

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

**BLA STN 125781/0**

**delandistrogene moxeparvovec (SRP-9001)**

**Ou Olivia Ma, DMPQ  
Reviewer**

**1. BLA#: STN 125781/0**

**2. APPLICANT NAME AND LICENSE NUMBER**

Name: Sarepta Therapeutics, Inc.

US License #: 2308

**3. PRODUCT NAME/PRODUCT TYPE**

Proper name: **delandistrogene moxeparvovec (SRP-9001)**

Proprietary name: **N/A**

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

- a. Pharmacological category: **Gene Therapy**
- b. Dosage form: **Solution for Infusion**
- c. Strength/Potency: **1.33E+13 vector genomes (vg)/mL**
- d. Route of administration: **Intravenous infusion**
- e. Indication(s): **Treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene**

**5. MAJOR MILESTONES**

- Application Receipt Date: September 28, 2022
- First Committee Meeting: October 24, 2022
- Filing Meeting: November 12, 2022
- Filing Action: November 27, 2022
- Internal Mid-Cycle Meeting: January 12, 2023
- Mid-Cycle Communication: January 24, 2023
- Late-Cycle Meeting: March 14, 2023
- Advisory Committee Meeting: May 12, 2023
- PDUFA Action Due Date: May 29, 2023
- Pre-License Inspection (PLI) of Catalent Biopark facility: February 21-24, 2023
- PLI of Catalent BWI facility: March 6-10, 2023
- PLI of Sarepta testing facility in Andover, MA: March 20-24, 2023

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

Reviewer/Affiliation	Section/Subject Matter
Ou Olivia Ma, OCBQ/DMPQ/MRB2	Drug substance, Drug Product, Facilities

**7. SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
Sep 28, 2022	STN 125781/0	
Jan 12, 2023	Amendment STN 125781/0/13 (Response to IR sent on Dec 27, 2022)	Reviewed and found acceptable
May 19, 2023	Amendment STN 125781/0/61 (Response to Catalent BWI inspection Form FDA 483)	Reviewed and found acceptable

**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) vials	yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	(b) (4) Vials	yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Stopper/ (b) (4)	yes	No DMF review required, information pertinent to container closure is provided in the BLA
STN (b) (4)	(b) (4)	Stopper, elastomeric formulations, coatings, films	yes	Deferred to OTP reviewers

**9. REVIEWER SUMMARY AND RECOMMENDATION****A. EXECUTIVE SUMMARY**

Sarepta Therapeutics, Inc. (Sarepta) submitted documentation to BLA STN 125781/0 to support licensure of delandistrogene moxeparvovec (SRP-9001), a gene therapy product intended to treat ambulatory patients with Duchenne muscular dystrophy (DMD) with a

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confirmed mutation in the DMD gene. CBER/DMPQ reviewed and evaluated the drug substance (DS) and drug product (DP) manufacturing processes and facilities proposed for use in the manufacture of SRP-9001. Information reviewed, evaluated, and documented in this memo includes data to validate and support the consistency of the manufacturing process and product quality; facility information which includes utilities, cross-contamination prevention measures, and maintenance of controlled environments; and equipment for use in the manufacturing (all product-contact equipment used in DS and DP manufacturing are single-use).

As part of the BLA review, three Pre- License Inspections (PLIs) were performed including the PLI of the DP manufacturing facility at Catalent Biopark in Baltimore, MD on February 21-24, 2023, DS manufacturing facility at Catalent BWI in Harmons, MD on March 6-10, 2023, and a DP release testing facility at Sarepta in Hanover, MA on March 20-24, 2023. Each PLI was documented in a separate establishment inspection report (EIR).

At the conclusion of the Catalent BWI inspection, a Form FDA 483 was issued on March 10, 2023 with two inspectional observations, to which the firm responded on March 31, 2023. At the conclusion of the Sarepta facility inspection, a Form FDA 483 was issued on March 24, 2023 with one inspectional observation, to which the firm responded on April 12, 2023. All inspectional 483 observations were deemed resolved, and both the Catalent BWI and Sarepta facilities were classified as Voluntary Action Indicated (VAI). No Form 483 was issued at the conclusion of the Catalent Biopark PLI, and this PLI was classified as No Action Indicated (NAI).

In addition to the PLIs, facility inspections were waived for the DP packaging and labeling facility of (b) (4), and the DP release testing facilities of (b) (4) in (b) (4). The inspection waivers were based on the evaluations of the facilities' inspection compliance histories. The inspection waivers are documented in a separate inspection waiver memo dated February 10, 2023.

This submission was granted priority review with 8-month review cycle.

