and Action Limits

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(b) (4)

WFI Generation System:

The WFI Generation System has a distillation unit that use (b) (4). This distillation unit operates in a (b) (4) mode at internal pressure (b) (4).

The action and alert levels for the WFI Generation System are the following:

Table No. 82: WFI Generation System Alert and Action Limits

(b) (4)

WFI Distribution System:

The WFI Distribution System consists of (b) (4) distribution loops that circulate constantly WFI generated from the distillation unit and stored in the (b) (4) storage tank at a temperature of (b) (4). These distribution loops are monitored for (b) (4). Also, a (b) (4)

The action and alert levels for the WFI Generation System are the following:

Table No. 83: WFI Generation System Alert and Action Limits

(b) (4)

Clean Steam

The firm indicated that the clean steam generation and distribution system is located in the (b) (4) and it produces (b) (4) steam at a pressure of (b) (4) and flow of (b) (4) distribution and storage system is used to produce the clean steam. The clean steam is used for the operation of the (b) (4) in the DS and DP manufacturing areas and (b) (4). Also, the clean steam is supplied to the (b) (4) area through a Point of Use (POU.) The alert and action limits of the clean steam are the following:

Table No. 84: Clean Steam Alert and Action Limits

(b) (4)

Compressed Gasses

VBI stated that the compressed air system generation and distribution system in SicVac Ltd. consists of (b) (4) compressors, (b) (4) compressed air. The compressed air is distributed to POU's with (b) (4) in the manufacturing areas.

The firm indicated that non-product contact compressed air is used for the operation of (b) (4) in the HBsAg DS and HBV DP manufacturing areas and laboratories.

VBI explained that (b) (4), and compressed air with (b) (4) are the other compressed gases used in the HBsAg (b) (4) manufacturing area and laboratories at SciVac Ltd. These gasses are supplied through (b) (4).

Below are the testing and criteria for the compressed gasses:

Table No. 85: Testing Conducted to Compressed Air

(b) (4)

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

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

The hardware and the software of the plant control and monitoring system consists of PLCs, HMI applications and servers, and HMI clients for operational and control system monitoring. The HMI applications are built in the server client configuration and use (b) (4) software. The HMI applications include the following components: synoptic screen representing the physical process being controlled and monitored, control screens to operate the systems and processes, login screen, current and history alarm screens; parameters, audit trail and trend screens. The HMI applications conduct the following operations: illustration of graphic visualization of the process status, human operation interface with systems, display and records process parameters and retrieves historical data.

Equipment

VBI listed the following equipment used for the manufacture of the DS and DP in SciVac Ltd.:

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

(b) (4)

[Redacted text block]

Product Contact Equipment Cleaning and Sterilization Studies

VBI provided a description of the Cleaning and Sterilization Studies conducted for the product contact equipment used for the DS and DP manufacture in SciVac Ltd., which is discussed below.

(b) (4)

[Redacted text block]

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(b) (4)

✓ **Reviewer Comments:** The facilities, utilities, computerized systems, equipment information in support for the manufacture of the DS and DP in Module 3.2.A.1 were reviewed from DMPQ standpoint. Also, the information in support for cleaning validation of the equipment used for the manufacture of the DS and DP in Modules 3.2.S.2.5 and 3.2.P.3.5 was reviewed from DMPQ standpoint. Addition clarification is required regarding VLR-0004004. In this BLA, the firm provided limited information in support for the facilities, utilities, computerized systems, equipment, cleaning and sterilization processes and EM monitoring in support for the manufacture of the DS and DP. See IR Questions #11, #12.a., #12.b., #12.c., #12.d., #12.e., #12.f., #12.g., #12.h., #12.i., #12.j., #12.k., #12.l., #12.m., #12.n., #12.o., #12.p., #12.q., #12.r. and #12.s. – 02/02/2021 (See Below.)

11. Please provide the following information in support of VLR-00004004, Version 2.0, “Process Performance Qualification of Sci-B-Vac;”

Summary that describes REP-0002732, “Equipment Capacity Increase and Facility Modernization.” Ensure to provide a summary of the testing conducted in these studies with their results and acceptance criteria. Also, ensure to include a summary that describes the deviations initiated in this study with their root causes and actions taken for resolution and closure, if applicable.

