

BLA STN #125610/0

Proper (non-proprietary) name:

voretigene neparvovec-rzyl

Proprietary name:

LUXTURNA

Manufacturer:

Spark Therapeutics, Inc.

Reviewers:

Lilia Bi, Ph.D.

Zenobia Taraporewala, Ph.D.

Robert Aksamit, Ph.D.

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Supervisory Reviewer:

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OTAT/CBER

DCGT CMC Review Data Sheet

1. **BLA#:** STN 125610
2. **REVIEW DATE:** December 8, 2017
3. **PRIMARY REVIEW TEAM:**
Medical Officer: Yao-Yao Zhu, MD
Medical Consult: Wiley Chambers, MD
Epidemiological Reviewer: Bethany Baer, MD
Pharm/Tox: Wei Liang, PhD
Product Quality: Lilia Bi, PhD; Zenobia Taraporewala, PhD; Robert Aksamit, PhD; Angela Whatley, PhD
DBSQC: Karla Garcia
Facilities: Rabia Ballica, PhD;
BIMO Reviewer: Carla Jordan
Statistics: Annie Lin. PhD
Labeling: Dana Jones
Lot Release: Marie Anderson, PhD.
RPM: Nevitt Morris, RN

4. **COMMUNICATIONS WITH APPLICANT AND OTAT:**

Communication/Document	Date
BLA Acknowledgement	May 26, 2017
BLA Filing Notification	July 14, 2017
Mid-Cycle Meeting	September 14, 2017
Late-Cycle Meeting	November 7, 2017

5. **SUBMISSION(S) REVIEWED:**

Original Submission and CMC amendments	Date Received	Review Completed (Yes/No)
Original submission	5/16/2017	Yes
Amendment #4	6/22/2017	Yes
Amendment #6	7/13/2017	Yes
Amendment #7	7/26/2017	Yes
Amendment #9	7/28/2017	Yes
Amendment #11	8/9/2017	Yes
Amendment #13	8/11/2017	Yes
Amendment #14	8/14/2017	Yes
Amendment #16	8/17/2017	Yes
Amendment #18	8/25/2017	Yes
Amendment #25	9/14/2017	Yes
Amendment #26	9/14/2017	Yes
Amendment #29	9/20/2017	Yes
Amendment #30	9/25/2017	Yes

Amendment #31	10/3/2017	Yes
Amendment #34	10/11/2017	Yes
Amendment #37	10/30/2017	Yes
Amendment #38	11/1/2017	Yes
Amendment #41	11/7/2017	Yes
Amendment #42	11/13/2017	Yes
Amendment #43	11/15/2017	Yes
Amendment #44	11/15/2017	Yes
Amendment #46	11/17/2017	Yes
Amendment #48	11/28/2017	Yes
Amendment #50	11/30/2017	Yes
Amendment #51	11/30/2017	Yes
Amendment #54	12/4/2017	Yes
Amendment #55	12/5/2017	Yes
Amendment #56	12/7/2017	Yes
Amendment #57	12/7/2017	Yes
Amendment #58	12/8/2017	Yes

6. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: LUXTURNA
- b. Trade Name: LUXTURNA
- c. Non-Proprietary/USAN: voretigene neparvovec-rzyl
- d. FDA UNII code: 2SPI046IKD

7. PHARMACOLOGICAL CATEGORY: Adeno-associated virus vector-based gene therapy

8. DOSAGE FORM: Suspension for injection

9. STRENGTH/POTENCY: Supplied concentration is 5×10^{12} vector genomes (vg) /mL. Requires 1:10 dilution prior to administration. Dose for each eye is 1.5×10^{11} vg in 0.3 mL.

10. ROUTE OF ADMINISTRATION: Sub-retinal injection only

11. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference
(b) (4)	(4)	(b) (4)	yes
		Pharmaceutical Closure (Stopper)	yes
		Pharmaceutical Closure (Stopper)	yes

- 12. INSPECTIONAL ACTIVITIES:** Pre-license inspection (PLI) of Spark Therapeutics, Inc. drug substance manufacturing facility was completed on August 25, 2017. PLI of manufacturing facility for drug product, (b) (4) , was waived.
- 13. CONSULTS REQUESTED BY DCGT:** N/A
- 14. PRECEDENTS:** First-in-class
- 15. ADMINISTRATIVE:**

A. Signature Block

Name and Title	Signature and Date
Reviewed by	
Lilia Bi, Ph.D. Chair, Review Committee Biologist, OTAT, CBER	
Zenobia Taraporewala, Ph.D. Biologist, OTAT, CBER	
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Steven Oh, Ph.D., Deputy Director, Division of Cellular and Gene Therapies, OTAT, CBER	
Raj K. Puri, M.D., Ph.D., Director, Division of Cellular and Gene Therapies, OTAT, CBER	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation:

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the new drug product voretigene neparvovec-rzyl. The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics. This information, along with post-marketing commitments (PMC) from Spark Therapeutics, Inc., satisfies the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products.

II. List Of Deficiencies To Be Communicated:

There are no outstanding CMC deficiencies to be communicated. However, the CMC postmarketing commitments agreed by the applicant and listed below in section III, will be communicated.

III. List Of Post-Marketing Commitments:

1. Spark Therapeutics, Inc. commits to provide the shipping validation study protocol for shipment of the Drug Product from the distributor to a clinical site (or to Spark Therapeutics, Inc.) by January 31, 2018. A final study report will be submitted as a “Postmarketing Commitment - Final Study Report” by June 30, 2018.
2. Spark Therapeutics, Inc. commits to complete the verification studies for the following assays:
 - a. (b) (4)
 - b. (b) (4) tests for particulate matter for the Drug Product and Diluent, performed by (b) (4).A final study report will be submitted as a “Postmarketing Commitment - Final Study Report” by March 31, 2018.
3. Spark Therapeutics, Inc. commits to perform an analysis of the lot release test results obtained from all Drug Substance (DS) and Drug Product (DP) lots manufactured within the first (b) (4) following approval, and evaluate if the acceptance criteria for LUXTURNA lot release tests (including the (b) (4)) continue to provide adequate quality control for DS and DP based on the new data obtained from those tests. A final study report will be submitted as a “Postmarketing Commitment - Final Study Report” by March 31, 2020.
4. Spark Therapeutics, Inc. commits to conduct stability studies on the HEK293 Master Cell Bank (MCB) used for drug substance manufacture. (b) (4)

(b) (4)
, “Postmarketing Commitment - Final Study Report” by March 31, 2018.

5. Spark Therapeutics, Inc. commits to qualify the (b) (4). A final study report will be submitted as a “Postmarketing Commitment - Final Study Report” by March 31, 2018.

IV. Review Of Common Technical Document- Quality Overall Summary Module 2:

The common technical document- Quality Overall Summary was reviewed. This section contains an overview of all aspects of the Module 3: Quality including the eCTD structure. Specific CMC issues were addressed within each section under Module 3 throughout this review memorandum.

V. Environmental Assessment or Claim of Categorical Exclusion:

The applicant (Spark Therapeutics, Inc.) submitted an environmental assessment (EA) in accordance with 21 CFR 25 in the original submission and per the recommendations in CBER’s Guidance for Industry (“Environmental Assessment of Human Drug and Biologics Applications” and “Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products”). In the EA, the applicant has estimated that about (b) (4) patients would receive voretigene neparvovec-rzyl yearly after marketing authorization. This would lead to the release of only trace amounts of voretigene neparvovec-rzyl into the environment, due to shedding through tears following patient administration, and this material is degraded into naturally occurring components.

The EA was based on aggregate quantitative data from biodistribution and shedding studies (both preclinical and clinical), lot release testing and related nonclinical studies, and a worst-case assumption in each case. Applicant has considered the known biology of the parental organism, adeno-associated virus serotype 2 (AAV2), the receiving environment, and the genetic modifications made to the product, when assessing the effect on the environment following exposure to voretigene neparvovec-rzyl. Specifically, voretigene neparvovec-rzyl is derived from wild type AAV2 which is non-pathogenic, single-stranded DNA genome-containing virus that is helper virus-dependent. Voretigene neparvovec-rzyl is unable to replicate independently, even in the presence of a helper virus, since it lacks essential genes required for rescue/packaging. The presence of the expression cassette is expected to confer a severe selective disadvantage to the genetically modified vector in the environment compared to wild type AAV2.

The Agency concludes based on the data and analysis presented in the EA, including the description of mitigation measures put in place for transport, product handling and waste treatment, that the potential effects of voretigene neparvovec-rzyl on the environment are negligible. No significant environmental impacts were identified and a finding of no significant impact (FONSI) was prepared.

VI. Primary Container Labeling Review:

Label examples provided in BLA submission:

Luxturna Vial Label:



NDC 71394-065-01
voretigene neparvovec-rzyl
 For subretinal injection
 5 x 10¹² vector genomes/mL
 One (1) single-dose vial, 0.5 mL per vial
 For Rx only; Must dilute before use
 Store at ≤ -65 °C; Discard unused portion
 Manufactured by
 Spark Therapeutics, Inc.
 US License No. 2056

Lot Exp

CLB-P-821-800-20562

Luxturna Diluent Vial Label:



NDC 71394-716-01
 Diluent for voretigene neparvovec-rzyl
 pH 7.3, containing 0.001%
 poloxamer 188
 For Rx only
 1.7 mL per vial; Store at ≤ -65 °C
 Manufactured for Spark Therapeutics
 By Nova Laboratories
 US License No. 2056

Lot Exp

CLB-P-821-800-20563

Luxturna Pouch Label:



NDC 71394-415-01
 Rx only

voretigene neparvovec-rzyl
LUXTURNA™

5 x 10¹² vector genomes/mL. No US standard of potency.
 One (1) single-dose vial of voretigene neparvovec-rzyl, 0.5 mL per vial
 Two (2) vials of Diluent for voretigene neparvovec-rzyl, 1.7 mL per vial
 Store at ≤ -65 °C. Dilute before use. Discard unused portion.
 For administration by subretinal injection
**See package insert for full prescribing information and instructions
 for dosage and administration**

2D
CODE

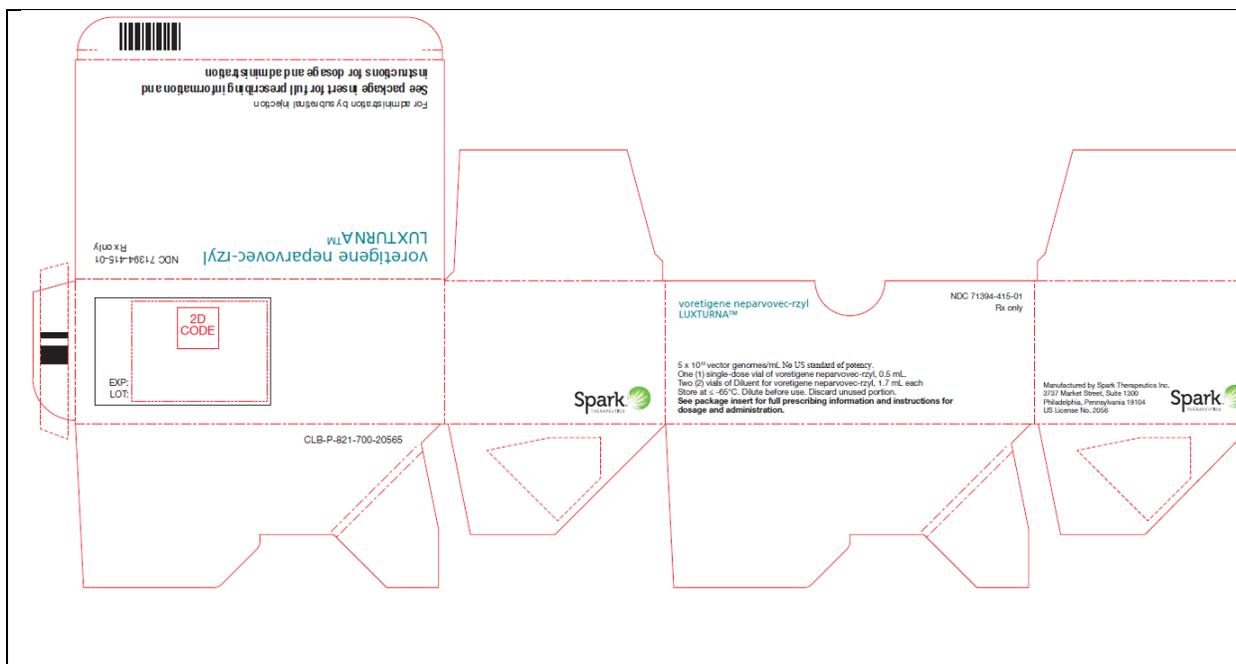
CLB-P-821-800-20564

Manufactured by Spark Therapeutics
 3737 Market Street, Suite 1300
 Philadelphia, Pennsylvania 19104
 US License No. 2056



EXP:
LOT:

Luxturna Carton Label:



VII. Review Of Common Technical Document- Quality Module 3:

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

3.2.S DRUG SUBSTANCE (DS)

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

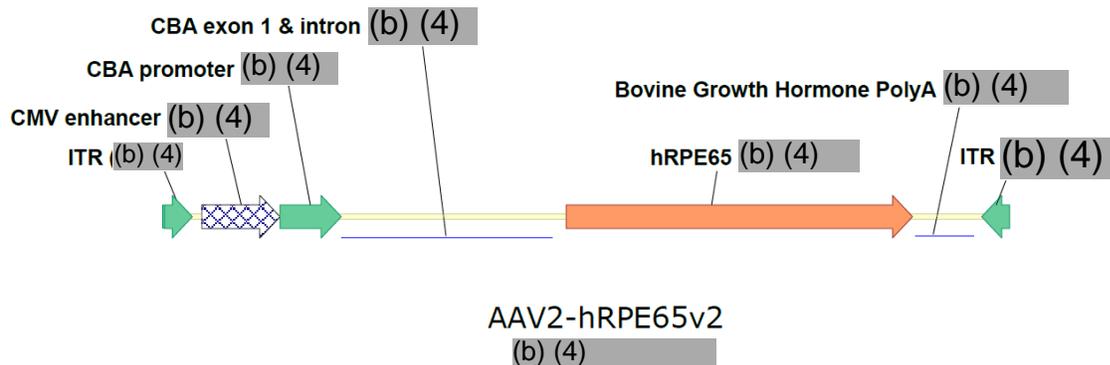
Proper (non-proprietary) name: voretigene neparvovec-rzyl

Proprietary name: Luxturna

3.2.S.1.2 Structure

The voretigene neparvovec-rzyl drug substance is an adeno-associated virus serotype 2-based vector containing the human RPE65 gene expression cassette containing the following components: 1) the cytomegalovirus (CMV) enhancer; 2) the chicken beta actin (CBA) promoter; 3) the CBA exon 1 and intron; 4) the cloned cDNA coding for human retinal pigment epithelium 65kDA protein (hRPE65); and 5) the bovine growth hormone polyadenylation (PolyA) region.

Figure 1. Voretigene Neparvovec-rzyl Vector Genome Diagram



The sequence of the DNA corresponding to the RPE65 transgene corresponds to the known normal human RPE65 sequence (NCBI [gi:67188783]). The annotated nucleotide sequence of voretigene neparvovec-rzyl is provided in BLA.

3.2.S.1.3 General Properties

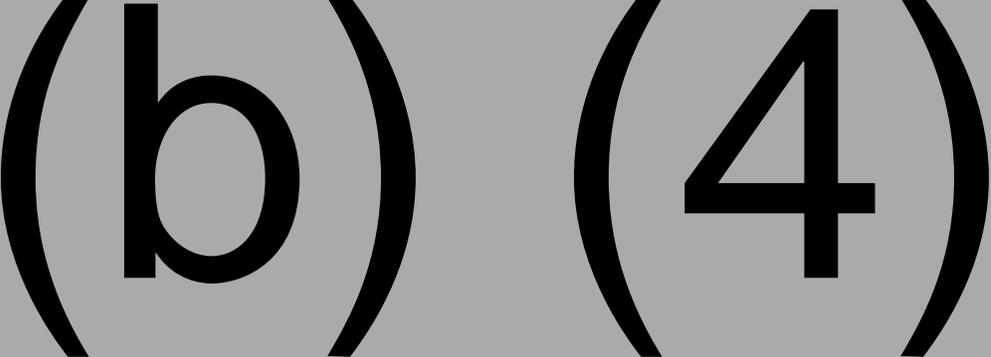
The voretigene neparvovec-rzyl (AAV2-hRPE65v2) drug substance is a clear, colorless solution at a concentration of 5×10^{12} vector genome-containing vector particles per milliliter in water for injection containing 180 mM sodium chloride, 10 mM sodium phosphate, 0.001 % (b) (4) P188. This formulation is slightly hypertonic with respect to normal saline, a feature that is incorporated to (b) (4)

(b) (4). The voretigene neparvovec-rzyl drug product is the same as the drug substance, except for the additional process of sterile filtration and filling in the final container.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Table 1. Voretigene Neparovec-rzyl DS Manufacturers and Testing Providers

Establishment Name, Address and Unique Facility Identifier	Contact Information for Person Responsible for Scheduling Inspections	Specific Manufacturing Operations Being Conducted
Spark Therapeutics, Inc.* 3737 Market Street, Suite 1300 Philadelphia, PA 19104 USA EIN#: 46-2654405 DUNS # 079498241	Paul Gil, Regulatory CMC Lead Phone: (215) 220-9328 E-mail: paul.gil@sparktx.com	Applicant and Drug Substance Manufacturer and Testing Laboratory
		

(b) (4)

*In this review memo, “Spark” is also used as an abbreviation for “Spark Therapeutics, Inc.”

3.2.S.2.2 Description of Manufacturing Process and Process Controls

3.2.S.2.2.1 Lot Scale

(b) (4) drug substance sub-lots ((b) (4)) are pooled and purified into one drug substance lot #(b) (4), which was manufactured into drug product lot #(b) (4).

