

**DMPQ review memo BLA 125814**

**CBER DMPQ CMC/Facility BLA Review Memorandum**

**BLA STN 125814**

**Pneumococcal 21-valent Conjugate Vaccine**

**Hector Carrero, Consumer Safety Officer, CBER/OCBQ/DMPQ**

1. **BLA#:** STN 125814/0

2. **APPLICANT NAME AND LICENSE NUMBER**

Merck Sharp & Dohme LLC, License #0002

3. **PRODUCT NAME/PRODUCT TYPE**

Non-Proprietary/Proper/USAN: Pneumococcal 21-valent Conjugate Vaccine

Proprietary Name: N/A

Abbreviated Name: V116

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

**Description:** V116 is prepared by [REDACTED]. The DP is filled into a 1.5 mL glass syringe assembly and stored at a temperature of 2–8°C.

**Dosage Form:** Solution for injection

**Strength/Potency:** Each 0.5 mL dose contains a total of 84 µg of the PnPs antigen (4 µg each of polysaccharide serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) conjugated to approximately 65 µg of CRM197.

**Route of Administration:** Intramuscular injection

**Indication:** Prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older.

5. **MAJOR MILESTONES**

Initial Modules Received	October 18, 2023
Module 3 Received	October 18, 2023
Application Filed	December 15, 2023
Mid-Cycle Meeting	N/A
Late-Cycle Meeting	N/A
Pre-License Inspections	Inspection waived for six facilities
Major Amendment Determination	N/A
PDUFA Action Date:	June 17, 2024

**6. DMPQ CMC/FACILITY REVIEW TEAM**

<b>Reviewer/Affiliation</b>	<b>Section/Subject Matter</b>
Hector Carrero, OCBQ/DMPQ/MRBII	3.2.S Drug Substance (as per CBER *SOPP 8401.4) 3.2.P Drug Product (as per CBER *SOPP 8401.4) 3.2.A.1. Facilities and Equipment (as per CBER *SOPP 8401.4)

**7. SUBMISSION(S) REVIEWED**

<b>Date Received</b>	<b>Submission</b>	<b>Comments/ Status</b>
10/18/2023	STN 125814/0.0	Quality Module and Completed Submission of BLA
5/9/2024	Amendment STN 125814/0.30	Response to most recent (b) (4) surface decontamination revalidation
5/17/24	Amendment STN 125814/0.32	Response to visual inspection acceptance criteria and results
5/31/24	Amendment STN 125814/0.34	Response to equipment qualification

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	(b) (4) Glass Prefillable Syringe (PFS)	Yes	Information pertinent to syringe barrel assembly. No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Primary Packaging Material Syringe	Yes	Information pertinent to syringe barrel assembly. No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Elastomeric Formulations, Coatings and Films	Yes	Information pertinent to plunger stopper. No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Rubber Compounds	Yes	Information pertinent to syringe barrel assembly. No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Contract Manufacturing Facility in (b) (4)		Information pertinent to (b) (4). No DMF review required, information pertinent to this facility is provided in the BLA

## 9. REVIEWER SUMMARY AND RECOMMENDATION

### A. EXECUTIVE SUMMARY

CBER received this electronic submission on October 18, 2023. Merck Sharp & Dohme LLC (Merck) submitted this BLA to provide information to support US market authorization of Pneumococcal 21-valent Conjugate Vaccine (also called V116). V116 is indicated for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in adults 18 years of age and older. V116 is supplied as a solution for intramuscular injection. V116 contains 21 distinct pneumococcal polysaccharides individually conjugated to the CRM197 carrier protein. The product is prepared by (b) (4)

The drug product (DP) is filled into a 1.5 mL glass syringe assembly and stored at a temperature of 2–8°C. To support this BLA, the firm provided facility information including facility design and containment strategies, equipment description and qualifications, cleaning validations, computer systems. Additionally, information was provided regarding container closure and integrity, process validation, including aseptic process simulations, stability studies and shipping validations.

The reviewed and evaluated information under DMPQ purview (as per CBER SOPP 8404.1) appears acceptable. All the identified deficiencies were addressed with the amendments in response to information requests.

CBER waived the pre-license inspections (PLI) in support of this BLA. All manufacturing facilities that manufacture drug substance and drug product are existing licensed facilities with an acceptable compliance history. A recommendation to waive the inspection for these facilities is documented in a waiver memo under BLA 125814/0.

**B. RECOMMENDATION**

**I. APPROVAL**

Based on the information reviewed in the BLA submission and amendments, approval is recommended.

The following facilities are used to manufacture V116 drug substance (DS) and drug product (DP):

- Merck (b) (4)
- (b) (4)
- Merck (b) (4) (Manufacture of the (b) (4))
- Merck (b) (4) (Formulation and filling of V116 drug product)

All manufacturing sites that produce drug substance intermediates, drug substances and drug product are existing licensed facilities. To date, all facilities have an acceptable compliance history.

**II. SIGNATURE BLOCK**

<b>Reviewer/Title/Affiliation</b>	<b>Concurrence</b>	<b>Signature and Date</b>
Hector Carrero Consumer Safety Officer OCBQ/DMPQ/MRBII	Concur	
Anthony Lorenzo Branch Chief, MRBII OCBQ/DMPQ	Concur	
Carolyn Renshaw Director, DMPQ OCBQ	Concur	

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



### 3.2.P.2.5 Microbiological Attributes

For details of the microbial attributes, refer to section 3.2.P.5 Control of Drug Product.

### 3.2.P.3 Manufacture

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

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities.

