



Date: December 10, 2017

BLA STN # 125610/0

Applicant: Spark Therapeutics Inc.
License# 2056

Product: AAV2-hRPE65v2 (Spark scientific name), voretigene neparvovec - rzy1 (nonproprietary name), Luxturna (proprietary name)

Active ingredients of drug product:
LUXTURNA is a suspension solution for subretinal injection containing 5E12 vector genomes per mL (in a 0.5 mL volume per single-use vial).

Inactive ingredients of drug product:
Sodium chloride, sodium phosphate, poloxamer 188.

Diluent ingredients: Sodium chloride, sodium phosphate, poloxamer 188, water for injection

Route of Injection: Subretinal

Proposed Indication for Use: For the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy.

Reviewer: Rabia Ballica, PhD, CBER/OCBQ/DMPQ/ MBR1

Lead office: OTAT

Supervisor: Carolyn Renshaw, Branch Chief/MBR1/DMPQ/OCBQ
OCBQ/DMPQ: John Eltermann, Director

Subject: DMPQ Review Memo for Biological License Application (BLA) - submitted electronically May 16, 2017
ADD (PDUFA): January 14, 2018
Target approval date: December 19, 2017

Purpose of

Submission: BLA for approval of AAV2-hRPE65v2 (voretigene neparvovec - rzy1)

Manufacturing Facilities:

1- Drug Substance Manufacturing and Testing at Spark Therapeutics Inc. located at 3737 Market St, Philadelphia, PA 19104
FEI#: 3011194531, DUNS#: 079498241

2- Drug Product and Diluent Manufacturing and Testing at (b) (4)

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RECOMMENDATION

There are no outstanding review and inspectional issues under DMPQ purview. Based on the evaluation of the information provided in the original BLA submission and its amendments, approval of BLA 125610/0 is recommended with the following inspectional consideration:

(b) (5), (b) (7)(E)

Please refer to “Summary” for more detail.

SUMMARY

Voretigene neparovec - rzyl (AAV2-hRPE65v2) is a gene therapy product and proposed for approval under BLA STN125610/0. Voretigene neparovec - rzyl (AAV2-hRPE65v2) is an adeno-associated viral type 2 (AAV2) gene therapy vector with a cytomegalovirus enhancer and chicken beta actin promoter driving expression of normal human retinal pigment epithelium 65 kDa protein (hRPE65) gene. This product is proposed for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy. The product should only be administered to patients with sufficient viable retinal cells.

Voretigene neparovec - rzyl is formulated as a sterile concentrate in solution (suspension) for subretinal injection containing 5E12 vector genomes (vg) per milliliter (mL), 180 mM sodium chloride, 10 mM sodium phosphate, 0.001% Poloxamer 188 (pH 7.3). It is supplied in a 0.5 mL extractable volume in a single-dose 2 mL vial, which requires a 1:10 dilution prior to administration. This product is for intraocular use and has an orphan drug designation for the treatment of inherited retinal dystrophy due to biallelic RPE65 mutations.

One (1) vial of drug product is co-packaged with two (2) vials of diluent and secured within a tray. The tray is inserted into an individual folding carton, and along with literature, is overwrapped with a sealed foil pouch. Primary packaging and labeling is performed at (b) (4) (Contract Manufacturer) and secondary packaging and labeling is done at (b) (4) (Contract Packager).

Drug substance (DS) is manufactured by Spark Therapeutics Inc. in PA (FEI#3011194531 for the manufacturing site located at 3737 Market St Philadelphia, PA 19104). Drug product (DP) and diluent are manufactured at a contract manufacturing site, (b) (4)

. Facility information and data provided in the BLA (3.2.a.1 *Facilities and Equipment*) were reviewed by CBER and found to be sufficient and acceptable.

CBER conducted a pre-license inspection (PLI) of Spark Therapeutics Inc, Philadelphia PA, from August 21 - 25, 2017 for voretigene neparovec - rzyl drug substance manufacturing. At the conclusion of this inspection, a Form FDA 483 was issued. The firm responded to the observations and the corrective actions were found to be adequate. This inspection was classified

as voluntary action indicated (VAI). (b) (5), (b) (7)(E) [redacted]
[redacted]
[redacted]
[redacted]

CBER had previously inspected the (b) (4) [redacted] location from (b) (4) [redacted]. All inspectional issues were resolved and the inspection was classified as VAI. The inspection of the (b) (4) facility is waived for voretigene neparvovec - rzył drug product manufacturing.

(b) (4) [redacted] performs DP testing. ORA conducted a routine surveillance inspection at (b) (4) [redacted] location from (b) (4) [redacted]. All inspectional issues were resolved and the inspection was classified as VAI. The inspection of this contract testing site is waived.

(b) (4) [redacted] conducts DP and diluent testing. ORA conducted a surveillance inspection of (b) (4) [redacted] from (b) (4) [redacted]. No Form FDA 483 was issued for this inspection and the inspection was classified as no action indicated (NAI).

(b) (4) [redacted] conducts DP testing. ORA conducted a routine surveillance inspection of this contract testing facility located in (b) (4) [redacted] from (b) (4) [redacted]. All inspectional issues were resolved and the inspection was classified as VAI. The inspection of this contract testing site is waived.

The DP and its diluent are filled into 2 mL (b) (4) [redacted] plastic vials (b) (4) [redacted], cyclic olefin polymer) in a (b) (4) [redacted] (Grade B_1) at the (b) (4) facility (3.2.P.7. Container Closure System). The plastic vials are stoppered with a 13 mm (b) (4) [redacted] grey chlorobutyl stopper (b) (4) [redacted] stopper) and sealed with a 13 mm (b) (4) [redacted] aluminum Flip-Off® design seal. The top surface and flange sides of the stopper are (b) (4) [redacted]. (b) (4) [redacted] testing was performed at (b) (4) [redacted] to evaluate the integrity of the container closure system stored at [redacted] for stability studies (October 16th Amendment). This test method was validated for the container closure system described above and the results were acceptable. Additionally, this testing will be performed at pre-determined intervals for ongoing stability evaluation. In addition, a (b) (4) [redacted] test method was validated to evaluate the integrity of the container closure system stored (b) (4) [redacted] for shipping studies, and the results were acceptable.

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

monitoring parameters (pre-, post-, and in operation) and (b) (4) integrity testing (including for (b) (4)). Media fill runs are performed on a (b) (4) basis to maintain validated state. Media fill results from the recent (b) (4) run (executed in Oct 2017) were acceptable.

Procedures were validated for decontamination, sanitization, and cleaning (where applicable) of the DP and DS manufacturing facilities and equipment. Equipment was also qualified (IQ/OQ/PQ) at both the manufacturing sites (*August 22nd Amendment*). Ready to sterilize stoppers and seals were sterilized by a validated (b) (4) process. (b) (4) vials are supplied as sterilized (ready to use).

Stability studies for the DP and its diluent are ongoing and available data met acceptance criteria for the parameters evaluated (*3.2.P.8 Stability*). Sterility testing was performed at release and result met the acceptance criteria. Sterility testing will also be performed at expiry. (b) (4) testing is performed at (b) (4) to evaluate the integrity of the container closure system stored at (b) (4) for stability studies. This integrity testing is performed at pre-determined intervals. The firm provides a post-approval commitment statement for ongoing stability studies.

In summary, approval of BLA STN 125610/0 is recommended. Note this BLA is approved approximately one month earlier (December 19, 2017) than its PDUFA deadline (January 14 2018). Also note the following post market commitments (PMCs).

The following PMCs were requested by the DMPQ and agreed by Spark

1- Following the 100% visual inspection, you should employ statistically sound sampling plans, and appropriate acceptance criteria for critical and major defects. The methodology and acceptance criterion for the statistical sampling plan should be based upon factors such as patient risk, product and container characteristics, and defect type. Risk factors such as the route of administration, patient population, and nature of the visible particulates should be used to develop appropriate acceptance criteria. We recommend that you submit the following post-approval commitment (PMC):

Spark Therapeutics, Inc. commits to revise procedures for visual inspection to incorporate statistically sound sampling plans (e.g., AQL) following the 100% inspection. The sampling plan will include appropriate acceptance criteria for critical and major defects. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" to include the procedure and the results of the revised visual inspection process for the next product lot manufactured.

2. We recommend that you perform (b) (4) as cleaning verification and submit a PMC as follows:

Spark Therapeutics, Inc. commits to perform (b) (4) as cleaning verification. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" to include the revised procedure for performing cleaning verification and the results of testing for the next lot manufactured.

REVIEW – Original BLA

Product Description and Proposed Clinical Use

The proposed indication for voretigene neparvovec – rzyl (AAV2-hRPE65v2) is to treat patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy. This product is developed for intraocular use. The product should only be administered to patients with sufficient viable retinal cells. The product is delivered in a total subretinal volume of 0.3 mL (300 µL) per eye. The individual administration procedures to each eye are to be performed on separate days.

Voretigene neparvovec -rzyl is formulated as a sterile concentrate in solution for subretinal injection containing 5E12 vector genomes (vg) per milliliter (mL), 180 mM sodium chloride, 10 mM sodium phosphate, 0.001% Poloxamer 188 (pH 7.3). It is supplied in a 0.5 mL extractable volume in a single-dose 2 mL vial, which requires a 1:10 dilution prior to administration.

Primary packaging and labeling is performed at (b) (4) (Contract Manufacturer) and secondary packaging and labeling is performed at (b) (4) (Contract Packager).

Primary packaging components include container, closure and seal. Container for the drug product (DP) and its diluent is a 2 mL (b) (4) plastic vial (b) (4), cyclic olefin polymer). Closure for the DP and its diluent container is a 13 mm (b) (4) chlorobutyl stopper (b) (4) Grey Chlorobutyl Rubber). Stoppered (b) (4) vials are sealed with a 13 mm aluminum Flip-Off® design seal (b) (4), 13 mm 6-bridge, ‘Flip-Off’ button long seal).

Secondary packaging components include tray, carton and sealable foil pouch. One (1) vial of drug product (5×10^{12} genome-containing vector particles per milliliter) is co-packaged with two (2) vials of diluent and secured within a tray. The tray is inserted into an individual folding carton, and along with literature, is overwrapped with a sealed foil pouch. Sealed foil pouches are placed in a payload box which is placed in a pre-qualified shipper with an electronic temperature monitor and (b) (4) (For additional information on the secondary packaging, refer to the review of the September 25th Amendment within this memo)

The mechanism of action of voretigene neparvovec –rzyl (AAV2-hRPE65v2) is gene augmentation to express the normal, functional RPE65 protein in affected cells of the retina. Voretigene neparvovec -rzyl employs the AAV vector as a delivery vehicle for an expression cassette encoding normal human RPE65; the recombinant vector is a non-enveloped icosahedral virion of approximately 26 nanometers in diameter. The parent adeno-associated serotype 2 virus (AAV2), used as a template for the vector, is a non-pathogenic, single-stranded DNA genome-containing, helper virus-dependent member of the parvovirus family.

Environmental Analysis (1.12.14): Provided

Environmental Assessment (EA) has been prepared in accordance with 21CFR25.15 (a) and is submitted with the BLA

Comment: Evaluation of EA is deferred to the product office.

Reprocessing and Reworking for Drug Substance and Drug Product (3.2.S.2.2.4 and 3.2.P.3.3.5):

The firm does not have reprocessing and reworking for drug substance (DS) and drug product (DP).

Manufacturers and Testing Facilities

Manufacturers and facilities for drug substance (DS), drug product (DP) and diluent manufacturing are listed in the table below.

Table 1 Facilities Table

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
<p>Spark Therapeutics Inc. 3737 Market St Philadelphia, PA 19104</p> <p>FEI: 3011194531 DUNS # 079498241</p> <p>Drug Substance Manufacturing and Testing (including Drug Product release testing for Vector Genome Identity by (b) (4), Vector Genome Concentration assay, (b) (4) assay, Purity testing, Gene Product Expression by (b) (4) assay)</p>	<p>Inspection</p>	<p>Yes</p>	<p>Yes</p>	<p>CBER August 21 -25, 2017 VAI</p>
<p>(b) (4)</p> <p>Contract Testing Laboratory for the following assays: -In Vitro Relative Potency of (b) (4) (for Drug Product release testing) -(b) (4) Assay</p>	<p>Inspection waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>ORA (b) (4) VAI</p>

<p>-Residual Host Cell DNA by (b) (4) [redacted] -Residual E1A DNA by (b) (4) [redacted] , -Residual Bovine Albumin by (b) (4) [redacted] -Residual HEK293 Protein by (b) (4) [redacted] -Residual (b) (4) [redacted] by (b) (4) [redacted]</p>				
<p>(b) (4) [redacted] [redacted]</p>	<p>Not Required</p>	<p>No</p>	<p>Yes</p>	<p>ORA January 04 -11, 2016 NAI</p>
<p>(b) (4) [redacted] [redacted] [redacted] [redacted] (raw material for use in Drug Substance Manufacturing)</p>	<p>Not required</p>	<p>No</p>	<p>Yes</p>	<p>Not inspected</p>
<p>(b) (4) [redacted] [redacted] [redacted] [redacted] Contract Testing Laboratory for the following assay: -In Vitro Relative Potency of (b) (4) [redacted] Assay (for Drug Product release testing)</p>	<p>Inspection Wavier</p>	<p>Yes</p>	<p>Yes</p>	<p>ORA (b) (4) [redacted] VAI</p>
<p>(b) (4) [redacted] [redacted] [redacted] [redacted] Contract Testing Laboratory for the following assays for Drug Substance: (b) (4) [redacted]</p>	<p>Not required</p>	<p>No</p>	<p>Yes</p>	<p>ORA (b) (4) [redacted] NAI</p>
<p>(b) (4) [redacted] [redacted] [redacted] [redacted] [redacted]</p>	<p>Not required</p>	<p>No</p>	<p>Yes</p>	<p>ORA (b) (4) [redacted] [redacted] NAI</p>

<p>(b) (4) Contract Testing Laboratory for Drug Substance: -(b) (4) -Concentration of Pluronic (for Drug Product release testing)</p>				
<p>(b) (4) Drug Product and Diluent Manufacturing and Testing: Aseptic Filling and Labeling of Drug Product, Diluent Manufacturer, Testing of Drug Product and Diluent for Sterility</p>	<p>Inspection Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>CBER (b) (4) VAI</p>
<p>(b) (4) Contract Testing Laboratory for DP: Drug product release testing for endotoxin, particulate and extractable volume</p>	<p>Inspection Wavier</p>	<p>Yes</p>	<p>Yes</p>	<p>ORA (b) (4) NAI</p>
<p>(b) (4) Secondary Packaging and Labeling</p>	<p>Not Required</p>	<p>No</p>	<p>Yes</p>	<p>ORA (b) (4), NAI</p>
<p>(b) (4) Identity Testing of Environmental Isolates</p>	<p>Not Required</p>	<p>No</p>	<p>No</p>	
<p>(b) (4) (b) (4) of stoppers, seals, tubing, labels and associated consumables</p>	<p>Not Required</p>	<p>No</p>	<p>No</p>	

DRUG SUBSTANCE MANUFACTURING AND TESTING (3.2.S)

Voretigene neparvovec - rzyl (AAV2-hRPE65v2) was derived from the naturally-occurring adenoassociated virus serotype 2 (AAV2), a member of the parvovirus family. The wild-type AAV virus consists of a single-stranded DNA genome encapsulated in a protein coat (refer to 3.2.S.1.2 Structure in BLA).

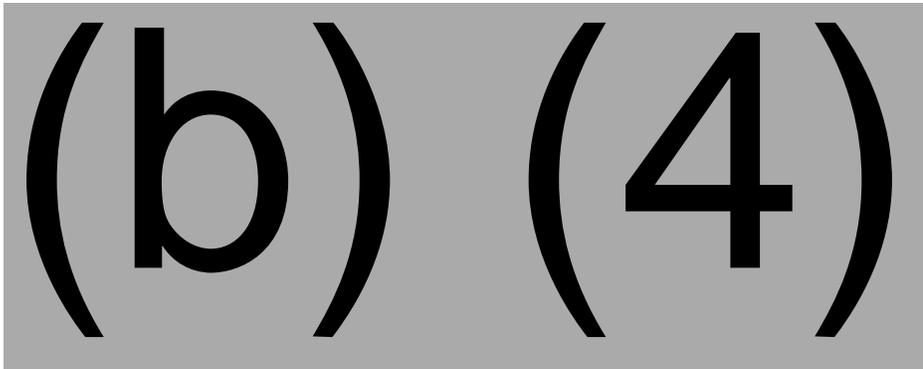
Drug substance (DS) is manufactured at Spark Manufacturing Facility located in PA. Pre license inspection (PLI) of this facility was conducted from August 21 to August 25, 2017 and this inspection was classified as VAI (refer to EIR).

The DS manufacturing process is comprised of (b) (4) sub-lots. (b) (4)

[Redacted]

A diagram showing the lineage of the sub-lots for the Process Performance Qualification (PPQ) lot (b) (4) is presented in Figure 1.

Figure 1. Lineage of the Process Performance Qualification Lot (b) (4)



Comment:

Note only one DS process validation lot (process performance qualification/PPQ) was manufactured. This is acceptable, because the drug product has an orphan drug designation for a rare disease.