3.2.S.2.2.2 Description of Manufacturing Process

The process used for manufacture of the voretigene neparvovec-rzyl Drug Substance is based on cell culture and transient transfection of adherent human embryonic kidney epithelial cells (HEK293 cells) with three plasmid constructs encoding: an expression cassette for normal human RPE65; AAV2 rep and capsid sequences; and helper virus-derived sequences required for packaging of the RPE65 cassette in recombinant AAV2 particles.

(b) (4)

[Redacted text block]

Step 1. Cell Culture Expansion:

(b) (4)

[Redacted text block]

(b) (4)
[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

Step 2: Transfection

(b) (4)
[Redacted text block]

(b) (4) [Redacted text block]

Step 3: Medium Exchange

(b) (4) [Redacted text block]

Step 4: Crude Cell Harvest

(b) (4) [Redacted text block]

Step 5: Tangential Flow Filtration ((b) (4))

(b) (4) [Redacted text block]

Step 6: Homogenization and (b) (4)

(b) (4) [Redacted text block]

(b) (4) [Redacted text block]

Step 7: Cation Exchange Chromatography

(b) (4) [Redacted text block]

[Redacted text block]

[Redacted text block]

Step 8: Density Gradient Centrifugation

(b) (4) [Redacted text block]

(b) (4)

Step 9: Buffer Exchange by (b) (4), Formulation and (b) (4) Filtration

(b) (4)

Reviewer comment: During the review and PLI it was discovered that Spark was having difficulty controlling the % of P188 in the final product formulation. To address this concern an advice IR was sent on October 25, 2017 suggesting that to reach the more accurate final P188 concentration, that the applicant (b) (4)

Spark responded in amendment #37 that they agree that the (b) (4)

to achieve a final concentration of 0.001%.

Reviewer's assessment: This is acceptable. No further comment.

Dilution and (b) (4) Filtration

(b) (4)

(b) (4)

Reviewer’s assessment: During batch record review it was noted that the storage temperature on the DS label was written as “Store (b) (4)”, which is not consistent with the proposed storage condition of (b) (4). An IR was sent to Spark on September 1, 2017, requesting that they revise the DS label. Applicant sent revised label in Amendment #25 listing storage temp as “(b) (4)”. A sample label with correct storage temperature is provided. The applicant’s responses are acceptable.

3.2.S.2.3 Control of Materials

3.2.S.2.3.1 Starting Materials

The starting materials for manufacture of voretigene neparvovec-rzyl Drug Substance consist of:

- a mammalian cell substrate (HEK293 Master Cell Bank (MCB))
- three purified recombinant DNA plasmids
 - pAAV2-hRPE65v2 (pCCVC-AAV2-hRPE65v2; Vector Plasmid)
 - pAAV2PKv2 (pCCVC-AAV2PKv2; Packaging Plasmid)
 - pAD2HPv2 (pCCVC-AD2HPv2; Helper Plasmid).

There are COAs provided for the starting materials, and they are reviewed in detail below.

3.2.S.2.3.1.1 Development and Characterization of Master Cell Bank

The HEK 293 MCB used to make voretigene neparvovec-rzyl was obtained by Spark from Children’s Hospital of Philadelphia (CHOP), who had the MCB manufactured under contract by (b) (4). The history of the HEK293 cells is as follows.

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

The MCB:

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

Table 2. Characterization of CHOP HEK293 MCB CHEKMC1.FP L/N (b) (4) for

(b) (4)

Test	Method	Study Number	Result
------	--------	--------------	--------

(b) (4)

Spark does not have a comprehensive stability study protocol on the HEK293 MCB. All they stated in the BLA submission is as following: "Expiry Period: On-Going Monitoring".

PMC: Spark Therapeutics, Inc. commits to conduct stability studies on the HEK293 Master Cell Bank (MCB) used for drug substance manufacture. (b) (4)

3.2.S.2.3.1.2 Plasmid Development History

The following three plasmids are required for the manufacture voretigene neparvovec-rzyl:

- pAAV2-hRPE65v2 (pCCVC-AAV2-hRPE65v2; Vector Plasmid): Vector Plasmid encoding a human retinal pigment epithelium 65 kDa (hRPE65) protein and regulatory elements flanked by AAV2 inverted terminal repeats (ITRs).
- pAAV2PKv2 (pCCVC-AAV2PKv2; Packaging Plasmid): Packaging Plasmid containing the AAV *rep* and *cap* genes coding for non-structural and structural proteins, respectively.
- pAD2HPv2 (pCCVC-AD2HPv2; Helper Plasmid): Adenovirus Helper Plasmid encoding the adenovirus type 2 genes *E2A*, *E4*, and *VA* RNAs required for AAV replication in HEK293 cells.

Vector plasmid pAAV2-hRPE65v2

The complete (b) (4) sequence for the vector plasmid was submitted in the BLA. The transgene hRPE65 is under transcriptional control of cytomegalovirus (CMV) enhancer and contains the chicken β -actin promoter (CBA) promoter, a Kozak sequence at the transcriptional start site, and the bovine growth hormone polyadenylation sequence. The hRPE65 expression cassette is inserted between AAV2 ITRs. The plasmid also contains the Kanamycin resistance gene, a (b) (4), and a bacteriophage lambda DNA stuffer to reduce reverse packaging of the plasmid backbone. The vector plasmid pAAV2-hRPE65v2 map is shown in the figure below.

The hRPE65 cDNA cloning was performed in the laboratory of Dr. Jean Bennet.

- The RPE mRNA was isolated from a human-derived RPE cell line, (b) (4).

Additional intermediate plasmid was created to incorporate the additional coding regions:

- Kan^R gene was excised from (b) (4)
- CMV enhancer and the CBA promoter, exon 1 and partial intron 1 of CBA, was excised from pAAVcu-ha1AT

Enhancements

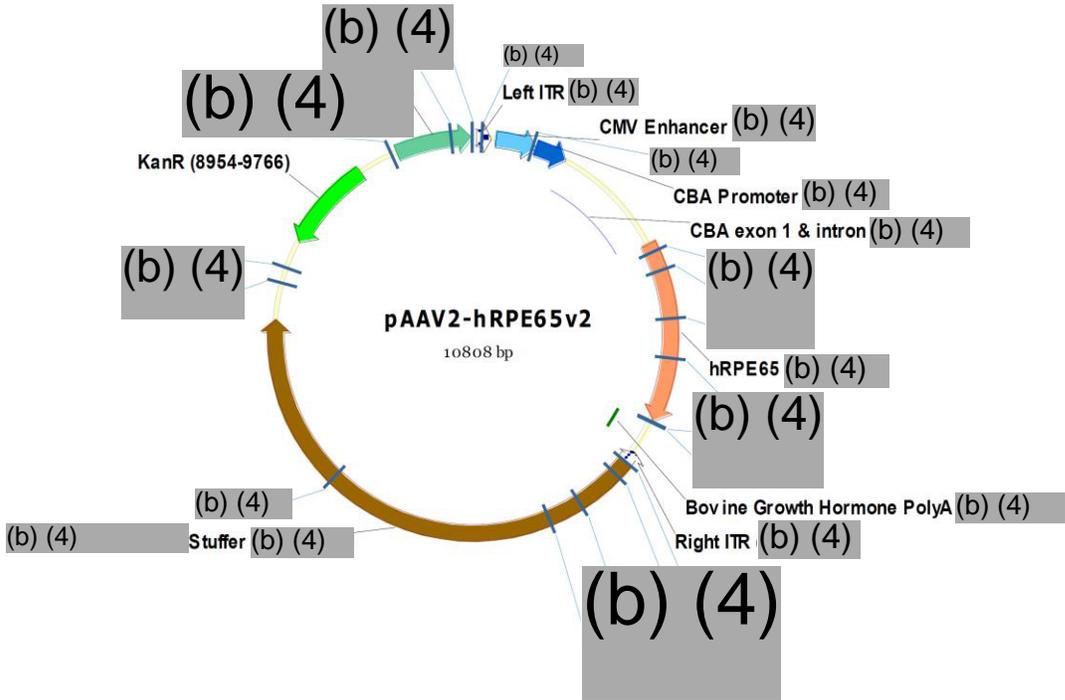
- The 5' UTR was changed to a introduce a Kozak sequence via (b) (4)
- The splice acceptor in the 5' UTR was also altered which increased expression efficiency of RPE65 but did not alter either the cellular specificity or biodistribution of the resultant AAV.

(b) (4)

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

Reviewer's assessment: the complete annotated plasmid sequence is provided in the BLA and the plasmid sequences are appropriate.

Figure 2. Vector Plasmid (pAAV2-hRPE65v2) Map

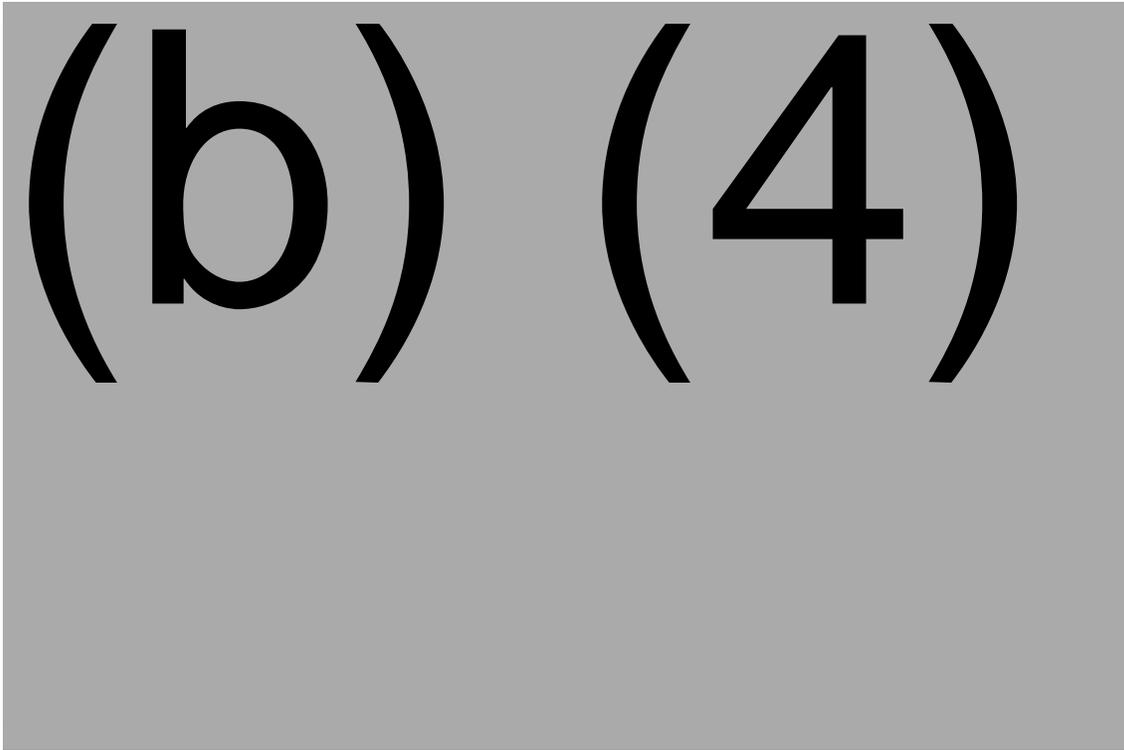


pAAV2PKv2 (Packaging Plasmid)

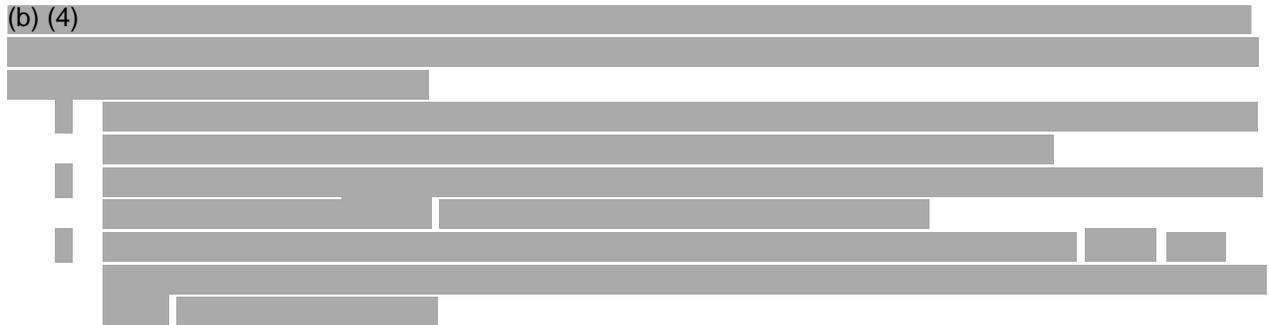
(b) (4)

[Redacted text block containing multiple lines of obscured information]

Figure 3. Packaging Plasmid (pAAV2PK) Map

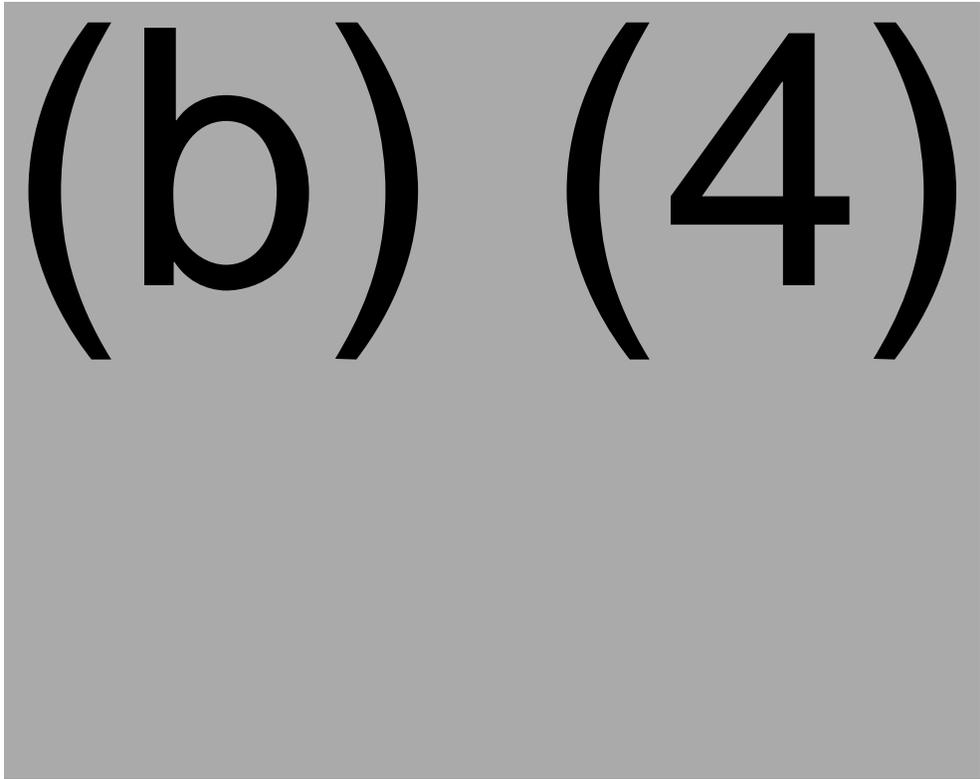


pAD2HPv2 (Helper Plasmid)



Reviewer's assessment: In response to an information request submitted 10/27/17 the Applicant submitted amendment #41 received by FDA on 11/7/17, which stated they do not have documentation on the source of the (b) (4) [redacted]. This is acceptable because the complete plasmid has been sequenced and shown to match the expected sequence, additionally, each incoming lot of plasmid is sequenced as well. The full annotated plasmid sequence for this plasmid is provided. A diagram of the plasmid map is provided in following figure.

Figure 4. Helper Plasmid (pAD2HPv2) Map



3.2.S.2.3.1.3 Preparation of Plasmids

(b) (4)
[Redacted text block]

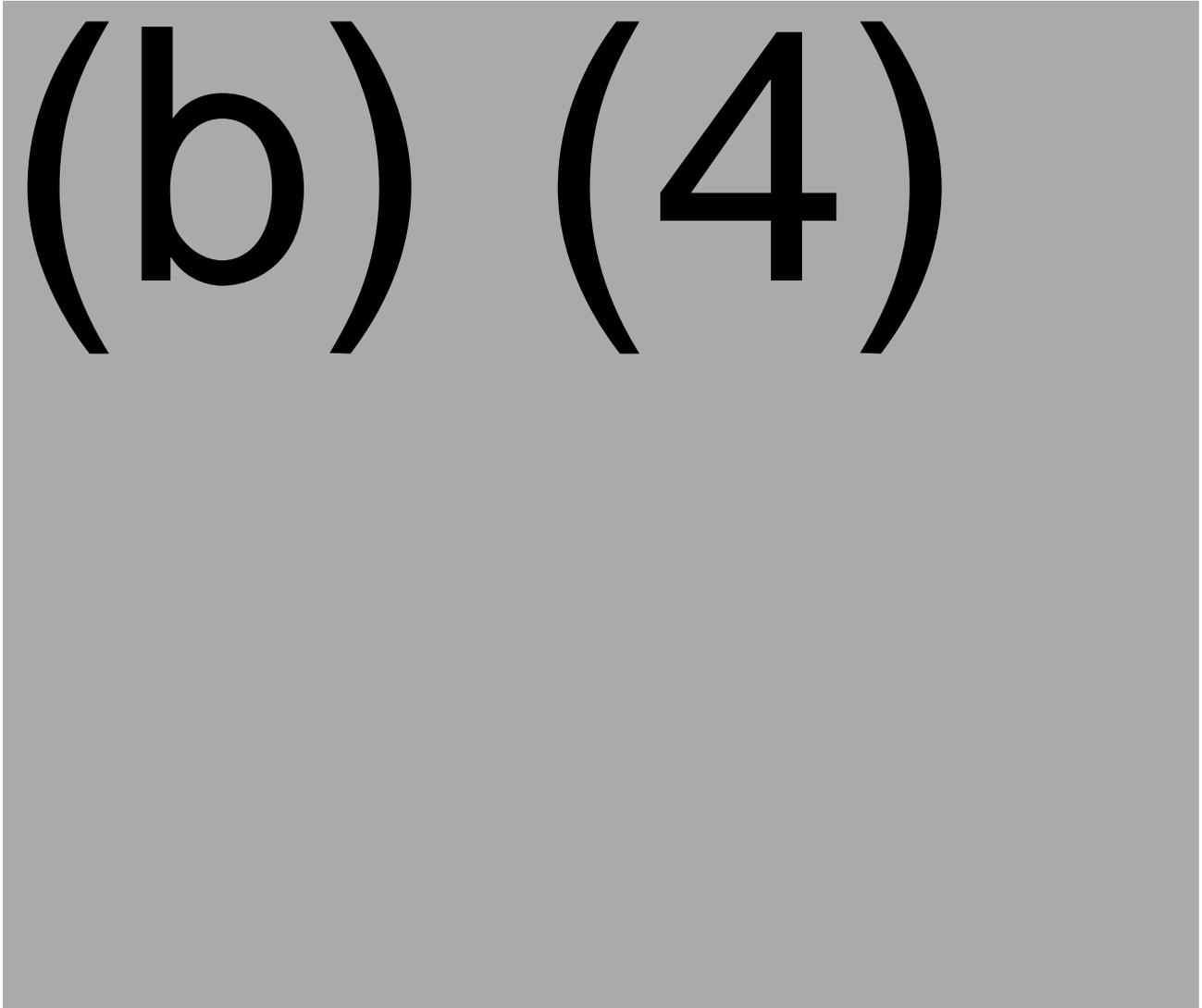
[Redacted text block]

Reviewer’s assessment: A detailed history for each Plasmid Cell Bank was provided in the BLA, and found to be acceptable.