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

V116 DP manufacturing process consists of (b) (4) main steps:

(b) (4)

(b) (4)

(b) (4)

(b) (4) Sterile filtration, filling, visual inspection, and storage – The (b) (4) is sterile filtered using a (b) (4) sterilizing filter. After sterile filtration, the (b) (4) is aseptically filled into syringes in the Grade (b) (4) . The filled syringes are automatically stoppered. During filling, in-process (b) (4) checks are performed to ensure the allowable syringe dose (b) (4) range is achieved. After each syringe is filled and stoppered, the syringe exits the (b) (4) and is transferred to the Automated Inspection Machine for 100% visual inspection for defects. After inspection, the syringes are placed into (b) (4) and stored at 2–8°C in preparation for packaging and labeling.

The DP is sterile filtered as it is filled into the syringe barrel assembly and stoppered with a plunger stopper to make a PFS. Final device assembly includes the addition of the plunger rod to the PFS. The combination product is defined as the syringe barrel assembly, filled, and stoppered, and with plunger rod inserted.

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

In-Process Controls (IPCs) and Critical Process Parameters (CPPs) for the DP manufacturing process are presented below:

### V116 DP Manufacturing IPCs and CPPs

Processing Step	Description	IPC/ CPP	Acceptance Criteria
Filling	Bioburden (b) (4)	IPC	(b) (4)
Filling	Bioburden (b) (4)	IPC	(b) (4)
Filling	Endotoxin (b) (4)	IPC	(b) (4)
Filling	Sterilizing Filter (b) (4) Test	IPC	Pass
Filling	Dose (b) (4)	CPP	(b) (4)

The IPCs in place for the combination product assembly are:

- (b) (4)
- 

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

##### Process Performance Qualification (PPQ)

(b) (4) consecutive batches were manufactured. All CPPs, IPCs and CQAs met the pre-determined acceptance criteria. The PPQ batch overview for both the formulation and syringe filling is presented below.

**V116 Formulation Batch to Fill Genealogy**

Formulation Batch Number	Formulated Batch Size <small>(b) (4)</small>	Fill Batch Number	Syringes Inspected	Date of Manufacture	Syringe
(b) (4)					

The formulation batch size for DP is qualified as (b) (4) for the (b) (4) batch size, and (b) (4) for the (b) (4) batch size.

Hold Times

**V116 Hold Times during PPQ**

V116 Hold Times	Start Time	End Time	Maximum Hold Time (hours)
(b) (4) Hold Time	(b) (4)	(b) (4)	(b) (4)
(b) (4) Storage Time	(b) (4)	(b) (4)	(b) (4)
Sterile Filling Time	Time (b) (4) is opened after docking the (b) (4)	Time of the last filled container	(b) (4)

The (b) (4) storage time was validated during the PPQ. Each batch was subject to a maximum (b) (4) storage time during the PPQ study. The shortest of the (b) (4) hold times, (b) (4), is the allowable limit based on the output of the PPQ. The sterile filling time and (b) (4) hold time were qualified as part of aseptic process simulation studies.

**V116 FFB/Fill Hold Times during PPQ**

Hold Times	Process Limit	(b) (4)	(4)
(b) (4) Storage Time (b) (4)	(b) (4)	(b) (4)	(4)
Sterile Filling Time (b) (4)	(b) (4)		
(b) (4) Hold Time (b) (4)	(b) (4)		

Critical Process Parameters

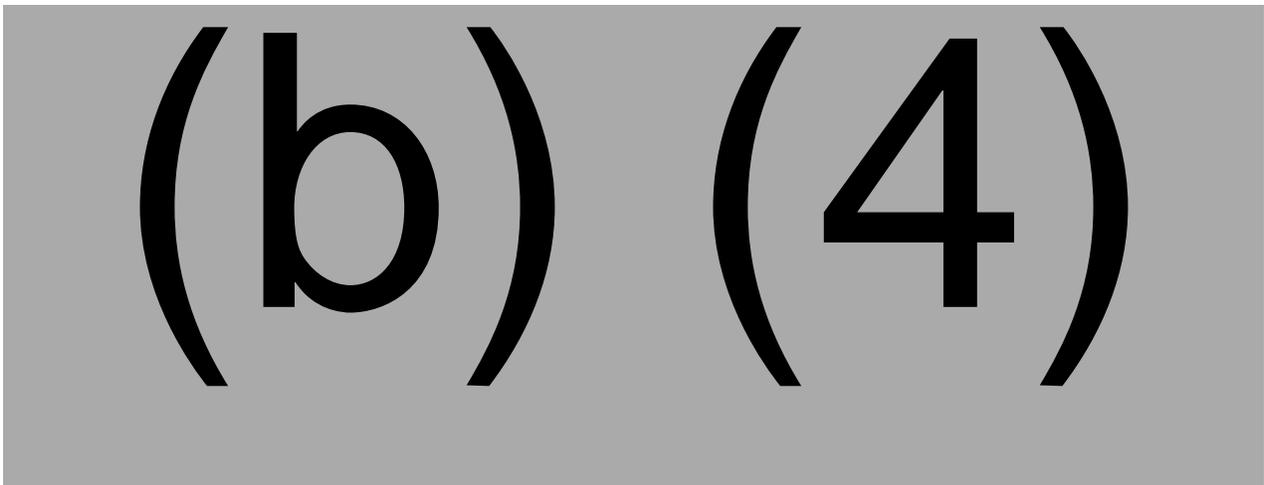
The CPP for the V116 filling process, along with the specification and qualification results are listed below. In-line fill (b) (4) checks ensure only filled syringes within the defined acceptance criteria are accepted by the filler and passed through to visual inspection. The CPP evaluated as part of the PPQ met specification.