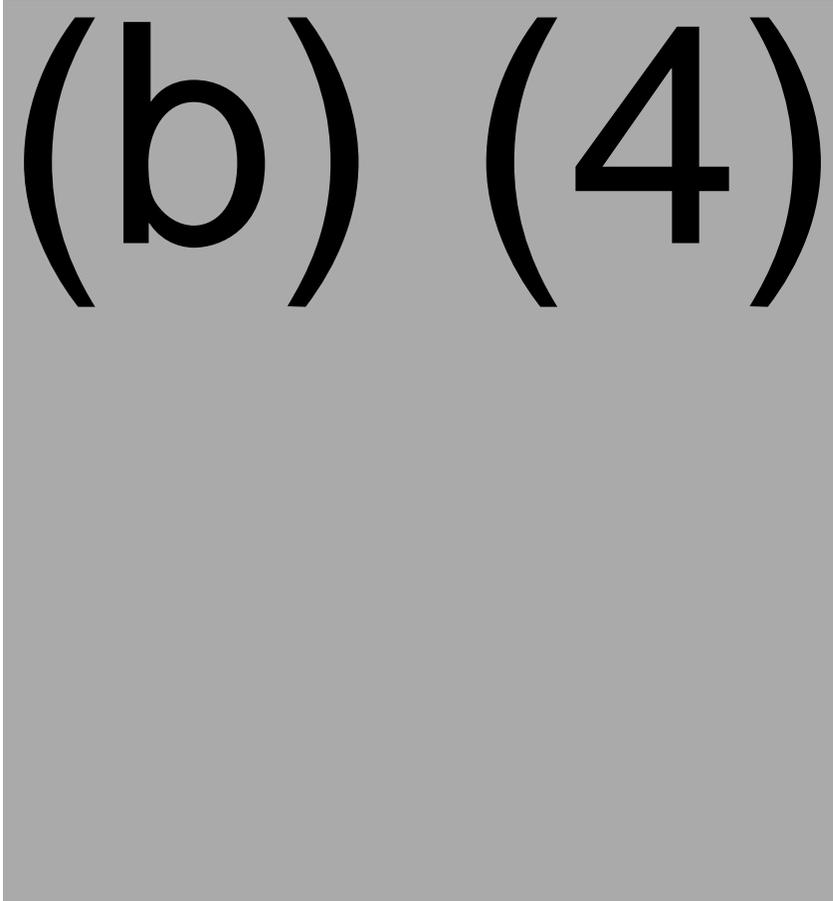
(b) (4)

[Redacted]

Description of Manufacturing Process and Process Controls
(3.2.S.2.2 and 3.2.S.2.6)

The drug substance (DS) is manufactured through the manufacturing steps illustrated in the process flow diagrams below, Figures 2 and 3. In the figures, microbial content controls (bioburden and endotoxin testing) are also indicated. Note that the DS manufacturing process is bioburden – controlled.

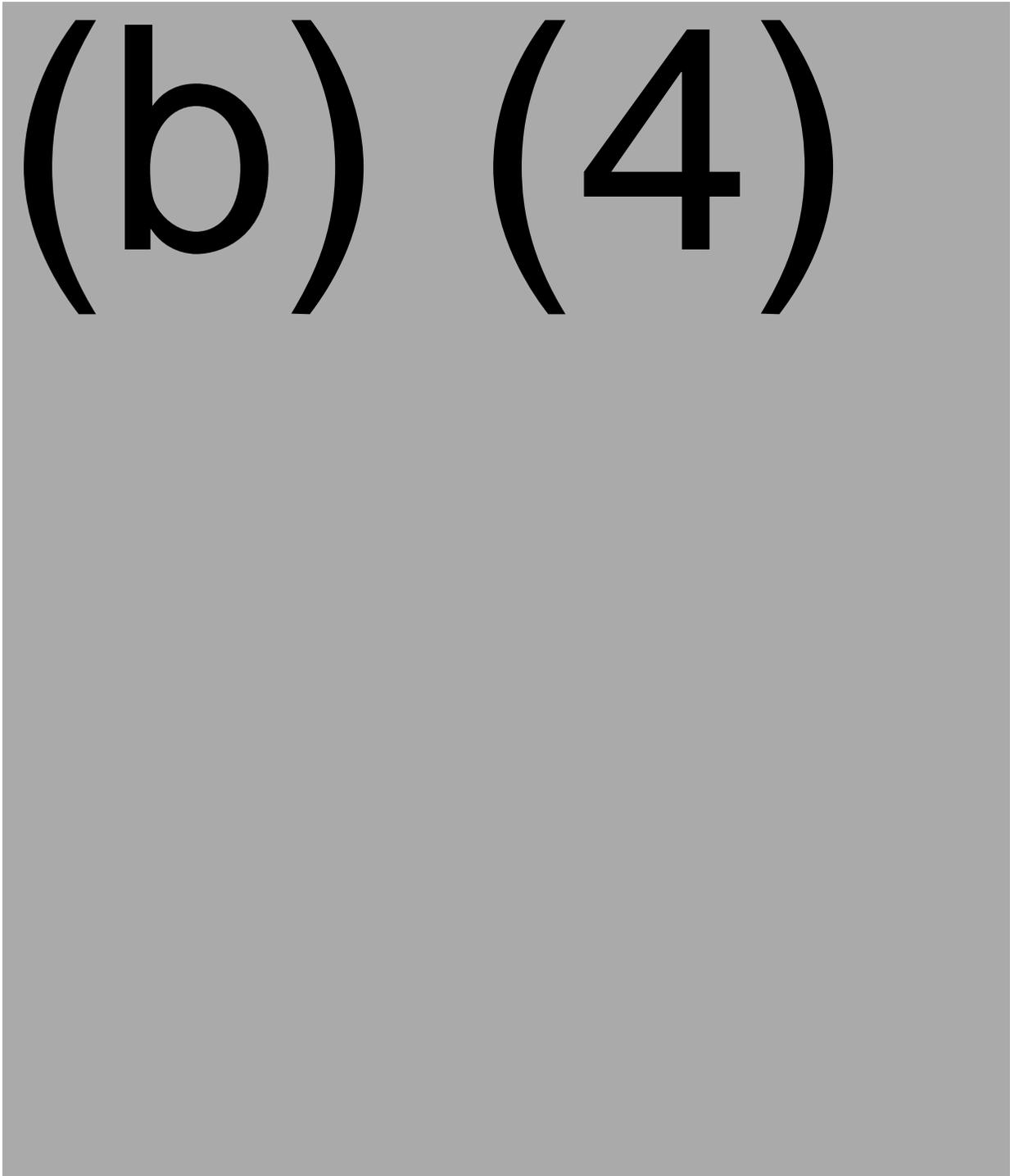
Figure 2. Manufacturing process and microbial content controls



Comment: Note that the PPQ lot (refer to PPQ batch analysis below) will not be distributed. During the PLI of Spark DS manufacturing facility, there was ongoing DS manufacturing campaign for voretigene neparvovec -rzyl.

Batch Analysis (3.2.S.4.4 Batch Analysis)

Table 5. Lot Release Data for Drug Substance Lot (b) (4)



(b) (4)

(b) (4) [Redacted]

Equipment IQ/OQ and Cleaning Validation

Comment: For equipment qualification and cleaning validation, refer to the review of Amendment 22, 2017 (IR# 2.5, IR# 2.6, IR# 2.7, and IR#2.10) within this review memo in addition to that for 3.2.a.1 Facilities and Equipment.

DRUG PRODUCT MANUFACTURING AND TESTING (3.2.P)

The Drug Product is a frozen aqueous solution concentrate that requires a 1:10 dilution with diluent prior to administration. The identical formulation of the inactive ingredients sodium chloride, sodium phosphate, and (b) (4) P188 in both the drug product (DP) and diluent ensures a consistent matrix of these excipients at all times during the dilution of the active substance.

The active substance is an adeno-associated virus serotype 2-based vector containing the human RPE65 gene expression cassette. The Drug Product is a solution for injection of 5×10^{12} vector genomes per mL (0.05 mg vector/mL). The finished product is a concentrate

containing 180 mM sodium chloride, 10 mM sodium phosphate, 0.001% (b) (4) P188, pH 7.3. It is supplied at a volume of 0.5 mL in a 2 mL (b) (4) vial and requires a 1:10 dilution with Diluent prior to administration.

Drug Product Development

(3.2.P.2 Pharmaceutical Development)

Phase I/II and III clinical material, using drug substance (DS) manufactured at The Children’s Hospital of Philadelphia (CHOP), was filled at two different manufacturing sites ((b) (4) and CHOP) into cryogenic vials. Moving toward commercialization, Spark Therapeutics has contracted with (b) (4) to manufacture voretigene neparvovec drug Product (DP) in Building (b) (4), their live virus facility. Additionally, the commercial DP container was changed to (b) (4) vials, with a standard container closure configuration. Table below summarizes changes to the DP filling process and container closure that have been implemented in the transition from clinical to commercial manufacturing.

Table 11. Historical Overview of DP Manufacturing Process (3.2.P.2 Pharmaceutical Development)

	Historical	Commercial
Fill Location	(b) (4)	(b) (4)
Fill Environment	(b) (4)	(b) (4)
Product Fill Volume	1 mL	0.5 mL
Container/Closure	(b) (4) Cryogenic Vial, with Silicone Gasket	2 mL (b) (4) gray, (b) (4) 13mm Stopper (b) (4) 13 mm Flip-Off Seal, 6-Bridge, Spark Green (b) (4)

(b) (4) is a privately owned pharmaceutical company which was established in (b) (4) to supply sterile and non-sterile compounded products to hospitals and pharmacies throughout the (b) (4). In (b) (4) moved to its current site at (b) (4) and diversified into the use of (b) (4)

Comment: For information on the (b) (4) facility, refer to the review of 3.2.a.1 for (b) (4) within the review memo. Additional information on the (b) (4) facility was requested and submitted in the August 22, 2017 Amendment.

Table 12. Drug Product and Diluent Engineering Lots (3.2.P.2 Pharmaceutical Development)

Batch Number	Date of Manufacture	Product or Diluent	Vials Manufactured	Batch Use
(b) (4)	(4)	Diluent	(b) (4)	ENG
		Simulated Vector		ENG
		Drug Product		ENG
		Diluent		ENG

Comment: Evaluation of the comparability analysis performed for the products manufactured (pre- PPQ lots/engr and clinical lots are compared to PPQ lot) is deferred to the product office.

Figure 9. Control Chart of Mixing Time for Drug Product Lots Produced at (b) (4)

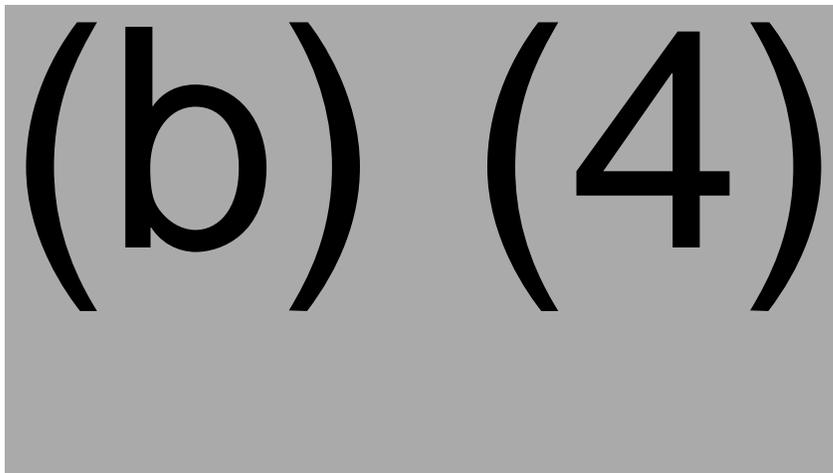


Table 13. Parameters and Controls for Shipping, Receipt, and Storage of Drug Substance

Critical Process Parameter	Target	Acceptable Range
Shipping and Storage Temperature	(b) (4)	
Transfer Time		

Table 14. Parameters and Controls for Thaw and Mix of Drug Substance

Operating Process Parameter	Target	Acceptable Range
Mix Time*	(b) (4)	
Mix Speed*		
In-Process Control		
(b) (4)		

**Comment: It is unclear how those limits for mixing are determined. Therefore, information on its validation was requested on September 5th and the response was received in October 5th Amendment*

Table 15. Parameters and Controls for Sterile Filtration

Critical Process Parameter	Target	Acceptable Range
Sterile Filtration Flow rate	(b) (4)	(b) (4)
Critical In-Process Control	Target	Acceptable Range
Filter Integrity Testing	PASS	(b) (4)
(b) (4)		

***Comment: It is higher than that of post-use integrity results - determined in the microbial retention studies, which is better.*

Table 16. Parameters and Controls for Drug Product Aseptic Filling

Operating Process Parameter	Target	Acceptable Range
Vial Fill (b) (4)	(b) (4)	(b) (4)

Table 17. Parameters and Controls for Inspection, Packaging, and Storage of Drug Product Vials

Operating Process Parameter	Target	Acceptable Range
Visual Inspection of Vials	100% of Vials Inspected	100% of Vials Inspected
In-Process Control	Target	Acceptable Range
Allowable Inspection Reject Limit	(b) (4)	(b) (4)
Time Product is held (b) (4) – Duration from Completion of Thawing to Transfer of Vials to Storage at ≤ -65 °C.	(b) (4)	(b) (4)

Reprocessing and/or reworking is not permitted as part of the manufacturing process

**Comment: It is unclear how the acceptable hold time is determined, but it was acceptable to the product office reviewers based on the evaluation of stability studies and study for the DP compatibility with the container closure system at (b) (4). The DP compatibility study supports (b) (4) at the (b) (4) per the product office reviewers.*

Vial filling, stoppering, and capping

(3.2.P.3.3 Description of Manufacturing Process & Controls)

Following filtration, the sterile DP solution is filled, stoppered and sealed* (b) (4). The vial filling process at (b) (4) utilizes a (b) (4) filling technology. Drug Product is filled into 2 mL (b) (4) vials to a predetermined filling (b) (4). This fill (b) (4) corresponds to a target fill volume of (b) (4) mL, which is based on the label claim of 0.5 mL and an (b) (4). Filled vials are stoppered with sterile serum stoppers, and manually crimped* in place with sterilized aluminum seals. Routine (b) (4) are performed periodically through the aseptic filling process to confirm that all vials tested are within the (b) (4) acceptable range. Labelled, inspection-passed vials** are packed into labelled, opaque, freeze-resistant bulk cartons. A tamper evident seal is applied to each carton. Once all inspection, labelling and packaging processes have been completed, the sealed cartons are transferred to storage at ≤ -65 °C. A maximum of (b) (4) is permitted between the end of the thawing process and completing transfer of the inspected and labelled vials to storage at ≤ -65 °C as shown in

**Comment: For additional information on capping and sealing, refer to the review of the October 16th Amendment within this review memo.*

***Comment: Information on inspection procedures were provided in the August 22nd, 2017 Amendment (IR# 3.8 and IR# 4.2).*

(b) (4)

[Redacted text block]

[Redacted text block]

Deviations

Comment: Information on deviations was submitted in the August 22nd Amendment (IR# 1).

Container and Closure System (3.2.P.7)

Container for the DP and its diluent is a 2 mL (b) (4) plastic vial (b) (4), cyclic olefin polymer). (b) (4) vials are supplied as sterilized (ready to use). Closure for the DP and its diluent container is a 13 mm (b) (4) chlorobutyl stopper ((b) (4) Grey Chlorobutyl Rubber). The top surface and flange sides of the stopper (no product contact) are (b) (4) stoppers are supplied as ready to sterilize.

The stopper is further sealed in place with a 13 mm aluminum Flip-Off® design seal ((b) (4), 13 mm 6-bridge, ‘Flip-Off’ button long seal). The sterilized seals are aluminum alloy with a (b) (4) and a polypropylene button.

Stoppers and seals are sterilized using a validated (b) (4) process*s at (b) (4). This contract facility ((b) (4)) is located at “(b) (4).

**Comment: The validation of (b) (4) process for the sterilization of stoppers, refer to the review of the August 22nd (IR# 3.10) and October 5th Amendments (IR# 4) within this memo.*

COA for stoppers** and vials are provided (21CFR 211.84 (d) (3)). A diagram and dimension information for stopper and vial are also provided.

****Comment:** COA (NO (b) (4)) for 13 mm (b) (4) Stopper for stoppers indicates that the stoppers are (b) (4) sterilized. Because these stoppers are also sterilized by (b) (4) at (b) (4), a justification was requested for double sterilization. In response, the firm indicated that a wrong one was submitted with the BLA and provided the correct one (indicates ready to sterilize) in the August 22nd Amendment (IR# 3.9). For additional information on the new COA, refer to the review of this Amendment.

Detailed information on container closure (CC) system used for the drug product (DP) and its diluent is provided in the tables below.

Table 18. Primary Container Closure System Description

Component	Description
Vial	2 mL (b) (4)
Stopper	(b) (4) Grey Chlorobutyl Rubber
Seal	(b) (4) 13 mm 6-bridge, Spark Lime Green (b) (4) 'Flip-Off' button long seal

Table 19. Component Supplier Information

Component	DMF Holder	Drug Master File Number
(b) (4)	(b)	(4)
Stopper Formulation		
Stopper		
Seal		

(b) (4)

(b) (4)

(b) (4)

**Comment: Evaluation of this study is deferred to the product office.*

Container Closure Integrity testing *

(CCIT performed by (b) (4) and associated reports provided)

Several studies were performed to assess container closure integrity (CCI) in the DP configuration. The CCI was verified at all exposed environmental conditions (including storage at (b) (4) for stability studies, (b) (4) for shipping and under (b) (4) conditions (refer to the review of the August 22nd Amendment review for the validation) (b) (4) at the (b) (4) facility).