3.2.S.2.3.1.4 Tests and Specifications for Plasmids

The manufacturer’s specifications for testing of new lots of plasmid are shown in following table. Confirmatory testing performed at Spark after receipt of new lots of plasmid prior to release is provided. All three plasmids passed manufacturer’s specifications and Spark confirmatory testing criteria to be released by Spark Quality Assurance for use in manufacture.

Table 3. (b) (4) Release Specification for Plasmids



(b) (4)

Table 4. Spark Specifications for Confirmatory Testing of New Lots of Plasmid



(b) (4)

Reviewer's assessment: the testing for plasmids is acceptable.

In response to an IR submitted on 11/7/17, in amendment #46 Spark stated that the plasmid cell banks are stored (b) (4)) as (b) (4) stocks at (b) (4) storage facility in dedicated

bins. The storage conditions are continuously monitored. This information also stated that there is no formal stability program for the bacterial cell banks and no expiration date has been set. As a production cell bank, the quality of the cell bank is being monitored over the lifetime of the bank through testing of the plasmid product for (b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

[Redacted]

3.2.S.2.3.2 Excipients

Excipients used to manufacture voretigene neparvovec-rzyl are in the table below.

Table 5. Excipients in the Drug Substance

Excipient	Manufacturer	Confirmatory tests
(b) (4) P188, (Poloxamer 188, Pluronic (b) (4))	(b)	(4)
(b) (4)		
Sodium Chloride (b) (4)		
(b) (4)		
(b) (4)		
(b) (4) WFI Quality Water, tested as (b) (4) Packaged Sterile Purified Water		

Reviewer's assessment: The MSS10025 for (b) (4) WFI Quality water states (b) (4)

[Redacted]

(b) (4)

Sodium

(b) (4)

The excipients are released based on the confirmation of the manufacturer’s COA and in-house testing by either Spark or a contract test laboratory. The applicant has included sample COAs and Material Specification Sheets (MSS) which lists the confirmatory testing and acceptance criteria completed by Spark or the contract test lab.

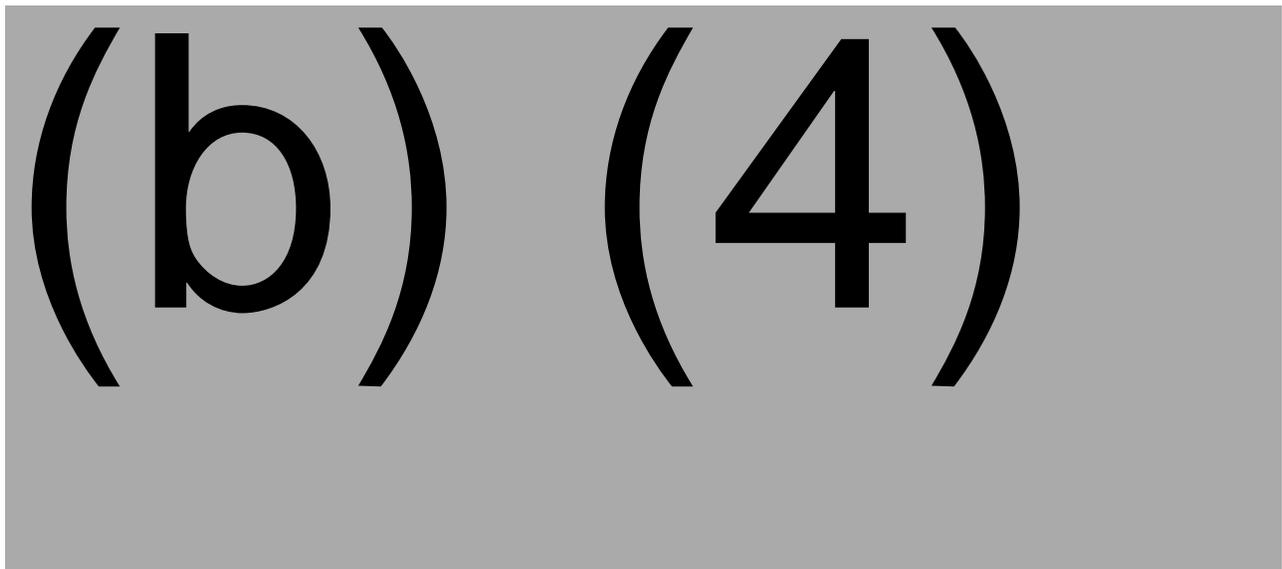
(b) (4)

Reviewer’s assessment: COAs and MSS are provided for all of the excipients and have been reviewed. The excipients are of appropriate quality and are adequately tested by the manufacturer and by Spark or a contract lab to confirm the information provided on the COA.

3.2.S.2.3.3 Raw Materials

Raw materials are purchased from qualified suppliers, and are either compendial quality (USP/NF or Ph.Eur) or undergo COA verification and/ or additional in-house testing against a list of specifications prior to use. The in house COA verification test for each raw material is listed on the MSS for each raw material. The raw materials used to manufacture the drug substance are listed in following table.

Table 6. Raw Materials



(b) (4)

(b) (4)

3.2.S.2.4 Controls of Critical Steps and Intermediates

A risk assessment was performed on each manufacturing process step to identify process parameters that impact safety and/or efficacy of the product. An evaluation of historical manufacturing at CHOP and Spark was used to identify a set of provisional critical process parameters (CPPs) and critical in-process controls (CIPCs) for the production of Drug Substance, and their associated control range.

3.2.S.2.4.1 Critical Operating Parameters

The process parameters and their corresponding Process Performance Qualification (PPQ) acceptance criteria were based on an Interim Control Strategy developed from a Failure Mode and Effects Analysis (FMEA) and a subsequent evaluation of historical manufacturing run data from (1) AAV2-hRPE65v2 CHOP manufacturing campaigns, (2) other AAV2 Clinical lots manufactured at CHOP which utilized the same manufacturing process as AAV2-hRPE65v2, and (3) AAV2-hRPE65v2 Engineering lots manufactured at Spark. The Initial Control Strategy defined parameter classifications based on their potential impact on product quality or and/or process consistency. Parameters and process controls were classified as described in the following Table.

Table 9. Definitions of Parameter Classifications

Parameter Classification	Definition
--------------------------	------------

CPP	<u>Critical Process Parameter</u> - A process parameter for which variability is expected to impact product quality ¹ . CPPs should be controlled within specified ranges to ensure the process produces the desired quality.
CIPC	<u>Critical In-Process Control</u> - A CIPC is a check (i.e. test or measure) performed during production to monitor and, if needed, to adjust the process to ensure the product quality is met.
CIPS	<u>Critical In-Process Specification</u> - A CIPS is a check (i.e. test or measure) performed during production to ensure the product quality is met. A CIPS is on the Certificate of Analysis.
OPP	<u>Operating Process Parameter</u> – Input parameter defined to ensure consistent manufacturing operations. An OPP is not expected to impact product quality.
IPC	<u>In-Process Control</u> – Output control defined to ensure consistent manufacturing operations. An IPC is not expected to impact product quality.
Parameter	<u>Parameter</u> – Additional parameters (inputs or outputs), which are neither critical nor operating parameters, will also be monitored during PPQ and CPV. These parameters do not impact product quality or consistency. No PPQ acceptance criteria have been set for this classification.

¹ Product quality is defined by the tests outlined in the Certificate of Analysis.

Table 10. Critical Process Parameters (CPPs) and In-Process Controls (CIPCs) for the Cell Culture Process

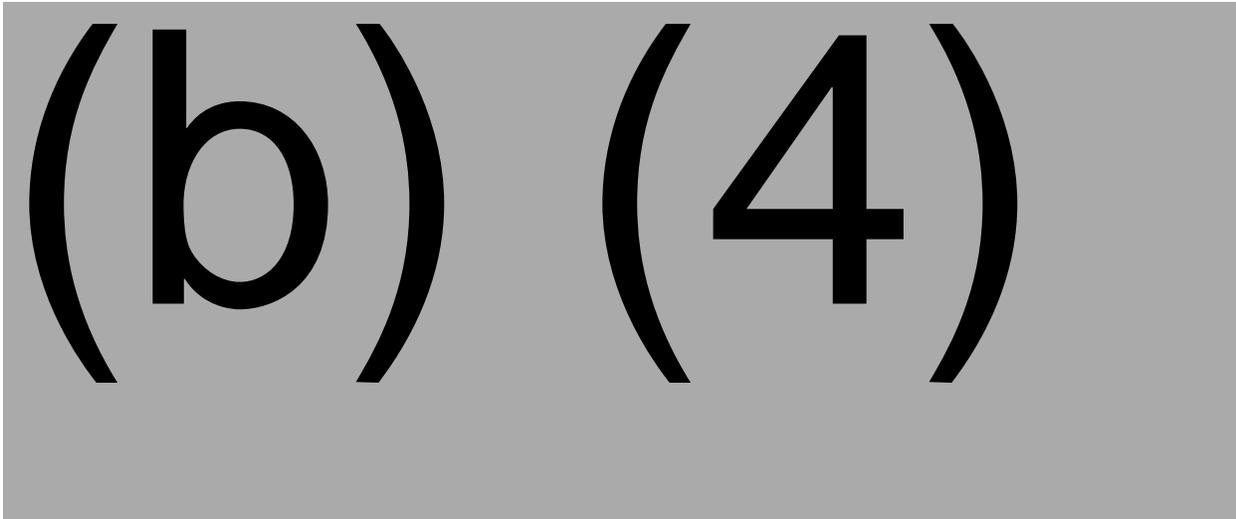


Table 11. Critical Process Parameters (CPPs) and In-Process Controls (CIPCs) for the Purification Process



(b) (4)

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

3.2.S.2.5 Process Validation and/or Evaluation

Validation of the process for manufacturing Drug Substance was to demonstrate the process is controlled to consistently deliver Drug Substance. The Process Performance Qualification (PPQ) was executed to confirm the Control Strategy developed during process design.

The PPQ validation was conducted by manufacturing one drug substance lot (b) (4) at Spark Therapeutics Manufacturing Facility. Manufacturing Drug Substance Lot (b) (4) (PPQ lot) was manufactured following a protocol outlined with pre-established acceptance criteria.

3.2.S.2.5.2 Process Performance Qualification (PPQ)

Step 1 PPQ Results: Cell Culture and Expansion

(b) (4)

Applicant's Cell Culture Process Conclusion

(b) (4)

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

3.2.S.2.6 Manufacturing Process Development

3.2.S.2.6.1 Manufacturing Process Development History

The manufacturing process for voretigene neparvovec-rzyl utilizes a three-plasmid transient transfection of adherent HEK293 cells in roller bottles for vector generation, cation exchange column chromatography and cesium chloride (CsCl) gradient (b) (4) centrifugation (b) (4) for product purification (Column-CsCl Process). The development of this process was performed at The Children’s Hospital of Philadelphia (CHOP) in the period 2004 – 2006 and evaluated as part of the IND 13408. Through 2014, the CHOP Core Facility had supported Chemistry, Manufacturing and Controls for (b) (4) investigational products used in (b) (4) clinical trials (Phase 1-3). The Column-CsCl Process developed for voretigene neparvovec-rzyl is a second-generation process which represents an extensive re-development and optimization of a previously established “(b) (4)” used to support early phase clinical development.

3.2.S.2.6.2 Control Strategy Development

The control strategy was developed to ensure that the voretigene neparvovec-rzyl commercial manufacturing process will consistently deliver Drug Substance. In place of a defined list of

Critical Quality Attributes (CQA), product quality was assessed by the Drug Substance attributes informed from the testing listed on the Certificate of Analysis used to release the CHOP Phase 3 clinical trial materials. The control strategy was developed using a risk-based approach based on product, process, and facility knowledge. Control strategy development for voretigene neparovvec-rzyl manufacture was divided into (b) (4) stages:

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

- | [Redacted]
- | [Redacted]
- | [Redacted]

(b) (4)

Reviewer's assessment:

The proposed BLA ranges are supported by the data obtained from the DOE studies, which are acceptable.

2.3.S.2.6.7 Comparability

A comparability evaluation was conducted to demonstrate that the voretigene neparvovec-rzyl Drug Substance produced at Spark Therapeutics is comparable to the Phase 3 clinical material manufactured at CHOP and that the change of manufacturing facility had no impact on the quality attributes of Drug Substance. The voretigene neparvovec-rzyl manufacturing process and unit operations employed at Spark Therapeutics to produce commercial Drug Substance are the same as those used to produce Drug Substance at CHOP during clinical development. The comparability evaluation was accomplished through a prospective study.

(b) (4)

(b) (4) [Redacted]

(b) (4) [Redacted]

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

Reviewer's comment: The SOPs used for each of the analytical procedures described below are listed for each test in Section 3.2.S.4.1 'Specification' in the BLA submission. However, most SOPs were not submitted in the BLA. Spark has submitted verification reports to show suitability of some compendial methods. For noncompendial methods, the validation data is submitted. Additional details for each assay follow:

3.2.S.4.2.1 Appearance by Visual Inspection

The 'Appearance by Visual Inspection' assay evaluates the visual appearance of color, clarity and presence of visible foreign particulate matter in (b) (4) Drug Product and Diluent using a compendial assay and is performed in accordance with (b) (4).

Verification

Reviewer's comment: No information in the submission. In Amendment #33, 1.4, the applicant notes that each analyst completes a robust three-step training prior to performing the test which includes an assessment of their ability to identify a defect with a product vial known to contain a defect. The applicant believes that the combination of the use of compendial standards along

(b) (4)

[Redacted text block]

[Redacted text block]

3.2.S.4.2.9. Vector Genome Identity by (b) (4)

The assay is performed on the (b) (4) DP and involves (b) (4)

[Redacted text block]

Validation:

The validation of the Vector Genome Identity by (b) (4) assay was performed at Spark. For the validation, (b) (4)

[Redacted text block]

(b) (4)

(b) (4)

Reviewer's comment: The validation is acceptable.

3.2.S.4.2.10. Vector Genome Concentration Assay

The purpose of this assay is to determine the titer of a vector preparation by quantifying the number of packaged genomes. The assay measures the amount of (b) (4) Adeno-associated virus (AAV) vector genomes (that are packaged and within capsid particles) in (b) (4) DP. (b) (4)

[Redacted text block]

Reported Results The vector genome concentration is reported in vector genome per milliliter (vg/mL).