## **B. RECOMMENDATION**

### **I. APPROVAL**

Based on the review of the information submitted to BLA 125781/0 and in conjunction with the PLIs and inspectional compliance history evaluations, the production process, facilities, equipment, and controls appear acceptable; approval is recommended with the following inspectional recommendation. CBER understands that the recommendation may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

- On the next inspection of Catalent Maryland (BWI), (b) (5), (b) (7)(E)

**Below** is a listing of the Drug Substance (DS) and Drug Product facilities to be included in the approval letter:

- DS manufacturing facility:  
Catalent Pharma Services  
Catalent Maryland (BWI)  
7555 Harmans Road  
Harmans, MD 20177, USA  
**FEI#:** 3015434301  
**DUNS#:** 116950534
- DP manufacturing facility:  
Catalent Pharma Solutions  
Catalent Maryland (BioPark)  
801 West Baltimore Street, Suite 302  
Baltimore, MD 21201, USA  
**FEI#:** 3015558590  
**DUN#:** 618890289

Below is the list of approvable Comparability Protocol(s) (CP):

- CP for conducting additional drug substance batches in manufacturing Suite (b) (4) at the Catalent BWI facility.

## II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Ou (Olivia) Ma/ Consumer Safety Officer OCBQ/DMPQ/MRB2	Concur	
Anthony Lorenzo / Branch Chief OCBQ/DMPQ/MRB2	Concur	
Carolyn Renshaw / Division Director OCBQ/DMPQ	Concur	

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**3.2.S DRUG SUBSTANCE**






(b) (4)



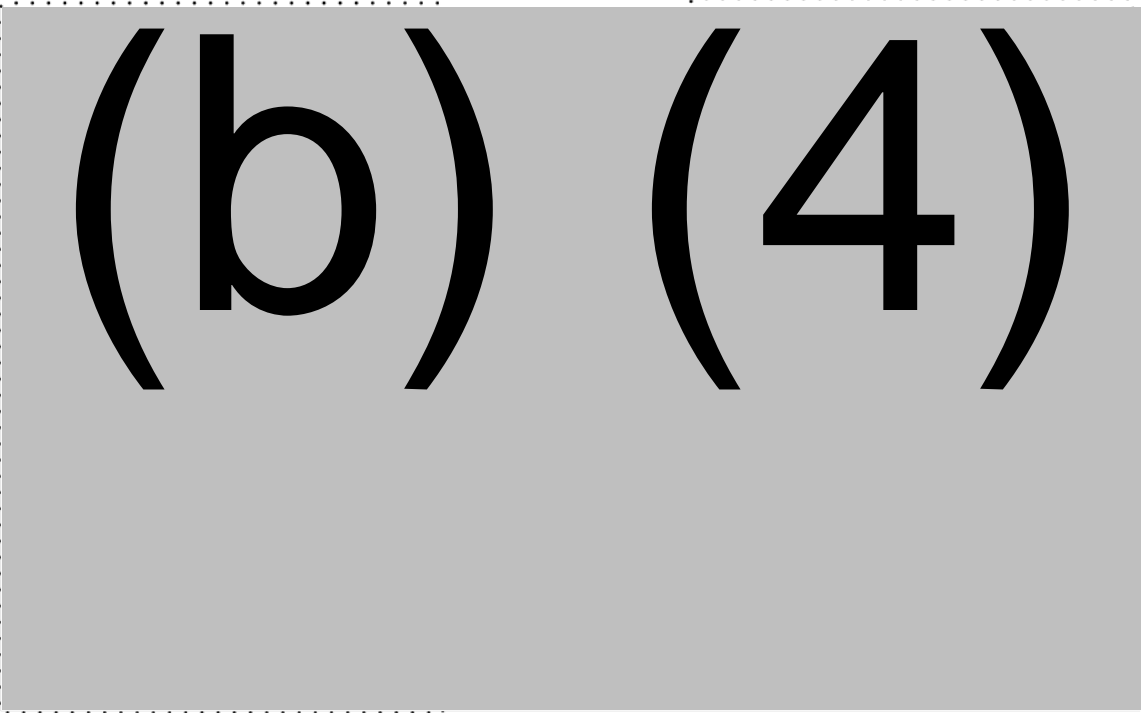
**3.2.S.2 Manufacture**

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

(b) (4)




(b) (4)



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

(b) (4)



### **3.2.P DRUG PRODUCT**

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

SRP-9001  $1.33 \times 10^{13}$  vg/mL solution for infusion (drug product) is supplied as a single-use, preservative-free, sterile, aqueous solution for intravenous infusion.

One vial contains 10 mL of  $1.33 \times 10^{13}$  vg/mL of Delandistrogene moxeparvovec (SRP-9001) formulated in a buffered solution of 20 mM Tromethamine/Tromethamine-HCl, 1 mM Magnesium chloride, 200 mM Sodium chloride, and 0.001% Poloxamer 188. Each vial contains an extractable volume of not less than 10.0 mL. The container closure system consists of a cyclic olefin polymer vial closed with a rubber stopper and sealed with an aluminum seal and plastic flip-off cap.