**Comment: An information request was made for missing and unclear information on CCIT September 25, 2017 and the response was submitted in the October 16th Amendment. Note that*

(b) (4)

(b) (4)

[Redacted]

Process Validation and/or Evaluation (3.2.P.3.5)

The PPQ was conducted using one manufacturing lot conducted at commercial scale starting from the receipt of drug substance Lot (b) (4) from Spark Therapeutics Inc. at (b) (4)

[Redacted]

(b) (4)

[Redacted]

The PPQ lot was evaluated using routine in-process testing and DP release testing. In addition to those tests, **the (b) (4) of filling process was sampled and tested for a subset of release tests to demonstrate consistency of the filling process** as evidenced by those pre-determined product quality attributes.

The firm indicates that the continued process verification will continue following one PPQ lot manufacturing for which the information is submitted in this BLA.

(b) (4)
[Redacted text block]

[Redacted text block]

Aseptic process validation (Media Fills Study - 3.2.P.3.5)

Comment: Because there was no non-viable particle monitoring in operation during filling, continuous non-viable particle monitoring is incorporated in media fill protocol as documented in September 11, Amendment. Refer to the review of this amendment within this memo.

Media fills are routinely performed by (b) (4) to monitor aseptic techniques and demonstrate that the aseptic filling process is consistent. Media fills are performed (b) (4) [Redacted]. This section summarizes the three Spark container closure-specific media fills conducted for commercialization: (b) (4) [Redacted] performed in 1Q2016.

Comment: Refer to the review of the November 16th Amendment in that results for a media fill run are reported. This media fill was performed as per the revised protocol that incorporated non-viable particle monitoring in operation for the (b) (4) [Redacted] upon request.

The three media fill studies were performed using the actual primary packing components (b) (4) [Redacted]. In all three studies, (b) (4) units were filled with the following interventions.

(b) (4) [Redacted text block]

DILUENT MANUFACTURING AND TESTING (3.2.P)

A diluent for voretigene neparvovec-rzyl drug product is manufactured at (b) (4) where the drug product is manufactured. For additional information, refer to Section 3.2.a.1 for the drug product and its diluent.

The Diluent for voretigene neparvovec-rzyl is a frozen aqueous solution containing an identical formulation of the inactive ingredients to that of the drug product (DP), without the active substance. As the DP is a concentrate/viral vector suspension, a 1:10 dilution with the diluent is required prior to administration; two diluent vials are needed to provide the 2.7 mL required to dilute 0.3 mL of DP. The identical formulation of the inactive ingredients sodium chloride, sodium phosphate, and (b) (4) P188 in both the DP and diluent ensures a consistent matrix of these excipients at all times during the dilution of the active substance.

Table 33. Product Diluent Formulation

Ingredient	Concentration	Function / Purpose
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sodium Chloride ((b) (4)) NaCl; FW 58.44 (b) (4)	180 mM	(b) (4)
(b) (4) P188 (Poloxamer 188, Pluronic (b) (4) ((b) (4)) HO(C ₂ H ₄ O) ₈₀ (C ₃ H ₆ O) ₂₇ (C ₂ H ₄ O) ₈₀ H; FW 7680 to 9510 Da (b) (4)	0.001%	(b) (4)
Water for Injection (WFI) Quality Water (b) (4)) (b) (4)	q.s.	Solvent

q.s. = quantum sufficit

(b) (4)

The diluent is supplied in 2 mL (b) (4) vials, like the DP. The Diluent is supplied at a volume of 1.7 mL and is composed of sterile water containing 180 mM sodium chloride, 10 mM sodium phosphate, 0.001% (b) (4) P188, pH 7.3.

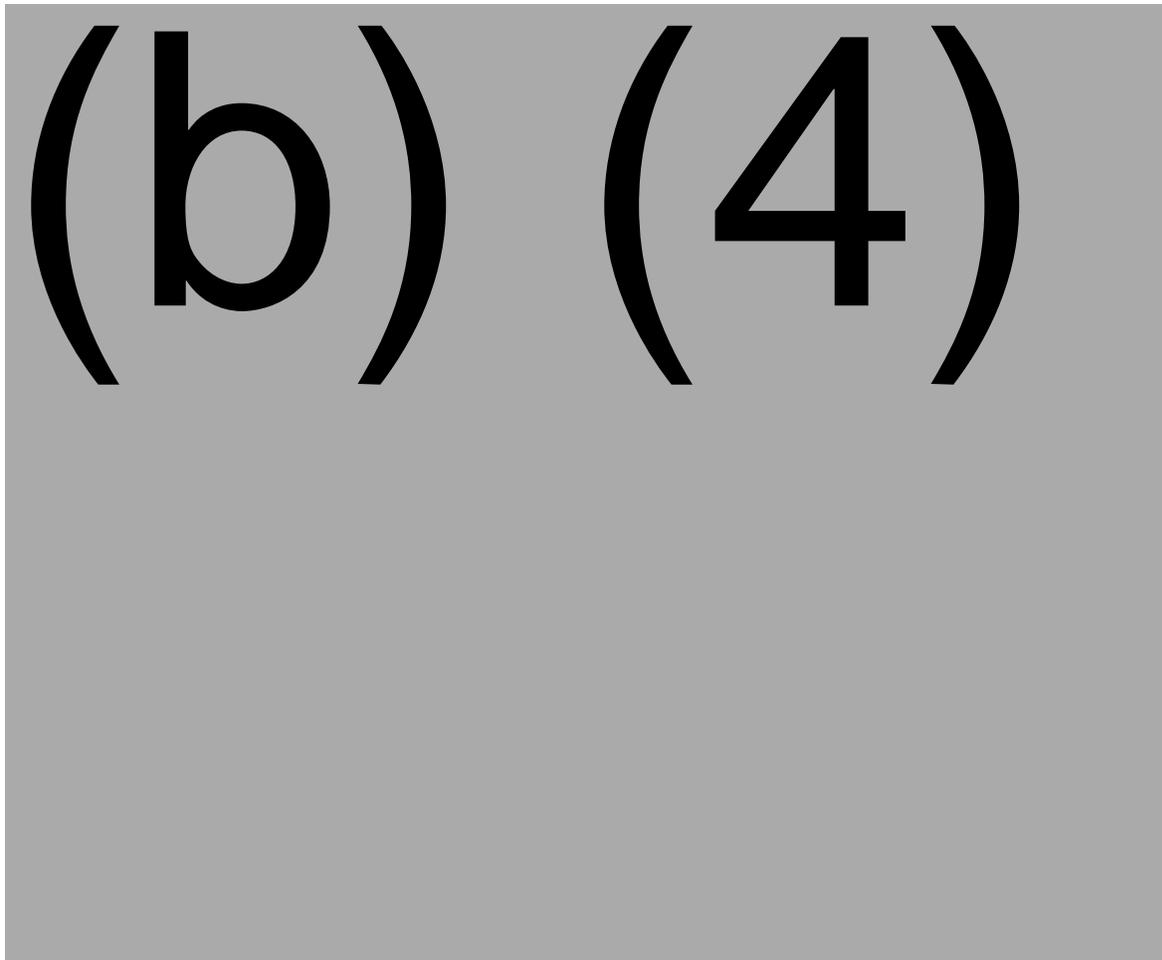
Container Closure System (3.2.p.7)

The container closure system used for the diluent is the same as the one used for the drug product.

Table 34. Diluent container closure system

Component	Description
Vial	2 mL (b) (4)
Stopper	(b) (4) gray, (b) (4) 13 mm stopper
Seal	(b) (4) 13 mm Flip-Off seal, 6-bridge, (b) (4) white, matte top button

Figure 13. Schematic of the Diluent Manufacturing Process (3.2.P.3.3 Description of Manufacturing Process & Controls - Diluent)



Description of Manufacturing Process & Controls – Diluent (3.2.P.3.3)

(b) (4)
[Redacted text block]

(b) (4)
[Redacted text block]

Table 35. Parameters and Controls for Diluent Solution Compounding

Operating Process Parameter	Target	Acceptable Range
(b) (4) P188 (b) (4)	(b)	(4)
Sodium Chloride (b) (4)		
Sodium Phosphate (b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
Total Formulated Diluent Solution (b) (4) (addition of WFI)		
Critical In-Process Control		
Formulated Diluent Solution pH	7.3	(b) (4)

(b) (4)
[Redacted text block]

Sterilization is accomplished by filtration through (b) (4)
[Redacted text block]

Table 36. Parameters and Controls for Sterile Filtration

Critical Process Parameter	Target	Acceptable Range
Sterile Filtration Flow Rate	(b) (4)	(b) (4)
Critical In-Process Control	Target	Acceptable Range
Filter Integrity Testing (b) (4)	PASS	(b) (4)
In-Process Control	Target	Acceptable Range
Duration from the Time Product Diluent Solution Preparation Starts to Completion of Aseptic Filtration into Filling (b) (4)	(b) (4)	(b) (4)

Comment: It is unclear how the time limit was determined. Evaluation of the processing time is deferred to the product office reviewers. According to the product reviewers, (b) (4) processing was acceptable, because results for the DP compatibility with the CC system (DP contains the diluent as inactive component) and stability studies were acceptable. The DP compatibility study supports (b) (4) hold time at (b) (4).

Duration from the time diluent solution preparation starts to completion of aseptic filtration (b) (4)

(b) (4)

[Redacted text block]

Comment: For capping and sealing, refer to the October 16th Amendment review.

(b) (4)

[Redacted text block]

to permit withdrawal of the labeled volumes.

(b) (4)

The vials are 100% visually inspected under (b) (4) light levels and defective vials are removed from the lot. An allowable inspection reject limit of (b) (4) of filled vials is specified, to ensure overall product losses are minimized. Labels will be applied directly to the vial immediately following inspection.

Labelled, inspection-passed vials are packed into labelled, opaque, freeze-resistant bulk cartons. A tamper evident seal is applied to each carton. Once all inspection, labelling and packaging processes have been completed, the sealed cartons are transferred to storage at ≤ -65 °C.

Table 37. Parameters and Controls for Inspection, Packaging, and Storage of Diluent Vials

Operating Process Parameter	Target	Acceptable Range
Visual Inspection of Diluent Vials	100% of Vials Inspected	100% of Vials Inspected
In-Process Control	Target	Acceptable Range
Allowable Inspection Reject Limit	(b) (4) of filled vials	(b) (4) of filled vials

Comment: Diluent is shipped with DP. Refer to the amendments for information on DP shipping validation.

Reprocessing and/or reworking is not permitted as part of the manufacturing process.

Process Validation

(3.2.P.3.5 Process Validation and/or Evaluation - Diluent)

Only one PPQ lot was manufactured for the process validation and evaluation. Because the product has an orphan drug designation for a rare disease, it is accepted (based on internal discussions). Also, note that manufacturing scale is very small (lab scale).

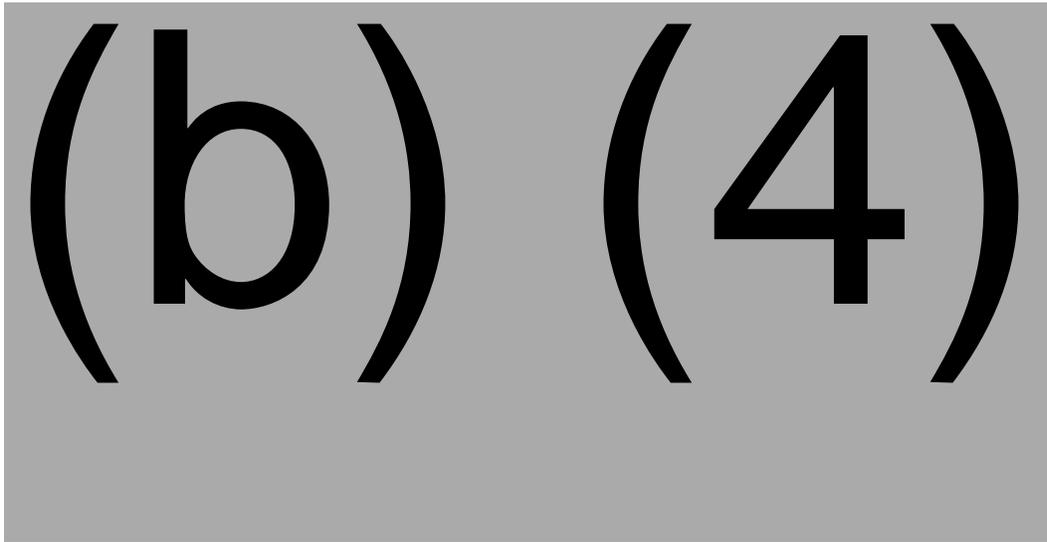
Table 38. Diluent Batches Used in Clinical, Engineering, and Stability Studies

Batch Number	Date of Manufacture	Batch Size	Fill Site	Batch Use
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Clinical & Stability
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Engineering & Stability
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Engineering
(b) (4)	(b) (4)	(b) (4)	(b) (4)	PPQ & Stability

¹Batch (b) (4) had a fill volume of (b) (4) in a (b) (4) cryovial.

(b) (4)

Figure 14. Filter Integrity (b) (4) Results for (b) (4) Filters (all above (b) (4), meeting the acceptance criteria)



Comment: The (b) (4) filter is used (b) (4) (Grade (b) (4) environment); whereas the (b) (4) filter is located within the (b) (4).

Batch Analysis

(3.2.P.5.4 Batch Analysis - Diluent)

Table 40. Diluent Release Data (Lot (b) (4))

Assay	Test Site	Method #	Acceptance Criteria	Results Lot (b) (4)
Appearance (Visual Inspection)	Spark Therapeutics, Inc.	QC028	Clear and colorless solution, free of visible particles	Clear and colorless solution, free of visible particles
pH	Spark Therapeutics, Inc.	QC020	7.3 (b) (4)	7.2
(b) (4)	Spark Therapeutics, Inc.	QC019	(b) (4) (b)	(b) (4)
Sterility	(b) (4)	SOP 1140	No growth	No growth
Endotoxin	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Concentration of Pluronic	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Particulate Matter	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Extractable Volume	(b) (4)	(b) (4)	(b) (4)	(b) (4)

***Comment:** *Particulate matters should have been evaluated for the drug product and its diluent based on the outline described in (b) (4). Refer to associated IR and Amendment (requested by the product office on July 21, 2017 and August 14th Amendment submitted in response).*

STABILITY (3.2.P.8)

Post – approval stability commitment is provided in Section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitments.

3.2.P.8.1 Stability Summary and Conclusions – Drug Product

The primary stability data consists of one PPQ lot of Drug Product (lot (b) (4) (DP)). At the time of submission, three months of stability data at three separate stability conditions (b) (4)) were available.

Table 41. Summary of Drug Product Stability Studies

Lot #	Stability	Drug Substance or Drug Product	Vialing Location	Fill Volume	Container Closure
(b) (4)	Primary	Drug Product	(b) (4)	0.5 mL	(b) (4) Vial ¹
(b) (4)	Supporting	Drug Product	Spark	0.5 mL	(b) (4) Vial ¹
(b) (4)	Supporting	Drug Product	(b) (4)	0.5 mL	(b) (4) Vial ¹
(b) (4)	Supporting	Drug Substance	Spark	0.5 mL	Cryovial ²
(b) (4)	Supporting	Drug Product	Spark	0.5 mL	(b) (4) Vial ¹
(b) (4)	Supporting	Drug Substance	Spark	0.5 mL	Cryovial ²
(b) (4)	Supporting	Drug Product	CHOP	(b) (4)	Cryovial ²
(b) (4)	Supporting	Drug Product	(b) (4)		Cryovial ²

¹Vial - 2 mL (b) (4), Stopper - (b) (4) gray, (b) (4) 13 mm, Seal - (b) (4) 13 mm Flip-Off seal, 6-bridge, Spark (b) (4) Green, matte top button (b) (4) 1.5 mL sterile polypropylene cryogenic vial, with silicone gasket

According to the information provided in the original BLA, the total shelf life of (b) (4) will be distributed as (b) (4) for the Drug Substance and (b) (4) for the Drug Product.

Up to (b) (4) of stability data are available at the (b) (4) storage condition for the CHOP clinical lot manufactured at (b) (4). Up to (b) (4) data are available at (b) (4) for the CHOP lot manufactured at CHOP. These data support the stability (including for sterility) of the product at the proposed shelf life when stored at the intended commercial storage conditions.

Table 42. Drug Product Stability Protocol (Lot (b) (4) (DP) – Primary Stability)

Study	Time Intervals								
	0 ¹	1W	2W	3W	1M	2M	3M	6M	9M
Long Term (b) (4)	A,C, D , E	NR	NR	NR	NR	A,B	A,B	A,B	A,B
Intermediate (b) (4)	A,C, D , E	NR	NR	NR	A,B	A,B	A,B	A,B	A
Accelerated (b) (4)	A,C, D , E	A	A,B	A	A,B	A,B	A,B	A,B	R
Study	Time Intervals (Months)								
	12M	18M	(b) (4)	(b) (4)	(b) (4)	(b) (4)			
Long Term (b) (4)	A,B, D	A,B	A,B, D	A,B, D	A,B, D	A,B,C, D , E			
Intermediate (b) (4)	A,B, D	NR	NR	NR	NR	NR			
Accelerated (b) (4)	NR	NR	NR	NR	NR	NR			

A = Appearance, pH, (b) (4) Genome Concentration, (b) (4), Expression by (b) (4)
 B = (b) (4) Potency Assay
 C = Genome ID, Endotoxin
D = CCIT
E = Sterility
 NR = no testing required at this time point for this study.
¹ Release data used as t=0 time point.