Reviewer's comment: The assay description is adequate. The SOP (QC.062) states that the (b) (4)

Validation

The validation of the AAV2-hRPE65v2 vector genome concentration by (b) (4) assay was performed at Spark according to the validation protocol and following ICH Q2 (R1) guidelines for analytical assay validation. The hRPE65 plasmid standard (lot (b) (4)

(b) (4) [Redacted text block]

The details are summarized in the table below:

Table 37. Validation Data: Vector Genome Concentration Assay

(b) (4)

(b) (4)

(b) (4)

3.2.S.4.2.15. In Vitro Relative Potency of (b) (4) by (b) (4) Assay

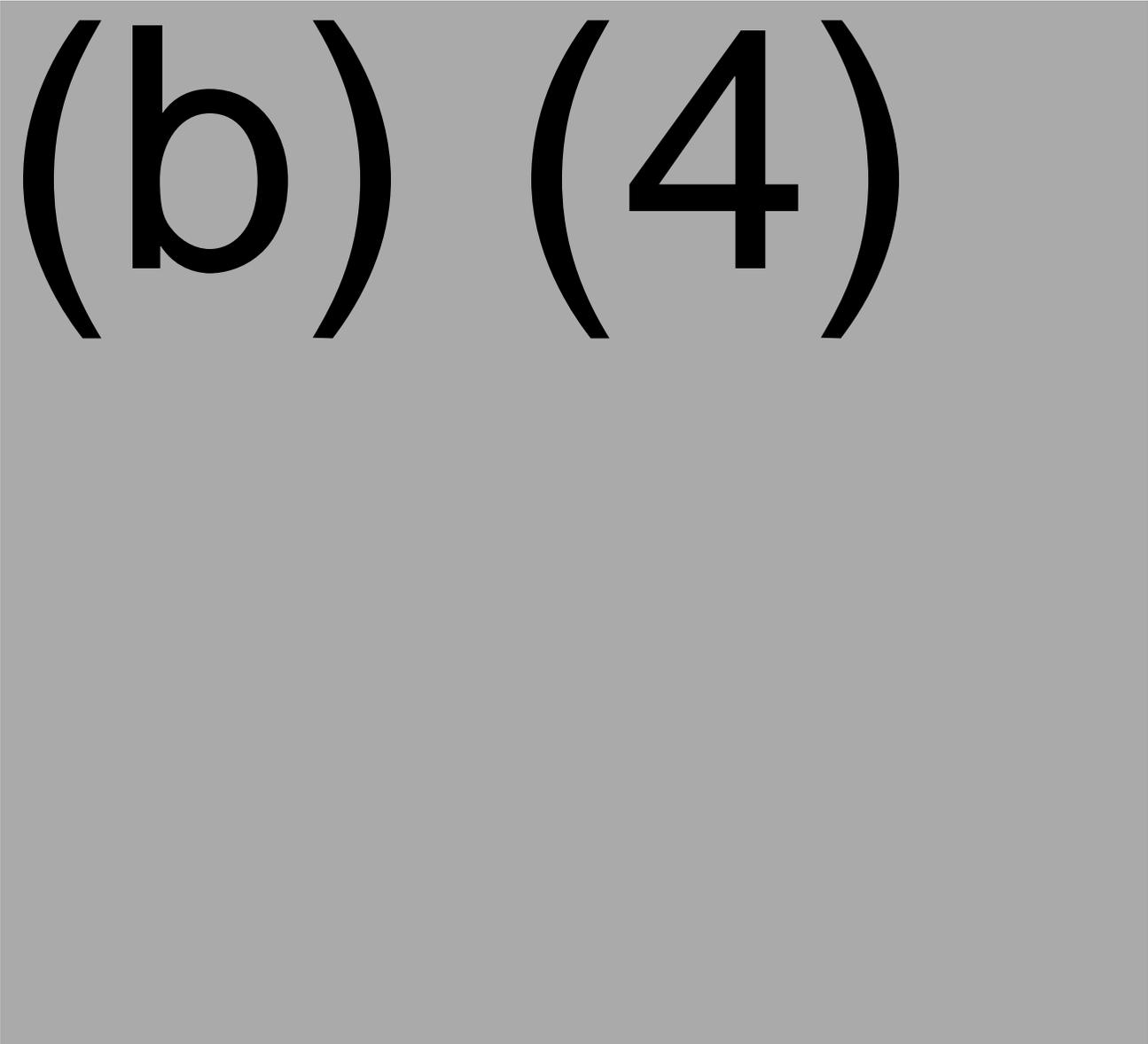
The purpose of this assay is to determine the relative (b) (4)

(b) (4)

Validation

The validation of AAV2-hRPE65v2 (b) (4) Method was performed by (b) (4). The reference standard (RS) used was AAV2-hRPE65v2 Lot (b) (4), the test article (DP) was Lot (b) (4)

Table 42. Validation Data: In vitro Relative Potency of (b) (4) by (b) (4) Assay



(b) (4)

All validation criteria were met and the assay was deemed suitable for its intended purpose.

Reviewer's Comment: The validation results demonstrate adequate assay control and sensitivity.

(b) (4) [Redacted]

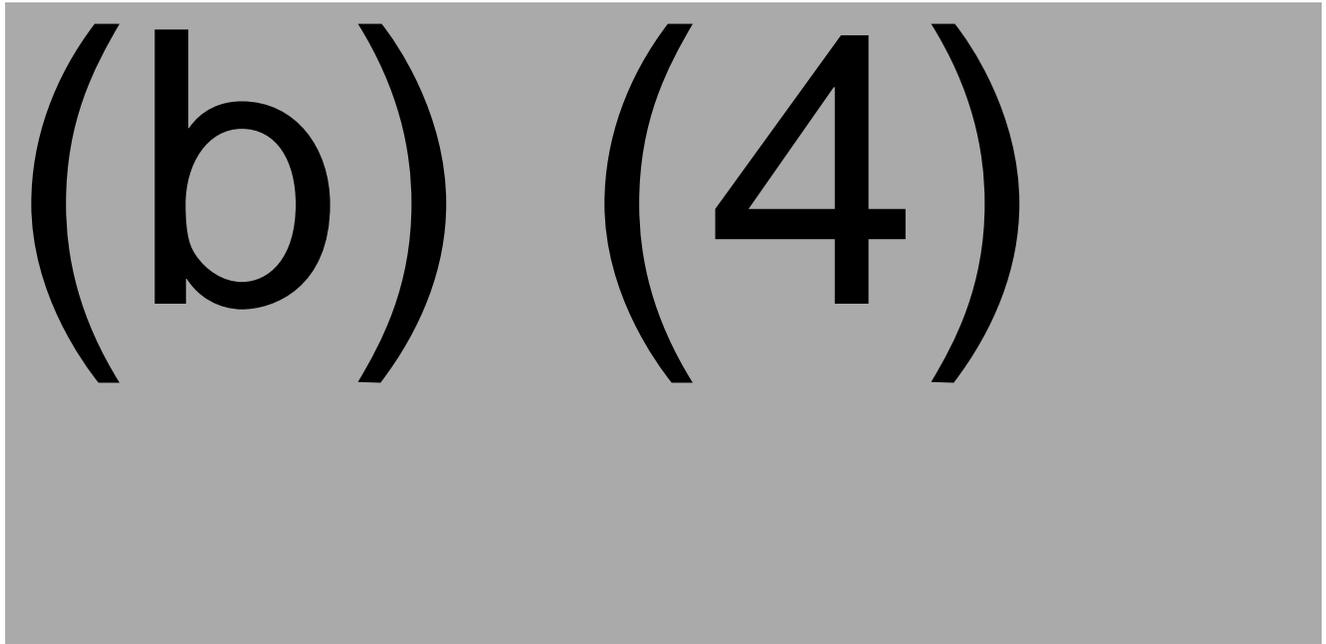
[Redacted]

[Redacted]

[Redacted]

[Redacted]

Table 47. Validation Data: Residual Cesium (Cs) by (b) (4)



Reviewer's comment: The assay validation is acceptable.

3.2.S.4.2.24. Concentration of Pluronic

The purpose of this assay is to measure (b) (4) P188 to demonstrate its final concentration in the (b) (4) Drug Product and Diluent because it is a formulation buffer excipient and to ensure it meets the specification. Quantitative determination of (b) (4) P188 is performed by (b) (4)

[Redacted text block]

Validation

The validation of Pluronic content (b) (4) was performed by (b) (4)

[Redacted text block]

[Redacted text block] Other validation criteria assessed (and corresponding results) are tabulated below:

Table 48. Validation Data: Pluronic content by (b) (4)

(b) (4)

Reviewer's Comment:

The report contains a discrepancy in the LOQ of the assay.

- Specifically: The LOQ of the assay is reported as (b) (4) in the validation summary and under Section 10 of the report but under Accuracy (Section 11) of the report, the LOQ is stated as (b) (4) (see text denoted under the asterisk mark above). Applicant was asked to clarify this discrepancy. In Amendment #33, 2.9i, applicant notes the study reports LOQ of 'Pluronic in

Solution' and LOQ for 'Pluronic in Sample; these values differ (b) (4)-fold because the samples are (b) (4). This is acceptable.

The validation report in the BLA does not contain data to support an update to the currently established LOQ ((b) (4)) levels for this assay; this information was noted during PLI while reviewing Deviation Investigation Report (open) DI 17-138 dated August 18, 2017. It is noted in that (DI) report that (b) (4) has expanded validation of this assay to include an assessment of the LOQ at the current LOD levels (S/N ratios and precision was calculated for (b) (4) replicate (b) (4) at the LOD level). The lower limit of specification for Pluronic content ((b) (4)) in the release plan is now above the newly established LOQ ((b) (4)) of the assay. Applicant was asked to clarify the LOQ for the assay. In Amendment #33, 2.9i, applicant notes that in DI17-138, review of existing validation data, revealed that the method was accurate, precise and in the linear range to support the same LOD and LOQ of (b) (4) 'Pluronic in sample'. Accordingly, the LOD/LOQ, linearity and range sections of the summary table have been revised to reflect the amended validation report to support the amended LOQ of (b) (4) "Pluronic in Sample". This is acceptable.

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4)

(b) (4)

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The stability protocol and a summary of results from the primary stability study for voretigene neparvovec-rzyl DS is provided. As only a limited amount of primary stability data is currently available, a summary of the supporting stability studies for the DS is also provided. All supporting stability data are from development studies.

Overview of Studies Performed

The primary stability study for (b) (4) was initiated in November 2016. All test methods used have been verified, validated, and/or qualified for their intended purpose. Testing at the (b) (4) stability time point has been completed (amendment #38 submitted November 1, 2017). Testing at additional time points is ongoing for this study which evaluates (b) (4). The stability data are presented below in section 3.2.S.7.1 Stability Summary and Conclusions.

Supporting stability studies consist of (b) (4) DP (b) (4) lots. Two sources of supporting stability data are available: the two clinical lots of voretigene neparvovec-rzyl, and (b) (4) sets of data from (b) (4) Engineering lots of material manufactured at Spark. The clinical lots were stored in polypropylene cryovials and are representative of the (b) (4) used to store (b) (4).

Data from both (b) (4) DP were pooled and evaluated as one data set for shelf life estimation. Discussion of all supporting stability data and corresponding shelf life estimates are in reviewer section 3.2.P.8.1 Stability Summary and Conclusion.

Primary And Supporting Stability Studies

The stability protocol for DS PPQ Lot #(b) (4) is provided in the first table below, and the proposed specifications for that same lot are provided in the second table below. The corresponding data is provided in review section 3.2.S.7.3 Stability Data. A summary of all DS supporting studies are provided in review section 3.2.P.8.1 Stability Summary and Conclusion.



(b) (4)

(b) (4)

Recommended Storage, Shelf Life, and Retest Period

Spark recommends storage at (b) (4) stability for DS. For additional details, please see review section 3.2.P.8.1 Stability Summary and Conclusion.

Pending the availability of material, Spark indicates additional testing at time points of (b) (4) may be performed after completion of the DS stability protocol. Testing will be performed to support revision of the expiry period for DS.

Reviewer Comments: During the late cycle telecon of 09 Nov 2017, Spark was notified that the statistical analyses that were submitted to the BLA for determination of expiration were not acceptable because estimates for functional properties were not performed. FDA communicated that Spark was welcome to suggest expiration based on real time stability data that followed Q5c. During the follow-up telecon on 16 Nov 2017, Spark and FDA agreed on (b) (4) 18 months expiration for DP. Spark submitted this information in amendment #48 received on 28 Nov 2017.

3.2.S.7.2 Post-Approval Stability Protocol

Post-Approval Stability Protocol

The provisional post-approval stability protocol for the DS is presented in the table below. Scheduled testing at time points earlier than (b) (4) may be removed and/or re-evaluated after

completion and analysis of long-term stability data from the PPQ lot and/or subsequent lots of DS placed on stability. Any revisions will be provided in a post approval supplement. The provisional stability specifications are the same as for DS lot (b) (4).

Table 60. Drug Substance Post-Approval Stability Protocol at (b) (4)



Reviewer comment: In accordance with amendment #48 submitted 28 Nov 2017, the above post-approval protocol was modified to include the (b) (4) assay.

Post-Approval Stability Study

In addition to reporting these ongoing stability results, Spark Therapeutics commits to the following:

- Complete the ongoing primary registration stability study.
- Commit to placing the next (b) (4) post-approval DS lots on stability following the Post-Approval stability protocol. Results will be reported in annual updates.

Reviewer comment: In accordance with amendment #48 submitted 28 Nov 2017, Spark modified the post-approval stability study in the BLA. The modification is the second bullet above.

Extension of Shelf Life

Any extension of the approved expiry period will be supported by data from the stability studies that will be filed as an update to the license with copies of the revised labeling.

3.2.S.7.3 Stability Data

Primary Stability Studies

The stability protocol for the primary stability study for DS is provided in review section [3.2.S.7.1](#). The associated primary stability data are summarized in the table below:

Table 61. Drug Substance Primary Stability Data - Long Term



(b) (4)

(b) (4)

3.2.P DRUG PRODUCT

3.2.P voretigene neparvovec-rzyl

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

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.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

The Drug Product solution composition was designed to be the same as the Drug Substance solution composition to enable a simple manufacturing process without requiring dilution of the Drug Substance to produce the final Drug Product.

Table 62. Drug Product Excipients

Excipient	Function	Quality Standard	Concentration
Sodium Chloride	(b) (4)	(b) (4)	180 mM
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4) P188	(b) (4)	(b) (4)	0.001 %
Water for Injection (WFI) Quality Water	Physiologically aqueous solvent	(b) (4)	quantum sufficit

There are no novel excipients used in the manufacture of the Drug Product.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The formulation of the Drug Product is similar to those previously used in a number of gene therapy clinical studies. Sodium phosphate is included to (b) (4). Sodium chloride is used to (b) (4). The slightly hypertonic formulation is based on formulation studies reported for a rAAV2-based vector (Wright, 2005) designed to prevent vector aggregation and provide long-term stability, (b) (4). The formulation includes a low concentration (0.001%) of the surfactant (b) (4) P188.

3.2.P.2.2.2 Overages and Overfills

(b) (4)

(b) (4)

3.2.P.2.2.3 Physicochemical and Biological Properties

The formulation was designed with the goal of developing a stable Drug Product that is physiologically compatible upon delivery and is similar to earlier gene therapy clinical formulations. The most common form of degradation of the Drug Product is loss of potency. The pH of the formulation is both physiologically compatible and suitable for stability of the Drug Product. The slightly hypertonic formulation provides sufficient ionic strength to (b) (4). The addition of (b) (4) P188 has been demonstrated to (b) (4).

3.2.P.2.3 Manufacturing Process Development

Phase 1 and 3 clinical material, using Drug Substance 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-rzyl Drug Product in Building (b) (4) of their live virus facility. Additionally, the commercial Drug Product container was changed to (b) (4) vials, with a standard container closure configuration.

Table 63. Historical Overview of DP Manufacturing Process

	Historical	Commercial
Fill Location	(b) (4) and Children’s Hospital of Philadelphia (2 nd Clinical Lot)	(b) (4)
Fill Environment	(b) (4)	(b) (4)
Product Fill Volume	(b) (4)	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)

3.2.P.2.3.1 Commercial Manufacturing Process Development

3.2.P.2.3.1.1 (b) (4) Background

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

 _____ Please see DMPQ review for details.

3.2.P.2.3.1.2 Manufacturing Process Development

The proposed commercial Drug Product manufacturing process was developed through processing experience and refinement over the course of several Drug Product lots executed at (b) (4). The successful transfer of process knowledge and completion of technology transfer activities was demonstrated by the ability of the commercial manufacturing site to perform the process and meet all current specifications and release test requirements for all executed engineering lots.

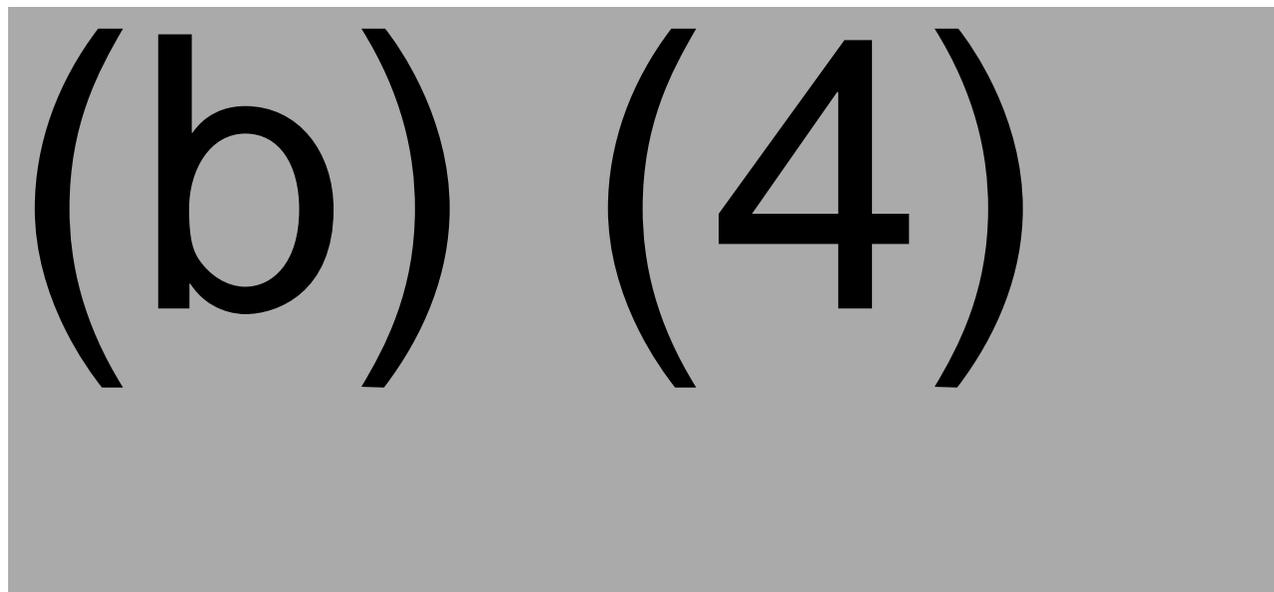
3.2.P.2.3.1.3 Engineering Lots

Engineering data was collected from four lots manufactured at (b) (4) from (b) (4). Engineering data was used to verify the parameter targets and determine manufacturing operating ranges to be used in the commercial manufacturing process as well as to develop batch records and standard operating procedures for use in the commercial production campaign at (b) (4). Engineering lots appear in following table.

Table 64. Drug Product and Diluent Engineering Lots

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

Data from the engineering lots has been assessed for extractable volume, particles per container, endotoxin and sterility. Data from engineering and PPQ lots has been assessed for (b) (4), infectivity and pluronic ((b) (4) P188) content.



Reviewer's assessment: The data provided are limited, however the data did not show significant difference in the tested analytical properties observed post-filtration. The data are acceptable for this step.