**V116 PPQ - Filling CPP Syringe**

Critical Process Parameter	Acceptance Criteria	(b) (4)	(4)
Syringe Filling Dose (b) (4)	Target: (b) (4) Range: (b) (4)	(b) (4)	(4)

In Process Controls

The IPCs evaluated as part of the PPQ were met as shown below:



Critical Quality Attributes

The CQAs for V116 DP, along with their specifications and qualification results are listed below:

**V116 PPQ - CQAs**

Test Method	Acceptance Criteria	(b) (4)
Appearance (Degree of Coloration)	Colorless Liquid (b) (4)	
Appearance (Opalescence)	Clear to Opalescent Liquid (Opalescence is (b) (4))	
Sterility	No Growth	
Endotoxin ((b) (4))	(b) (4)	
Syringeability	Liquid is dispensed from the needle in an even stream; no evidence of needle blockage	
Recoverable Volume (mL)	0.500(b) (4)	

In addition to CQA testing, PPQ samples were taken at equal timepoints during the batch. The PPQ samples, number of sampling locations, and acceptance criteria are provided below.

**PPQ Testing Sampling Plan**

Attribute	Process Step	# of Sample Locations	Acceptance Criteria	Statistical Evaluation (Y/N)
Bioburden	(b) (4)	(b) (4)	(b) (4)	N
Recoverable Volume	Filling	(b) (4)	(b) (4)	Y

A statistically based sampling plan was derived for a sub-set of filling attributes to ensure the PPQ demonstrates high probability of meeting quantitative critical quality attributes across the batch. For recoverable volume, the high performance prediction interval fell within the specification limits. The Lower Specification Limit = 0.50 mL and the Upper Specification Limit = (b) (4) mL.

Drug Product Release Testing

The final product testing was performed as per established specifications. The evaluation criteria included: sterility, and endotoxin, recoverable volume and syringeability.

**Lot Release testing results for PPQ lots**

Release test	Acceptance criteria
Sterility	No Growth
Bacterial endotoxins	(b) (4)
Recoverable Volume	0.500(b) (4) mL
Syringeability	Liquid is dispensed from the needle in an even stream; no evidence of needle blockage

All (b) (4) PPQ batches met the release specification acceptance criteria listed above.

Deviations

Deviations were noted during the PPQ runs. These deviations were due to human error, instrument/system error, and environmental monitoring (EM) excursions. The EM deviations were due to sample handling error after batch completion, and (b) (4) in the (b) (4) prior to entry to the (b) (4). All deviations and EM excursions were investigated and closed. The deviations were appropriately addressed and determined by the firm to have no impact on the process, product, or performance qualification.

**Reviewer's Comments:** *The PPQ appears to have been appropriately performed and is adequate to support the manufacture of V116 DP. The PPQ lots met all acceptance criteria for process control and release testing under DMPQ purview. Evaluation of the acceptability of the other testing and manufacturing parameters for these lots is deferred to the assigned OVRP reviewer. The deviations under DMPQ purview appear to have been appropriately investigated and resolved with no adverse impact on the PPQ or the manufactured lots; other deviations not under DMPQ purview are deferred to the assigned OVRP reviewer.*

Validation of Sterile Filtration

(b) (4)

(b) (4)

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

(b) (4)

### 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 final product release tests and acceptance criteria microbial attributes under DMPQ purview are acceptable. The evaluation of the rest of quality attributes and acceptance criteria is deferred to the OVRR

Test	Acceptance Criteria
Sterility	No Growth
Endotoxin	(b) (4)

Recoverable volume (0.50<sup>(b) (4)</sup> mL) and syringeability (liquid is dispensed from the needle in an even stream; no evidence of needle blockage) are also evaluated as part of release.

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

Refer to section 3.2.P.7 Microbiological Attributes for assessment of container closure integrity testing (CCIT).

#### 3.2.P.5.4 Batch Analyses

The batch analysis data presented for the (b) (4) PPQ lots manufactured appear acceptable. Sterility and endotoxin results for the PPQ lots met the acceptance criteria (“no growth” for sterility, and (b) (4) for endotoxin). Recoverable volume and syringeability criteria were also met.

**Reviewer’s Comments:** *The batch analysis results are acceptable. Review and evaluation of all other parameters not under DMPQ purview for the lots manufactured to support the BLA are deferred to the OVRR reviewer.*

**3.2.P.8 Stability**

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

Evaluation of the acceptability of the stability data and the overall testing plan is deferred to the assigned OVRP reviewer. The PPQ lots available data for DMPQ to review were the CCI and sterility at time 0 (release); all lots met the criteria of integral container and no growth. The firm is performing CCIT at 0, 12, (b) (4) months per annual stability protocol. Merck committed to submit sterility and CCI long-term stability data (b) (4) for (b) (4) to support a drug product shelf life of up to 18 months stored at 5 ± 3 °C protected from light.

***Reviewer’s Comments:** The proposed shelf-life and storage conditions with respect to microbial quality and/or sterility assurance appear appropriate. I defer to the OVRP reviewer for a full assessment of the stability testing plan and results.*

**3.2.A APPENDICES**

The following table includes a full listing of all facilities associated with the BLA submission.

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	CMO	Comments
<p>Facility: Merck Sharp &amp; Dohme LLC                      (b) (4)                      (b) (4)                      FEI#: (b) (4)                      Manufacturing of drug substance intermediate                      (b) (4)                      Combination Product Assembly, DP Labeling, Finished Product Release for Distribution</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>No</p>	<p>ORA                      VAI                      (b) (4)</p>

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	CMO	Comments
<p>Facility: (b) (4)</p> <p>██████████</p> <p>██████████</p> <p>██████████</p> <p>FEI#: (b) (4)</p> <p>Manufacturing of drug substance intermediate (b) (4)</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>Yes</p>	<p>ORA NAI (b) (4)</p>
<p>Facility: MSD (b) (4)</p> <p>██████████</p> <p>██████████</p> <p>██████████</p> <p>FEI#: (b) (4)</p> <p>Manufacturing of drug substance and drug product (b) (4)</p> <p>██████████ DP Release Testing</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>No</p>	<p>ORA NAI (b) (4)</p>