***Comment:** Because there was no CCIT data for zero time point), I asked Spark to identify the location of that data in the submission (indicated as “D” for time zero point in the table above). In response, Spark indicated that CCIT would not be performed at release and expiry, because sterility testing is performed, and CCIT would be performed in lieu of sterility testing in accordance with the 2008 FDA guidance, “Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products”. This is acceptable. For additional information, refer to the t-con memo uploaded in EDR (dated October 24, 2017).*

Table 43. Drug Product Shelf-life Specification PPQ Lot (b) (4) (DP)

Test	Method	Limits
Appearance	Spark / SOP.QC.028	Clear, Colorless Solution
pH	Spark / SOP.QC.020	(b) (4)
(b) (4)	Spark / SOP.QC.069	(b) (4)
Purity by (b) (4) Assay	Spark / SOP.QC.003	(b) (4)
Vector Genome Concentration Assay	Spark / SOP.QC.062	(b) (4)
(b) (4)	Spark / SOP.QC.081	Report Result
<i>In Vitro</i> Relative Potency of (b) (4) by (b) (4) Assay	(b) (4)	(b) (4)
Vector Genome Identity by (b) (4)	Spark / SOP.QC.067	Positive for hRPE65v2
Endotoxin	(b) (4)	(b) (4)
CCIT	(b) (4)	Pass
<i>In Vitro</i> Relative Potency of (b) (4) Assay	(b) (4)	(b) (4)

Table 44. Drug Product Shelf-life Specification PPQ Lot (b) (4) (DP)

Test	Method	Limits
Appearance	Spark / SOP.QC.028	Clear, Colorless Solution
pH	Spark / SOP.QC.020	(b) (4)
(b) (4)	Spark / SOP.QC.069	(b) (4)
Purity by (b) (4) Assay	Spark / SOP.QC.003	(b) (4)
Vector Genome Concentration Assay	Spark / SOP.QC.062	(b) (4)
(b) (4)	Spark / SOP.QC.081	Report Result
<i>In Vitro</i> Relative Potency of (b) (4) by (b) (4) Assay	(b) (4)	(b) (4)
Vector Genome Identity by (b) (4)	Spark / SOP.QC.067	Positive for hRPE65v2
Endotoxin	(b) (4)	(b) (4)
CCIT	(b) (4)	Pass
<i>In Vitro</i> Relative Potency of (b) (4) Assay	(b) (4)	(b) (4)

3.2.P.8.1 Stability Summary and Conclusions - Diluent

All available test results from both the primary stability studies at all stability storage conditions tested (b) (4) met specifications. In addition, all results across the (b) (4) supporting stability study on the CHOP clinical diluent were observed to

be stable and met specification (including for sterility testing) throughout the entire duration of the study (*For the stability protocol and available data, refer to Section “3.2.P.8.1 Stability Summary and Conclusions – Diluent” in the BLA*). Sterility testing is performed at release and expiry.

Based on the available primary and supporting stability data, the shelf life of (b) (4) determined for the Drug Product is also supported for the diluent. Additional long-term stability test results will continue to be tested to ensure that the (b) (4) shelf life is supported.

Comment: *Evaluation of the stability studies is deferred to the product office reviewers.*

FACILITIES AND EQUIPMENT – Spark (3.2.a.1)

Drug substance manufacturing and testing facility located at 3737 Market Street, Suite 1300, Philadelphia, PA will be used for commercial manufacturing of drug substance (DS). The Spark facility is approximately (b) (4) and site operations include research and development, manufacturing, quality and administrative functions. The facility does not manufacture or manipulate beta-lactam or cephalosporin compounds.

The DS manufacturing facility on the (b) (4) (FEI: 3011194531, DUNS # 079498241) was inspected from August 21 to August 25, 2017 and this pre-license inspection was classified as VAI (Voluntary Action Indicated). For additional information, refer to EIR for this inspection.

The Spark facility is served by a building management system (BMS) which provides automated control and maintenance monitoring of the primary air handling unit, exhaust fans, terminal units, reheat coils, humidifier, fan powered terminal units, chilled beams, and HEPA fan filter units. The BMS controllers are powered from normal and standby power sources to assure continuous and consistent control. The system is provided with a server/workstation with a stand-alone uninterruptible power supply (UPS) capable of backup at full load. Each BMS controller is capable of peer-to-peer communication for sharing of point status and valve information.

The Spark manufacturing areas are provided with an environmental monitoring System (EMS) which provides dedicated, validated environmental monitoring of environmental parameters (room temperature, relative humidity and differential pressures within the (b) (4) areas) and micro-environments and associate equipment (freezers, refrigerators, incubators, fan filter units, and oxygen monitors). The EMS provides a graphical user interface which allows the user to display and manage data. This interface allows adjusting schedules and set points, acknowledging alarms, tracking pressure, temperature and humidity readings. The EMS functions as the primary data historian for the GMP manufacturing facility and the data gathered supports batch release and demonstrates that the GMP environment is in a state of control. Operation and Performance of the EMS was qualified through the testing summarized below:

DS manufacturing (cell culture and purification) for (b) (4)

Suite (b) (4)

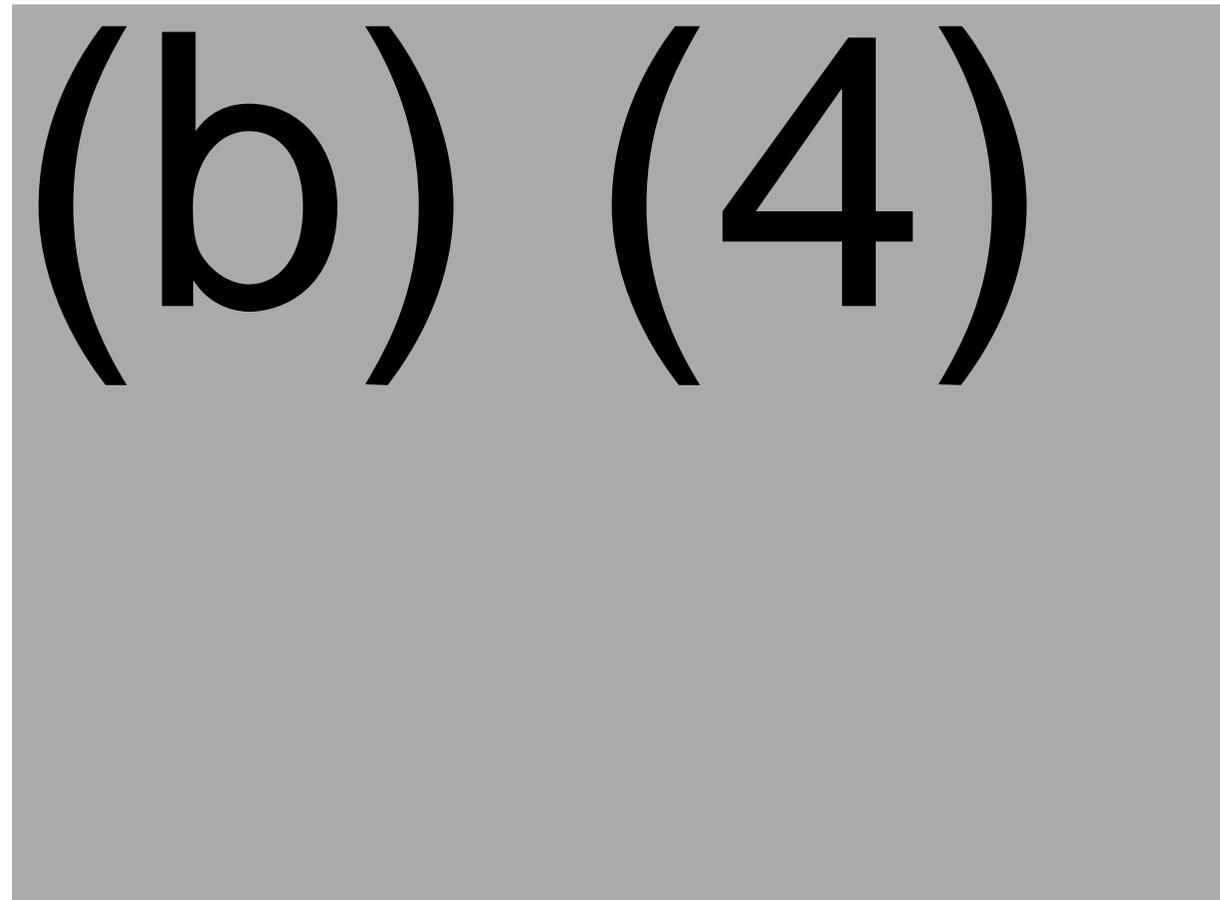
(b) (4)

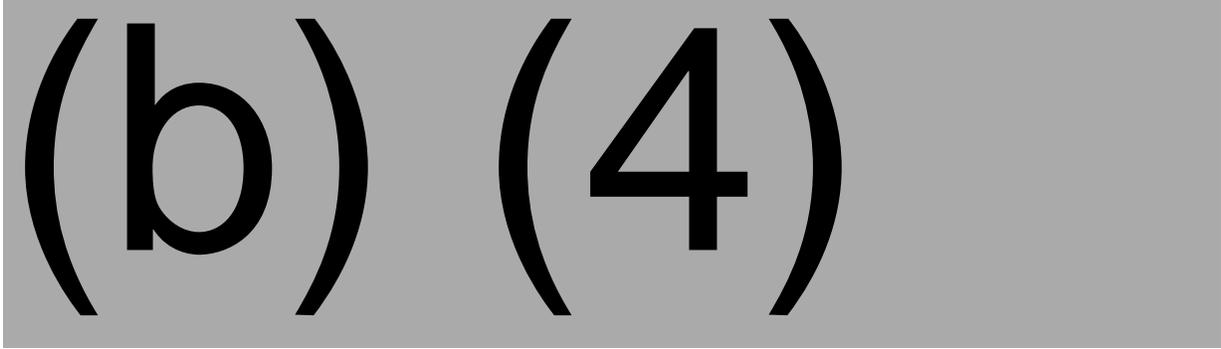
The firm provided flow diagrams for personnel, material, product and waste. The firm also provided information pressure cascade in the manufacturing facility to maintain containment. No objectionable issues are noted.

Comment: Airlock (b) (4) for entry to the rooms (b) (4) (cell culture) and (b) (4) (purification) is designed to (b) (4)

These design features are appropriate to maintain viral containment.

Table 45. Spark Facility Rooms*





**Areas highlighted in bold are used in voretigene neparvovec DS manufacturing*

Classification of the cleanrooms was initially performed and is performed periodically as per the requirements of ISO **(b) (4)** .

(b) (4) [Redacted text block consisting of approximately 10 lines of greyed-out content]

Room classification and periodic re-classification: Acceptance criteria for the certification of the Spark **(b) (4)** controlled areas were established with Spark user requirements specifications and included the following activities:

(b) (4) [Redacted text block consisting of approximately 10 lines of greyed-out content]

The following table lists the initial EM alert and action levels that were established based on compendial guidance **(b) (4)** , baseline EM levels and appropriateness by room classification. EM alert and action levels will be routinely assessed and adjusted as appropriate based on trend data. If action level conditions are exceeded, investigations for root cause are conducted.

Actions taken include adequate investigation into the source, potential impact on product, and measures taken to prevent recurrence.

FACILITIES AND EQUIPMENT – (b) (4) (3.2.a.1)

Drug Product (DP), voretigene neparvovec (AAV2-hRPE65v2), and its diluent are manufactured at (b) (4) [redacted]. Sterility testing on this gene therapy (viral vector) product and its diluent is also performed at (b) (4) [redacted] is a contract manufacturer.

The (b) (4) contract manufacturing site for the manufacture of a viral vector ((b) (4) [redacted] vector) was previously inspected under (b) (4) [redacted] by FDA/CBER back in (b) (4) [redacted] and this inspection was classified as VAI (Voluntary Action Indicated). (b) (4) [redacted] vector product is used in manufacturing of a (b) (4) [redacted] product, (b) (4) [redacted]. The inspection of the (b) (4) facility is waived based on the information provided in the BLA and FDA inspection history.

(b) (4) [redacted], which is a contract manufacturer, is located at (b) (4) [redacted].

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

[redacted]
[redacted]
[redacted]
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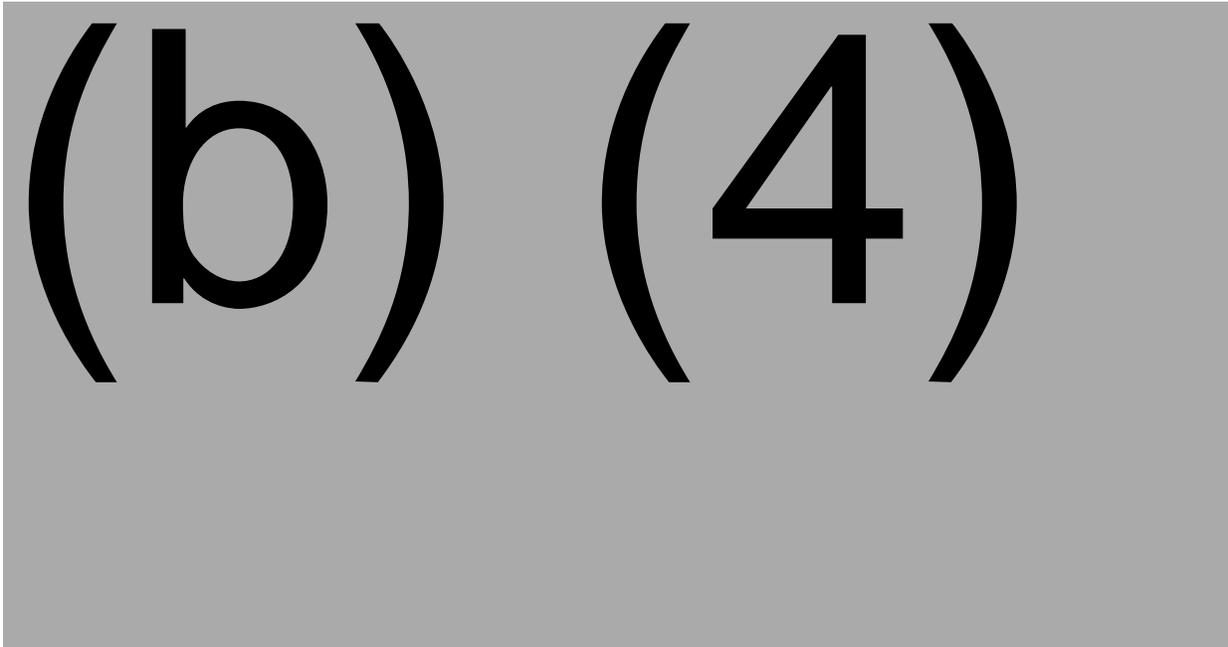
[redacted]
[redacted]
[redacted]

[redacted]
[redacted]
[redacted]
[redacted]

(b) (4) [redacted], is a multi - product manufacturing site with buildings for production including and formulation of multiple types of clinical trial materials for early development (Phase 1-3) projects and commercial, licensed products. The site does not manufacture or manipulate beta-lactam or cephalosporin compounds.

Voretigene neparvovec DP and its diluent are manufactured in Building (b) (4) [redacted], a dedicated facility for the manufacture of live biologics. Building (b) (4) [redacted] is a (b) (4) [redacted] dedicated live biologics facility commissioned in (b) (4) [redacted] with validation completed in (b) (4) [redacted]. Building (b) (4) [redacted] is a multi-product (product) manufacturing site. This building was inspected from (b) (4) [redacted] under (b) (4) [redacted] for a (b) (4) [redacted]. This inspection was classified as VAI (Voluntary Action Indicated). Refer to the associated EIR for information on quality system, production system, facility and equipment system and laboratory and materials controls system.

Table 50. (b) (4) Building (b) (4) Facility Rooms

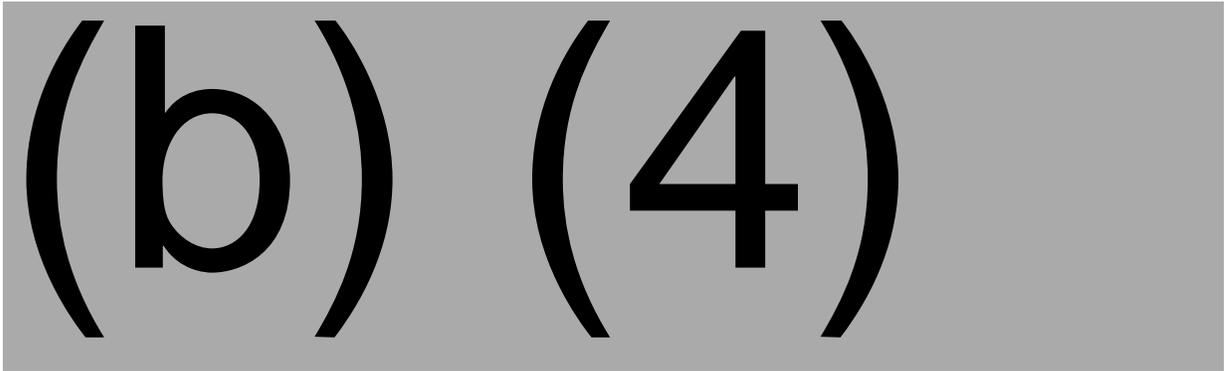


AAV2-hRPE65v2 DP and its diluent are manufactured in Suite (b) (4) [redacted] while (b) (4) [redacted] vector is manufactured in (b) (4) [redacted]. Filling Suite (b) (4) [redacted] is being used as the microbiological laboratory (where sterility testing performed on the DP and its diluent) and contains the (b) (4) [redacted] used for the sterility test and processing of environmental monitoring samples.