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

Refer to section 3.2.P.7 Container Closure System for the primary container closure system description, specifications, and its qualification (per DMPQ purview).

### 3.2.P.2.5 Microbiological Attributes

The SRP-9001 drug product is manufactured as a sterile DP by aseptic processing, and supplied as preservative-free, single-use vials. The DS is manufactured using a

(b) (4) to the DP (b) (4) process. As part of the aseptic filling process, DP solution is filtered through (b) (4). DP is aseptically filled using a validated process, and all product-contact components are either received sterile or sterilized during validated process. The container closure integrity of the primary packaging systems was demonstrated by (b) (4) testing with a detection limit of (b) (4). DP is subject to sterility and endotoxin testing as part of the release process, with acceptance criteria of no growth and (b) (4), respectively. Assurance of container closure system integrity during shipping was established by the shipping validation study.

**Reviewer's Assessment:** *The microbial attributes and control strategy appears acceptable. The (b) (4) controlled DS manufacturing process is reviewed in Section 3.2.S.2.4. The sterile filtration steps are reviewed in Sections 3.2.P.3.3 and 3.2.P.3.4. DP filling aseptic process validation, as well as product-contact material sterilization process validation are reviewed in Section 3.2.P.3.5. Container closure integrity testing validation is reviewed in Sections 3.2.P.5.3 and 3.2.P.7.*

### 3.2.P.3 Manufacture

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

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

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

The SRP-9001 DP manufacturing process is performed at Catalent Maryland (Biopark) facility in Baltimore, MD, and include the following steps.

Formulation buffer preparation: formulation buffer is prepared by (b) (4). The final concentration of the formulation buffer is 20 mM Tris, 200 mM sodium chloride, 1 mM magnesium chloride, 0.001% poloxamer 188, and (b) (4). The formulation buffer is tested for (b) (4).

(b) (4)

Sterile filtration: The formulated bulk drug product solution is sterile (b) (4).

(b) (4)

Aseptic filling, stoppering, and capping: Aseptic filling, stoppering, and capping is performed on (b) (4)

Each vial is filled to the target fill volume and fill (b) (4) checks are manually performed at predefined intervals throughout the fill.

Visual inspection: All filled vials are manually inspected for container closure and solution defects within (b) (4). Vials passing the 100% manual visual inspection process are then sampled for an Acceptable Quality Limit (AQL) visual inspection.

Freeze and storage: The drug product vials are frozen and stored at  $\leq -60^{\circ}\text{C}$ .

Labeling and packaging: Drug product is transferred to the secondary packaging site. Labeling and packaging operations are performed at (b) (4)

Long-term storage: The final drug product vials are stored at  $\leq -60^{\circ}\text{C}$ .

Drug product batches produced at Catalent Biopark are numbered using the following nomenclature: A-634-SRP9001-20-XXXX, with A: Drug Product; 634: designation of company (Sarepta); SRP9001: designation of drug product; 20: (b) (4) XXXX: (b) (4)

***Reviewer's Assessment:*** Adequate information is provided for the DP process description. Description and assessment of controls associated with critical steps operating and performance parameters, in-process controls and hold-times are provided in sections 3.2.P.3.4 Controls of Critical Steps and Intermediates, and 3.2.P.3.5 Process Validation.

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

The formulation buffer is (b) (4)

**Reviewer's Assessment:** Microbial control strategy including sterility assurance steps and in-process control testing appears suitable. The bioburden testing (b) (4) is in place to ensure contamination control of the drug product (b) (4) processing and reduce the risk of sterility failure. (b) (4) integrity test is in place to ensure no microbial breach of the sterilizing filter.

Maximum in-process hold times for each process step have been identified. Review of the microbial qualities in support of the maximum hold time for the formulation buffer is reviewed in Section 3.2.P.3.5. Evaluation of all other maximum allowable hold time studies is deferred to OTP reviewers. Validation of aseptic filling is reviewed in section 3.2.P.3.5.

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

1 page determined to be not releasable: (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)

DP specifications under DMPQ purview are reviewed in section 3.2.P.2.5 Microbiology Attributes.

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

CCIT and its method validation is reviewed in Section 3.2.P.7 Container Closure System. Evaluation of other analytical methods is deferred to OTP and DBSQC reviewers.

#### 3.2.P.5.4 Batch Analyses

Batch analyses results are provided for (b) (4) lots that were manufactured from (b) (4) with the commercial process. These batches cover nonclinical lots, clinical lots, engineering runs, and DS and DP process validation batches including the three consecutive DP PPQ lots (b) (4). Batch sizes range from (b) (4) vials.