Firm Responses: VBI explained that REP-0002732, Version 1.0, Effective Date June 23, 2019 is the interim validation report that describes the status from the qualification studies of the utilities, facilities, and equipment in support for the Project Validation Plan (PVP) VAL-0001654. This PVP describes the activities in support for the (b) (4) of SciVac Ltd. manufacturing facility.

The firm indicated that VLR-0003177, Version 1.0, Effective Date February 15, 2021 is the final report that describes the final status from qualification studies of the utilities, facilities, and equipment in support for the PVP VAL-0001654. They stated that all qualification studies of the utilities, facilities and equipment were completed, prior to initiate the PPQ Studies in support for the manufacture of the DS and DP in SciVac Ltd. This report also provides a list of the reports from these qualification studies.

VBI explained that REP-0000909, Version 1.0, Effective Date August 2018, describes the changes implemented to the utilities, facilities, and equipment in support for the increase of manufacturing capacity in SciVac Ltd. These changes were the following:

(b) (4)

[Redacted text block containing approximately 15 lines of obscured content]

The firm stated that the above changes described in REP-0000909 were discussed with the agency in a Type C meeting in October 2018.

✓ **Reviewer Comments:** REP-0002732, VLR-0003177 and REP-0000909 were reviewed and found acceptable from DMPQ standpoint. These reports describe the activities conducted in support for the manufacturing capacity increase at SciVac Ltd.

12. Please provide the following information in support of Module 3.2.A.1, “Facilities and Equipment;”
 - a. The number of Point of Use (POUs) of the Water for Injection (WFI), Pure Steam and Compressed Gasses Systems installed in the manufacturing areas. Ensure to indicate if (b) (4) are installed at the Compressed Gasses POUs.

Firm Responses: VBI provide a list of the POU's for the WFI, Clean Steam and Compressed Gasses Systems installed in the DS and DP manufacturing areas at SciVac Ltd. They stated the following POU's for each of the above utilities:

- WFI: (b) (4) POU's

(b) (4) [Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]

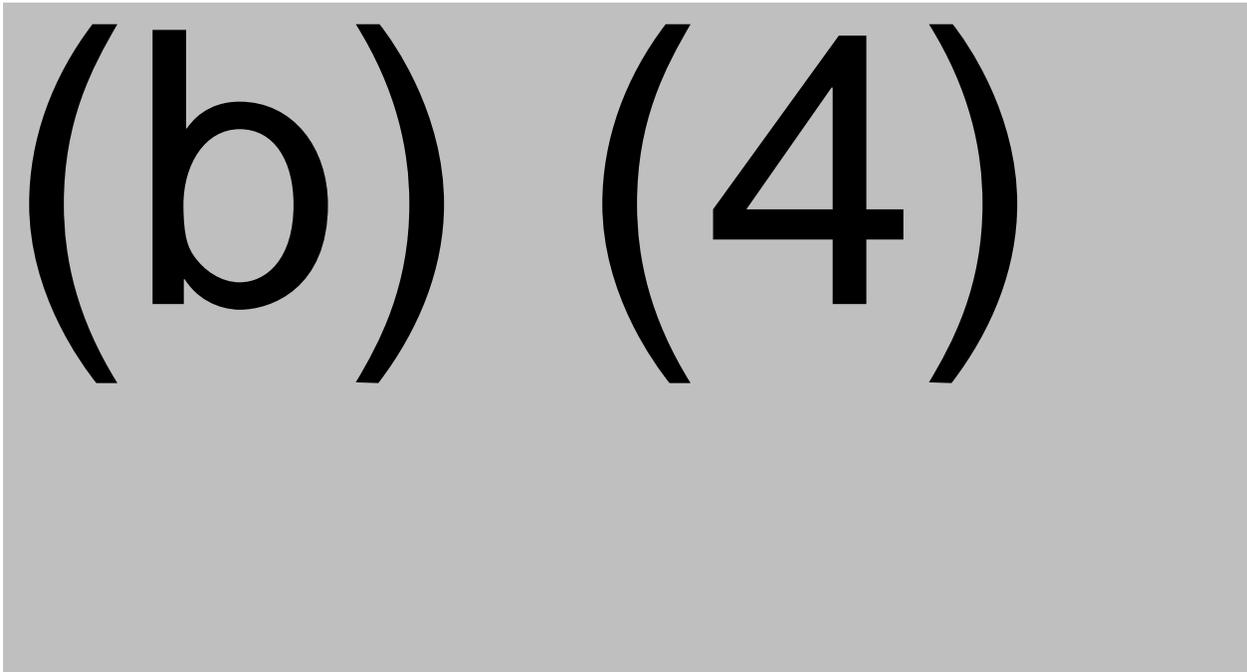
The firm clarified that (b) (4) are installed in the POU's from the compressed gases.