3.2.P.2.3.2 Control Strategy

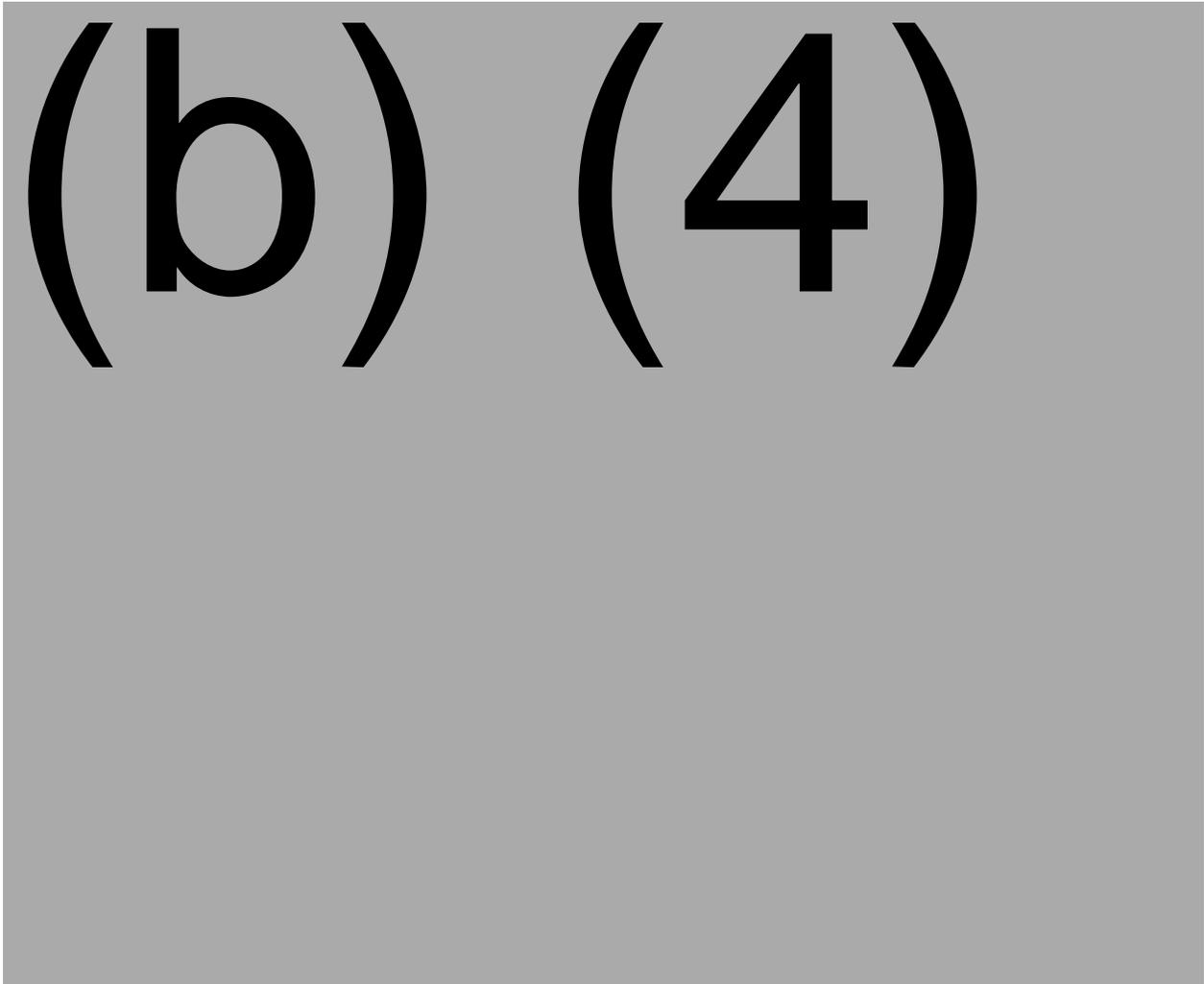
The Drug Product control strategy was developed by conducting an evaluation based on product, process, and facility knowledge. The resulting combination of process controls and product tests are employed to ensure product quality and patient safety. The control strategy was developed using the quality attributes for Drug Product lot release that were in place for process

performance qualification (PPQ) execution. These quality attributes were established as the control strategy CQAs.

Engineering lots data was collected from four lots manufactured at (b) (4) from (b) (4). Engineering data was used to verify the parameter targets and determine manufacturing operating ranges to be used in the commercial manufacturing process as well as to develop batch records and standard operating procedures for use in the commercial production campaign at (b) (4). The engineering run data was used to determine/verify the parameter targets and manufacturing operating ranges to be used in the GMP comparability run as well as the process performance qualification.

Each Drug Product manufacturing parameter was evaluated and classified as critical or not critical and then acceptable ranges were established as shown in following table.

Table 66. Classification and Rationale for Process Controls and Parameters



(b) (4)

(b) (4)

3.2.P.2.3.3 Comparability

A comparability evaluation was conducted by Spark to demonstrate that the voretigene neparvovec-rzyl Drug Product produced at (b) (4) is comparable to the CHOP material used in the Phase 3 pivotal clinical study and that the change in manufacturing facility and container closure has had no impact on product quality. Following are data of analytical results for side-by-side testing from Drug Product comparability study:

Table 67. Comparability Results for Side-by-Side Testing

(b) (4)

Reviewer's Assessment: Although the Release Specification ranges for In Vitro Relative Potency tests are wide, the real "Comparability Results for Side-by-Side Testing" of (b) (4) Lot (b) (4) and CHOP Lot (b) (4) are very close, showing the two product lots are comparable.

3.2.P.2.6 Compatibility

The primary packaging components of the container closure system are in direct contact with the Drug Product. Compatibility of the vial and stopper with the Drug Product has been demonstrated during primary and supporting stability studies located in Drug Product Module 3.2.P.8.1. Stability studies demonstrate Drug Product compatibility and stability in the proposed container closure system.

The results of compatibility studies of the diluted Drug Product with administration devices are provided in Module 3.2.R.4 Medical Device Compatibility.

Device Compatibility

Device compatibility studies were performed to demonstrate no product loss due to non-specific adsorption to device contact surfaces during handling of SPK-RPE65 which includes thaw, storage, loading and delivery in the administration devices. Three studies measured the recovery and stability of voretigene neparvovec-rzyl vector using device components listed in the Surgical Training Manual (injection cannulas, syringes and extension tubes, listed in the table below) that are commercially available FDA Class I devices and EMA CE mark devices for ophthalmic use. The studies were conducted to test extended storage conditions post-thaw and in the device.

Table 68. Delivery Devices Listed in the Surgical Training Manual

Product Description	Manufacturer	Reference Number	510(k) Numbers
Cannulas			
PolyTip [®] cannula 25 g/38 g 25 x 28 mm cannula with 38 g (0.12 mm) x 5 mm tip	MedOne Surgical, Inc. Sarasota FL	3219	Exempt
De Juan/Awh subretinal injection cannula 25 g/41 g 41 g (0.10 mm) tip	Synergetics, Inc. USA - Bausch & Lomb, Inc. O'Fallon MO	12.03.25	Exempt
Retinal hydrodissection cannula 20 g/39 g 20 g shaft with 39 g inner diameter flexible tip	Storz Ophthalmic - Bausch & Lomb, Inc. Rochester NY	ED7365	Exempt
Extension Tubes			
Ocular irrigation tube 6" (15.2 cm), ID 0.8 mm, OD 1.6 mm male/female Luer connections	Eagle Labs Rancho Cucamonga CA	169-30L-6	Exempt
High pressure extension tube 6" (15.2 cm), ID 1.4 mm, OD 2.29 mm, PVC tube with male and female Luer-lok [™] connections	MedOne Surgical, Inc. Sarasota FL	3243	Exempt
Syringes			
BD Luer-Lok [™] 1-mL disposable syringe Has 1/100 mL graduation	Beckton, Dickinson & Company Franklin Lakes NJ	309628	K941562

Medallion® 1-mL syringe Fixed male Luer connector, flat grip	Merit Medical Systems, Inc. South Jordan UT	MSS011	K875196
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Table 69. Compatibility Study Summary

Study # (*design)	Subretinal Injection Device Components			Product Lot # (titer)	Study Conclusion:
	Cannula	Extension Tube	Syringe		
Study 1: TR2016-046* (* as described below)	Polytip® 25g/38g MedOne Surgical	High Pressure MedOne Surgical, Inc.	1mL Polycarbonate Luer-Lok Tip Becton Dickenson & Co	(b) (4)	
Study 2: TR2016-049 (* as described below)	De Juan/Awh 41g/25g Synergetics USA Bausch & Lomb	Ocular Irrigation Eagle Labs	1mL Polycarbonate Luer-Lok Tip Becton Dickenson & Co		
Study 3: Wright and Zelenia report (** as described below)	Hydro-dissection Bausch & Lomb Storz Cannula	Ocular Irrigation Eagle Labs	Becton, Dickinson & Company		

The three studies (listed above) were designed to document stability and recovery of SPK-RPE65 under worst-case conditions: extended duration of storage [in syringe after thaw and dilution, and in the device (cannula and tubing)] during the steps of product preparation and administration and low product concentration (Study#3).

Study#3 was performed to show compatibility of AAV2-hRPE65v2 (voretigene neparvovec-rzyl) with the Bausch & Lomb Storz Cannula for early human clinical studies (Phase I), and the study report was provided in IND 13408 Serial 0006). Study#3 is also briefly described below.

Studies#1 and 2: These two compatibility studies had the following common steps*, briefly:

- Thaw and dilution of the Drug Product: (b) (4)

- Storage in Syringe: (b) (4)


(b) (4)

(b) (4)

- █ [Redacted]
- █ [Redacted]
- █ [Redacted]

[Redacted]

Reviewer's comment: *The compatibility data is acceptable.*

- *The applicant has demonstrated compatibility of the Becton and Dickinson Storz Cannula using a CHOP vector lot and not the Spark lots. This is acceptable, since both the CHOP and Spark lots were formulated with 0.001% Pluronic, and compatibility was demonstrated with a very low concentration of the vector, i.e., vector that was highly diluted (b) (4) instead of 1:10 dilution proposed for clinical use).*
- *The applicant also notes that biocompatibility using Medallion® 1-mL syringe hasn't been tested because like the 1 ml Becton and Dickinson syringe, the Medallion® 1-mL syringe 510(k) # K875196 (Merit Medical Systems, Inc) mentioned in the surgical*

manual, is an alternative to 1mL BD syringe and is manufactured using similar polycarbonate material. This is acceptable.

- The applicant also notes that Spark does not propose to limit the device components to any specific brand because of the use of (b) (4) P188 in the formulation and because of the compatibility data generated to date. **This is acceptable** as there tends to be little variation in the materials used for ophthalmic instruments among various device manufacturers.
- The AAV2-RPE65 lot used in the device compatibility study authored by Wright and Zeleniaia, dated 31 Oct 2007, is AAV2-hRPE65v2 Lot (b) (4). This lot is not in the Spark Lot History list provided under the BLA submission. In Amendment #33, 6.2.1, the applicant notes that Lot (b) (4) is a non-clinical lot (described under Module 4 and used in multiple toxicity studies in dogs and monkeys), manufactured using the standard CHOP (b) (4)-roller bottle process, formulated with 0.001% Pluronic, but not tested for Pluronic content. **This is acceptable** as no loss in vector was noted in the study.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Table 70. Drug Product Manufacturer(s)

Establishment Name, Address and Unique Facility Identifier	Contact Information for Person Responsible for Scheduling Inspections	Specific Manufacturing Operations Being Conducted
(b)	(4)	Aseptic Filling and Labeling of Drug Product, Diluent Manufacturer, Testing of Drug Product and Diluent for Sterility
		(b) (4) of stoppers, seals, tubing, labels and associated consumables
		Contract Testing Laboratory for: Endotoxin, Particulate Matter, Extractable Volume

(b) (4)	(b) (4)	Packaging and Labeling
		Distribution of Drug Product
		Backup distribution of Drug Product
		Container Closure Integrity Testing

*In this review memo, “(b) (4)” is also used as an abbreviation for (b) (4)

3.2.P.3.2 Batch Formula

The Drug Product formulation is a solution of vector at a concentration of approximately 5×10^{12} vector genomes per milliliter (corresponding to approximately 0.05 mg vector / mL) in Water for Injection (WFI) quality water containing 180 mM sodium chloride, 10 mM sodium phosphate, 0.001% (b) (4) P188®, pH 7.3.

Table 71. Drug Product Formulation

Ingredient	DP Concentration	Function / Purpose
SPK-RPE65 AAV2-hRPE65v2 Spark Therapeutics, Inc.	0.05 mg/mL (5×10^{12} vector genomes/mL)	Vector (Active Ingredient)
(b) (4)		

Sodium Chloride (b) (4) NaCl; FW 58.44 (b) (4)	180 mM	(b) (4)
(b) (4) P188 (Poloxamer 188, Pluronic) (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

3.2.P.3.3 Description of Manufacturing Process and Process Controls

3.2.P.3.3.1 Schematic of the Manufacturing Process

Drug Substance (Bulk Vector), formulated at Spark Therapeutics, is (b) (4) to (b) (4) where it is processed into Drug Product by (b) (4) filtration and filling into (b) (4) vials. There is no change in formulation or dilution from Drug Substance to Drug Product.

3.2.P.3.3.2 Preparation of (b) (4) for Manufacturing

The batch process begins with the cleaning, preparation, loading and sterilization of the (b) (4). All the production equipment and components required for processing are (b) (4). Items are initially (b) (4).

(b) (4)

3.2.P.3.3.3 Description of Manufacturing Process

A narrative description of the Drug Product manufacturing process is provided below.

Shipping, Receipt, and Storage of Drug Substance

(b) (4)

Drug Substance Thaw and Mix

(b) (4) [Redacted text block]

Pool and Mix for Homogeneity

(b) (4) [Redacted text block]

Sterile Filtration

(b) (4) [Redacted text block]

[Redacted text block]

Vial Filling, Stoppering, and Capping

Following filtration, the sterile Drug Product solution is filled, stoppered and sealed (b) (4) [Redacted text block]

acceptable range.

Inspection, Bulk Packaging, and Storage

Following containment break (opening the (b) (4) to the room environment), the finished product vials are immediately transferred to the inspection room. The finished product vials are 100% visually inspected 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 vials 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. 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.

3.2.P.3.3.5 Reprocessing and Reworking

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

3.2.P.3.3.4 Controls of Critical Steps and Intermediates

The controls of the critical steps of the commercial manufacturing process for voretigene neparvovec-rzyl Drug Product are summarized in following tables:

Table 72. Critical Process Parameters (CPPs) and Acceptance Ranges

(b) (4)

Table 73. Critical In-Process Controls (CIPCs) and Acceptance Ranges

(b) (4)

Table 74. Processing Time Limits for the Drug Product Manufacturing Process

Process Time Limit Description	Time Limit
Time limit from the completion of Drug Substance thawing to the transfer of finished Drug Product vials to storage at ≤ -65 °C.	(b) (4)

3.2.P.3.3.5 Process Validation and/or Evaluation

Process validation and evaluation was conducted using one manufacturing PPQ lot at commercial scale, starting from the receipt of Drug Substance Lot (b) (4) from Spark

Therapeutics at (b) (4) . Drug Substance PPQ Lot (b) (4) used as Drug Product Manufacturing PPQ Lot (b) (4) for the Drug Product.

The PPQ lot was evaluated using routine in-process testing and Drug Product 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.

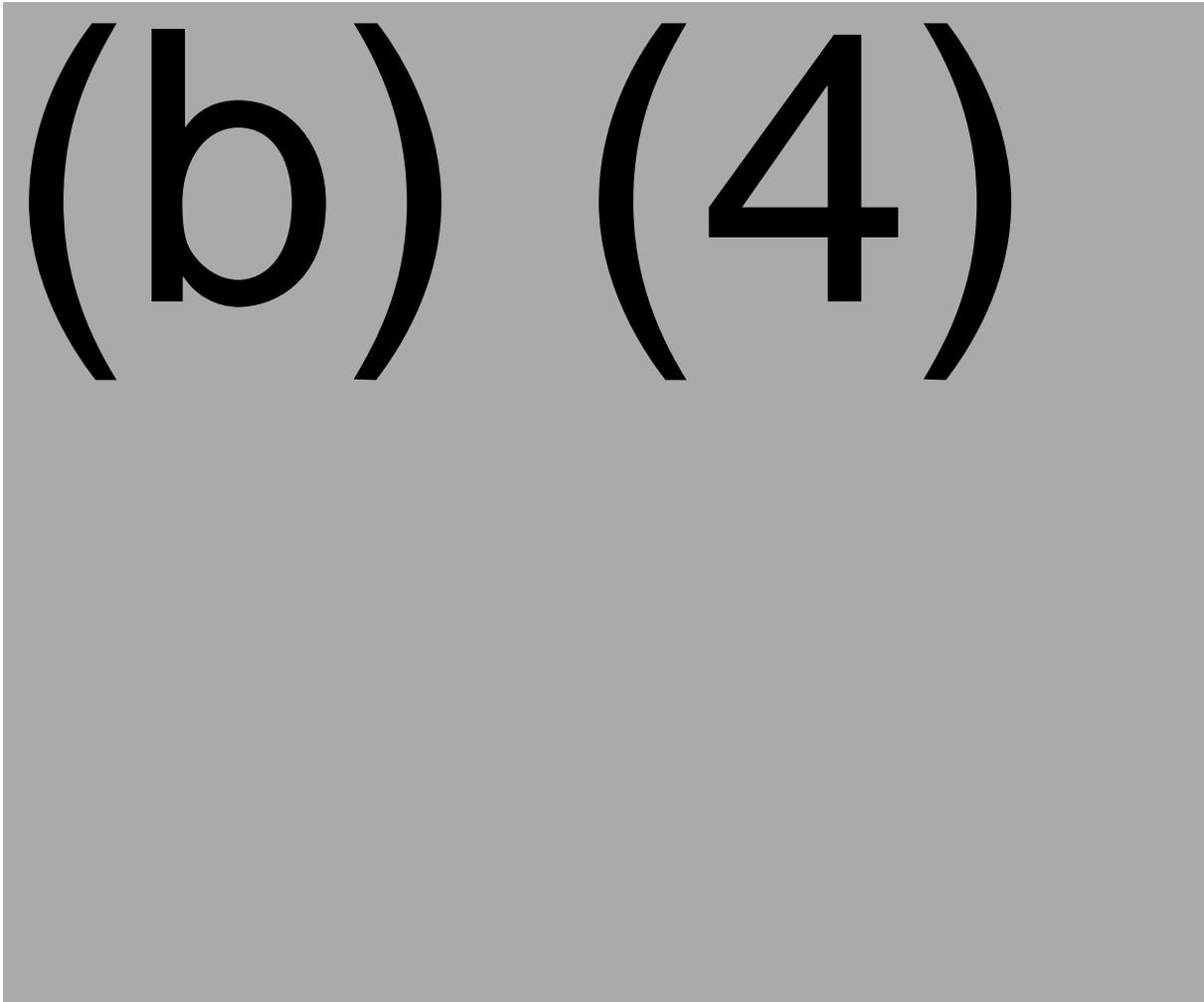
3.2.P.3.5.2 Process Performance Qualification (PPQ)

The objective of the PPQ was to demonstrate that the shipping, thawing, filtration, and filling steps of the manufacturing process are controlled effectively at the commercial scale to produce Drug Product that consistently meets the established product quality acceptance criteria.