Major differences between filling suites (b) (4) [redacted] and (b) (4) [redacted] are as follows:

- (b) (4) [redacted]
- (b) (4) [redacted]

Table 51. Other Manufactured Products and Shared Equipment in Suite (b) (4)



GMP product storage units such as refrigerators and freezers in shared areas are periodically re-qualified (refer to Section 3.2.a.1 of BLA 125610 submission and Establishment Inspection Report for (b) (4) under (b) (4)). Equipment critical to aseptic processing undergoes re-qualification on an (b) (4) basis, including:

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

The DP and its diluent are filled in (b) (4) (Grade (b) (4) area). Before filling, (b) (4) and testing are performed.

Non-viable particle monitoring is performed (b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

AMENDMENT REVIEW - August 22, 2017

This amendment was submitted in response to the July 31st IR.

1. Please provide a summary of deviations occurred during Drug Substance (DS), Drug Product (DP) and Diluent PPQ runs. This summary should include a summary of incidents, investigations, results of root-cause analyses and implemented CAPAs (where applicable).

Reviewer Comment: Deviations, OOSs and associated CAPAs were evaluated during the August 21-25th PLI of the Spark manufacturing site located in PA (refer to EIR for this PLI). This evaluation covered the deviations occurred at (b) (4)

2. Regarding DS manufacturing at Spark Therapeutics Inc.:
 - 2.1. Risk assessment for EM
 - 2.2. EM frequency for (b) (4) areas
 - 2.3. It is unclear from the information provided in the BLA submission whether non-viable particulate monitoring is performed during dynamic conditions in Biological Safety Cabinets (BSCs). Please comment. If not performed, please provide a justification/rationale for not performing non-viable particulate monitoring during dynamic conditions.

Spark Response 2.1.

A risk assessment, **TD2015-023 - Environmental Monitoring Risk Assessment** Statement, was conducted **to identify risk-based sample locations** for the Spark Therapeutics controlled environment manufacturing rooms. An Environmental Monitoring Risk Evaluation Method (EM-REM) was utilized to select risk-based Environmental Monitoring (EM) sample locations based on people, activity and potential contamination sources present in the rooms.

Reviewer Comment: Addressed. EM risk assessment is adequate.

Spark Response 2.2.

SOP.QC.002 - Routine Environmental Monitoring defines the (b) (4) sampling of viable air, non-viable particles, and viable surface sampling for the classified areas.

Reviewer Comment: Acceptable. Refer to the referred table under "Facilities and Equipment – Spark). Frequency of EM (for non-viable particulate, viable air and viable surface using (b) (4) for (b) (4) areas are provided in SOP.QC.002 ((b) (4) EM for all areas). A description of sampling locations and alert and action limits for EM are also provided. No objectionable issues are noted.

Spark Response 2.3.

Non-viable particle counts are not performed during dynamic conditions in the Biological Safety Cabinets (BSCs). The manufacturing process design and controls provide a low bioburden process under dynamic conditions in BSCs. (b) (4)

. Viable surface samples are taken immediately following processing in the BSC.

Reviewer Comment: Acceptable.

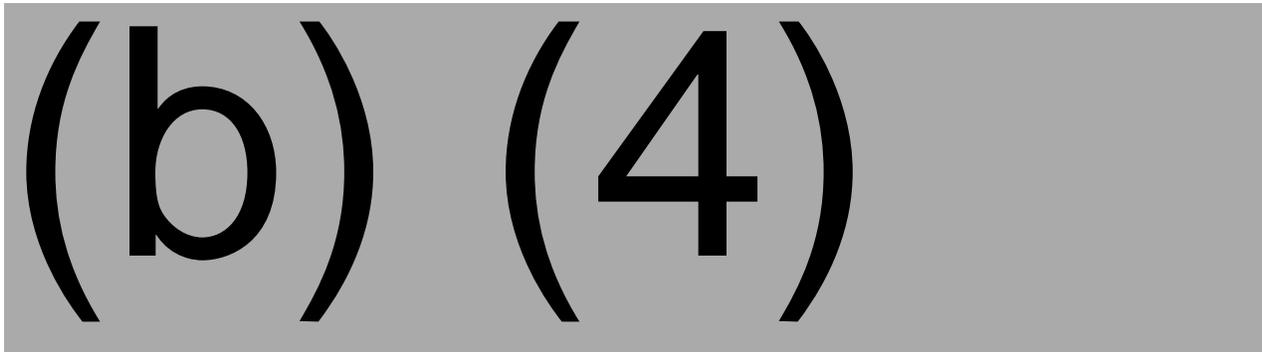
-The firm did not provide a sound justification for not monitoring non-viable particle monitoring. However, it is acceptable, because there are (b) (4)

. Also note (b) (4)

2.4. Please provide cleaning frequency for BCSs and (b) (4) areas.

Spark Response 2.4.

Table 1 describes the cleaning frequency for the Biosafety Cabinets (BSCs), the (b) (4) areas.



Reviewer Comment: Acceptable. Note that changeover and cleaning procedures were evaluated during the PLI (refer to EIR).

2.5. Please provide a summary of cleaning validation (including protocol and data) for TFF^{(b) (4)} system, homogenizer, chromatography system and (b) (4) centrifuge/rotor. Please ensure that acceptance limits are provided for cleaning parameters evaluated during validation such as for (b) (4) that you indicated in the BLA submission. Please also indicate frequency of equipment cleaning and whether there is any qualified pre-use flushing procedure (e.g., with either WFI or buffer as appropriate) for TFF systems (to remove storage solution for TFF^{(b) (4)} and potential extractables/leachables).

- (b) (4) [Redacted]

2.6. We note from the information provided in Section 3.2.a.1 (on page 12) that glassware washer and steam sterilizer have been qualified, but associated qualification reports are not included in the submission. Please provide a copy of those qualification reports.

Spark Response:

The glassware washer and steam sterilizer are used to aid in minimizing bioburden entering into the manufacturing facility. The glassware washer and steam sterilizer are used to sanitize buckets used for facility cleaning and carboys used for process waste collection/transport. Installation and Operational Qualifications were performed however, a Performance Qualification was not required based on the type of components cleaned and sterilized.

(b) (4) [Redacted]

[Redacted]

Reviewer Response: Acceptable.

The autoclave validation is adequate for the intended use. During the PLI, It was noted that autoclave is used for carboys and buckets used in sanitization/cleaning that do not have any product-contact and washer is not used for voretigene neparvovec manufacturing, because all equipment (except for homogenizer, TFF^{(b) (4)} system and chromatography system as described above), accessories, containers, tubings, connectors, stirrers, tubes, tissue flasks, roller bottles and so on are single use. In summary, nothing is sterilized for commercial manufacturing.

According to S-011 IOQ Report - 1600TISS Glassware Washer and S-011 Test Report - 1600TISS Glassware Washer Spray Coverage, washer was qualified using (b) (4) solution (for the assessment of complete washing coverage and removal/efficient washing) for intended

use. The validation is adequate. Note that nothing is washed for commercial manufacturing (verified during the PLI).

2.7. Please provide a summary of OQ (or PQ if applicable) for incubators (CO₂ and roller bottle incubators), TFF systems (TFF (b) (4)) and (b) (4) chromatography system. Alternatively, you may submit a copy of actual qualification reports (that contain protocol and data).

Spark Response 2.7.

IOQ and PQ protocols were prepared and executed in accordance with the site Validation Master Plan. Summaries for the requested protocols are provided as follows: Roller Bottle Incubators (Equipment IDs (b) (4)) IOQ and PQ protocols were prepared and executed for each of the Roller Bottle Incubators. The executed IOQ protocols ((b) (4) IOQ - Roller Bottle CO₂ Incubator and (b) (4) IOQ - Roller Bottle CO₂ Incubator) demonstrate that each incubator was installed correctly, all alarms functioned as required and measured temperatures within each chamber were within the required process range of (b) (4) and CO₂ was within the process range of (b) (4) through empty chamber temperature and CO₂ distribution studies. The executed PQ protocols ((b) (4) PQ - Roller Bottle Incubator and (b) (4) PQ - Roller Bottle CO₂ Incubator) demonstrate that all measured temperatures within each chamber were within the process range of (b) (4) and CO₂ was within the process range of (b) (4) with a fully loaded chamber (roller bottles in all (b) (4) positions) through temperature and CO₂ distribution studies. PQ testing also included open door and power loss testing.

CO₂ Incubators (Equipment IDs (b) (4))

IOQ and PQ protocols were prepared and executed for each of the CO₂ Incubators. The executed IOQ protocols ((b) (4) IOQ - CO₂ Incubator and (b) (4) IOQ - CO₂ Incubator) demonstrate that each incubator was installed correctly, all alarms functioned as required and all measured temperatures within each chamber were within the process range of (b) (4) and CO₂ was within the process range of (b) (4) through empty chamber temperature and CO₂ distribution studies. The executed PQ protocols ((b) (4) PQ - CO₂ Incubator and (b) (4) PQ - CO₂ Incubator) demonstrate that all measured temperatures within each chamber were within the process range of (b) (4) and CO₂ was within the process range of (b) (4) through fully loaded chamber ((b) (4)) temperature and CO₂ distribution studies. PQ testing also included open door and power loss testing.

TFF System (Equipment ID (b) (4)) The TFF System consists of (b) (4)

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

(b) (4) Given the nature of this set-up no equipment qualification was required to be performed.

(b) (4) Chromatography System (Equipment ID (b) (4)) In accordance with the Commissioning and Qualification Plan for the (b) (4) (b) (4) chromatography system IOQ protocol), an IOQ protocol was prepared and executed for the

(b) (4) Chromatography System. This IOQ protocol is comprised of hardware and software ((b) (4)) tests, including an executed 21CFR Part 11 compliance test protocol with results summarized in TR2014-006 – Summary Report for the for the IQ-OQ for the (b) (4) with (b) (4) Control - (b) (4) . The executed IQ ensures the (b) (4) installation adheres to all applicable approved design intentions as well as user and process requirements, and demonstrates successful conformance with the following (b) (4) installation requirements: Personnel Suitability Verification, Document Verification, Computer System Performance, (b) (4) Installation Verification, Instrument Configuration Verification, Software Settings & Components

The executed OQ provides documented evidence that the (b) (4) operates as intended throughout all its anticipated operating ranges and successfully conforms with the following operational functions:

(b) (4)

[Redacted]

The executed 21 CFR Part 11 compliance test protocol provides documented evidence to demonstrate that the (b) (4) software is in compliance with 21 CFR Part 11 and successfully conforms with the following testing functions:

(b) (4)

[Redacted]

Reviewer Comment: *Acceptable.*
Actual documents for Equipment IQ/OO/PQ were also reviewed during the PLI. Equipment qualification was adequately performed and documented. I found that equipment qualification was an excellent work and one of the best qualifications I have reviewed so far.

2.8. Please indicate filter type (e.g., cartridge, capsule), membrane area and manufacturer for TFF and (b) (4) filters used in PPQ run.

Spark Response 2.8.

Table 4 describes the filters used in the PPQ run in the order where they are used in the process.

Table 4 Filter Information by Process Step

Reviewer Comment: Addressed.

During the August PLI, it was found out that Filter (b) (4) from (b) (4) was not used in the DS PPQ (b) (4) lot; (b) (4) filter was used in PPQ manufacturing and engineering runs. The firm indicated that (b) (4) filter would be used for commercial manufacturing, which is the same filter as the ones used at (b) (4) for the DP and its diluent filtrations. Therefore, this change was communicated with both DMPQ and the product office during the PLI. Because this change was not a significant change, it was decided to review this filter change under this BLA and approve it. Supporting information for this change was requested on September 5, 2017. Refer to the review of October 5th Amendment submitted in response to the September 5th information request.

2.9. Please describe how you decontaminate and dispose viral biological waste. Please provide a copy of decontamination validation report. If not validated, please provide a justification/rationale.

Spark Response 2.9.

Biological waste is collected in either leak-proof carboys or drums. It is decontaminated by (b) (4). This decontaminated waste is collected by a licensed vendor and disposed.

Reviewer Comment: The firm has a procedure in place for decontamination that was reviewed during the PLI, but not validated. Because the biological waste was removed by a licensed vendor and disposed, it is acceptable.

2.10. Please provide a qualification report demonstrating effectiveness of facility cleaning/sanitization procedures.

Spark Response 2.10.

TD2015-024 - Disinfectant Efficacy Study Rationale provides rationale for the selection of materials and microorganisms utilized in the disinfectant efficacy studies for the surfaces that are cleaned and disinfected at Spark Therapeutics.

DCR-3383 - Disinfectant Efficacy Study Summary is the report for the disinfectant efficacy studies based on TD2015-024 and performed at a Contract Testing Lab (b) (4), including (b) (4). This study includes testing with (b) (4) microorganisms (b) (4). Environmental isolates will be utilized in TP2017-043 - Disinfectant Efficacy Study.

DCR-3383 - Disinfectant Efficacy Study Summary: The following disinfectants are used in the study: (b) (4)

Minimum (b) (4) log reduction was acceptance criteria. Results met this acceptance criteria.

A disinfectant efficacy study, **TR2016-099 - Virus Inactivation Solution Study Using (b) (4)**, was performed for (b) (4) to evaluate viral inactivation in solution, including cytotoxicity, (b) (4).

A disinfectant efficacy study, **TR2016-100 - Virus Inactivation Study Using (b) (4)**, was performed for (b) (4) to evaluate viral inactivation on surfaces, including cytotoxicity, (b) (4).

TR2016-100 - Virus Inactivation Study Using (b) (4)
A disinfectant efficacy study was performed for (b) (4). The surfaces evaluated through this study were (b) (4). The study consisted of a (b) (4)

for all disinfectant, surface, and virus combinations. The results showed that (b) (4) contact time with (b) (4) inactivates the single stranded DNA.

Reviewer Comment: *Acceptable. All the validation studies listed in the response are adequate.*

-Note different surfaces are used in the validation studies.

-Also note that in the virus inactivation study, (b) (4) is used. This virus is a non-enveloped single stranded (ss) DNA virus (b) (4) DNA genome and in (b) (4) in

diameter), like adeno associated virus (AAV). Note that the adeno-associated virus (AAV) genome is also a linear single-stranded DNA (ssDNA) molecule. Therefore, use of (b) (4) is acceptable. Single stranded DNA virus is also a worst case virus for inactivation/cleaning purposes, because inactivation of DNA viruses are more difficult compared to that of enveloped viruses.

3. Regarding DP manufacturing at (b) (4)

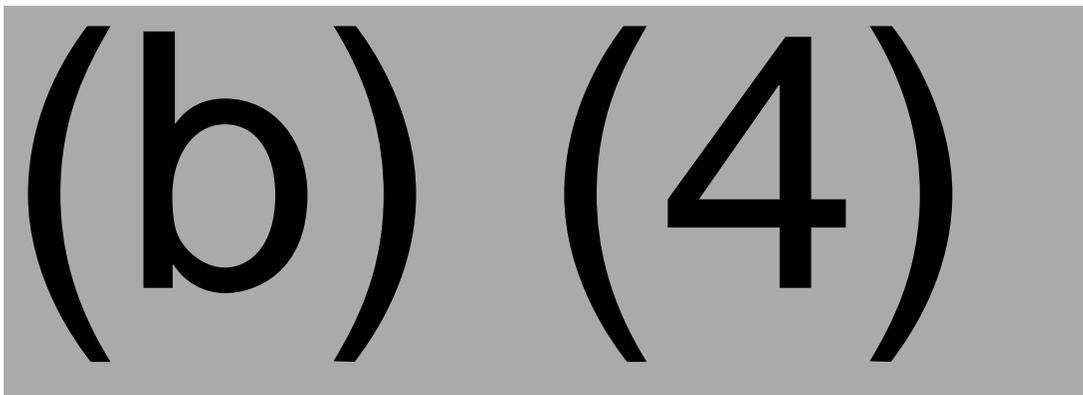
3.1. Please provide SOP (s) or a detailed description of procedures for the following:

- Segregation, labeling and tracking procedures in shared (multi-product) areas and equipment to prevent mix-ups and cross contamination
- voretigene neparvovec 100% DP visual inspection and labeling procedures
- Change over procedures for shared (multi-product) areas and equipment

Spark Response 3.1.

- Segregation, labelling and tracking procedures in shared (multi-product) areas and equipment to prevent mix-ups and cross contamination: (b) (4) SOP 1904 – Line Clearance. Instructions for labelling appear in the BMR under section ‘INSPECTION, SAMPLING AND LABELLING OF VIALS’.
- Voretigene neparvovec 100% DP visual inspection and labelling procedures: (b) (4) SOP 1208 - Visual Inspection for Particulate Contamination Instructions for labelling appear in the BMR under section ‘INSPECTION, SAMPLING AND LABELLING OF VIALS’.
- Change over procedures for shared (multi-product) areas and equipment: (b) (4) SOP 1076 - Use of (b) (4). Instructions for ensuring areas and equipment clear prior to processing also appear in the BMR and in Table 5.

Table 5 (b) (4) Change Over Procedures



Reviewer Comment: 100% inspectional procedures per SOP 1208 are acceptable, but AQL sampling along with defect categories needed to be addressed in a PMC (For this PMC, refer to PMC#1 under “Summary” section of this memo).

-Sealed plastic clear container closure system is visually inspected for visible particulates, low/over-fill and seals as per SOP1208. Associated inspectional categories are listed in SOP 1208 as follows: (b) (4)

-Note extractable volume is measured as a release testing (refer to Table 32 of this memo).

-Also note vial fill (b) (4) is measured (for results, refer to Figure 15 of this memo)

(b) (4) SOP 1904 (Version 2, dated June 8, 2016) – Line Clearance: Line clearance and room cleaning are recorded in logs and batch records, where required. This SOP describes procedures for removal of stuff (e.g., all materials, documentation) for the previous manufacturing campaign/run, cleaning/sanitization of shared equipment and room (where applicable as noted in SOP). No objectionable issues are noted.