✓ **Reviewer Comments:** *The firm's response is acceptable.*

b. *Diagrams for the WFI, Pure Steam and Compressed Gasses Distribution Systems.*

Firm Responses: VBI provided copies from the following diagrams for the WFI, Clean Steam and Compressed Gasses Distribution Systems:

Table No. 102: Diagrams for the WFI, Clean Steam and Compressed Gasses Distribution Systems



These diagrams illustrate the components from the above utilities systems and their POU's.

✓ **Reviewer Comments:** *The above diagrams were reviewed and found acceptable.*

c. *Summary that describes the Operational and Performance Qualification (OP/Q) Studies for the WFI and Pure Steam System. Ensure to provide a summary of the testing conducted with their results and acceptance criteria. Also, ensure to include a summary that describes the deviations initiated in these studies with their root causes and actions taken for resolution and closure, if applicable.*

Firm Responses: (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

(b) (4)

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(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

✓ **Reviewer Comments:** *The summaries that described the OP/Q Studies for the WFI and Pure Steam Systems were reviewed and found acceptable.*

- d. *Summary that describes the routine monitoring program for the WFI, Pure Steam and Compressed Gasses Systems. Ensure to provide a list of the sampling locations in the manufacturing areas. Also, ensure to indicate the sampling frequencies, acceptance criteria and actions to be taken in the case of an excursion during the routine monitoring of these systems.*

Firm Responses: VBI provided a summary that describes the routine monitoring programs for the WFI, Pure Steam, and Compressed Gas Systems as follows:

- WFI Routine Monitoring Program:

The WFI Routine Monitoring Program consists of the (b) (4) sampling of the (b) (4) WFI POUs located in the utilities, DS and DP manufacturing areas for (b) (4) and (b) (4). Also, (b) (4) testing is conducted in (b) (4) basis in the (b) (4) POUs located at the (b) (4) of the WFI distribution loops. (b) (4) are (b) (4) monitored in the (b) (4) WFI distribution loops. The (b) (4) instruments are connected to the Plant Control and Monitoring System. The alert and action limits for the (b) (4) for the WFI are the following:

Table No. 105: WFI Routine Monitoring Program Alert and Action Limits

(b) (4)

(b) (4)

- Clean Steam Routine Monitoring Program:

The Clean Steam Routine Monitoring Program consists of the (b) (4) sampling of (b) (4) Clean Steam POUs located in the (b) (4) rooms of the DS and DP manufacturing areas for (b) (4). The alert and action limits, and actions taken if there is an excursion in the Clean Steam sample that exceeded the action or alert limit are the same as for the WFI Routine Monitoring Program.

- (b) (4) Compressed Air and Compressed Gasses Routine Monitoring Program:
The (b) (4) Compressed Air Routine Monitoring Program consists of the (b) (4) monitoring of the POU's located in the DS and DP manufacturing areas for (b) (4) (b) (4). The acceptance criteria for these testing is the following:

Table No. 106: (b) (4) Compressed Air Routine Monitoring Program Acceptance Criteria

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(b) (4)

A large rectangular area that has been completely redacted with a solid grey fill. The text "(b) (4) (b) (4)" is visible in the center of this redacted area.

In the case of an excursion in the (b) (4) Compressed Air or Compressed Gasses sample that exceeded the action limit the action taken is to initiate a deviation to identify the root cause and initiate a CAPA (as needed).