3.2.P.3.5.3 PPQ Results

All process parameters and controls met the PPQ acceptance criteria as shown in the table below.

Table 75. Drug Product PPQ Process Performance



(b) (4)

(b) (4)

Reviewer's assessment: The Drug Product manufacturing validation was performed on the PPQ DP lot. All manufacturing process parameters were met. The PPQ lot was successfully processed and met the proposed commercial Drug Product specifications.

Additional PPQ Testing During Filling

In addition to performing routine sampling and release testing, additional in-process Drug Product vial samples were collected from the (b) (4) of the filling process to verify the routine sampling plan and to demonstrate consistency of the filling process as evidenced by those product quality attributes.

Table 76. Expanded PPQ Sampling

(b) (4)

(b) (4)

(b) (4)

Microbial Retention Study

The testing results indicate that exposure of the solution did not alter the ability of the (b) (4) filter to retain a challenge of (b) (4) at levels (b) (4). (b) (4) was retained on all filters tested. Additionally, the solution did not inhibit the ability of (b) (4) to pass through the (b) (4) filter control.

Reviewer comment: Based on the data generated at (b) (4), the (b) (4) filter is an appropriate filter for sterile filtering Drug Product solution.

3.2.P.3.5.5 Aseptic Process Simulation (Media Fills)

Media Fill Results

All acceptance criteria were met, none of the units were contaminated, all growth promotion tests of broth passed.

3.2.P.3.5.6 In-Process Hold Studies

The Drug Product is manufactured as a “continuous process,” where there is no in-process hold.

3.2.P.3.5.7 Validation of the Shipping Process

At the secondary packaging and labeling site, one vial of DP and two vials of Diluent will be placed in a carton with literature and overwrapped within a sealed foil pouch, and shipped in an ISC at $\leq -65^{\circ}\text{C}$ from the secondary packaging site to (b) (4) for storage and subsequent distribution to a limited number of Centers of Excellence for administration to patients.

Reviewer’s assessment: The shipping validation from the distributor (b) (4) to the Centers of Excellence is not provided in this BLA and is requested as a PMC.

Shipping validation will focus on transportation hazards such as temperature, shock, vibration and pressure that the DP and Diluent may encounter for both the semi-finished packaging presentation and the finished product packaging presentation within the commercial supply chain. The following will be applied when evaluating the results of the shipping studies:

- Packaging Inspection: DP and Diluent vials and packaging will be 100% visually inspected for damage and defects

- DP and Diluent Analytical Testing: DP and Diluent will be tested for select quality attributes and evaluated against control vials
- Shipping Temperature Profiles: The temperatures within the ISC will be verified to have maintained $\leq -65^{\circ}\text{C}$ throughout the shipping processes

CMC Reviewer Comments for the above description of product validation and Amendment #16: Deficiencies are:

- *A plan with little detail is provided; no shipping validation has been performed*
- *A third party logistic provider has not been selected; shipping expectations for the 3PL are not provided*
- *There is no indication the shipping validation will be completed before commercial operations*
- *No information regarding shipping container configurations that account for the different product formats shipped from (b) (4) or from (b) (4).*
- *Whether or not actual shipments or simulations are planned*
- *What testing will be performed pre- and post-shipping; in amendment #16 Spark proposed not to do testing.*

The deficiencies were confirmed and addressed in amendments 16, 25, 29, 30 and the mid-cycle meeting. At the mid-cycle meeting with Spark on 14 Sep 2017, FDA emphasized the importance of immediately beginning the shipping validation for DP and completing the shipping validation for DS. FDA requested that Spark provide a plan and a date when FDA could expect the product shipping validation reports. Spark provided this information in amendment 30; the expected date for the validation reports is November 30, 2017.

Spark requirements for selection of 3PL distributor are provided in amendment 25. These are

- Capable of storing product securely in validated freezers at $\leq -65^{\circ}\text{C}$
- Must utilize an approved courier service capable of executing secure shipments (via ground or air) in shipping containers that have demonstrated capability of maintaining product at $\leq -65^{\circ}\text{C}$. Selected 3PL and courier service employed must have extensive cold chain experience and routinely utilize (b) (4) shipping containers and temperature monitoring capability.
- Must comply with (b) (4), Good Storage and Distribution Practices for DPs
- Adheres to cGMP and GDP guidelines in a fully developed Distribution Management System
- Inventory Control Process featuring daily inventory counts of Spark DP
- Distribution site(s) within the US to ensure supply chain continuity

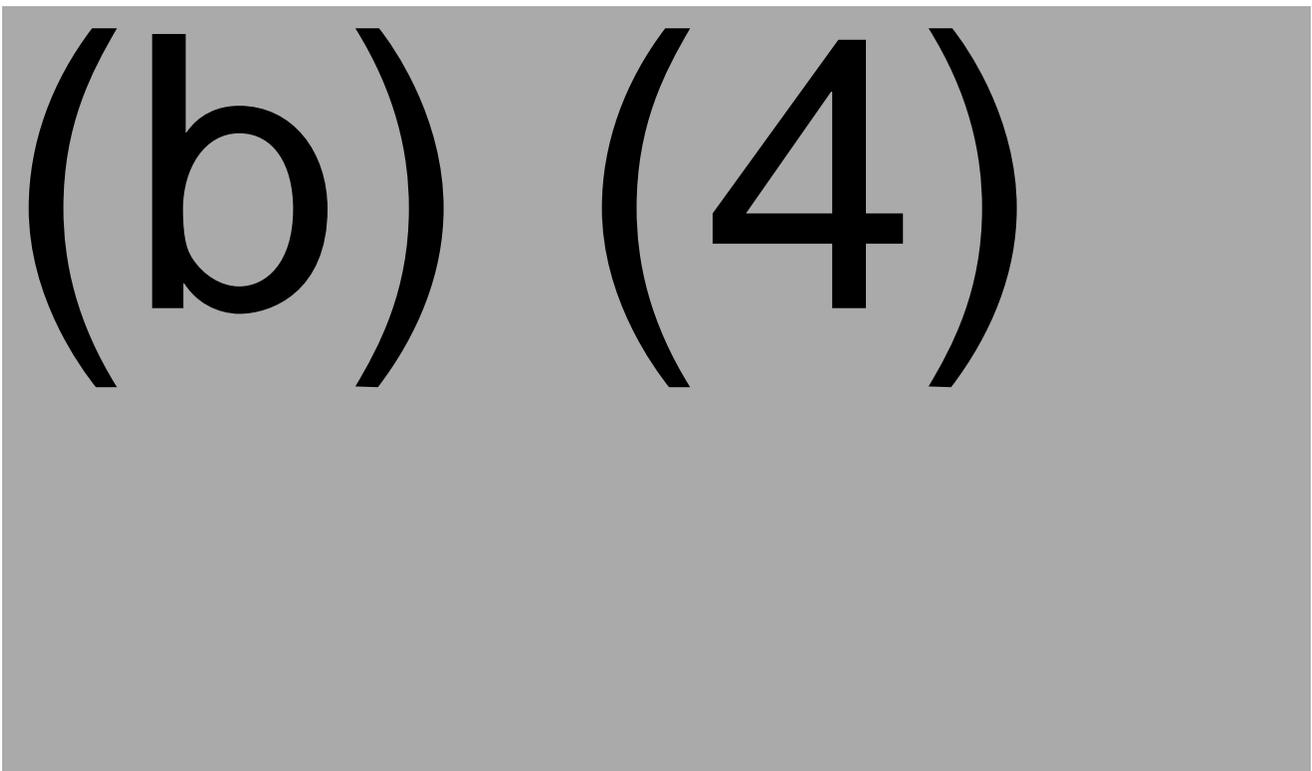
As a follow-up to the FDA IR of 01 Sep 2017 and the mid-cycle meeting of 14 Sep 2017, Spark provided a revised Shipping Validation Plan.

- DP and Diluent shipping validation will encompass shipping of DP and Diluent from the manufacturer, (b) (4), to the final packager, (b) (4) utilizing a pre-qualified (b) (4) shipper. DP and Diluent will be in

(b) (4) packed to prevent movement of contents. A temperature monitor will be placed in the shipment to record temperatures during transit.

- (b) (4) is (b) (4), approximately (b) (4) transport. It is anticipated that this segment, including ground transfers, will comprise a same day delivery.
- DP and Diluent will be shipped in the final packaging configuration from (b) (4) to Spark in the US utilizing a pre-qualified (b) (4) shipper. The final packaging configuration will include one vial of DP and two vials of Diluent in a tray with a product leaflet placed on top, all enclosed within a carton. The carton is then placed in a foil pouch which is sealed using a bar sealer. Shipments will be comprised of (b) (4) units of the final packaging configuration, packed to prevent movement of the contents. Due to a limited availability of DP vials, co-packaged units of Diluent vials will be used to fill out the shipments. A temperature monitor will be placed in the shipment to record temperatures during transit.

In Amendment 30 in response to discussion between FDA and Spark, the following figure was submitted to indicate the proposed packing of product.



- (b) (4) to Spark is (b) (4), approximately (b) (4). It is anticipated that this segment, including ground transfers and customs clearance, will comprise a delivery of less than (b) (4). If material from (b) (4) is received in under (b) (4), Spark will keep the shipment in the (b) (4) shipping container for a full (b) (4) prior to unloading the shipment and assessing temperature profile, damage and putting product on test.
- Spark will conduct the shipping study utilizing the Spark Philadelphia location as a representative shipping destination to simulate shipment durations from (b) (4) to the 3PL

location (s). These shipments represent a worst case shipping duration in that there are no shipping destinations in the continental US that would constitute a shipping leg greater than the air/ground shipment duration from (b) (4) to Philadelphia.

- DP will be placed in the worst-case locations within the shipping configuration (for example, (b) (4)) for all shipments. Remaining positions will contain Diluent to ensure the thermal mass of the shipment is representative of actual shipments.
- DP shipping validation will include three runs.
- Shipping temperature profiles and absence of damage will be evaluated.
- DP and Diluent will be tested pre- and post-shipment as shown in the table below. Acceptance criteria will be the same as for lot release.

Table 78. Quality Testing for Drug Product and Diluent Shipping Validation

Drug Product Quality Testing	Diluent Quality Testing
pH	pH
(b) (4)	(b) (4)
Appearance	Appearance
Vector genome titer	
(b) (4)	
Expression by (b) (4)	
(b) (4)	

Supportive Data for Drug Product Shipping from (b) (4) to Spark:

- Engineering lot utilized to support comparability of manufacturing for the site change from CHOP to Spark. All release acceptance criteria for this DP lot, (b) (4) were met.
- DP PPQ lot (b) (4) samples manufactured at (b) (4) and encompassing the majority of the lot were shipped to Spark and placed on stability. Lot release criteria were met.

The shipping conditions for these lots are representative of the condition under which DP will be shipped from (b) (4) to the 3PL with respect to distance, time, temperature and mode of transportation.

DP and Diluent vials will be shipped from the 3PL provider (provider not yet determined) in the final packaging configuration which is the pouch described above, (b) (4) and a temperature monitor. Shipments may be as small as one unit in a size-appropriate (b) (4) shipper.

Packing procedures will be provided for (b) (4) in a separate response to the Mid-Cycle Communication. Packing procedures for the 3PL will be provided upon selection of the provider in the coming weeks.

A telecon between Spark and FDA was held September 19, 2017 to discuss this plan. The telecon issues were documented in an IR request and responses by Spark to the IR were provided in amendment 30 and incorporated into this review. The following issues were discussed:

- FDA requested the final shipping reports with full data by October 31, 2017; Spark will look into the details of the shipping plan and get back to us with the likely date for receipt of the reports. Amendment 30 indicates that Spark anticipates a final report summarizing the

results of the DP shipping validation will be provided no later than November 30th. Should the anticipated date change, Spark will provide an update to FDA.

- It would aid the reviewers to have images of the packing steps, e.g., the packing configuration that occurs at (b) (4) such as the placement of the product and diluent vials in a tray, the tray in the carton, and the carton in the sealed pouch. In amendment 30, one image was provided of the vials in the tray and Spark expects to provide more at a later date.
- Spark will space the 3 shipments of product by at least (b) (4).
- Spark will provide a justification for not including the (b) (4) potency assay as part of testing for the shipping validation. The justification in amendment 30 is the scarcity of available product at the current time, time required for performing the assay and the FDA requested timeline. Spark will rely on the results of the (b) (4) assay. The reviewer finds this information acceptable.
- Spark will notify FDA if shipping validation plans change.

Reviewer comments: The reviewer believes an acceptable compromise has been reached whereby the Applicant will begin product shipping validation and we accept using partial but sufficient amounts of product for shipping and quality evaluation and agree to use Spark as a destination in place of a 3PL distributor.

Report TR2017-044 was received as amendment #54, received 04 Dec 2017, and describes Performance Qualification for DP PPQ Lot (b) (4) and Diluent Lot (b) (4) to demonstrate that the DP shipping process is adequate and reproducible in maintaining the required temperature and quality of DP and diluent during shipments from the manufacturer (b) (4) to the secondary packaging site (b) (4) and from the secondary packaging site to the US for distribution. The following shipping acceptance criteria were successfully performed for three separate shipments:

- *No visible damage or defects to container, final packaging, or load*
- *All shipments maintained temperature of $\leq 65^{\circ}\text{C}$ throughout the shipping process*
- *All pre- and post-shipment QC testing met established specifications*

Per FDA request (amendment #30 received 25 Sep 2017) a photograph of the shipping configuration is included.

FDA requested three separate shipments on three separate days. Report TR2017-044 shows that Spark did not do this. (b) (4) transportation shipments from (b) (4) were reported as follows: shipment 1 was on 17 Oct 2017 and transit time was (b) (4), shipment 2 was on 17 Oct 2017 and transit time was (b) (4), and shipment 3 was on 17 Oct 2017 and transit time was (b) (4). The same date and transit time indicate the 3 shipment were made together.

For (b) (4) shipments from (b) (4) to Spark, shipment 1 was on 30 Oct 2017 and transit time was (b) (4), shipment 2 was on 30 Oct 2017 and transit time was (b) (4), and shipment 3 was on 30 Oct 2017 and transit time was (b) (4). Spark notes that although the 3 shipments occurred the same day, each shipment was (b) (4).

As a whole, the information in report TR2017-044 and the demonstrated stability of DP at $\leq 65^{\circ}\text{C}$ in the stability studies indicate that the product can be successfully shipped from (b) (4) and from (b) (4) to Spark although the results are not as robust as they could be since some shipments occurred together. Validation of shipment of DS from (b) (4) and from (b) (4) to the US is acceptable.

During the BLA review, a Distributor for the DP was identified (see Amendment #58, received on 08 Dec 2017) as (b) (4) with sites in (b) (4). Spark will distribute from the (b) (4); the (b) (4) site is currently planned as a backup only for business continuity and risk management.

In amendment #58, the applicant indicated that DP will be stored at the approved storage condition of $\leq 65^{\circ}\text{C}$ in qualified freezers at (b) (4). Duration of storage at each location is variable. At (b) (4), it is anticipated that DP will be stored for (b) (4) days prior to shipment. However, depending upon production schedules, DP can be stored at (b) (4) at the approved storage conditions for the duration required with no specified time limit other than shelf life. At (b) (4), commercial distribution periods have yet to be determined. The applicant's intent is to store DP at (b) (4) and distribute as product demand determines, up to the entirety of shelf life.

Additional shipping validation studies were requested to demonstrate that the (b) (4) has adequate processes in place to ensure that DP lots will be properly shipped to the clinical site. This resulted in the PMC listed below. This is acceptable.

PMC: Spark Therapeutics, Inc. commits to provide the shipping validation study protocol for shipment of the Drug Product from the distributor to a clinical site (or to Spark Therapeutics, Inc.) by January 31, 2018. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by June 30, 2018.

Regarding the Labeling:

Initially, Drug Product and Diluent vials will be labeled at (b) (4), prior to freezing.

(b) (4)

Instructions for the labeling of the vials and boxes are described within the batch manufacturing record (BMR) - Inspection, Sampling and Labeling of Vials.

(b) (4) SOP1249, Generation and Control of Labels has been used to ensure that the printing and application of labels is controlled in accordance with cGMP guidelines and internal (b) (4)

procedures. This general SOP will be superseded by a product specific SOP for voretigene neparvovec-rzyl Drug Product and Diluent prior to commercial production.

3.2.P.3.5.8 Continued Process Verification

Continued process verification was initiated after the completion of the PPQ. The process will continue to be evaluated using the parameters and their acceptance criteria as outlined in the PPQ for a minimum of two additional manufacturing runs. This evaluation will be conducted to provide assurance that during routine production, the process remains in a state of control. The CPV program will be updated through the life-cycle of the product as more data is available to ensure consistency of the manufacturing process.