(b) (4) SOP 1208 - Visual Inspection for Particulate Contamination (Version 13, issue date May 11, 2017): This SOP describes procedures for training procedures, inspection of area, line clearance and set up, and inspection.

-6.7 High reject rates:

6.7.1. An AQL inspection must be performed on batches that have a reject rate (b) (4) to demonstrate the effectiveness of the initial inspection in identifying all rejects.

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

(b) (4) SOP 1076 Use of (b) (4) (Version 9, issue date May 11, 2017): This SOP describes procedures for training, inspection of (b) (4)

[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]

No objectionable issues are noted.

3.2. Please provide a copy of cleaning and decontamination validation reports for filling (b) (4) and transfer (b) (4) (b) (4) used in voretigene neparovec DP and Diluent manufacturing.

Spark Response 3.2.

The following documents are provided:

(b) (4) (refer to September 5th IR and associated October 5th Amendment). No issues are noted for the validation of (b) (4) decontamination.

3.3. Please provide a floor plan/diagram of equipment/items in the (b) (4) .

Spark Response 3.3

Attached are the Floor plan/diagram of equipment/items in the (b) (4)
[Redacted]

Reviewer Comment: Diagrams should have provided with a description of (b) (4) during filling. Because a description of (b) (4) was not provided, additional information was requested on September 5, 2017. Refer to the review of October 5th Amendment within this memo for the description of (b) (4). I note from the diagrams that there is (b) (4). This was also verified during the meeting with Spark for the BLA submission walk-through.

3.4. Please provide a copy of a (b) (4) total particle qualification of the (b) (4) at rest and in operation.

Spark Response 3.4

(b) (4)
[Redacted]

[Redacted]

[Redacted]

would thus aspirate viral aerosols around the filling room. Therefore, particle sampling “In Operation” during filling is not performed. (b) (4) also refers to the following EU GMP regulation in Annex 1 for not performing non-viable particle monitoring in operation: “For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter* or present a hazard, e.g. live organisms and radiological hazards.”

Therefore, August 18th information request was made following an internal discussion with the DMPQ management on the issue described above:

We note from the information provided in your BLA 125610 that (b) (4) does not monitor non-viable particles in operation during AAV2-hRPE65v2 product filling in (b) (4) because of contamination risk for particle counter with viral aerosols. Under this circumstance, non-viable particle monitoring in operation can be performed during media fill runs, because viral product is not used for media fill. Please incorporate non-viable particle monitoring in operation into your media fill protocol for (b) (4) and provide the revised protocol.

The response to the August 18th IR was received in an amendment to the file on September 11, 2017. The response is acceptable.

Because data from the media fill run with the revised media fill protocol would not be available up until November 10, 2017, another information request was made on September 5, 2017 for the data submission due November 12, 2017:

Please provide data (results of EM and media fill) from the media fill run being executed September 26 through October 10, 2017. Please ensure that nonviable particle monitoring in operation (as you agreed in the e-mails dated August 29 - August 31, 2017) will be performed during this media fill run.

The response to the IR above was received on November 15, 2017. Refer to the review of the November 15th amendment.

3.5. Please provide a copy of decontamination validation report for viral biological waste. If there is no validation, please provide a justification/rationale.

Spark Response 3.5

(b) (4) INV444-01 - (b) (4) Report - Decontamination Study Investigation into the (b) (4) of AAV Vector RPE65 for Spark Therapeutics is provided. This study was designed and executed by (b) (4) for Spark Therapeutics to investigate the (b) (4)

waste in Building (b) (4) and is handled in accordance with (b) (4) SOP 1321 - Control of Waste - Building (b) (4).

Reviewer Comment: *Addressed. It appears that no liquid waste is not generated during filling and any viral contaminated surfaces are decontaminated by (b) (4).*

(b) (4) SOP 1321 - Control of Waste - Building (b) (4) (Version 2; Issue date: July 12, 2013): In this SOP, procedures for solid waste handling and surface decontamination of the waste bags (b) (4) and liquid waste handling per SOP 1408. The solid waste is sent to for incineration by an approved contractor.

6.2 Liquid waste:

6.2.1 Any liquid waste produced within Building (b) (4) will be sent via drain to the Building (b) (4) waste storage tank. For checking and emptying of waste storage tank refer to SOP 1408.

(b) (4) INV444-01 - (b) (4) Report - Decontamination Study Investigation into the (b) (4) of AAV Vector RPE65 for Spark Therapeutics: In this report, the (b) (4)

protocol was performed in accordance with SOP 1843 in order to verify the decontamination procedure. In any case, SOP 1408 appears to be the one for liquid waste handling.

3.6. Please provide a copy of actual microbial retention study report(s) for sterilizing grade/(b) (4) filters - used in voretigene neparvovec DP and Diluent manufacturing.

Spark Response 3.6

Spark technical document TD2016-079 - Filter Microbial Retention is provided. The purpose of this study was to provide (b) (4) retention data for (b) (4) membranes after exposure to the candidate test product, voretigene neparvovec Diluent.

All protocol acceptance criteria were met. The test data obtained from evaluating voretigene neparvovec Diluent revealed that exposure to this solution at its processing conditions does not alter the ability of the (b) (4) filter, pores size (b) (4), to (b) (4)

[Redacted text block]

Reviewer Comment: Acceptable.

Note that the microbial retention validation study was performed only with the diluent, not with the product. Because the drug product are sterile filtered using (b) (4)

, there is limited supply of the product, the DP is formulated in the diluent, the route of the product administration is not via intravenous injection and the final product and its diluent are tested for sterility, the microbial retention validation with the diluent is acceptable. Also note that post integrity testing acceptance criterion is (b) (4)

Summary of the validation: Impact of Pluronic (b) (4) (major formulation component of the diluent and the drug product) on the (b) (4)

The purpose of the microbial retention study was to provide (b) (4)

3.7. Please provide a qualification report for mixing to ensure DP homogeneity (performed prior to sterilizing grade/(b) (4) filtration). If DP mixing process is not qualified, please provide a justification/ rationale.

Spark Response 3.7

A qualification study has not been performed for mixing pooled Drug Substance to ensure Drug Product homogeneity. There are several reasons for not performing a formal mixing study: A Drug Substance batch consists of (b) (4)

(b) (4)

Appearance, pH, (b) (4), Vector Genome titer, particulate matter and concentration of Pluronic were assessed at (b) (4) of filling for both Drug Product lots. Results were consistent at (b) (4) for all testing.

Reviewer Comment: *Acceptable because of the justifications 1-3 provided above. Also refer to Figure 9 “Control Chart of Mixing Time for Drug Product Lots Produced at (b) (4)” within this review memo (in that results were within the limits).*

3.8. It is unclear from the information provided in your BLA submission whether there is AQL sampling for DP 100% visual inspection. Please comment and provide associated acceptance limits. If there is no AQL sampling, please provide a justification/rationale. Please also indicate the total qualified time for DP visual inspection and labeling.

Spark Response 3.8

All Drug Product vials are 100% inspected in accordance with SOP 1208 – Visual Inspection. The reject limit is (b) (4) of filled vials. There is no AQL sampling due to batch sizes. As stated in the Drug Product Batch Manufacturing Record (BMR), there is a cumulative maximum time of (b) (4) permitted between the end of the thawing process, and completing transfer of the inspected and labelled vials to storage at ≤ -65 °C: Specific BMR instruction The time the product is held at (b) (4) after thawing must be recorded, during the filling, inspection and packaging processes, and must not exceed a total period of (b) (4).

Reviewer Comment: *Acceptable based on the limited supply/availability of the DP. However, it needs to be performed, because AQL inspection is non-destructive. For the associated PMC (PMC#1), refer to “Summary” section of this memo.*

SOP 1208 indicates AQL inspection for high reject rates:

6.7 High reject rates

6.7.1 An AQL inspection must be performed on batches that have a reject rate (b) (4) to demonstrate the effectiveness of the initial inspection in identifying all rejects.

Because defect/reject categories and AQL inspection is not addressed in the response, a PMC (post marketing commitment) request is made (refer to “Summary” section of this BLA)

3.9. We note from the information provided in the certificate of analysis (COA) for (b) (4) 13 mm stoppers (COA-NO (b) (4) for 13 mm (b) (4) Stopper - attached to Section 3.2.P.7 Container Closure System) that these stoppers are indicated as (b) (4) – sterilized (ready to use). We also note that (b) (4) stoppers are (b) (4) at (b) (4) prior to use in the filling of voretigene neparvovec DP in (b) (4) (Section 3.2.P.7 Container Closure System and pages 69-71 /228 of (b) (4) Batch Record submitted with the BLA submission). Therefore, it is unclear why (b) (4) stoppers are sterilized again ((b) (4) at (b) (4)). Please comment and provide a rationale/justification for the additional sterilization of the stoppers prior to use in DP and Diluent manufacturing.

Spark Response 3.9

The correct Certificate of Conformance (CofC) for (b) (4) QC code) stoppers ((b) (4) Quality Certificate - (b) (4) Stopper CofC) is attached. An incorrect CofC for stoppers was previously included in Section 3.2.P.7.1 Drug Product. The stoppers are provided ready to sterilize (RS), they are not already sterilized. (b) (4)

Reviewer Comment: *Addressed.*

An incorrect COA for stoppers was previously included in Section 3.2.P.7.1 Drug Product. The correct one is provided as noted in the response.

3.10. It is also unclear from the information provided in the BLA submission whether sterility test result on the COA of the (b) (4) stoppers (b) (4) at (b) (4) has been verified for the use in voretigene neparvovec DP manufacturing. Please comment. If not verified, please provide a justification/rationale.

Spark Response 3.10

Sterility test details (from (b) (4)) have been provided.

- (b) (4) INV380-01 - Microbiological Validation of (b) (4) Sterilisation is attached. This initial validation was executed using 20mm (b) (4) Stoppers ((b) (4)). Spark uses the 13mm version of these stoppers.

- (b) (4) INV380-02 - Microbiological Validation of (b) (4) Sterilisation is attached. This is the re-validation, using 20mm “Flip Tear Up” overcaps. (b) (4) approach is to rotate (b) (4) items through the validation program.

Reviewer Comment: *Because the validation reports are provided for 20 mm stoppers, additional information was requested on September 5, 2017:*

We note from the information provided in your August 22nd Amendment that a sterilization validation report is provided for (b) (4) of 20mm stoppers. Please provide a justification/rationale for not providing a validation report specific for 13 mm (b) (4) stoppers used for voretigene neparvovec drug product and the diluent.

The response to the IR above was received on October 5, 2017. Refer to the review of October 5th Amendment for the response.

3.11. Please provide a copy of the study performed at (b) (4) to demonstrate that (b) (4) the closed DP container closure system (b) (4).

Spark Response 3.11

(b) (4) **INV473** - Report on the Extent of (b) (4) into (b) (4) Stoppered and Sealed (b) (4) Vials is provided.

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

Reviewer Comment: Acceptable based on the information provided in (b) (4) INV473.

(b) (4) **INV473 - Report on the (b) (4) into (b) (4) Stopped and Sealed (b) (4) Vials**

(b) (4)

(b) (4)

(b) (4)

4. Diluent Manufacturing at (b) (4) :

4.1. Please provide your qualification report for mixing to ensure diluent homogeneity. If diluent mixing process is not qualified, please provide a justification/ rationale.

Spark Response 4.1

No study performed: rationale for not performing. A qualification study has not been performed for mixing formulated Diluent to ensure homogeneity. There are several reasons for not performing a formal mixing study:

(b) (4)

(b) (4)

[REDACTED]

Reviewer Comment: Acceptable because of the reasons/justifications - provided under 4 and 5 of the response.

4.5. It is unclear from the information provided in the BLA submission whether there is AQL sampling for diluent 100% visual inspection. Please comment and provide associated acceptance limits. If there is no AQL sampling, please provide a justification/rationale. Please also indicate the total qualified time for diluent visual inspection and labeling.

Spark Response 4.2

All Diluent vials are 100% inspected in accordance with (b) (4) SOP 1208 – Visual Inspection for Particulate Contamination. The reject limit is (b) (4) of filled vials. There is no AQL sampling due to batch sizes. As stated in the Diluent BMR, there is a cumulative maximum time of (b) (4) permitted between the end of the thawing process, and completing transfer of the inspected and labelled vials to storage at ≤ -65 °C. Specific BMR instruction:

The time the product is held at (b) (4) after thawing must be recorded, during the filling, inspection and packaging processes, and must not exceed a total period of (b) (4).

Reviewer Comment: Acceptable.
100% visual inspection is acceptable based on PMC#1 (regarding AQL and defect categories).
Refer to the “Reviewer’s comment under IR# 3.8 (page 94).

AMENDMENT REVIEW - September 11, 2017

This amendment was submitted in response to the August 18th information request.

1. We note from the information provided in your BLA 125610 that (b) (4) does not monitor non-viable particles in operation during AAV2-hRPE65v2 product filling in (b) (4) because of contamination risk for particle counter with viral aerosols. Under this circumstance, non-viable particle monitoring in operation can be performed during media fill runs, because viral product is not used for media fill. Please incorporate non-viable particle monitoring in operation into your media fill protocol for (b) (4) and provide the revised protocol.

Spark Response 1

(b) (4) has revised the media fill protocol (SPA004, Simulation of SPK-RPE65 Vector or Diluent Manufactures) to include the monitoring of non-viable particles in operation.

Reviewer Comment: Addressed.

The firm provided the requested protocol. This protocol is for media fill runs for up to (b) (4) filled vials and revised to include non-viable particle monitoring in operation when Spark drug product (AAV2-hRPE65v2) is filled in the (b) (4).

The introduction of continuous particle monitoring of the (b) (4) during the filling process is referenced on the following pages: 3, 9, 17-18, 21-22, 46, and 59. Specific instruction for performing particle counting throughout the filling operation is found on pages 46 and 59

“Simulated filling process for up to (b) (4) filled vials”

Product: Simulation of SPK-RPE65 vector or diluent manufactures

Fill (b) (4) : (b) (4); Bulk volume: (b) (4)

-2mL vial, (b) (4) clear COP polymer, RU Vac, Sterile

(b) (4) article: (b) (4) - (b) (4) x 2 ml clear (b) (4) plastic vials (sterile; ready to use)

-13mm (b) (4) injection stopper

(b) (4) article: (b) (4) Grey)

-13mm US Green ‘Flip-off’ button long seal overcap

(b) (4) design: (b) (4)

On page 46 (out of 82): In process particle counting

(b) (4)
[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

September 27-29 e-mail Communication

With a September 27th e-mail, a detailed description for sealable foil pouch is requested (not an information request; *refer to the original e-mail uploaded in EDR*). This foil pouch is used to overwrap the carton (secondary packaging) containing container closure systems (*refer to September 25th Amendment*).

The following information is provided:

The foil pouch (images attached) is sourced by (b) (4) from a third party vendor in the (b) (4)

1. The pouch is made of a retortable aluminum foil laminate, approximate thickness is 0.101 mm.
 - a. The tensile strength is (b) (4)
 - b. Provides protection from permeability of oxygen, water vapor, and light
 - i. Permeability of other gasses not evaluated
 - c. The pouch is a non-sterile secondary packaging component
 - d. The pouch is suitable for chilling and is utilized at ultra-low temperatures
2. The pouch is supplied to (b) (4) pre-sealed on three sides. After insertion of the carton, the open side is sealed at (b) (4) using a bar heat-sealer
 - a. (b) (4) visually confirms integrity of the seal during packaging operations
3. The foil pouch will be evaluated for damages before and after shipments during the drug product shipping validation, which will include shipping of Drug Product and Diluent in the final packaging configuration (within the pouch) from (b) (4) to Spark Therapeutics.
 - a. The final report for the Drug Product shipping validation will document the condition of all packaging components comprising the final packaging configuration, including the foil pouch

Comment: *It is unclear from the information provided whether (b) (4) into the sealed pouch. This was clarified in the November 2, 2017 Amendment. Pouch (not padded) is made of aluminum which conducts heat better than plastics.*

AMENDMENT REVIEW - September 25, 2017

This amendment was submitted in response to the product office IR. Because the information contained in this amendment is also under DMPQ purview, this amendment is also reviewed.

Summary of the information under DMPQ purview:

The following is a description of the overall packaging configuration:

- Two Drug Product vials and one diluent vial are placed in the tray which is subsequently placed in a carton (secondary package)
- A prescribing information insert is laid on top of the vials and the carton is closed
- The closed carton is placed in a foil pouch and sealed
- 30 foil pouches are placed in a payload box
- The payload box is placed in a pre-qualified (b) (4) shipper with an electronic temperature monitor and (b) (4)



The other packaging materials (i.e. foil pouch, payload box, etc.) are on order pending delivery and photographs are currently not available to Spark. Spark will provide photographs of the final packaging configurations including all components in the final validation report.

(b) (4)

[Redacted text block]

Larger Payload

(b) (4)

[Redacted text block]

Smaller Payload

(b) (4) [Redacted text block]

(b) (4)

Spark anticipates that a final report summarizing the results of the Drug Product shipping validation will be provided no later than November 30th. Should the anticipated date change due to unexpected events, Spark will provide an update to the FDA accordingly.

Comment: The configurations described above are acceptable. Because the shipping validation protocol was handled by the product office, the review and evaluation of associated amendment is deferred to the product office reviewers.