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	CMO	Comments
<p>Facility: MSD (b) (4)</p> <p>(b) (4)</p> <p>FEI#: (b) (4)</p> <p>Manufacturing of drug product (Formulation, filling), DP Release Testing, Stability</p>	Waiver	Yes	Yes	No	<p>ORA VAI (b) (4)</p>
<p>Facility: (b) (4)</p> <p>(b) (4)</p> <p>FEI#: (b) (4)</p> <p>DP Release Testing, Stability</p>	Waiver	Yes	Yes	Yes	<p>ORA VAI (b) (4)</p>
<p>Facility: Merck Sharp &amp; Dohme LLC</p> <p>(b) (4)</p> <p>FEI#: (b) (4)</p> <p>Primary Labeling, Combination Product Assembly, Finished Product Release for distribution</p>	Waiver	Yes	Yes	No	<p>ORA NAI (b) (4)</p>

**Merck** (b) (4)

The (b) (4) building (b) (4) facility is used for the manufacture of pneumococcal polysaccharides DS intermediate. Building (b) (4) is a shared building that contains multiple manufacturing areas for other products. The manufacture of PnPs occurs in (b) (4) different areas of building (b) (4). (b) (4) is used for manufacturing of the (b) (4) PnPs DS intermediates present in V116 vaccine, these (b) (4). (b) (4) is a dedicated production facility for the manufacture of V116 novel PnPs (b) (4) (serotypes (b) (4)). See below for manufacturing area specific information.

(b) (4)  
Building (b) (4) is a multi-product area which manufactures the (b) (4) PnP (b) (4) (serotypes (b) (4)) used as DS intermediates for the V116 vaccine. (b) (4)

According to Merck, the HVAC systems and other utilities were qualified prior to use in the manufacture of the company's other commercial vaccines. Since the initial qualification routine monitoring of these systems has been in place with acceptable results. Cleaning and sterilization validation studies for all equipment have been completed. Periodic evaluation of the validated cleaning and sterilization procedures is performed per site procedures.

The (b) (4) facility has (b) (4) floors and is operated in conformance with current good manufacturing practices (CGMPs). Environmentally classified process suites are located on the (b) (4) floor and mechanical support systems are located on the second floor. The main manufacturing steps at (b) (4) are (b) (4).

**Reviewer's Comments:** Limited information was provided regarding equipment qualification; an IR was sent to the firm and the firm provided a response in amendment STN 125814/0.34. The response is summarized as follows and appears sufficient:

New equipment at (b) (4) includes (b) (4)  
Merck stated that product contact equipment was qualified by

completing IQ/OQ/PQ as per the company's Engineering and Quality management systems. A combination of the following is used to qualify equipment:

- Installation qualification (IQ) to provide documented evidence that the equipment is installed as intended to comply with critical installation requirements.
- Operational qualification (OQ) to provide documented evidence that the equipment operates as intended to comply with critical operational requirements.
- Performance qualification (PQ) to provide documented evidence that the equipment performs effectively and reproducibly according to the predetermined critical parameters in its operating environment, based on process method and product specification. When PQ is applicable to the equipment qualification strategy, the requirements are determined based on the local procedures for the equipment and its function.

The [redacted] successfully completed IQ, OQ, and PQ. The [redacted] was qualified prior to use in the [redacted]-batch PQ study and all equipment was qualified prior to use in manufacturing.

The cleaning and sterilization validation for the new equipment is described below. Merck stated that new equipment in the [redacted] facility includes the [redacted]

[redacted] validation runs were executed for the [redacted] and all results met the acceptance criteria. The following testing was conducted on the initial CVs along with the accompanying acceptance criteria:

(4)	[redacted]
[redacted]	[redacted]

The [redacted] sanitization qualification consisted of [redacted]; all criteria were met.

(4)	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The initial cleaning validation of the [redacted] consisted of [redacted] total runs: [redacted] consecutive runs with the worst-case rack ([redacted]) and [redacted] single runs with

the non-worst-case (b) (4). The following testing was conducted on (b) (4) along with the accompanying acceptance criteria:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

After the initial sterilization validation, the production (b) (4) was replaced with an equivalent (b) (4). Requalification of the (b) (4) sterilization cycle requires (b) (4) for both the (b) (4) cycles. The (b) (4) sterilization qualification results met the acceptance criteria. The (b) (4) sterilization qualification is ongoing. The (b) (4) sterilization PQ testing and acceptance criteria:

(b) (4)

(b) (4)

(b) (4)

**Reviewer Comments:** Merck (b) (4) is an FDA-licensed facility which manufactures PnPs used for the currently approved (b) (4)

(b) (4)

(b) (4)

(b) (4)

The (b) (4) facility is routinely inspected and has an acceptable compliance history with no outstanding issues identified. This facility has been previously inspected by US FDA with an acceptable outcome.

(b) (4)

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

(b) (4) [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

**MSD (b) (4)**

The Merck (b) (4) facility is already approved for (b) (4) and has experience manufacturing (b) (4). However, (b) (4) building dedicated to the new V116 vaccine. The facility and equipment information for the (b) (4) building is reviewed below. Building (b) (4) is a dedicated facility for the manufacture of (b) (4) from the DS intermediates: serotype-specific activated PnPs and CRM197 protein. Each PnP is conjugated to the CRM197 carrier protein.

(b) (4) consists of (b) (4) floors. The (b) (4) floor consists of (b) (4) and the (b) (4) floor for main processing activities. The (b) (4) floor encompasses (b) (4) manufacturing suites (b) (4)

(b) (4). The suites contain equivalent processing equipment to allow concurrent MBC manufacture. The (b) (4) areas on the (b) (4) floor and the main (b) (4) processing rooms on the (b) (4) floor are Grade (b) (4) classification.