✓ **Reviewer Comments:** The routine monitoring programs for the WFI, Pure Steam and Compressed Gasses Systems were reviewed and found acceptable.

e. Summary that describes the Operational and Performance Qualification (OP/Q) Studies for the HVAC System, Laminar Air Flow (LAF) hoods. Ensure to provide a summary of the testing conducted with their results and acceptance criteria, including differential pressure, air changes, temperature, relative humidity, EM and others testing in static (at rest) and dynamic (at operational) conditions. Ensure to provide a summary of the activities conducted under dynamic (at operational) conditions, such as simulation of manufacturing processes and others. Also, ensure to include a summary that describes the deviations initiated in these studies with their root causes and actions taken for resolution and closure, if applicable.

Firm Responses: VBI provided a summary that describes the OP/Q Studies for the HVAC system and LAF Hoods in SciVac Ltd.

(b) (4)

[Redacted]

(b) (4)

(b) (4)

[Redacted]

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

(b) (4)

[Redacted]

[Redacted]

(b) (4)

(b) (4)

[Redacted]

(b) (4)

(b) (4)

(b) (4)

✓ **Reviewer Comments:** *The summaries that describe the OP/Q Studies for the HVAC System and the LAF hoods were reviewed. The OQ Studies for the HVAC System and the OP/Q Studies for the LAF hoods were found acceptable. Additional clarification was required regarding the deviations associated to the excursions in the viable particulate count of the airlocks and its respective CAPA. They were discussed in the RIE.*

f. *Summary that describes the routine Environmental Monitoring (EM) Program of the manufacturing areas, including Grades A, B, C, D; and including Laminar Air*

Flow (LAF) hoods, (b) (4) and others. Ensure to include a list of the sampling locations in the manufacturing areas. Also, ensure to indicate the sampling frequencies, acceptance criteria and actions to be taken in the case of an excursion during the routine EM.

Firm Responses: VBI provided a summary that describes the routine EM Program for HBsAg DS and HBV DP manufacturing areas, LAF hoods and QC Micro Sterility Laboratory including sampling locations, frequencies, acceptance criteria and actions taken in the case of EM excursions.

The acceptance criteria, sampling locations and actions taken in the case of an excursion in support for the personnel monitoring were discussed in the firm's response to the IR Question #12.p. and were found acceptable

The viable particulate count (b) (4) is conducted using (b) (4). The non-viable particulate count is continuous monitored through the (b) (4) and Monitoring System.

Diagrams 116-30-5740, "Micro Test Map," Version 4, Date February 17, 2021 illustrates the sampling points for the viable particulate count (b) (4) and Diagram 116-30-5741, "Particle Test Map," Version 5, Date February 17, 2021 illustrates the sampling points for the non-viable particulate count in the DS and DP manufacturing areas, LAF hoods and Sterility testing area.

The EM sampling frequencies during manufacturing and routine are the following:

Table No. 114: EM Sampling Frequencies During DS and DP Manufacturing and QC Micro Sterility Laboratory

(b) (4)

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

(b) (4)

Table No. 117: Non-Viable Particulate Count Acceptance Criteria

(b) (4)

VBI indicated that the following actions are taken in the case of an excursion in the EM and personnel monitoring:

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

• The following items have to be evaluated in the investigation:

- (b) (4)

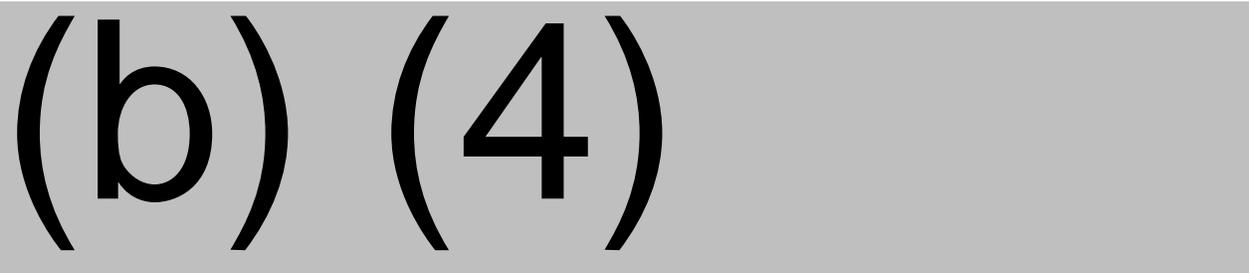
(b) (4)

✓ **Reviewer Comments:** The routine EM Program for the DS and DP manufacturing areas, LAF hoods and QC Micro Sterility Laboratory was reviewed and found acceptable.