AMENDMENT - October 5, 2017

This amendment was submitted in response to the DMPQ IR dated September 5, 2017

1. Regarding drug product and diluent shipping validation:

We note from the information provided in your BLA 125610 that no shipping validation was conducted for the drug product and diluent - filled into their primary container closure systems at (b) (4). Please provide a shipping validation protocol for voretigene neparvovec (AAV2-hRPE65v2) drug product and the diluent along with associated validation data. Shipping validation should be performed with the actual primary container closure system used in PPQ lot and commercial manufacturing. Because the diluent primary container closure system is the same as that of the drug product (2 ml (b) (4) vial, 13 mm (b) (4) chlorobutyl stopper with (b) (4) seal), shipping validation can be performed with the diluent in its primary container closure system if there is no sufficient drug product at this time (by information request due date). Shipping validation protocol for the diluent should include at least the following:

1.1. Detailed description of the diluent primary container closure system and contents of the shipping container (e.g., number of diluent vials, dimensions of the shipping container, amount of (b) (4), temperature monitoring device, and others if any).

Spark Response 1.1

A detailed plan for Drug Product shipping validation has been provided in previous 1.11.1 IR response (sequence 0029).

1.2. Detailed description of shipping conditions (e.g., shipping by air in cabin, frozen diluent at <65° C, and shipping temperature, pressure and duration) and monitoring. We recommend that three shipments be considered for the validation studies and actual and worst case shipping conditions be challenged in the shipments.

Spark Response 1.2

FDA has indicated that they accept this Spark's shipping validation plan and Spark is committed to providing a final report to the agency by November 30, 2017.

1.3. Detailed description of inspection and testing being performed upon delivery of the shipping container. For the diluent shipping validation, testing should include for, but not limited to, primary container closure system integrity, pH and appearance. Container closure system integrity (CCIT) can be evaluated with (b) (4) into the primary container closure system, because shipment is (b) (4).

Spark Response 1.3

Spark has conducted a study to assess the potential (b) (4) into the Drug Product container closure system after storage (b) (4). (b) (4) Container Closure Integrity Program: (b) (4) Post-Storage Over (b) (4), LTN 40961. (Module 3.2.P.7 Drug Product) The study was performed employing a (b) (4) test method for confirming the container closure integrity of the client 2mL (b) (4) vial packages with (b) (4) and (b) (4) target fill volumes post-storage over (b) (4). The fill volumes represent the target fill volumes for Drug Product and Diluent vials. The study considered potential (b) (4) after storing in a (b) (4) shipper for a period of at least (b) (4). The study concluded that (b) (4) was observed in the Drug Product container closure system following storage (b) (4).

Reviewer Comment on Response 1.3.: *In the original BLA submission LTN 40961 was not referred/cited in any way (just included in Section 3.2.p7 folder) to be evaluated. In response to this IR, it is referred for intended use qualification. This technical report is acceptable for the validation of CCIT for the vials stored (b) (4). Refer to the review of this report within this memo under “Container Closure System” (in prior to “Stability” section).*

1.4. Please also provide a shipping validation protocol with the same information above for voretigene neparvovec drug product along with product testing plan. If associated data is not available, please provide a date for submitting validation data. Alternatively, if the diluent and product are shipped in the same shipping container, you may combine the protocols.

Spark Response 1.4

FDA has indicated that they accept this Spark’s shipping validation plan and Spark is committed to providing a final report to the agency by November 30, 2017.

1.5. If secondary packaging and labeling will be performed at (b) (4) in (b) (4) and then shipped to US, your shipping protocol may also need to include transport for secondary packaging. For example, it should include type of transport (ground or air) and transport time and conditions from (b) (4). In this case, the primary container closure system in its secondary package will be shipped from (b) (4) to US. If there is any additional transport in US, then that may also need to be included in the shipping validation. If any of these additional transports are not incorporated in your shipping validation, please provide a rationale /justification.

Spark Response 1.5

A detailed plan for Drug Product shipping validation has been provided in previous 1.11.1 IR response (sequence 0029).

Reviewer Comment on the IR#1: *Shipping validation report would be provided by November 30, 2017. CCIT for shipping validation is not requested following an internal discussion. Instead, additional information on CCIT methods and their validations were requested on*

September 25, 2017 (response due October 12, 2017). Because the shipping validation protocol was handled by the product office, the review and evaluation of associated amendment is deferred to the product office reviewers. Note Shipping validation study report became a PMC (PMC request by the product office)

DMPQ IR due October 16, 2017

1. Please clearly indicate container closure integrity test (CCIT) method (s) used for the drug product and diluent container closure (CC) systems (used for PPQ lot and commercial manufacturing). Please also indicate CCIT conditions along with acceptance criteria for testing. If CCIT method used for CC systems stored at (b) (4) (such as CCIT used for stability studies) is different than that for CC systems stored (b) (4) , please ensure that CCI testing conditions and acceptance criteria are indicated for each of the test methods used.
2. We cannot locate validation report (s) for CCIT method (s) used in the integrity evaluation of the product and diluent CC systems – stored (b) (4) . Please provide those validation reports (including protocol and data). Please ensure that CCIT method validation (s) are conducted with voretigene neparovec drug product and/or its diluent under appropriate conditions that represent actual manufacturing conditions (such as with CC systems used in PPQ / commercial lot manufacturing and stored at (b) (4) etc.).
3. Please also compare the (b) (4) values used at (b) (4) filler with the data presented in the (b) (4) (tr-2010-014.pdf which is provided in the submission).

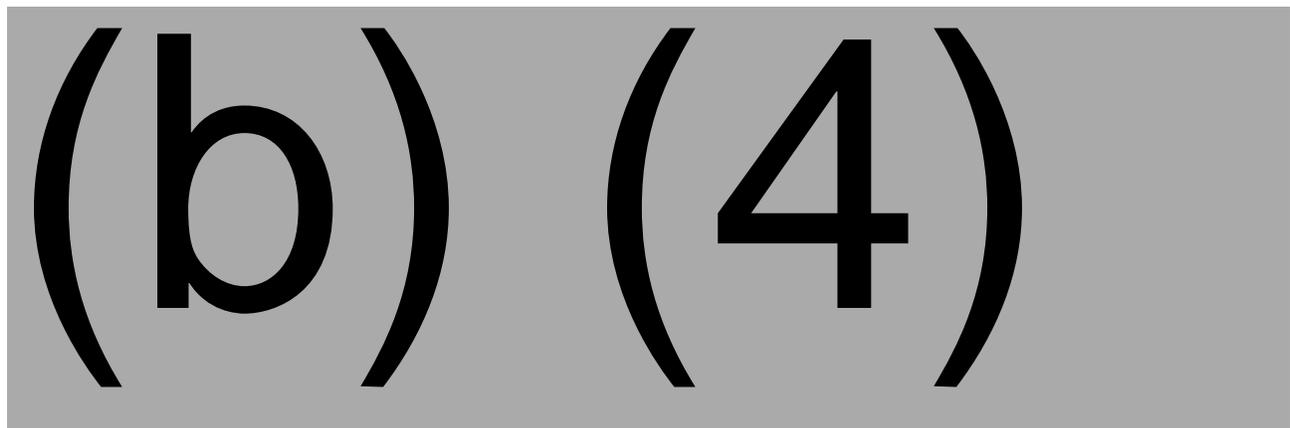
2. Regarding the information provided in the August 11nd Amendment:

2.1. Please provide a detailed description of the equipment present in (b) (4) during voretigene neparovec drug product and diluent filling (in Filling Suite (b) (4)).

Spark Response 2.1

Photographs of a (b) (4) were provided in a previous 1.11.1 IR response (sequence 0017). A detailed description of the equipment present in the (b) (4) during Drug Product and Diluent filling is provided in Table 1 and Table 2.

Table 1. Equipment for Use in Filling (b) (4)



(b) (4)

Table 2 Equipment for Use in Transfer (b) (4)

(b) (4)

Reviewer Comment: *Addressed.*

Major equipment in the (b) (4) (filling) (b) (4) (b) (4). Crimping is performed (b) (4).

2.2. We note that (b) (4) decontamination qualification report is provided only for (b) (4) (b) (4) in response to July 31st information request, not for (b) (4) (b) (4). Please provide a copy of the qualification report (including protocol and data) for (b) (4) (b) (4) decontamination, which was conducted with (b) (4) (b) (4) (summarized under 3.2.A.1.1.3 Equipment in 3.2.A.1 Facilities and Equipment – (b) (4)).

Spark Response 2.2

(b) (4)

(b) (4)

In summary, all acceptance criteria was met and (b) (4) (b) (4)

(b) (4)

3. We note from the information provided in the BLA submission that (b) (4) are also manufactured in (b) (4) (in Filling Suite, (b) (4)). Please provide a copy of qualification reports for cleaning and decontamination of (b) (4) after manufacturing these viruses. If qualification reports are the same as the ones provided for AAV2-hRPE65v2, please provide a scientific rationale/justification for using the same validation protocols/procedures.

Spark Response 3

Three separate decontamination studies have been performed, see Table 3. For each viral product, all product contact parts are either dedicated or disposable and destroyed via clinical waste after filling and (b) (4). Only large pieces of equipment (i.e. balances) are cleaned and reused, none of these items are product contact.

Table 3. Decontamination Studies/Investigational Validation

Investigational Validation		
Doc #	Version	Title
INV444	1	Decontamination Study: Investigation into the (b) (4) of AAV Vector RPE65 for Spark Therapeutics (summarized in TD2016-033)
INV497	1	Investigating the (b) (4)
INV551	1	Decontamination Study: Investigation into the Effectiveness of decontamination after (b) (4)

Reviewer Comment: *Acceptable, because the firm evaluated (b) (4) used for decontamination on the inactivation/decontamination of (b) (4).*

(b) (4)

INV497: *This study investigates the (b) (4)*
Decontamination raw data is provided and appear to be acceptable, but no conclusion is made for this study.

INV551: This study utilizes a methodology similar to the one used in INV497. This study concludes that a (b) (4) procedure of (b) (4) is sufficient to inactivate the virus on stainless steel, PVC and glass surfaces.

4. We note from the information provided in your August 22nd Amendment that a sterilization validation report is provided for (b) (4) of 20mm stoppers. Please provide a justification/rationale for not providing a validation report specific for 13 mm (b) (4) stoppers used for voretigene neparvovec drug product and the diluent.

Spark Response 4

There is no specific validation report for 13mm stoppers. The (b) (4) vial stoppers is determined by the (b) (4), regardless of the specific size of stopper. All stoppers whether 13mm or 20mm, are (b) (4) into the same type and size of box, following SOP1183, Packaging and (b) (4) Requirements for Materials Sterilized by (b) (4), and receive the same (b) (4) at (b) (4). (b) (4) certificates for the 13mm stoppers (SKM_C30817092208070 and SKM_C30817092208090), (b) (4) item (b) (4), are provided. The (b) (4) certificates indicate that the 13mm stoppers used in the manufacture of Spark Drug Product and Diluent received the same (b) (4), as the 20mm stoppers.

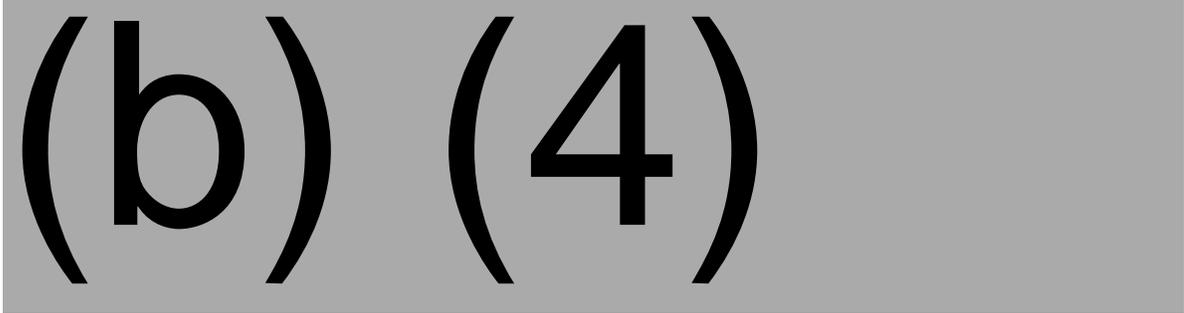
Reviewer Comment: *Acceptable, because the validation based on the size and type of (b) (4) box. Note that the type and size of the (b) (4) box packed with 20mm stoppers are the same as those of the box packed with 13mm stoppers. The stoppers are packaged in small cardboard boxes ((b) (4)).*

Information from INV380 for qualified (b) (4) of stoppers (refer to August 22, 2017 Amendment):

This validation study was performed in accordance with ISO11137-2- 2013 and demonstrates that the (b) (4) for injection stoppers (as defined in SOP1183 and SOP1153) provides a sterility assurance level (b) (4).

The 20mm (b) (4) stoppers were inspected and then packed in packs of (b) (4). They were (b) (4)

(b) (4)



5. During the pre-license inspection of your drug substance manufacturing site from August 21 to August 25, 2017, for commercial manufacturing, you initiated a change for the (b) (4) . You indicated that the (b) (4) . Please provide the following information for this change:

5.1. A copy of the document created per your change control SOP for the (b) (4) :

Spark Response 5.1

As discussed during the PLI, Change Control CC17-072 was executed to capture the change of the (b) (4) . Additionally, Change Control CC17-079 was executed to further align the operational procedure and parameters utilized at (b) (4) for the voretigene neparvovec Drug Product.

Reviewer Comment: *Addressed. This change for the (b) (4) step in the drug substance manufacturing is an improvement, because operating parameters (b) (4) . Evaluation of the information on (b) (4) to this filter is deferred to the product office.*

The (b) (4) was changed in A2B1 RPE65 Rev 4 .0 (effective 08May2017) via the DCR to a (b) (4) catalog number (b) (4) . Spark Material Specification Sheet number 10131 (Refer to Attachment 1). The (b) (4) specifications are summarized as follows (refer to Attachment 2 for (b) (4) Specifications Sheet)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

5.2 A copy of COA for the new (b) (4).

Spark Response 5.2

(b) (4) is a copy of the COA for the (b) (4).

Reviewer Comment: *Addressed.*

5.3. Established operating conditions/ranges for the new (b) (4)

Spark Response 5.3

This is described in CC17-079

Reviewer Comment: *Acceptable because the (b) (4) is qualified for the (b) (4) and operating conditions are similar those used at (b) (4).*

-CC17-079 change control document describes (b) (4) procedures, which appear to be similar to the (b) (4) procedures performed at (b) (4) (contract DP manufacturing site located in UK). In any case, impact of this change (not likely there would be any impact) may need to be assessed with one DS lot manufactured using the new (b) (4) (refer to IR# 5.5). Evaluation of the need for this assessment is deferred to the product office.

5.4. A copy of the revised batch record for the (b) (4) of the drug substance using the new (b) (4) at Spark Therapeutics, Inc.

Spark Response 5.3

A copy of the updated batch record pages is included in CC17-079.

Reviewer Comment: *Addressed.*

Note that the information under IR#5 was requested to gather supporting information for the (b) (4) change (IR 5.1-5.5) to be reviewed for approval under this BLA

5.5. Available data from currently ongoing commercial drug substance manufacturing.

Spark Response 5.5

The Drug Substance lot that was in progress during the PLI has just completed. No results are currently available.

Reviewer Comment: Because there is no manufacturing data available for this change, supporting data could be followed up either during next routine inspection or by the product office in an annual report. In any case, release specifications for commercial lots manufactured with this change/using the (b) (4) need to be met. In summary, evaluation of any commercial lot manufactured with this change is deferred to the product office if the product office does not have any issues with this change.

AMENDMENT REVIEW - October 16, 2017

(in response to IR on September 25, 2017)

1. Please clearly indicate container closure integrity test (CCIT) method (s) used for the drug product and diluent container closure (CC) systems (used for PPQ lot and commercial manufacturing). Please also indicate CCIT conditions along with acceptance criteria for testing. If CCIT method used for CC systems stored at (b) (4) (such as CCIT used for stability studies) is different than that for CC systems stored (b) (4), please ensure that CCI testing conditions and acceptance criteria are indicated for each of the test methods Used.

Spark Response 1

CCIT was not a release test for the Drug Product and Diluent PPQ lots and is not an intended release test for commercial batches of Drug Product and Diluent. Drug Product and Diluent are tested for sterility as part of release testing.

The 2mL (b) (4) vial, 13 mm (b) (4) serum stopper and 13 mm (b) (4) Flip Off seal (container closure system for Drug Product and Diluent) were assessed for CCIT in supporting (b) (4) studies referenced in Module 3.2.P.7.4.

The (b) (4) study Technical Report 2010-014 for (b) (4) 2 mL RU Vial-Ready Pack Stopper CCI Evaluation demonstrated CCI using a (b) (4) method. The (b) (4) study Container Closure Integrity of Rubber-stoppered Glass and Plastic Vials Stored at (b) (4) demonstrated that CCI was maintained under cold conditions, including (b) (4) storage utilizing (b) (4) analysis to measure (b) (4) of vials.

The CCIT performed for the PPQ lot is driven by its stability programs, which utilize CCIT in lieu of sterility. CCIT is performed in the Drug Product and Diluent stability programs, by (b) (4) services, utilizing the (b) (4) method. This method is utilized to assess the integrity of a pharmaceutical package by (b) (4). The method is applicable to all container/closure systems comprised of elastomer stoppers secured to containers with crimped aluminum seals as detailed in (b) (4) Method Summary and (b) (4) Validation Summary (VR-111).

Reviewer Comment: Acceptable.

- The firm did not address the IR, because there are no testing conditions indicated along with acceptance criteria. Instead, the same information provided in the original BLA is repeated. It appears that the firm wants me to figure it out (did as follows).
- In the IR, CCIT is not indicated as a release test. Therefore, 1st paragraph in the response is not relevant either. Also, note that this method is not indicated anywhere in the original BLA and associated validation report is not included in the BLA submission.