Merck provided a site map of the (b) (4) facility, and the flow diagrams for personnel, product, materials, and waste. A description of the flows is described below in the “Facility Flow Diagrams” section.

### Facility Flows

Merck provided the facility flow diagrams and narratives in the BLA submission and stated that the flows are defined in approved SOPs. The rooms are designed to provide appropriate flow for personnel, material, equipment, and waste to or from the manufacturing room. All employees with access to classified spaces are trained on the approved flow procedures and must demonstrate proficiency in cleanroom gowning. The information is reviewed below:

#### Material Flow

The flow of (b) (4) through the facility is controlled via site procedures. The transfer of materials involves the cleaning and removal of protective layering from materials. Materials are sanitized when going from lower classification to higher classification (e.g., Grade (b) (4) to Grade (b) (4)). Entry and exit of materials to and from all graded areas is controlled via site procedures.

#### Product Flow

The flow of product throughout the classified manufacturing areas is controlled per site procedures. There is a dedicated (b) (4) for product removal.

#### Waste Flow

Disposal of all process waste generated in (b) (4) is controlled via site procedures. The manufacturing suite has a dedicated waste exit airlock.

#### Personnel flow

Personnel are trained in gowning requirements prior to entry to the (b) (4) production areas and personnel flow is controlled via site procedures. Personnel are responsible for the movement of product, raw materials, buffers, and equipment throughout the classified manufacturing areas. There are separate personnel airlocks in and out of the manufacturing area.

**Reviewer’s Comments:** Overall, the facility flows described and illustrated in diagrams appear to be appropriate to support the manufacturing process.

### HVAC

The HVAC system in building (b) (4) was qualified in (b) (4). The classified areas in (b) (4) are categorized as Grade (b) (4). For Grade (b) (4) and Grade (b) (4) areas, air is supplied at a rate of (b) (4) air changes per hour and (b) (4) air changes per hour, respectively. A positive pressure differential is maintained from the Grade (b) (4) processing areas to adjacent lower

grade areas. Room pressure, temperature and relative humidity conditions are continuously monitored and alarmed.

There are (b) (4) AHUs servicing the manufacturing area. The air is HEPA filtered prior to entry into the classified manufacturing areas. HEPA filters are changed if testing or repairs indicate a change is necessary.

**AHUs supporting (b) (4) Manufacture**

Air Handling Unit	Rooms Served	Room Classification
A large rectangular area is completely redacted with a solid grey background. In the center of this redacted area, the text "(b) (4)" is written in a large, bold, black font. The "(b)" is on the left and the "(4)" is on the right, with a space between them.		

**Reviewer's Comments:** The HVAC system and design in the (b) (4) facility used for (b) (4) appears to be acceptable.

EMPQ

The environmental monitoring performance qualification (EMPQ) was executed by sampling multiple test sites in each room. Sample locations were determined using an EM risk-based design to determine the appropriate number, location, and type of environmental samples for the PQ and subsequent routine EM program. The PQ consisted of (b) (4) phases: (b) (4) (b) (4) The PQ included Grade (b) (4), Grade (b) (4) and Grade (b) (4) rooms used in manufacturing operations. The testing in the cleanrooms included (b) (4). The EMPQ also included criteria to qualify environmental controls, such as temperature, humidity, and differential pressure. The following action limits were used during HVAC PQ.

(b) (4)

One excursion was noted that included an active microbial air result exceeded the action limit in Grade <sup>(b) (4)</sup>; the retest met the criteria.

***Reviewer's comments:** The EMPQ appears to have been appropriately performed.*

### **Environmental Monitoring**

Environmental monitoring (EM) is performed in all classified areas. The facility is routinely monitored for <sup>(b) (4)</sup> levels as required per area classification according to the established standard operating procedures. The sampling locations include active air samples ( <sup>(b) (4)</sup> ), passive air (<sup>(b) (4)</sup> ), and microbial surfaces. The routine testing frequency and limits required for each classified area are specified in site procedures.

Action limits excursions during routine EM are handled per standard procedures; the event is documented, and investigation and corrective actions performed as required.

(b) (4)

**Reviewer's comments:** *The EM program appears adequate.*

### Facility Cleaning

Approved and qualified disinfectant and sporicidal agents are used to clean the manufacturing area in (b) (4); all activities are documented. Additionally surface sanitizing agent is used to sanitize items prior to entry to the processing area. Disinfectant efficacy studies are carried out according to procedures. Procedural controls for cleaning are in place and are monitored through the routine environmental program.

**Reviewer's Comment:** Limited details were provided in the submission; however, the facility has an established compliance history and has an acceptable compliance status.

### Utilities

Clean utilities in (b) (4) include WFI, (b) (4).

#### WFI

Water for injection (WFI) is used during (b) (4) manufacture, equipment cleaning, and generation of clean steam. The WFI system consists of (b) (4)

The qualification of the WFI system in (b) (4) was completed over a 4-week period in 2019. The (b) (4) PQ and routing monitoring testing and action limits are presented below.

(b) (4)

All PQ results met the criteria.

The routine monitoring testing frequency and locations are established based upon the application of the system. All routine monitoring action limit excursions are investigated per site procedures.