- g. List of computerized/automated systems and their use in support of the manufacture of HBsAg Bulk Drug Substance and Sci-B-Vac Drug Product. Ensure to include all computerized/automated systems that control and monitor HVAC, supporting utilities and process equipment.

Firm Responses: VBI provided a list of the computerized/automated systems used in the manufacture of the DS and DP in SciVac Ltd. are the following:

Table No. 118: Computerized/Automated Systems



✓ **Reviewer Comments:** The list of the computerized/automated systems used in the manufacture of the DS and DP was reviewed and found acceptable. The back-up and restore actions in support for disaster recovery for the computerized systems were reviewed in the RIE.

- h. Summary that describes the Validation Studies conducted on the computerized/automated systems used in the manufacture of HBsAg Bulk Drug Substance and Sci-B-Vac Drug Product, including the systems that control and monitor HVAC, WFI, Pure Steam and Compressed Gasses Systems. Ensure to provide a summary of the testing conducted with their results and acceptance criteria. Also, ensure to include a summary that describes the deviations initiated in these studies with their root causes and actions taken for resolution and closure, if applicable. If the Validation Study of the computerized/automated systems was conducted as part of the Qualification Study for the equipment, ensure to make cross-reference to the Qualification Study for the equipment.

Firm Responses: VBI provided a summary that describes the Validation Studies conducted to the computer and automated systems used in the manufacture of the DS and DP at SciVac Ltd.

The Validation Study of the Plant Control and Monitoring System includes the (b) (4)

No deviation was initiated in the Validation Study of the Plant Control and Monitoring System.

The Validation Studies of the (b) (4) included the verification of 21CFR Part 11 Compliance and sequence of operation. No deviation was initiated in these Validation Studies.

The Validation Studies of the (b) (4) trail and 21CFR Part 11 Compliance. The firm indicated that one deviation was initiated during the (b) (4)

The Validation Study of the automated system for the (b) (4) is discussed in the response to the IR Question #12.I.

✓ **Reviewer Comments:** The summary that describes the Validation Studies conducted to the computer and automated systems used in the manufacture of the DS and DP was reviewed and found acceptable.

- i. Summary that describes the equipment used for the labeling and packaging of Sci-B-Vac Drug Product.

Firm Responses: VBI stated that the (b) (4) Labeling Machine is the equipment used for the labeling of vials. They clarified that the packaging is conducted manually. Below is an illustration of this labeling machine.

(b) (4)

(b) (4)

This labeling machine applies the self-adhesive labels that contains relevant information and batch details from a label roll to the exterior of the vials. This machine operates at a speed of (b) (4) labels per minute. The labeling operation starts (b) (4)

(b) (4) In the labeling station, where the vials are labeled.

(b) (4)

✓ **Reviewer Comments:** *The firm's response is acceptable.*

j. Clarify the terms (b) (4) " in Tables 20 and 21 from Module 3.2A.1 "Facilities and Equipment".

(b) (4)

(b) (4)

(b) (4)

(b) (4)

✓ **Reviewer Comments:** The firm's response is acceptable.

- k. Summary that describes the (b) (4) used for the (b) (4) used for HBsAg (b) (4) steps. Ensure to provide diagrams that illustrate the (b) (4) Please indicate the testing conducted to these (b) (4) verification prior use.

(b) (4)

✓ **Reviewer Comments:** The descriptions of the (b) (4) used for the (b) (4) used for HBsAg (b) (4) steps in SciVac Ltd. were reviewed and found acceptable.

- l. Summary that describes the Operational and Performance Qualification (OP/Q) Studies for the equipment used in the manufacture of HBsAg Bulk Drug Substance and Sci-B-Vac Drug Product, including labeling and packaging of Sci-B-Vac Drug Product. Ensure to provide a summary of the testing conducted with their results and acceptance criteria. Also, ensure to include a summary that describes the deviations initiated in these studies with their root causes and actions taken for resolution and closure, if applicable.