Reviewer’s assessment: The CPV study protocol was provided in amendment #37, received on 10/30/2017 and the protocol is acceptable. The applicant proposed to include the Continued Process Verification study report as a part of the Annual Report. The proposal is acceptable.

3.2.P.4 Control of Excipients

No excipients are added during Drug Product manufacturing. The excipients in the Drug Product are introduced during Drug Substance manufacturing. These excipients are described in [3.2.S.2.3 Control of Materials](#).

3.2.P.5 Control of Drug Product

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

Specification

The Drug Product tests and specifications are presented in table below. Compendial methods are noted and referenced.

Table 79. Drug Product Specifications

Assay	Test Site/Method #	Acceptance Criteria
Physicochemical		
Appearance (Visual Inspection)	Spark / QC028	Clear and colorless solution, free of visible particles
pH	Spark / QC020	(b) (4)
(b) (4)	Spark / QC019	(b) (4)
Concentration of Pluronic (µg/mL)	(b) (4)	(b) (4)
Extractable Volume (mL)	(b) (4)	(b) (4)
Identity		
Vector Genome Identity by (b) (4)	Spark / QC067	Positive for hRPE65v2
Concentration		

Vector Genome Concentration Assay (vg/mL)	Spark / QC062	(b) (4)
Activity/Potency		
Vector Infectious Titer Assay (vg/IU)	Spark / QC069	(b) (4)
Gene Product Expression by (b) (4) Assay	Spark / QC033	Positive for hRPE65v2 gene expression
<i>In Vitro</i> Relative Potency of (b) (4)	(b) (4)	(b) (4)
<i>In Vitro</i> Relative Potency of (b) (4) Assay	(b) (4)	(b) (4)
Purity		
Purity by (b) (4) Assay (%)	Spark / QC003	(b) (4)
Safety		
Endotoxin (IU/mL)	(b) (4)	(b) (4)
Particulate Matter	(b) (4)	(b) (4)
Sterility	(b) (4)	No Growth

Reviewer’s comments:

The acceptance criteria listed in table above include the revised criteria for pH, (b) (4), in vitro relative potency of (b) (4) by (b) (4) assay, in vitro relative potency of (b) (4) assay, and the specification for particulate matter, as agreed upon by the applicant (for details please refer to the Sections below under ‘Justification of Specification’ and to Sections 3.2.P.5.2, 2.3.S.4.1 and 3.2.S.4.5 under the respective assays). These revised acceptance criteria should be listed as the final acceptance criteria in Lot Release Protocol.

The units reported for endotoxin testing have been revised from EU/ml to IU/ml considering DBSQC’s IR (Amendment #55, received on 12/05/2017), informed the applicant that CBER has discontinued the U.S. Reference Standard Endotoxin (EU) roughly five years ago, and the only Reference Standard Endotoxin available now is the International Standard (IU). Since the EU and IU are equal units, and the EU standard is no longer available or used, so IU should be used from now on.

PMC: *Spark Therapeutics, Inc. commits to perform an analysis of the lot release test results obtained from all Drug Substance (DS) and Drug Product (DP) lots manufactured within the first (b) (4) following approval, and evaluate if the acceptance criteria for LUXTURNA lot release tests (including the (b) (4) assay, (b) (4) by (b) (4), residual plasmid DNA, and residual cesium) continue to provide adequate quality control for DS and DP based on the new data obtained from those tests. A final study report will be submitted as a “Postmarketing Commitment - Final Study Report” by March 31, 2020.*

Justification of Specification

Reviewer's comment: The approach used for DP specification was the same as that for DS; acceptance criteria were established based on a tolerance interval statistical approach using the historical process performance manufacturing data as described under Section 3.2.S.4.5.

For pH, (b) (4), Vector Genome Identity by (b) (4)

The specification remains the same for (b) (4) Drug Product; details are covered under [3.2.S.4 Control of Drug Substance](#).

Vector Genome Concentration by (b) (4)

The Drug Product specification of (b) (4) is (b) (4) of the label claim (5×10^{12} vg/mL). The Drug Product acceptance criterion is (b) (4)

(b) (4)

The justification is covered in [3.2.S.4 Control of Drug Substance](#).

In vitro Relative Potency of (b) (4) Assay

The Drug Product acceptance criterion for the (b) (4) Enzyme (b) (4) Potency assay is (b) (4)

(b) (4)

(b) (4)

(b) (4) [Redacted]

(b) (4) [Redacted]

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

Reviewer's comment: The SOPs used for each of the analytical procedures described below are listed for each test in Section 3.2.P.4.1. However, most SOPs were not submitted in the BLA. Several (b) (4) Drug Product release assays are the same, so only the release assays unique to Drug Product are described below and the related validation/verification information. The applicant has submitted verification reports to show suitability of some compendial methods. The (b) (4) potency assay is the only non-compendial release assay that is performed for Drug Product release (b) (4). Note, in Amendment #48, 2.1, the applicant has committed to add the (b) (4) potency assay to (b) (4)

[Redacted] . This is acceptable.

3.2.P.5.2.1 In vitro Relative Potency of (b) (4) Assay

The purpose of the 'In vitro Relative Potency of (b) (4) Assay' is to determine potency of the Drug Product gene expression product, RPE65, the retinal pigment epithelium-specific 65kDa protein (RPE65), a critical enzyme of the vertebrate visual cycle and encoded by RPE65 (gene). (b) (4)

[Redacted]

Reviewer's comments: The validation report was submitted under Amendment #42. The validation criteria set for the assay were met. Note that 'Repeatability' under Intermediate Precision was not assessed. The applicant reasons that the assay set up makes the assessment of repeat samples impractical because the (b) (4)

. This is acceptable, considering the (b) (4) results between analyst and from day to day for each target concentration ((b) (4)) are far lower than the set acceptance criteria; accordingly, the values for repeatability would be expected to be in that range too or lower.

The validation report for the (b) (4) Potency assay is comprehensive and the validation results show reasonable assay control for a multi-step quantitative biological assay. The validation is acceptable.

3.2.P.5.2.2 Endotoxin

The Endotoxin assay is conducted for quantitative determination of endotoxin in (b) (4)

. Refer to DBSQC review. No issues were found.

3.2.P.5.2.3 Particulate Matter

The Particulate Matter assay is a standard operating procedure for determining the quantity of particulate matter in small volume injections that is conducted using a (b) (4) in accordance with compendial methods (b) (4) and (b) (4). (b) (4)

. Results are reported as the number of particles $\geq 10 \mu\text{m}$ per container and the number of particles (b) (4).

Reviewer's comment: The Drug Product testing and specification for Particulate Matter was revised; specifically, applicant will use testing by (b) (4) used instead of (b) (4). Given that the Drug Product is diluted 1:10 in Diluent, the applicant proposed testing Drug Product according to (b) (4) with acceptance limits of (b) (4) and (b) (4). This was acceptable, and applicant was notified that if all DP lots are diluted prior to administration, then the particulate matter testing for the Diluent should also comply with (b) (4). Applicant has agreed to this, and specification for Drug Product, Section 3.2.P.5.1 and Diluent Section 3.2.P.5.1 has been modified accordingly. Please refer to the following communications with the applicant: Amendment #9, 1.4; Amendment #14, 1.1, and Amendment #25, 1.7.

Verification for (b) (4): Performance characteristics examined to demonstrate the suitability of this procedure for particulate analysis of AAV2-hRPE65 drug product (assay verification) should be included. In Amendment #31 1.2.1, applicant noted that verification for this compendial procedure method is not required as it is a basic compendial test procedures that is routinely performed (this is according to (b) (4) Verification of Compendial Procedures). The

applicant notes that for sub-visible particulate testing, the environment test as defined in (b) (4) is the basis for (b) (4). This is not adequate to assess the matrix effects and thus to demonstrate suitability of the procedure for the product. In Amendment #37, 6.1, the applicant has agreed to verify the assay with the diluent (same buffer composition as the buffer used for DS/DP formulation) due to limited availability of Drug Product sample. **The study report will be submitted as a PMC within 90 days of approval of the BLA (Amendment #48, 10.1).**

3.2.P.5.2.4 Extractable Volume

Volume confirmation of the extractable volume is performed using the (b) (4). Volume confirmation of the extractable volume is a standard operating procedure performed in accordance with compendial methods (b) (4).

Reviewer’s comment: Verification report for (b) (4) is not submitted. In Amendment #31, 1.2.1, applicant noted that verification for this compendial procedure is not required as it is a basic compendial test procedures that is routinely performed (this is according to (b) (4) Verification of Compendial Procedures). The applicant contends that Extractable Volume: (b) (4) is a basic compendial test procedure that does not require verification. **This is acceptable.**

3.2.P.5.2.5 Sterility

The Sterility test is conducted as described in a standard operating procedure for the determination the presence of viable microorganisms in Drug Product in accordance with compendial methods (b) (4) and (b) (4). Refer to DBSQC review. DBSQC reviewer has identified no issues.

3.2.P.5.4 Batch Analyses

A summary of batch information for Drug Product lot (b) (4) and batch analysis data are provided in following two tables. All results meet the acceptance criteria defined in the specification.

Table 81. Drug Product Summary Information

Lot #	Fill Date	Batch Use	# Vials	Container Closure	Volume	Fill Site
(b) (4)	(b) (4)	PPQ	(b) (4)	2 mL (b) (4) gray, (b) (4) 13 mm stopper, 6-bridge, Spark Lime Green (b) (4) ‘Flip-Off’ button long seal	0.5 mL	(b) (4) Building (b) (4)

Table 82. Drug Product Lot (b) (4) Analytical Result

Assay	Test Site/Method #	Acceptance Criteria for process	Revised Commercial Acceptance Criteria	Lot # (b) (4)

		qualification study		
Physicochemical				
Appearance (Visual Inspection)	Spark / QC028	Clear and colorless solution, free of visible particles	Clear and colorless solution, free of visible particles	Clear and colorless solution, free of visible particles
pH	Spark / QC020	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Spark / QC019	(b) (4)	(b) (4)	371
Concentration of Pluronic (µg/mL)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Extractable Volume (mL)	(b) (4)	(b) (4)	(b) (4)	0.5
Identity				
Vector Genome Identity by (b) (4)	Spark / QC067	Positive for hRPE65v2	Positive for hRPE65v2	Positive for hRPE65v2
Concentration				
Vector Genome Concentration Assay (vg/mL)	Spark / QC062	(b) (4)	(b) (4)	5 X 10 ¹²
Activity/Potency				
(b) (4)	Spark / QC069	(b) (4)	(b) (4)	(b) (4)
Gene Product Expression by (b) (4)	Spark / QC033	Positive for hRPE65v2 gene expression	Positive for hRPE65v2 gene expression	Positive for hRPE65v2 gene expression
<i>In Vitro</i> Relative Potency of (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
<i>In Vitro</i> Relative Potency of (b) (4) Assay	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Purity				
Purity by (b) (4)	Spark / QC003	(b) (4)	(b) (4)	(b) (4)
Safety				
Endotoxin (EU/mL)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Particulate Matter	(b) (4)	(b) (4)	(b) (4)	11 at (b) (4) 1 at (b) (4)
Sterility	(b) (4)	No Growth	No Growth	No Growth

Reviewer's comment: Lot (b) (4) has met all release criteria but is not planned for use as a commercial lot (per the information provided by the applicant during PLI). Acceptance criteria for commercial manufacturing have been revised. A separate column has been added to the above table. The PPQ lot met the revised AC.

3.2.P.5.5 Characterization of Impurities

Expected Impurities:

- Particulate Matter; Section 3.2.P.5.2.3
- Excipients: Section 3.2.P.2.1
- Leachables from Container Closure System(s): Section 3.2.P.7

Identification of Drug Product Impurities:

Table 83. Quantitation of Particulate Matter for Drug Product Lot (b) (4)

Impurity Test	Method	Specification	Manufacturing Site/Lot Number Spark/SPAd003
Particulate Matter	(b) (4)	(b) (4)	11 particles per container (b) (4) 1 particle per container (b) (4)

Reviewer's comment: The particulate matter for Lot (b) (4) is well below the specification set under (b) (4). Note, the applicant has agreed to revise this specification and that for the diluent to meet (b) (4). Refer to Reviewer's Comments under Section 3.2.P.5.2.3. Lot (b) (4) will meet (b) (4) specifications (b) (4). Particulate matter content was reported for Lot (b) (4) and the data shows that particulate matter content for Lot (b) (4) would also meet the release criteria for (b) (4). Amendment #9, under 1.4.

3.2.P.6 Reference Standards or Materials

The same reference standard is utilized for the Drug Product as the Drug Substance. Information on the reference standard is provided in 3.2.S.5, Reference Standards or Materials.

3.2.P.7 Container Closure System

Table 84. Description of the Container Closure System

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

(b) (4) [Redacted]

[Redacted]

[Redacted]

Component supplier information and references to MFs are provided in the table below. Spark has obtained Letters of Authorization to cross reference these MFs.

Table 85. Component Supplier Information

Component	DMF Holder	Drug Master File Number
(b) (4)	(b) (4)	(b) (4)
Stopper Formulation	(b) (4)	(b) (4)
Stopper	(b) (4)	(b) (4)
Seal	(b) (4)	Not Applicable

Vial

The materials of construction for vials and stoppers comply with the current version of the compendia. The components may be tested in-house or accepted on the basis of the supplier's

COA or Certificate of Conformance. Acceptance criteria are provided in the following tables. The specifications for the vials are provided in the next table. A sample Quality Certificate with test results is presented in COA no. (b) (4) .

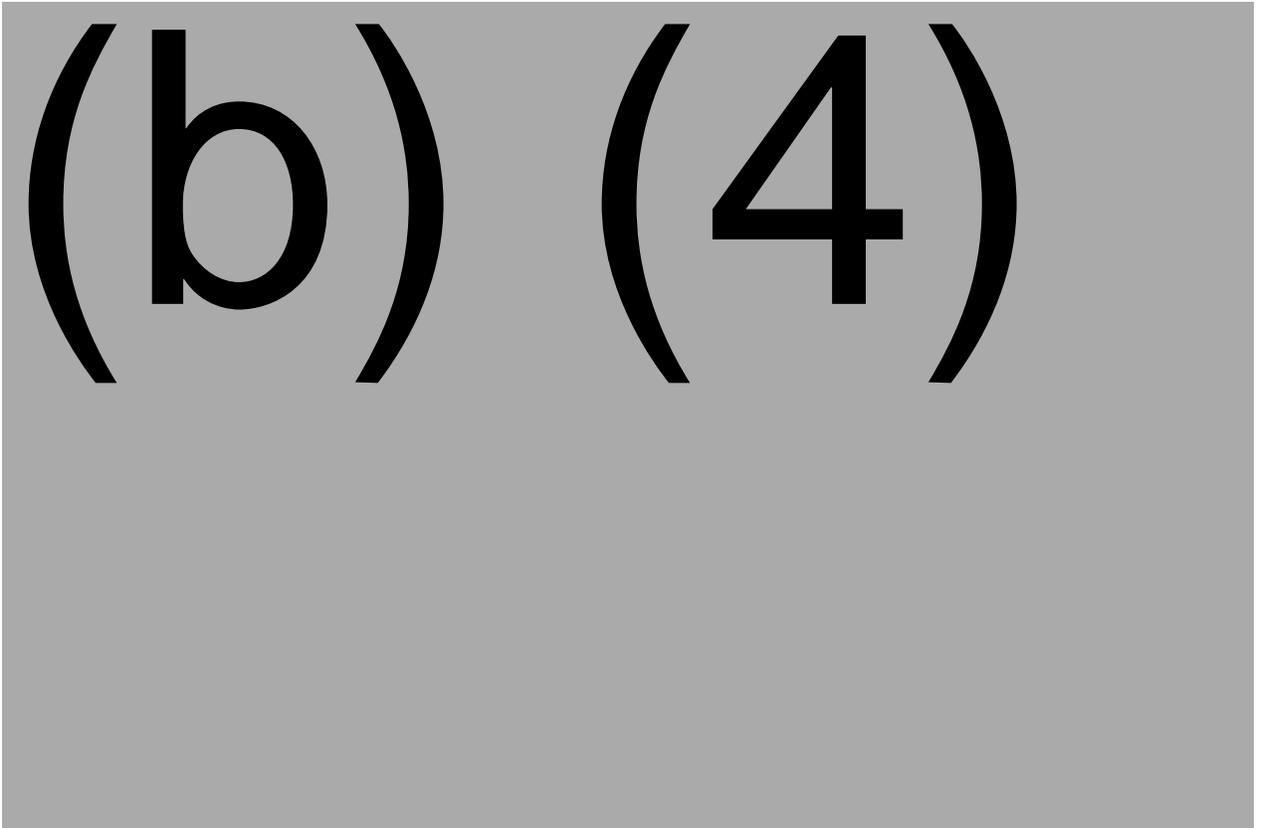
Table 86. Vial Release Specifications



Stoppers

Specifications for the stoppers are provided in COA no. (b) (4) and the next table.

Table 87. Stopper Release Specifications



Seals

Spark has sourced and acquired inventory of seals and, in turn, supplies these seals to (b) (4) prior to scheduled fills. At (b) (4), the seals are cleaned, dried, and repackaged for (b) (4) sterilization by (b) (4).

Table 88. Seal Release Specifications



3.2.P.7.2 Component Sterilization

The (b) (4) vials are purchased pre-sterilized, read to use. The stoppers are subdivided at (b) (4) and (b) (4) sterilized at (b) (4) prior to use. The seals are subdivided and each pack is labeled with preparation details and sterilized by (b) (4).

3.2.P.7.3 Compatibility, Toxicity and Biological Test Data

Although the (b) (4) storage condition for DP mitigates concerns for extractables and leachables, a study was performed by (b) (4) on the combination of a 2 ml (b) (4) vial and a (b) (4) 13 mm (b) (4) gray stopper with (b) (4). A semi-quantitative extractables profile was created for each component making up the container closure system for voretigene neparvovec-rzyl DP.