(b) (4) [Redacted text block]

(b) (4)

[Redacted]

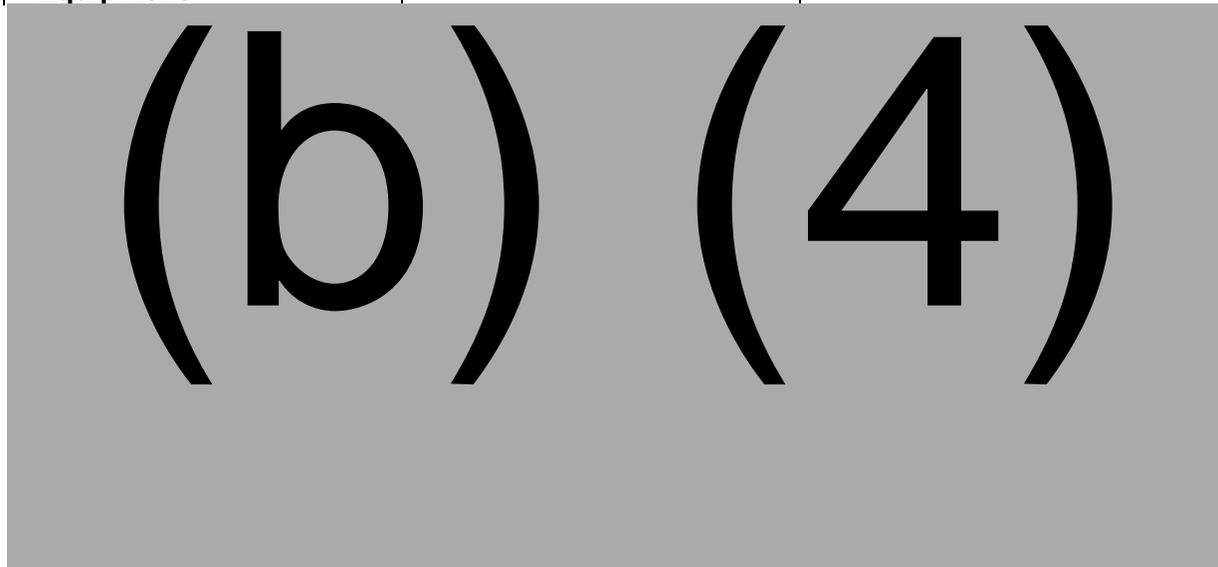
*Reviewer's Comments:* The WFI, (b) (4) appear appropriate to support manufacturing of (b) (4). The qualification, monitoring and specifications of the systems are acceptable.

**Equipment**

The major product contact equipment used in the manufacture of (b) (4) is constructed of (b) (4). All equipment in each group is considered equivalent.

**Major Product Contact Equipment in (b) (4) Manufacture**

Major Processing Equipment	System ID	Process Step
<b>(b) (4)</b>		

Major Processing Equipment	System ID	Process Step
		

**Reviewer's Comments:** Limited information was provided regarding equipment qualification; an IR was sent to the firm and the firm provided a response in amendment STN 125814/0.34. The response is summarized as follows appears sufficient:

Per Merck, the (b) (4) product contact equipment including the (b) (4) [redacted], were qualified using Factory Acceptance Testing (FAT), Site Acceptance Testing (SAT), and qualification stages (IQ, OQ, PQ). PQ can be incorporated into the Process Performance Qualification (PPQ) depending on the equipment. All equipment was successfully commissioned and qualified prior to use in the (b) (4) manufacturing process, including PPQ.

(b) (4) [redacted]

Equipment Cleaning

(b) (4) is a dedicated facility containing (b) (4) manufacturing trains ( (b) (4) ) for the manufacture of (b) (4). All equipment in (b) (4) is considered equivalent. (b) (4) are equipped with separate (b) (4) systems that clean all direct and indirect

reusable product contact equipment associated with (b) (4) manufacture. The (b) (4) used for the cleaning cycles are functionally equivalent.

All reusable product contact equipment used in the manufacture of (b) (4) are cleaned after use. The (b) (4) cleaning cycles were validated with a minimum of (b) (4) consecutive runs for the (b) (4), and (b) (4) validation runs for the (b) (4) per site procedures. The efficacy of the cleaning procedures was evaluated by (b) (4)

The following tests were performed for cleaning validation studies: (b) (4). A hardest to clean worst-case process soil approach was applied to cleaning validation studies. The cleaning validation studies also incorporated dirty hold time and clean hold time for the process.

**Summary of Cleaning Validation Studies for (b) (4) Equipment**

Equipment	Validated Cleaning Procedure
(b)	(4)

The following testing was conducted on all the CVs listed in the table above along with the accompanying acceptance criteria.

(b) (4)

All acceptance criteria were met. The deviations encountered during the validation studies were due to out of specification (b) (4) results due to inadequate procedure information, (b) (4) sample tested using the incorrect procedure, and incorrect (b) (4) limits due to a wrong calculation. All deviations were resolved and closed. Periodic monitoring of validated procedures is conducted to demonstrate that the equipment cleaning procedures continue to be effective.

**Reviewer's Comments:** *The routine cleaning processes at (b) (4) appear to be appropriate. The deviations appeared to have been appropriately resolved and determined to have no impact on the cleaning validation.*

Equipment Sanitization

(b) (4) sanitization methods are applied to equipment prior to use in manufacturing for (b) (4) control. Performance qualification is performed to demonstrate that (b) (4) sanitization procedures are effective, reliable, and reproducible, and provide a SAL of at least (b) (4). Initial performance qualification studies consist of at least (b) (4) consecutive validation cycles on the associated equipment. Sanitization qualification is carried out under production conditions, where time and/or temperature settings were monitored. The temperature distribution throughout the equipment assembly was monitored using (b) (4) placed at defined locations. (b) (4) are used to determine the accumulated physical lethality ( $F_0$ ) within the system over pre-determined exposure times.

All reusable product contact equipment is (b) (4) sanitized by a (b) (4) cycle or autoclave. The purpose of the validation studies is to achieve (b) (4) for product contact components used for (b) (4) controlled process steps. The equipment includes (b) (4). Components downstream of (b) (4) such as (b) (4) are sterilized by the vendor via gamma irradiation. The (b) (4) is dispensed into (b) (4) assemblies from single use vessels.

(b) (4) cycles were validated for the following reusable product contact equipment: (b) (4).