Firm Responses: VBI provided a summary that describes the equipment used for DS and DP manufacturing with their OP/Q Studies, which are discussed below:

(b) (4) [Redacted]

(b) (4)

(b) (4)

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

(b) (4)

(b) (4) [Redacted]

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

(b) (4)

[Redacted]

[Redacted]

✓ **Reviewer Comments:** The summary that describes the equipment used for DS and DP manufacturing with their OP/Q Studies was reviewed and found acceptable.

m. Summary that describes procedures for the manual washing, automated washing (b) (4) sterilization using autoclave, (b) (4) (SOP) of the equipment, (b) (4), filters, (b) (4), small components, glassware, and other product-contact surfaces used in the manufacture of HBsAg Bulk Drug Substance and Sci-B-Vac Drug Product.

Firm Responses: VBI provided a summary that describes the procedure for the manual and automated washing, and the sterilization processes of the equipment and components used in the manufacture of the DS and DP in SciVac Ltd.

The firm explained that equipment used for DS and DP manufacturing has the following Dirty Hold Time (DHT):

- DHT of (b) (4) of the equipment used for DS manufacturing
- DHT of (b) (4) of the equipment used for DP manufacturing.

VBI stated that the clean equipment has a Clean Hold Time (CHT) on (b) (4) prior to be sterilize. (b) (4).

The following equipment is manually washed in segregated washing rooms located in the DS and DP manufacturing areas:

(b) (4)

[Redacted]

[Redacted]

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

(b) (4)

(b) (4)

✓ **Reviewer Comments:** The summary that describes the procedure for the manual and automated washing, and the sterilization processes of the equipment and components used in the manufacture of the DS and DP in SciVac Ltd. was reviewed and found acceptable.

- n. Summary that describes the Cleaning Validation Studies for manual washing and automated washing (washer machines, (b) (4)) methods. Ensure to provide a summary of the testing conducted with their results and acceptance criteria. Ensure to describe Dirty and Clean Hold Times (DHT and CHT) validated in these Studies. Also, ensure to provide a description and diagrams of the load configurations in support for the washing of stoppers, glassware and

components used for manufacturing and evaluated in the Cleaning Validation Studies for the washing machines. Ensure to include a summary of deviations initiated in these studies with their root cause and action taken for correction and resolution, if applicable.

Firm Responses: VBI provided a summary that describes the Cleaning Validation Studies for the manual washing and automated washing methods, which is discussed below. (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

(b) (4)

[Redacted]

(b) (4)

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

(b) (4)

✓ **Reviewer Comments:** The summary that describes the Cleaning Validation Studies for the manual washing and automated washing methods in SciVac Ltd. was reviewed. The summary that describes the Cleaning Validation Studies for the filters and the (b) (4) in support for the (b) (4) was discussed in Section 3.2.A.1 of this memo. Additional clarification was required regarding the Cleaning Validation Study for the buffer preparation vessels. It was reviewed in the RIE and discussed in the RIE memo.

- o. Summary that describes the Validation Studies for the sterilization (b) (4) sterilization using (b) (4) of the equipment used in the manufacture of HBsAg Bulk Drug Substance and Sci-B-Vac Drug Product, including the sterilization of stoppers used for the filling of Sci-B-Vac Drug Product. Ensure to provide a summary of the testing conducted with their results and acceptance criteria. Ensure to provide a description and diagrams of the temperature dataloggers placement in the equipment/loads in support for these Validation Studies. Ensure to include a summary of deviations initiated in these studies with their root cause and action taken for correction and resolution, if applicable.

Firm Responses: VBI indicated that no (b) (4) is conducted on the equipment used for the DS and DP manufacturing.