Selbty-28 R0 Validation Summary (VR-111) addresses the question in the IR, because this validation is conducted for the CCIT/(b) (4) Testing method for the CC system used for the drug product and diluent (2 ml (b) (4) vials + 13 mm (b) (4) rubber stoppers). Note that this test method was also used for the same CC system approved under BLA 125518/0 (refer to the review memo for BLA 125518/0) and the applicant for BLA 125518/0 clearly indicated acceptance criterion and testing conditions. In the previously approved BLA 125518/0, the acceptance criterion for the (b) (4) was reported as (b) (4) as a **pass/fail criterion** for (b) (4) Testing to differentiate non-defective and defective samples by the (b) (4) test. Note that this criterion is the same as what is established with VR-111 Validation by (b) (4) (submitted with this Amendment). In summary, any samples having the (b) (4) of (b) (4) at (b) (4) will be rejected according to the pass/fail criteria. And, Spark should have extracted this acceptance criterion from the validation report in response to the IR.

Document Number: VR-111

Method Title: Report for the Validation of 2ml (b) (4) containers at (b) (4) for use with (b) (4)
Standard Test Method (b) (4); **Revision:** 0; **Effective Date:** 28 March 2013

Validation Summary

The validation for (b) (4) was based off of (b) (4) Testing on Pharmaceutical Packaging" which had been previously validated and reported following an approved validation plan.

(b) (4) method validation was executed using protocol VP-108 and focused on testing (b) (4) containers at (b) (4). The validation parameters detailed included method precision of (b) (4) and intra-laboratory precision. The Method precision and intra-laboratory precision were demonstrated on 2 ml (b) (4) vials using 13 mm. (b) (4) rubber stoppers.

The data generated provides sufficient substantiation that the analysis of 2 ml (b) (4) vials can be determined using (b) (4) detection at (b) (4).

Through this validation, a new failing (b) (4) was established using the (b) (4)

All the fills are done at (b) (4).

(b) (4)

The apparatuses, reagents, and instrument parameters are detailed in the report and subsequent method. The report and method also include details of sample preparation and instrument set up.

2. We cannot locate validation report (s) for CCIT method (s) used in the integrity evaluation of the product and diluent CC systems – stored at (b) (4) . Please provide those validation reports (including protocol and data). Please ensure that CCIT method validation (s) are conducted with voretigene neparvovec drug product and/or its diluent under appropriate conditions that represent actual manufacturing conditions (such as with CC systems used in PPQ / commercial lot manufacturing and stored at (b) (4) etc.).

Spark Response 2

The (b) (4) CCIT study is included in Module 3.2.P.7.4, (b) (4) Analysis Container Closure Integrity Program: (b) (4) Post-Storage (b) (4) (LTN 40961). This study was a supporting study, conducted as confirmation of what the (b) (4) reports concluded for the container closure system stored (b) (4) . In the (b) (4) study, Spark included vials prepared at (b) (4) to demonstrate consistency to what was found in the laboratory setting. The study employed a (b) (4) test method for confirming the CCI of the 2 mL (b) (4) vial packages with (b) (4) and (b) (4) target fill volumes (corresponding to Drug Product and Diluent fill volumes) after storage (b) (4) . Results of the study confirmed CCI of the 2 mL (b) (4) vials post storage (b) (4) conditions.

Reviewer Comment: *Addressed.*

- Validation information for the storage (b) (4) to support shipping is submitted with the original BLA, but was not cited/ referred in any section of the submission. It is noted in and reviewed with this amendment. Refer to the review of LTN 40961(validation

report) under “Container and Closure System” section before the diluent manufacturing section within this memo.

The validation (LTN 40961) is acceptable. Because there is no secondary package and sealable pouch used in this validation study, testing conditions represent the worst case conditions for shipping. Note that this CCIT is not included in the shipping validation report.

- The validation report for the CCIT method used for stability studies in lieu of sterility is submitted with this amendment upon request. The validation is acceptable. This report indicates the acceptance criterion and testing conditions for the (b) (4) testing as documented under IR#1 above.
3. Please also compare the (b) (4) values used at (b) (4) filler with the data presented in the (b) (4) (tr-2010-014.pdf which is provided in the submission).

Spark Response 3

(b) (4)

[Redacted]

Reviewer Comment: Acceptable.

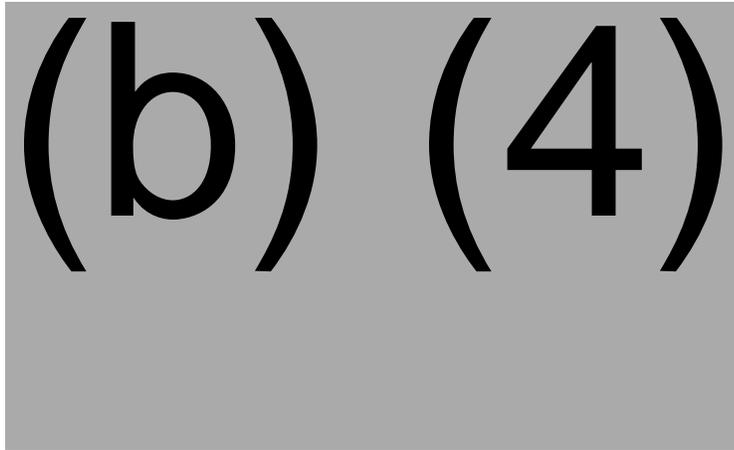
The following information is from the Internet:

(b) (4)

[Redacted]

[Redacted]

[Redacted]



Communication with the Firm

(via e-mail, tcon etc.)

Communications with Spark on CCIT (October 24-20, 2017) and sealable pouch (September 29-27, 2017 and October 25, 2017) are uploaded in EDR.

Reviewer's evaluation of the information discussed via e-mails:

- Note that the validation studies for (b) (4) to support shipping of the drug product and its diluent were conducted (b) (4) and is not used as a sterile barrier. Because the validation studies are performed under a worst case condition such as without a pouch (made of a retortable aluminum foil laminate, which does not have any padding/insulation material that interfere with cooling) and secondary package, no further question would be raised for the validation of packaging sealing and (b) (4) into the pouch. Note that aluminum foil is a good conductive material, which is suitable for chilling and heating (its heat transfer properties are better compared to carton and plastics). Also note that the data for CCIT showed that the CC system integral even without the capping (refer to).
- For additional information on secondary package (product and diluent trays in carton box), foil pouch and payload box, refer to the September 25, 2017 Amendment and its review within this memo.
- Note that information on shipping validation is being submitted by November 30, 2017 in response to the information requests from both the product office and DMPQ (September 5th DMPQ IR). Also note that DMPQ decided not to ask for CCIT testing for shipping validation (based on the DMPQ internal communication for the use of a pouch and CCIT validations conducted to support shipping). In any case, (b) (4) of the drug product that would be evaluated for shipping will indicate whether there is any (b) (4), because (b) (4). Evaluation of the shipping validation with respect to (b) (4) and other quality attributes (included in the shipping validation protocol) is deferred to the product office reviewers.
- Note shipping validation study report became a PMC (request by the product office)

AMENDMENT REVIEW – November 02, 2017

1. You indicated in your October 25th 2017 e-mail that the sealable foil pouch is utilized to (b) (4) during product shipments. However, this intended use is not indicated in the original BLA submission and any of its amendments. Please provide a clear description of your intended use for the pouch along with associated validation information (including validation protocol summary and data). If the intended use is not validated, please provide your plans and a timeframe for validating.

Spark Response 1

Although the sealable foil pouch provides (b) (4), it is not a secondary packaging component required for product integrity. Included in Module 3.2.P.7.4, primary component container closure integrity (CCI) has been demonstrated through Spark-executed studies (LTN 40961—(b) (4) Container Closure Integrity Program: (b) (4) Post-Storage (b) (4) and INV473—Report on the (b) (4) Stopped and Sealed (b) (4) Vials), as well as several (b) (4)-referenced studies. Additionally, CCI is monitored and confirmed as part of the Drug Product and Diluent stability programs. The supplier, (b) (4), performs release testing and provides a declaration of compliance and specification sheet for each lot. In addition, to verify strength and integrity, (b) (4) testing is performed on a sample (b) (4) from the start of each box of (b) (4) produced. At (b) (4), the labeled vials of voretigene neparovec and Diluent are placed into a carton (which is also labeled), the package insert is added, and the contents are placed into the three-sided foil pouch which is then heat-sealed and labeled. A shipping validation study on the packaged product is currently in execution. The pouch and all packaging components will be 100% visually inspected (post-shipment) for the presence of damage and/or effects. (b) (4) will not specifically be evaluated as part of this study however, product quality will be measured. Results of the shipping validation will be provided on 30 Nov 2017 as previously committed.

Reviewer Comment: Acceptable, because:

- I agree with the firm that this pouch will not contribute to CC integrity, because LN40961 has demonstrated that CC system is integral even without secondary packaging components. Note that a CCIT method ((b) (4) test method) was validated under worst case conditions for the CC system stored (b) (4) to support shipping studies (refer to LTN 40961), because secondary packaging components (e.g., carton box and sealable pouch) were not used. For additional information on the validation of the (b) (4) test method (LTN 40961), refer to section “Container and Closure System” within this memo.
- Sealable pouch is not used as a sterile barrier

- The firm implies that shipping validation results for quality attributes are sufficient. I agree with this as well, because (b) (4) (which will be evaluated for shipping).

AMENDMENT REVIEW – November 15, 2017
(in response to September 5th IR due November 12, 2017)

1. Please provide data (results of EM and media fill) from the media fill run being executed September 26 through October 10, 2017. Please ensure that non-viable particle monitoring in operation (as you agreed in the e-mails dated August 29 - August 31, 2017) will be performed during this media fill run.

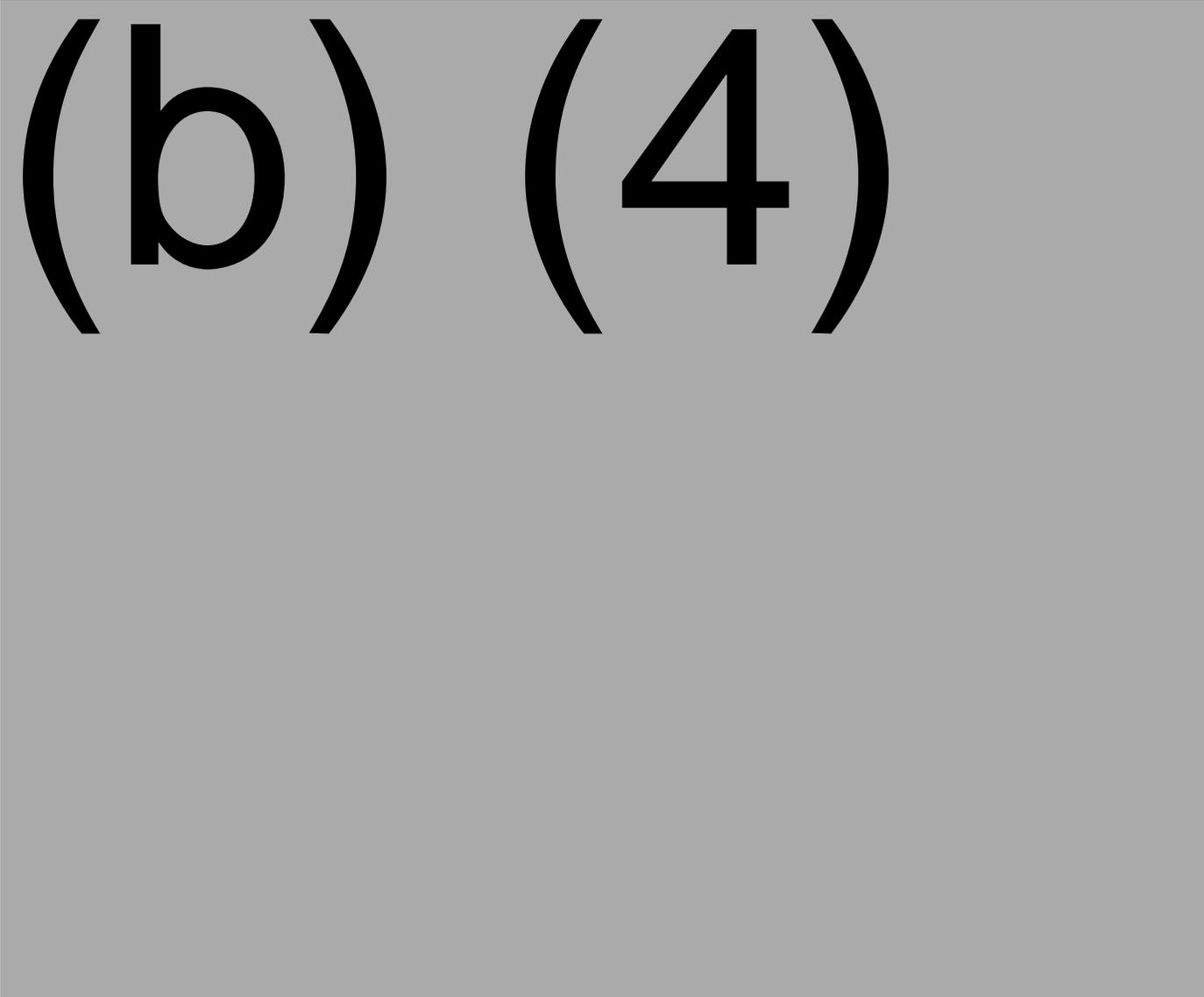
Spark Response 1

(b) (4) performed a media fill for Spark Therapeutics on October 5, 2017, lot number (b) (4). EM and media fill results are included in (b) (4) **Media Fill Microbiological Report. Continuous non-viable particle monitoring in operation was performed during this media fill.** Particle counting data is included as (b) (4) Media Fill Particle Count Data (b) (4). Particle counting results and an assessment of the data are detailed in (b) (4) Fill Particle Rationale.

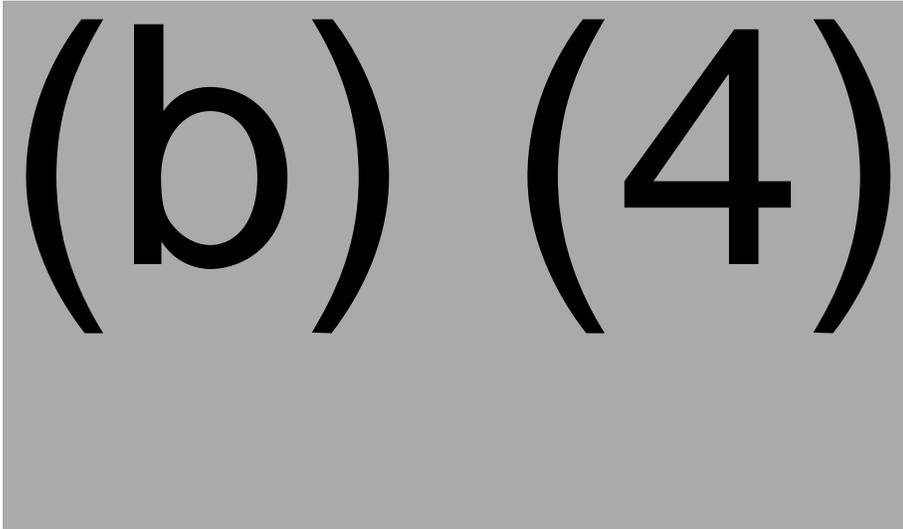
(b) (4) performed a media fill for Spark Therapeutics on October 5, 2017, lot number (b) (4). EM and media fill results are included in (b) (4) **Media Fill Microbiological Report.** Continuous non-viable particle monitoring in operation was performed during this media fill. Particle counting data is included as (b) (4) **Media Fill Particle Count Data** (b) (4). Particle counting results and an assessment of the data are detailed in (b) (4) Media Fill Particle Rationale.

Reviewer Comment 1: EM and media fill results are acceptable, except for the results of non-viable particle monitoring in operation. Refer to the OCBO assessment for the results of non-viable particle monitoring in operation below.

From (b) (4) **Media Fill Microbiological Report:**



(b) (4) *Media Fill Particle Count Data* (b) (4) :



Reviewer Comment 2 (on results of continuous non-viable particle monitoring):
Acceptable based on the OCBQ assessment and the results of particulate matter testing at release and during the DP filling (refer to Tables 24 and 25 in this memo).

(b) (4) [Redacted text block consisting of multiple lines of greyed-out content]

- The issue summarized above was internally discussed (OCBQ):

As the materials (b) (4) that are generating particles have been sterilized, there shouldn't be an issue of contamination (microbial). As for particulate monitoring in general, there seems to be some question on whether it is necessary beyond the initial qualification, however it would be useful to show whether there was a problem with the HEPA or (b) (4) filter – especially when the particulate monitoring is continuous. With (b) (4), there are clear ups and downs in the particulate counts which suggest that it is due to manipulations (b) (4), not a problem with the (b) (4) ability to maintain aseptic conditions. This, along

with the media fill data and passing product particulate testing results according to (b) (4), should allow us to justify the spikes in particulate levels without requiring additional controls at this time.

Reviewer Final Comment: *The response is acceptable.*

OTHER AMENDMENTS

Amendments pertaining PLI:

- SOPs and forms provided in the August 8th Amendment was requested for pre-inspection preparation. Those SOPs were evaluated during the PLI.
- A copy of SOPs provided in the November 22nd Amendment was requested by Cecily Jones to write up her sections for EIR. Those SOPs were evaluated during the PLI
- Spark's response to 483 observations was submitted in the September 8th Amendment and memo evaluating the response was uploaded in the EDR

Comment: *Note that the shipping validation that was supposed to be submitted by November 30, 2017 has become PMC.*