Under DMPQ purview, the batch analyses testing including sterility and endotoxin tests and the acceptance criteria are no growth and (b) (4), respectively. All batches met the sterility acceptance criteria, and all batches met the endotoxin acceptance criteria with the highest endotoxin level at (b) (4).

**Reviewer's Assessment:** Lots included in the batch analyses appear suitable, including the three consecutive DP validation runs. There were no deviations for the batch testing under DMPQ purview. Additional data for batches manufactured by an archived process ("Process A") were also provided. As this process is no longer being used for SRP-9001 DP manufacturing, the analyses are not included in this review.

### 3.2.P.7 Container Closure System

#### Components of the Container Closure System

The container closure system consists of cyclic olefin polymer (COP) vials, stoppered with grey rubber stoppers, and further sealed with aluminum seals with flip-off plastic caps. The components of the container closure system are listed in Table 5:

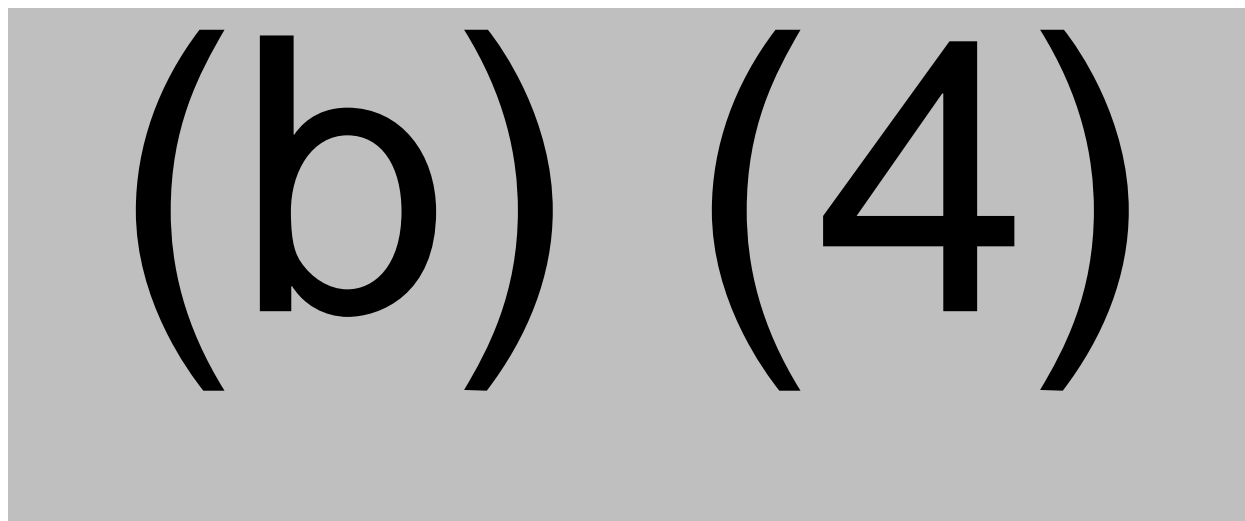
Table 5. SRP-9001 DP Container Closure Components

Component	Description	Manufacturer	Standards
Vial	10-mL, cyclic olefin polymer (b) (4)	(b) (4)	(b) (4)

Component	Description	Manufacturer	Standards
Stopper	20-mm, (b) (4) grey chlorobutyl rubber stopper with (b) (4) barrier on product contact side, (b) (4) coating on non-product side	(b) (4)	(b) (4)
Cap	20-mm, aluminum shell with polypropylene flip- off cap overseal	(b) (4)	Not applicable (no product contact)

All components in the SRP-9001 DP primary packaging system are received sterile and ready to use. The specifications for the vials, stoppers and caps are summarized in Table 6. The components of the container closure system are released against these specifications based on the Certificate of Analysis (CoA) provided by the manufacturer.

Table 6. SRP-9001 DP Container Closure Specifications



The selected container closure system (CCS) for the drug product is commonly used in the industry for cell and gene therapies due to its performance properties of break resistance and structural integrity under cryogenic storage conditions. The cyclic olefin polymer (COP) (b) (4) are chosen for the primary container closure since SRP-9001 vials are stored at  $\leq -60^{\circ}\text{C}$  and polymer vials are more robust and supportive than glass at low temperature. Rubber stoppers and COP polymer have more similar coefficients (than glass) of thermal expansion, reducing the risk of ingress.

The secondary packaging consists of an opaque, tamper-evident, rigid paperboard carton. The carton provides physical protection for the vials during storage and shipping.