(b) (4)

[Redacted list of equipment]

The following criteria were met for the (b) (4) qualification:

(b) (4)

[Redacted list of criteria]

(b) (4) [Redacted]

The following criteria were met for the (b) (4) sanitization qualification:

(b) (4) [Redacted]

A maximum and minimum worst case load assessment was executed on the (b) (4) [Redacted] loads:

(b) (4) [Redacted]

The PQ for the (b) (4) loads included a (b) (4) [Redacted]. The purpose of these studies is to (b) (4) [Redacted]. All results passed.

The (b) (4) [Redacted] studies met the following criteria:

(b) (4) [Redacted]

**Reviewer's Comments:** *The sanitization validations appear to have been appropriately performed. The data demonstrate the effectiveness of the sanitization processes for reducing bioburden.*

**Line Clearance/Cross contamination**

Merck stated that engineering controls, gowning requirements and flow patterns within

the facility have been designed to maintain cleanliness and minimize contamination/cross-contamination. The (b) (4) manufacturing process is a (b) (4) process that occurs upstream of sterile filtration. (b) (4)

The HVAC system including HEPA filters support room classification, differential pressure cascades, and temperature and humidity controls. Facility access is restricted in controlled and classified areas.

Preparation of the production area occurs prior to the next batch. Batch changeover in the classified area is performed per written procedures and includes:

- Removal of batch-specific materials
- Cleaning of room and reusable equipment

Single use components including (b) (4) are sterilized by the vendor. Additionally, all (b) (4) used in the manufacturing process are (b) (4).

Cleaning, disinfection, and decontamination is performed at a defined frequency with approved and qualified chemical agents. Cleaning agents and disinfectants are qualified by performing disinfectant efficacy studies. Additionally surface sanitizing agent is used to sanitize items prior to entry to the processing area. Procedural controls for cleaning are monitored through the routine environmental program ensuring that microbial control for all classified areas in (b) (4).

**Reviewer's Comments:** The (b) (4) is a dedicated facility currently manufacturing (b) (4) DS and seems to have appropriate controls and procedures to prevent contamination and cross contamination.

### Computer Systems

(b) (4) uses the following automation systems in (b) (4) manufacture:

- (b) (4) - primary automated production system for monitoring and controlling manufacturing
- (b) (4) - controls the weigh and dispense of raw materials
- (b) (4) - Data acquisition and model execution; allows real time follow-up of the product quality and enhances increased process understanding of information acquired from (b) (4).

The computer systems involved with the manufacture of (b) (4) have been validated in accordance with 21 CFR Part 11 and compliance with electronic records/signatures requirements. The computerized system validation policy is in alignment with Good Automated Manufacturing Practice guidance documentation and uses a risk based and science-based approach, as well as lifecycle methodologies. IQ, OQ, and periodic

validation maintenance are described in site procedures. Validation activities are managed through approved protocols with associated testing and acceptance criteria. A periodic review is performed and includes operating history and system performance, change controls, and security.

**Reviewer's Comments:** *The computer systems used for (b) (4) at the (b) (4) facility appear acceptable.*

### **MSD (b) (4)**

The (b) (4) site is a multi-product facility and approved to conduct formulation and filling of DP for similar, approved commercial products. This facility manufactures other vaccines, biologicals, and small molecule products. There are no beta-lactams, cytotoxic products, live or attenuated virus or microbiological products manufactured at the (b) (4) site. The aseptic manufacture and primary packaging operations for vaccine drug product are performed in the (b) (4) which contains the production area and the (b) (4). The (b) (4) houses the facility warehouse and additional support areas such as a (b) (4) area. The production area consists of a (b) (4) are controlled to Grade (b) (4) classification. Syringe and vial filling are performed within a Grade (b) (4) located in a Grade (b) (4) room.

**Reviewer Comments:** *MSD (b) (4) is an FDA-licensed facility which manufactures currently approved pneumococcal vaccines, (b) (4). The (b) (4) facility at (b) (4) used for V116 is also used in the manufacture of the above approved vaccines. The facility information including HVAC, environmental monitoring, utilities, contamination control, computer systems, and equipment qualifications were previously reviewed under (b) (4). The (b) (4) facility has an acceptable compliance history with no outstanding issues identified. This facility has been previously inspected by US FDA with an acceptable outcome. New information regarding this facility was provided in the submission and is reviewed below and includes the most recent critical equipment sterilization revalidation studies provided by Merck to support the manufacture of V116 DP.*

### **Equipment**

All reusable major product contact equipment used for the V116 DP is constructed of (b) (4) with surfaces which are sanitary by design.

Equipment Cleaning

The product-contact equipment for the manufacture of V116 DP consists of (b) (4) and re-usable equipment including (b) (4). Equipment cleaning is validated via automated (b) (4) cycles or automated equipment washer (b) (4) cycles. A minimum of (b) (4) satisfactory studies for product contact equipment was required to validate the cleaning procedure. The validation approach considered equipment configurations, dirty and clean equipment hold times using reduced cleaning cycles. Cleaning validation for the following equipment was performed using V116 product as soil.

**Overview of V116 DEHT Grouping Strategy**

Equipment	Grouping Description	Total No. of Runs Required per Group

There are (b) (4) that are considered equivalent. (b) (4) is comprised of components from the (b) (4) of the drug product manufacturing process. (b) (4) is comprised of components from the (b) (4) that are used during the filling process. (b) (4) consists of components from the (b) (4) . (b) (4) consists of components from the (b) (4) load.

The following testing was conducted on all the CVs listed in the table above along with the accompanying acceptance criteria.

--

All results met the acceptance criteria. All validated cleaning processes are re-assessed annually.