The firm provided a summary that describes the Validation Studies for the (b) (4)

(b) (4)

(b) (4)

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

(b) (4)

[Redacted text block]

✓ **Reviewer Comments:** The summary that describes the Validation Studies for the (b) (4) used for the sterilization of components and materials used in DS manufacturing area was reviewed and found acceptable. The summary that describes the (b) (4) used for the sterilization of components and materials used in DP manufacturing area was discussed in Section 3.2.A.1 of this memo

p. List of the sampling locations, frequency, and acceptance criteria for personnel monitoring. Ensure to indicate the actions to be taken in the case of an excursion during the personnel monitoring.

Firm Responses: VBI provided a list of the sampling locations, frequency, and acceptance criteria for personnel monitoring in SciVac Ltd. as follows:

Table No. 132: Personnel Monitoring Sampling Locations, Frequency and Acceptance Criteria

(b) (4)

(b) (4)

The firm stated that (b) (4) are used for the personnel monitoring.

VBI clarified that the actions taken in the case of an excursion during the personnel monitoring are the same as for the EM. These actions were discussed in the firm's response to the IR Question #12.f.

✓ **Reviewer Comments:** *The list of the sampling locations, frequencies, and acceptance criteria for personnel monitoring in SciVac Ltd. and the actions were taken in the case of an excursion during the personnel monitoring were reviewed and found acceptable*

q. *List of cleaning and disinfectant agents used for the cleaning of manufacturing areas and equipment in support of the manufacture of HBsAg Bulk Drug Substance and Sci-B-Vac Drug Product.*

Firm Responses: VBI provided a list of the cleaning and disinfectant agents used for the cleaning of manufacturing areas and equipment in support of the manufacture of the DS and DP as follows:

Table No. 133: Cleaning and Disinfectant Agents

(b) (4)

(b) (4)

✓ **Reviewer Comments:** The list of the cleaning and disinfectant agents used for the cleaning of manufacturing areas and equipment in support of the manufacture of the DS and DP was reviewed and found acceptable.

r. Summary that describes the cleaning procedures for the manufacturing areas, including the cleaning frequencies and actions to be taken if the cleaning cannot be conducted at the established frequency.

Firm Responses: VBI provided a summary that describes the cleaning procedures for the manufacturing areas, including cleaning frequencies and action to be taken if the cleaning cannot be conducted at the established frequencies which is discussed below.

(b) (4)

(b) (4)

Table No. 134: Components Used for the Cleaning of DS and DP Manufacturing Areas

(b) (4)

(b) (4)

The firm indicated the cleaning frequencies in the DS and DP manufacturing areas as follows:

Table No. 135: Cleaning Frequencies in the DS and DP Manufacturing Areas

Cleaning Frequency	Items Cleaned
(b) (4)	(4)

(b) (4)

✓ **Reviewer Comments:** The summary that describes the cleaning procedures for the manufacturing areas, including cleaning frequencies and action to be taken if the cleaning cannot be conducted at the established frequencies was reviewed and found acceptable.

- s. Summary that describes the Cleaning and Disinfectant Agents Effectiveness Study of the cleaning agents used for the cleaning of manufacturing areas and equipment. Ensure to provide a summary of the testing conducted with their results and acceptance criteria. Ensure to include a summary of deviations initiated in this study with their root cause and action taken for correction and resolution, if applicable.

Firm Responses: VBI provided a summary that describes the Cleaning and Disinfectant Agents Effectiveness Study of the agents used for the cleaning of the manufacturing areas and equipment below.

The firm explained that Disinfection Effectiveness Studies of non-product contact surfaces in Grade ^{(b) (4)} area was conducted using (b) (4) methods. They indicated that the Disinfection Effectiveness Studies of non-product contact surfaces in Grade ^{(b) (4)} area was conducted using the (b) (4) method.

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

(b) (4)

The firm explained that the purpose of the (b) (4) Study is to verify the effectiveness of the cleaning program after changes were implemented. Changes were done to improve the cleaning program in the Grades (b) (4) areas and they were found effective according to the summary of the results reported in Table 138 from this memo.

- ✓ **Reviewer Comments:** *The summary that describes the Cleaning and Disinfectant Agents Effectiveness Study of the agents used for the cleaning of the manufacturing areas and equipment was reviewed. Additional clarification is required regarding the Cleaning and Disinfectant Agents Effectiveness Study for (b) (4) . It was reviewed in the RIE and discussed in the RIE memo.*