#### CCIT by (b) (4) Testing

CCIT by (b) (4) testing is performed to define the crimping settings and is part of the stability testing program. (b) (4) testing is performed by (b) (4) and the test

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method has been validated for the SRP-9001 container closure system per (b) (4)

(b) (4)

(b) (4)

(b) (4)

**Reviewer's Assessment:** It appears acceptable to use (b) (4) solution filled vials as surrogate for the SRP-9001 drug product. The (b) (4) limit and quantitation limit of the (b) (4) test for the SRP-9001 drug product container closure appear to be appropriately validated.

(b) (4)

(b) (4)

(b) (4)





(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)




### 3.2.P.8 Stability


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

The stability studies include storage for up to (b) (4) months at the long-term condition of  $\leq -60^{\circ}\text{C}$  or at accelerated condition of (b) (4). The proposed shelf life is 12 months stored at  $\leq -60^{\circ}\text{C}$ .

(b) (4) batches of drug product are being evaluated on stability, including (b) (4) primary stability lots (registration stability batches) and (b) (4) process validation batches. The vials are stored in only one configuration (upright) on stability (b) (4)



For both storage conditions, container closure integrity testing is scheduled for 12, (b) (4)



(b) (4) sterility is tested at study start with an acceptance criterion of no growth, and endotoxin testing is scheduled for 0, 6, 12, (b) (4) months with an acceptance criterion of (b) (4). For the (b) (4) storage condition, additional CCIT was performed at (b) (4) months.

Stability data of up to 12 months storage at both conditions were provided and sterility, endotoxin and CCIT testing all conform to acceptance criteria.





**Reviewer's Assessment:** *The sterility, endotoxin and CCIT testing schedules on the stability study appear acceptable. The testing results support the shelf life of 12 months stored at  $\leq -60^{\circ}\text{C}$  from DMPQ perspective.*





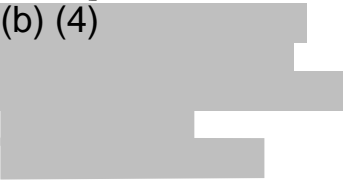
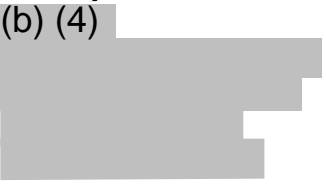
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## Facilities Table

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Manufacturing/ Testing activities	Inspection ? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required ?	Comments
<b>Facility:</b> Sarepta Therapeutics 100 Federal Street Andover, MA 01810, USA <b>FEI#:</b> 3012807588 <b>DUNS#:</b> 072827382  DS Release and Stability Testing; DP Release and Stability Testing	Inspection	Yes	Yes	Pre-license Inspection for STN 125781/0, VAI, Mar 20-24, 2023
<b>Facility:</b> (b) (4)      DS In-Process and Release Testing; DP Release and Stability Testing	Waiver	Yes	Yes	Surveillance inspection, VAI, (b) (4)
<b>Facility:</b> (b) (4)       DP Release Testing	Waiver	Yes	Yes	Surveillance inspection, VAI, (b) (4)
<b>Facility:</b> (b) (4)      Master Cell Bank and Working Cell Bank Manufacturing and Testing	Not required	No	Yes	Site has been decommissioned and no further activities will occur here.

Manufacturing/ Testing activities	Inspection ? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required ?	Comments
<b>Facility:</b> (b) (4)  DS Release and Stability Testing	Not required	No	Yes	
<b>Facility:</b> (b) (4)  Master Cell Bank and End of Production Cell Bank Testing	Not required	No	Yes	
<b>Facility:</b> (b) (4)  Working Cell Bank and End of Production Cell Bank Testing; DS Release Testing	Not required	No	Yes	
<b>Facility:</b> (b) (4)  Master Cell Bank, Working Cell Bank and End of Production Cell Bank Testing; DS Release Testing	Not required	No	Yes	

Manufacturing/ Testing activities	Inspection ? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required ?	Comments
<b>Facility:</b> (b) (4)   Master Cell Bank and End of Production Cell Bank Testing	Not required	No	Yes	
<b>Facility:</b> (b) (4)   DS In-process Testing	Not required	No	Yes	
<b>Facility:</b> (b) (4)  DS Release Testing; (b) (4) Cell Bank and (b) (4) Release Testing	Not required	No	Yes	
<b>Facility:</b> (b) (4)  (b) (4) Cell Bank and (b) (4) Manufacturing, Testing and Storage	Not required	No	No	Surveillance inspection, NAI, (b) (4)



Manufacturing/ Testing activities	Inspection ? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required ?	Comments
<b>Facility:</b> (b) (4) (b) (4) Release Testing	Not required	No	No	
<b>Facility:</b> (b) (4) (b) (4) Release Testing	Not required	No	No	
<b>Facility:</b> (b) (4) (b) (4) Cell Bank Release Testing	Not required	No	No	
<b>Facility:</b> (b) (4) (b) (4) Cell Bank and (b) (4) Lot Storage	Not required	No	No	