**Reviewer's Comments:** *The equipment cleaning processes at (b) (4) appear to be appropriate.*

### Equipment Sterilization

After cleaning, all product-contact equipment undergoes sterilization prior to manufacturing. The (b) (4) is decontaminated via (b) (4), and equipment is sterilized via (b) (4). The objective of sterilization validation is to demonstrate that a sterilization cycle provides a minimum SAL of (b) (4) probability of microbial survival or better. The sterilization cycles are challenged by performing the sterilization validation study using a (b) (4)

A summary of the methods of sterilization at the (b) (4) facility are presented below:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The initial (b) (4) surface decontamination cycle validation included: (b) (4)

(b) (4)

Periodic revalidation is performed for the (b) (4) decontamination cycle for the (b) (4).

The most recent (b) (4) revalidation results met the criterion of 'No growth', demonstrating a minimum (b) (4) reduction in the BI challenge population distributed around the (b) (4). The (b) (4) revalidation results met the criteria of (b) (4)

There are (b) (4) already qualified autoclaves ( (b) (4) ) at (b) (4) for manufacturing V116. Temperature sensors and BIs with worst-case challenge of (b) (4) are used for load qualification studies. The autoclave loads for the processing of V116 include (b) (4). The autoclave loads are revalidated (b) (4). The worst-case load is requalified (b) (4), other loads are requalified every (b) (4).

The results for the most recent revalidation runs met the following criteria:

(b) (4)

(b) (4)



The [redacted] are already qualified. The most recent revalidation results met the following acceptance criteria:

(4)



**Reviewer's Comments:** *The sterilization and sanitization validations appear acceptable. The data demonstrate the effectiveness of the processes.*

### 3.2.R Regional Information (USA)

#### □ Combination Products

Merck provided Quality System information for the combination product and compliance with 21 CFR Part 4 Section 4.4 (b)(1) and the following provisions from the device Quality System regulation requirements during development and manufacturing of the combination product.

- 21 CFR 820.20 Management Responsibility

Merck and the manufacturers of device components have established Commercial Quality Agreements outlining the responsibilities between the companies for the commercialized finished product. Periodic management reviews are performed.

- 21 CFR 820.30 Design Controls

The design control system implemented for the development of the combination product addresses the following elements: design and development planning, design inputs, design outputs, design review, design verification, design validation, design transfer, design changes, and risk assessments. Changes that potentially affect product quality or system compliance are managed through a formal change management process.

The device risk management in place includes a risk management plan, hazardous situations and harms list, hazard identification tools such as failure mode effect analysis (FMEA), an evaluation of patient risk that includes identification and verification of risk control measures, and a summary of device risk management per (b) (4). The company concluded that all residual risks were reduced as far as possible, and the combination product is safe and effective for its intended use.

Merck provided the following studies performed for the combination product:

*CCI Testing of the DP Assembled syringe (combination product PPQ)*

A PPQ study performed to support the assembly process of the plunger rod into the PFS to produce a combination product. The study consisted of (b) (4) distinct final assembly batches each at both (b) (4) sites, with a minimum batch size of (b) (4) units. The study included (b) (4) syringe batches. All acceptance criteria were met. The sample testing and acceptance criteria included:

(b) (4)

Syringeability is assessed as part of the recoverable volume method, by visually observing the passage of the product through the syringe needle during the execution of the compendial method. The test is to ensure that the liquid is dispensed in an even stream and there is no evidence of needle blockage or other conditions which could interfere with the discharge of the vaccine.

*CCI Testing, combination product after Shipping Studies*

CCI testing was performed on (b) (4) samples each of (b) (4) different configurations. The different configurations include combination product and combination product post simulated shipping from both manufacturers ((b) (4)) of syringe barrel assembly. All samples passed the test demonstrating acceptable container closure integrity (No leaks detected).

Syringe Functionality

Syringe functionality is determined by the (b) (4)

(b) (4) The method is based on the principles described in (b) (4). The DP pre-filled syringes are tested for (b) (4)

(b) (4) was performed to demonstrate functionality of (b) (4) syringes. (b) (4) was performed on (b) (4) samples each of (b) (4) different configurations. The different configurations include combination product and combination product post simulated shipping from both manufacturers ((b) (4)) of syringe barrel assembly. The acceptance criteria for this testing were (b) (4). All test results met the acceptance

criteria.

#### Recoverable Volume Testing

Recoverable volume was tested to demonstrate essential performance functionality of both (b) (4) syringe assembly. Testing was performed on (b) (4) samples each of (b) (4) different configurations. The different configurations include combination product and combination product post simulated shipping from both manufacturers ((b) (4) ) of syringe barrel assembly. The results were required to meet a minimum k-value of (b) (4) in addition to meeting the specification of 0.500(b) (4) mL. The (b) (4)-value is the calculated tolerance interval factor that indicates confidence and probability that samples will fall within the required specification. All results met the acceptance criteria.

- 21 CFR 820.50 Purchasing Controls

The supplier or manufacturer selection is executed per established process for supplier management and procurement. An audit is performed as part of the quality assessment for the selected supplier. Quality agreements are documented with suppliers and contract manufacturers. Quality oversight of the device manufacturers is described in approved procedures. Additionally, the performance of suppliers/contractors is monitored and periodic assessments are carried out to verify conformity. Specifications are established to control the incoming medical devices or device components to meet design requirements.

- 21 CFR 820.100 Corrective and Preventative Action (CAPA)

The Quality System includes procedures for the evaluation of deviations, customer complaints and observations from internal audits and inspections. Investigations into the root cause are executed and documented. Corrective and preventive actions are implemented, and verification of effectiveness of these actions is performed. Periodic reviewed of nonconformities is performed.

**Reviewer's Comments:** *The information provided appears adequate. Merck fills other products in syringes and has a history with the device and controls. The combination product information was already reviewed under Vaxneuvance BLA 125741 and found acceptable.*