Manufacturing/ Testing activities	Inspection ? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required ?	Comments
<b>Facility:</b> (b) (4) (b) (4) Cell Bank and (b) (4) Lot Storage	Not required	No	No	
<b>Facility:</b> (b) (4) DP Stability Testing	Not required	No	No	Container closure integrity test for stability

### Catalent BWI DS Manufacturing Facility

#### Facility Design

SRP-9001 drug substance is manufactured at Catalent BWI facility located in Harmans, Maryland. Catalent BWI is a multi-product manufacturing facility for commercial and clinical manufacturing of gene therapy products. The following product types are manufactured at Catalent BWI facility:

- AAV vectors for gene therapy (adeno-associated virus vectors)
- AAV vectors for gene editing/cell therapy (CAR-T cell)
- Non-replicating recombinant adeno-associated virus
- Master Cell Banks (HEK293, Lentiviral, (b) (4))

Catalent BWI facility consists of (b) (4)



(b) (4)

## DS Shipping Validation

(b) (4)

## Catalent Biopark DP Manufacturing Facility

### Facility Design

SRP-9001 drug product is manufactured at Catalent Biopark located on the University of Maryland, Baltimore campus. The building is approximately (b) (4) square feet, and consists of corporate office, general laboratory, and GMP manufacturing areas including areas for formulation, filling, visual inspection, and cell banking. Catalent Biopark is a multi-product facility specializing in the commercial and clinical manufacturing operations of gene therapy products including adeno-associated viral vector, recombinant protein, and oncolytic adenoviral vector. The site also manufactures working cell banks (293T cells) and has the capacity of producing recombinant protein using mammalian cells. Among these products, SRP-9001 is the first product seeking commercial approval.

For SRP-9001 production, DP aseptic filling, stoppering and capping take place in Room (b) (4) which is a Grade (b) (4) within a Grade (b) (4) space. Room (b) (4) DP formulation and sterile filtration take place in the (b) (4) in Grade (b) (4) Room (b) (4) DP formulation buffer is prepared in Room (b) (4) (Grade (b) (4))

All Grade (b) (4) manufacturing space is accessed through Grade (b) (4) material air lock (MAL) and personnel air lock (PAL), which then connect to the Grade (b) (4) corridor. Material transfer requires (b) (4) as containers of materials move through the facility.

The facility enforces strict training and gowning requirements for the manufacturing areas. Entry into the Grade (b) (4) manufacturing hallway is gained by passing through a locker room and putting on appropriate gowning. Access to the Grade (b) (4) manufacturing

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area is through a (b) (4) airlock configuration. Passage between the classified hallway and formulation suites, equipment wash/storage/prep areas is through additional airlocks to minimize cross contamination and maintain overall cleanliness.

Where specifications allow, all equipment and components are prepared for aseptic processes using validated autoclave cycles in a qualified, (b) (4) -supplied autoclave. All other equipment, media, and components are supplied in a qualified, aseptic, or sterile condition by appropriate vendors or prepared under an approved compliant aseptic procedure.

All controlled, classified areas are cleaned and sanitized on a regular basis per a Standard Operating Procedure. Standard Operating Procedures describe the frequency and type of cleaning and sanitization to be performed for each production area. Sanitizing agents are qualified for effectiveness on clean room surfaces using representative micro-organisms, including selected environmental isolates. House environmental isolates are selected based on the environmental program from which data is reviewed on regularly.

### **Prevention of contamination and cross-contamination**

Prevention of contamination and cross-contamination is ensured through engineering, procedural, and manufacturing controls.

The facility design is the primary infrastructure supporting contamination control. Exposed surfaces in classified areas are constructed with smooth, non-porous materials to minimize contamination and withstand repeated cleaning. Flat surfaces and recesses are minimized to reduce the potential for contaminate accumulations; false ceilings are sealed; and sinks and drains are not within Grade (b) (4) areas.

A dedicated Air Handling Units (AHUs) controls the manufacturing areas on the (b) (4) floor, with HEPA filtration for (b) (4). Pressure differentials and airlocks are set up to ensure area classifications and Biosafety Level (BSL) qualification. Primary containment to prevent contamination includes using (b) (4)

Procedural controls are established for material, personnel, and waste flows including gowning requirements, use of airlocks, spillage handling, and restricted key card access. All equipment that has direct product contact for SRP-9001 manufacture is single use.

Activities to clean and inactivate possible virus residues include (b) (4). All cleaning, decontamination and sterilization processes and reagents are qualified. Cleaning and changeover procedures are performed between products campaigns.

**Reviewer's Comment:** The facility containment features, and cross-contamination control procedures appear acceptable. The cleaning and changeover procedures were evaluated during the PLI of February 21-24, 2023. (b) (4) cleaning and decontamination is defined by approved SOP. After each filling and prior to product changeover, (b) (4)

surfaces are decontaminated by ready-to-use (b) (4) with sterile (b) (4) after a (b) (4) contact time. (b) (4) decontamination is documented in the filling machine usage logbook. No issues were noted; procedures appeared acceptable.

### Facility cleaning and disinfectant effectiveness studies

**Reviewer's Comment:** Facility cleaning and disinfectant effectiveness were reviewed during the PLI of February 21-24, 2023 and found acceptable. Refer to Establishment Inspection Report for details.

### Critical Utilities

#### Water

Water For Injection (WFI) used for manufacturing is sourced from qualified vendors and is not produced on site. Purified Water (PW) systems are not utilized for the manufacturing process but for the (b) (4) (e.g., (b) (4) ). The PW system is qualified and meets (b) (4) for (b) (4)

**Reviewer's Comment:** The WFI used in manufacturing is not produced on site. The qualification and monitoring of (b) (4)-PW appears acceptable. Water system was evaluated in detail during the PLI of February 21-24, 2023; no issues were noted.

#### HVAC

The Heating, Ventilation and Air Conditioning (HVAC) systems that support the cleanrooms are designed to purify and condition the air supplied to the suites through filtration, predefined air changes per hour and control of temperature, relative humidity, and differential pressures. The AHUs provide the cleanrooms with (b) (4) HEPA-filtered air to achieve the appropriate temperature, humidity, airflow, and positive pressure to meet the (b) (4) classification for each cleanroom. HEPA filters are rated 99.99% efficient and HEPA certification is performed per (b) (4) standards.

AHU (b) (4) controls the entire SRP-9001 manufacturing areas, including the Grade (b) (4) and Grade (b) (4) manufacturing areas, Grade (b) (4) airlocks, and Grade (b) (4) hallways, preparation suites and gowning rooms.

Cleanroom temperatures are maintained between (b) (4) while relative humidity (RH) is maintained between (b) (4). Cleanrooms and airlocks are controlled with an interlocking system to maintain positive pressure differentials and minimize reverse airflow.

The room pressurization conceptual design is for all cleanrooms to be positive to the external environment. Differential Pressures are maintained between adjacent areas within the suite based on the intended work being performed (upstream, downstream, and fill/finish) in the area. Room pressurization is controlled to maintain the minimum differential pressure levels to provide the level of contamination control as appropriate. DP levels and alarms are continuously monitored by the (b) (4) system.

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HVAC and HEPA filters are requalified (b) (4) . The (b) (4) (Fill Finish Suite) GMP HVAC was last qualified over a (b) (4) period from (b) (4) .

**Reviewer's Comment:** The HVAC zoning and pressure differential control appear acceptable. The requalification of the HVAC was reviewed in detail during the PLI of February 21-24, 2023. Refer to the Establishment Inspection Report for details.

Please note that in this BLA submission, Sarepta stated that the HVAC and HEPA are requalified (b) (4) at Catalent Biopark. Per "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice", HEPA filter leak test shall be performed twice a year for Grade A and Grade B manufacturing areas. This requirement was conveyed to Catalent Biopark during the February 21-24, 2023 inspection, and Catalent Biopark updated the HVAC requalification SOP promptly to reflect this change.

### Computer Systems

The automatic filler is controlled by HMI Panel. Filling settings (e.g., line speed) are entered before each filling, and no electronic data are generated during filling.

The software systems used at Catalent Biopark facility are the same as the ones used at Catalent BWI facility, except that (b) (4) Process Control System is not used at Catalent Biopark. Refer to the Computer Systems section under Catalent BWI facility for details.

**Reviewer's Comment:** A general description of the computer systems used at the Catalent Biopark facility was provided and reviewed. The computer systems appear acceptable.

### Equipment

After formulation, (b) (4)

Major reusable equipment used in the SRP-9001 DP manufacturing process is summarized in Table 14:

Table 14. List of SRP-9001 DP Manufacturing Equipment

Equipment	Product Contact	Product Dedicated
Freezer	No	No
(b) (4)	No	No
(b) (4)	No	No
(b) (4)	No	No

(b) (4) filling machine	No	No
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All reusable equipment was determined to not be in direct contact with product, and the non-product contact equipment is cleaned according to established procedures. Major process equipment utilized in drug product manufacturing has been qualified. For the (b) (4) filling machine, filling volume performance qualification was completed to verify the fill accuracy and capability.

In addition to these cleaning procedures, a (b) (4) is completed after viral agent processing. The (b) (4) includes a (b) (4). Decontamination verification is achieved through (b) (4).

A risk assessment was performed to identify the risks associated with cleaning verification/validation of equipment used in the manufacturing of SRP-9001 drug product. Based on the outcome of the assessment, it was determined that cleaning verification/validation was not required.

Note that the SRP-9001 filling process does not use an (b) (4) but instead, uses a (b) (4) the filling line. Contamination control and sterility assurance for SRP-9001 drug product is achieved through the use of onsite- or pre-sterilized, single-use processing components for filtration and filling operations.

**Reviewer's Comments:** Equipment used in the SRP-9001 DP manufacture is not product contact. Equipment qualification is reviewed during the PLI of February 21-24, 2023; no issues were noted. (b) (4) qualification is reviewed in the Sterilization section below.

## Sterilization


Filling (b) (4) Sterilization by (b) (4)

The filling (b) (4) is the only material that has product-contact after the sterilizing filtration step. The filling (b) (4) is single-use and received sterilized and ready-to-use. Sterilization is performed at (b) (4).

(b) (4)





(b) (4)

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**Reviewer's Assessment:** The validation of the (b) (4) of the filling<sup>(b) (4)</sup> includes dose map study, worst-case evaluation, (b) (4) monitoring, (b) (4), and low verification dose study. The study design and results appear acceptable.

Filter Sterilization by (b) (4)

(b) (4)


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After initial qualification, the equipment and sterilization parameters are revalidated (b) (4). The last requalification for (b) (4) are Mar 07, 2022 and Apr 07, 2022, respectively, and all studies met the predefined acceptance criteria.

**Reviewer's Assessment:** The validation of the filter sterilization, including heat distribution, heat penetration and biological indicator challenge studies appear appropriate. (b) (4) qualification is further reviewed during the PLI of February 21-24, 2023 and no issues were noted.







Sterile Filtration Validation

A filter validation study was conducted to provide bacterial retention data for the sterilization filter used to (b) (4) drug product. (b) (4)

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

(b) (4)



### **Environment Monitoring**

The cleanroom manufacturing spaces for SRP-9001 include (b) (4) and Aseptic Fill areas. Each area is designed and qualified to meet requirements for Grades (b) (4) cleanroom classifications per (b) (4) standards.

The Environmental Monitoring Performance Qualification (EMPQ) was performed to evaluate the flow of personnel, materials, air as well as the gowning and sanitization practices throughout the manufacturing space. The qualification consisted of (b) (4) of static monitoring and (b) (4) of dynamic monitoring. Non-viable particulate sample sites were selected as outlined in (b) (4). All other environmental

monitoring sample sites were established based upon risk-based analysis of the EMPQ data.

Action limits for non-viable particulates and viable particulates are described in Table 16 and Table 17:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

An EMPQ was performed during the HVAC requalification of (b) (4), and no excursion was noted.

The routine environmental monitoring (EM) program consists of viable and non-viable particulate air sampling and viable surface sampling. Routine and in-process monitoring is performed at pre-defined frequencies to ensure a continued state of environmental control in the cleanrooms and BSCs. EM locations are selected according to the site's risk assessment. Surface sites were selected throughout the facility based upon worst-case locations, proximity to process, probability of operator contact, equipment locations or materials of construction. All data and facility environmental isolates are trended, analyzed, and summarized on a (b) (4) basis. EM monitoring frequency is summarized in Table 18.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

No EM excursion was reported.

**Reviewer's Comment:** The EMPQ and routine EM program appear acceptable. EM, including deviations, was reviewed in further detail during the PLI of February 21-24, 2023. Refer to Establishment Inspection Report for details.

## Aseptic Process Validation

At Catalent Biopark facility, initial Aseptic Process Qualification requires (b) (4)

(b) (4)

(b) (4)

(b) (4)

No growth was observed in any vials, and all growth promotion studies pass.

**Reviewer's Assessment:** Catalent Biopark's media fill qualification and requalification program appear adequate, and the interventions are appropriately designed. SRP-9001 aseptic filling parameters and container specifications appear to be (b) (4) by the recent media fills, (b) (4)

(b) (4)

*this appears acceptable.*

### Shipping Validation



(b) (4)

(b) (4)

(b) (4)

[REDACTED]

(b) (4)








**Reviewer's Assessment:** *It appears acceptable for the shipping validation to focus on thermal control and package integrity, as product-specific attributes are conserved when stored at  $\leq -60^{\circ}\text{C}$  as verified in the stability study. Temperature control, packaging integrity, and CCIT all met pre-defined acceptance criteria. Shipment from the manufacturing site Catalent BioPark to the finished goods packaging site (b) (4) as well as the finished goods packing site (b) (4) to the Specialty Pharmacy or End User appear to be appropriately qualified.*

### 3.2.R Regional Information (USA)

#### Comparability Protocol

(b) (4)





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(b) (4)