The scope of the study included duplicate extraction of one lot of each component in various solvents. Extracts were analyzed by:

- (b) (4)

(b) (4) risk-based assessment was performed on observed organic extractable species.

There were no significant (b) (4) detected via (b) (4) in any of the extracts of the (b) (4) Vials. There were no significant (b) (4) detected via (b) (4) in the (b) (4) extracts of the Stoppers. Detailed results are provided in Extractables Study Report 2016000300. A risk-based analysis was performed to determine the requirements for leachables testing. Results are included in the report. Given the frozen condition for DP storage, it was determined that there is a low risk for leachables.

3.2.P.7.4 Container Closure Integrity

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) and under (b) (4) conditions). In the first supporting study, (b) (4) demonstrated CCI using a (b) (4) method for the (b) (4) 2 ml, 13 mm RU vial, (b) (4) Gray (b) (4) RU 13 mm serum stopper, and 13 mm Flip Off® seal combination of components. Results of this CCI study can be found in Technical Report 2010-014 for (b) (4) 2 ml RU Vial-Ready Pack Stopper CCI Evaluation. In another (b) (4) study with these components, (b) (4) demonstrated that CCI was maintained under cold conditions, including (b) (4) storage. Results of the CCI are presented in Container Closure Integrity of Rubber-stoppered Glass and Plastic Vials Stored at (b) (4).

In another supporting study, (b) (4) confirmed CCI (b) (4) by demonstrating that (b) (4) did not penetrate the closed SPK-RPE65 (b) (4) vials under extended (b) (4) conditions. CCI was confirmed in this study by demonstrating that no (b) (4) penetrated the container closure system during an (b) (4) cycle, which is (b) (4) the end of SPK-RPE65 vial filling process.

CCI was confirmed in a study conducted by (b) (4) using vials filled and finished at (b) (4). This 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 DP and Diluent) post-storage (b) (4). Results of the study confirmed CCI of the 2 ml (b) (4) vials post storage (b) (4) conditions.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The stability protocol and results for the primary stability study using the Process Performance Qualification (PPQ) Drug Product (lot #(b) (4)) are provided and summarized. As only a limited amount of primary stability data is currently available, data from a series of supporting stability studies has also been provided. The data from the supporting stability studies performed at Spark has been used to generate shelf-life estimates based on statistical analyses. Additional data from the ongoing primary stability study will be provided as it becomes available in order to support the proposed shelf-life.

Reviewer comment: amendment #16 submitted on August 17, 2017 has 6-month stability data and amendment #38 submitted on November 1, 2017 has 9-month stability data.

3.2.P.8.1.1 Overview of Studies Performed

The primary stability data were obtained for one PPQ lot of DP (lot (b) (4) (DP)). At the time of submission, 3 months of stability data at 3 separate stability conditions (b) (4) are available. All test methods used have been validated and/or qualified for their intended purpose.

Two sources of supporting stability data are available: the two clinical lots of voretigene neparvovec-rzyl, and five sets of data from three Engineering lots of material manufactured at Spark (see tables below).

The two clinical lots were (b) (4) filtered prior to being hand filled into polypropylene cryovials. (b) (4)

(b) (4) of the Spark Engineering lots were evaluated in (b) (4) presentations for each lot:

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

The container is expected to have a greater impact on the stability profile of the AAV2-hRPE65v2 material than the mechanism and location of filling (i.e., hand-filling at Spark vs. metered peristaltic pump-filling at (b) (4)). Any material stored in (b) (4) vials is treated as DP whereas those stored in polypropylene cryovials are treated as (b) (4). The Applicant claimed that the (b) (4) DP samples from a single lot were tested independently, and that these samples may be considered as separate samples yielding separate data sets.

CMC reviewer comment: DS and DP samples from a single lot stored in different containers are were not considered independent samples for the analysis by the reviewer.

Table 89. 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
	Supporting	Drug Product	Spark	0.5 mL	(b) (4) Vial ¹
	Supporting	Drug Product	(b) (4)	0.5 mL	(b) (4) Vial ¹
	Supporting	Drug Substance	Spark	0.5 mL	Cryovial ²
	Supporting	Drug Product	Spark	0.5 mL	(b) (4) Vial ¹
	Supporting	Drug Substance	Spark	0.5 mL	Cryovial ²
	Supporting	Drug Product	CHOP	1 mL	Cryovial ²
	Supporting	Drug Product	(b) (4)		Cryovial ²

¹ Vial - 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

² (b) (4) 1.5 mL sterile polypropylene cryogenic vial, with silicone gasket

Shelf life estimates were determined based on statistical modeling of the quantitative stability data for the Spark manufactured material. Data from voretigene neparvovec stored both in polypropylene and (b) (4) containers were used. Stability profiles were statistically consistent for data from voretigene neparvovec stored in both cryovials and (b) (4) vials and justified combining results for statistical analysis of the Vector Genome Concentration, (b) (4), pH and Vector Purity by (b) (4) results. Spark has determined that the available data support a shelf life of (b) (4) according to ICH Q1E. (b) (4)

The (b) (4). And, they claimed that this best meets the needs for time between DS manufacture and DP manufacture and distribution of the DP.

CMC Reviewer Comments: The proposed shelf life was not acceptable, based on the limited amount of data that they provided.

IRs sent 04 Aug 2017 requesting 6-month stability data and 19 Sep 2017 requesting 9-month stability data informed Spark that the DP expiration date should be based on real time stability data. At the late cycle meeting telecon of 07 Nov 2017, Spark was notified that the statistical analyses that were submitted in the BLA to determine expiration were not acceptable because estimates for functional properties of the DP were not performed. FDA communicated that Spark was welcome to suggest an expiration based on real time stability data that followed Q5c. FDA agreed to discuss this issue during a follow-up telecon. On 15 Nov 2017, FDA received a pre-read file from Spark that proposed an expiration for DS of (b) (4) and an expiration for DP of 18 months. During the telecon of 16 Nov 2017, FDA agreed with the proposed expirations for DS and DP.

3.2.P.8.1.2.1 Primary Stability Studies, Results and Discussion

The primary stability study for DP ((b) (4) (DP)) is summarized in the following table. Stability data at (b) (4)

Table 90. Primary Stability Studies for Drug Product

Lot #	Purpose	Drug Substance Mfg Site	Drug Product Mfg (Fill) Site	Fill Date	Storage Conditions ¹	Available Data (Months)	Status
(b) (4) (DP) (PPQ)	Process Performance Qualification	Spark	(b) (4)	November 2016	(b) (4)	3, 6, 9	Ongoing
					(b) (4)	3, 6, 9	Ongoing
					(b) (4)	3, 6	Ongoing

¹ Temperatures of (b) (4), ≤ -65 °C, and (b) (4) are all considered to be the accepted storage temperatures when stored in a (b) (4) stability chamber and should be interpreted as the same storage condition.

The protocol for the primary stability and the specifications against which the data are assessed are provided in following tables:

Table 91. 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.

Table 92. 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)

Results from the primary stability study demonstrate product stability for at least 9 months at the long term storage conditions. Several attributes show a decline at the accelerated condition of (b) (4) over the 3 and 6 month periods, which demonstrates the stability-indicating property of the associated test methods. The test methods used for the PPQ lot have been fully optimized, qualified, and/or validated, as appropriate.

3.2.P.8.1.2.2 Supporting Stability Studies, Results and Discussion

The two sources of supporting stability data are summarized in the table below.

Table 93. Supporting Stability Studies for Drug Product

Lot#	Purpose	DS Mfg Site	DP Mfg (Fill) Site	Fill Date	Storage Conditions	Available Data (Months)	Status
(b) (4)	Engineering #4	Spark	Spark	October 2015	(b) (4)	12	Ongoing
	Engineering #3	Spark	(b) (4)	22 Dec 2015		12	Ongoing
						6	Completed
						6	Completed
	Engineering #3	Spark	NA	September 2015		12	Ongoing
						6	Completed
						3	Completed
	Engineering #1, Container Material Study (b) (4) vial)	Spark	Spark	July 2015		12	Ongoing
						18	Ongoing
						6	Completed
						1	Completed
	Engineering #1, Container Material Study (Cryovial)	Spark	NA	July 2015		12	Completed
						18	Completed
6					Completed		
						1	Completed
Clinical	CHOP	CHOP	February 2014	(b) (4)	Completed		
Clinical	CHOP	(b) (4)	January 2007	(b) (4)	Completed		

Results from the two clinical lots of DP manufactured at CHOP and used for all the clinical studies support the stability of the DP. Specifications were met throughout the duration of both studies ((b) (4) for lot (b) (4) and (b) (4) for lot (b) (4) when stored at the (b) (4) storage condition. The results demonstrate the consistency of the product when stored at the (b) (4) storage condition.

Statistical analyses were applied to the Spark supportive stability data to examine both container-based differences as well as to extrapolate shelf life estimates. An initial study focused on lot (b) (4) (Engineering Lot 1), which was stored in three containers of different materials to determine if any statistically significant differences existed based on the container material in

which the DP was stored across the (b) (4) different stability conditions monitored (b) (4) . Data from (b) (4) assays with numerical outputs (vector genome concentration, (b) (4) , pH, and purity by (b) (4)) were examined. All (b) (4) responses showed very little change across time at both (b) (4) regardless of container material. Most importantly, pH was not observed to significantly change over time at any of the (b) (4) stability conditions, but a significant difference in the measured pH value was observed across container material types, with glass vials reporting higher pH values than DP stored in either (b) (4) vials or cryovials. Based on this result, only data from DP stored in either (b) (4) vials or cryovials were used to determine shelf life estimates.

Reviewer comments: Of the (b) (4) numerical output assays, only (b) (4) of them provided data amenable to statistical analysis for shelf life estimation. The analyses produced shelf life estimates from genome concentration of (b) (4) .

For (b) (4) , the shelf life estimates were (b) (4) .

These estimates were incomplete because functional assays of viral vector were not included. See review section [3.2.P.8.1](#) for additional information.

3.2.P.8.1.2.3 Forced Degradation Studies

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted]

(b) (4)

(b) (4)

[Redacted]

3.2.P.8.1.3 Reviewer Conclusions and Recommended Shelf Life

Spark applied statistical modeling of the supporting engineering lots to estimate a shelf life of (b) (4) for storage at $\leq 65^{\circ}\text{C}$. This estimate is based on a combined analysis of (b) (4) DP samples and stability testing of two stability-indicating, structural properties of voretigene neparvovec, genome concentration and (b) (4). One functional property of voretigene neparvovec was available for the engineering lots but the data were too variable for analysis of shelf life. The Spark statistical analysis for each test follows the advice given in (b) (4). This guidance also recommends the individual analysis of all quantitative stability-indicating tests, and the test with the shortest estimated shelf life would be used for product shelf life. Stability data from the primary lot at (b) (4) showed that RPE65 (b) (4) and RPE65 expression by (b) (4) are functional, stability-indicating tests. These two tests were not performed for the engineering or clinical supporting lots. Because of the lack of functional tests in the Spark shelf life estimation, Spark's statistical estimation of shelf life was not accepted. Instead, data from the primary DP stability lot will be used to recommend DP shelf-life ((b) (4)).

With receipt of amendment #38 on November 1, 2017, Spark has now submitted 9 months of primary stability data that include both structural and functional tests. The 9-month data

indicate voretigene neparvovec is stable at $\leq -65^{\circ}\text{C}$. Based on the time from pulling samples for analysis to receipt of stability data at FDA, the reviewer estimates 12-month data could be available during the first week in February 2018 and 18-month data could be available during the first week in August 2018. A rigorous estimate of shelf life would be 9 months; a conservative estimate of shelf life would be 12 months; a less conservative estimate of shelf life, but supported by stability data for engineering lots (12 months) and clinical lots ((b) (4) [redacted]), would be 18 months for DP. The clinical lots manufactured in the CHOP facility and the lots manufactured in the Spark facility are comparable. The reviewer suggests 18 months shelf life that can be extended when more primary data are available.

Reviewer Comments: During the late cycle telecon of 09 Nov 2017, Spark was notified that the statistical analyses that were submitted to the BLA for determination of expiration were not acceptable because estimates for functional properties were not performed. FDA communicated that Spark was welcome to suggest expiration based on real time stability data that followed Q5c. During the follow-up telecon on 16 Nov 2017, Spark and FDA agreed on (b) (4) [redacted] 18 months expiration for DP. Spark submitted this information in amendment #48 received on 28 Nov 2017.

3.2.P.8.2 Post-Approval Stability Study

Post-Approval Stability Protocol

The provisional post-approval stability protocol for DP is presented in below. Scheduled testing at time points earlier than 12 months may be removed and/or re-evaluated after completion and availability of long term and intermediate stability data from the PPQ lot and/or long term stability data from subsequent lots of DP placed on stability. Any revisions will be provided in a submission. The provisional stability specifications are unchanged from the BLA specifications.

Table 94. Drug Product Post-Approval Stability Protocol (Long Term Stability Study: (b) (4) [redacted] Storage Condition)

0 ¹	6	9	12	18	(b) (4) [redacted]
A,C,E,F	A,B,F	A,B	A,B,D,F	A,B,F	(b) (4) [redacted]

¹ Release data used as t=0 data point.

A = Appearance, pH, (b) (4) [redacted], Titer by (b) (4) [redacted]

Gene Expression (b) (4) [redacted]

B = Potency

C = Genome ID, Endotoxin

D = CCIT

E = Sterility

F = (b) (4) [redacted] Potency

Reviewer comment: In accordance with amendment #48 submitted 28 Nov 2017, the above post-approval protocol was modified by including the (b) (4) [redacted] potency assay.

Post-Approval Stability Study

In addition to reporting the results from the ongoing stability studies, Spark Therapeutics commits to the following:

- Complete the ongoing registration lot stability studies.
- Commit to placing the next (b) (4) post-approval DP lots on stability following the Post-Approval stability protocol.

Reviewer comment: In accordance with amendment #48 submitted 28 Nov 2017, Spark modified the stability protocol for ongoing stability studies in the BLA. The modification is the second bullet above.

Extension of Expiry Period

Any extension of the approved expiry period will be supported by data from long-term stability studies that will be filed to the application with copies of revised labeling.

3.2.P.8.3 Stability Data

CMC Reviewer Comments: This section provides stability data for both the primary stability study consisting of the Spark PPQ lot, and the supporting stability studies, consisting of CHOP clinical lots and Spark engineering lots. The data are summarized in multiple tables. The first table directs the reader to the next three tables that contain the primary data for the DP, PPQ lot (b) (4). The data are analyzed and discussed in module 3.2.P.8.1. A summary of the length of time the supporting lots were assessed for stability is found in the table of supporting lots.

3.2.P Diluent

3.2.P Diluent.1 Description and Composition

The Diluent for voretigene neparvovec-rzyl (Diluent) is a frozen aqueous solution containing an identical formulation of the inactive ingredients to that of the Drug Product without the active substance.

3.2.P Diluent.3 Manufacturing

3.2.P Diluent.2 Pharmaceutical Development

Table 95. Diluent Excipients

Excipient	Function	Quality Standard	Concentration
Sodium Chloride	(b) (4)	(b) (4)	180 mM
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

(b) (4) P188	(b) (4)	(b) (4)	0.001%
Water for Injection (WFI)	Physiologically aqueous solvent	(b) (4)	quantum sufficit

Formulation Development

The formulation of the Diluent is identical to the Drug Product to ensure a consistent matrix of these excipients during and after dilution of the Drug Product. Thus, the functions of the formulation excipients in the Drug Product, as well as the rationale for their use, extend to the same excipients in the Diluent.

Table 96. Diluent Batches Used in Clinical, Engineering, and Stability Studies

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

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

(b) (4)

(b) (4)

Manufacturing Process Control Strategy

The control strategy was designed to ensure that the Diluent commercial manufacturing process will consistently deliver Diluent with the specified product quality. Process control is achieved through control of excipients, process parameters, in-process controls, in-process specifications, and release testing.

Container Closure System

The container closure system for the Diluent is a 2 mL (b) (4) vial, closed with a 13 mm serum stopper, and then secured with a 13 mm aluminum flip-top seal. This is the identical container closure system for voretigene neparvovec-rzyl Drug Product.

Compatibility (Diluent)

The primary packaging components of the container closure system are in direct contact with the Diluent. Compatibility of the vial and stopper with the Diluent has been demonstrated during primary and supporting stability studies.

3.2.P Diluent.3.1 Manufacturer

(b) (4)

3.2.P Diluent.3.2 Batch Formula

Table 97. 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	180 mM	(b) (4)
(b) (4) (Poloxamer 188, Pluronic (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	0.001%	(b) (4)
Water for Injection (WFI) Quality Water (b) (4)) (b) (4)	q.s.	Solvent

3.2.P Diluent.3.3 Description of Manufacturing Process and Process Controls

Preparation of (b) (4) P188 (b) (4)

(b) (4)

Diluent Solution Compounding

(b) (4)

(b) (4)

Sterile Filtration

Sterilization is accomplished by filtration through (b) (4)

(b) (4)

Vial Filling, Stoppering, and Capping

Following filtration, the Diluent is filled, stoppered and sealed (b) (4)

Diluent is filled into 2mL (b) (4) vials to a predetermined filling (b) (4). This fill (b) (4) corresponds to a target fill volume of (b) (4), which is based on the label claim of 1.7 mL (b) (4). Filled vials are stoppered with sterile serum stoppers, and manually crimped in place with sterilized aluminum seals.

(b) (4) are performed periodically thorough the aseptic filling process to confirm that all vials tested are within the (b) (4) acceptable range.

Inspection, Bulk Packaging, and Storage

Upon (b) (4), the filled vials are stored at (b) (4) to await visual inspection. 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 loses 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.

Diluent Shipment

During commercial distributions, the Diluent is shipped (at ≤ -65 °C) from the filling site to the secondary packaging and labeling site in insulated shipping containers (ISC) of semifinished vials (vials with primary labels applied).

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

Table 98. Critical Process Parameters (CPPs) and Acceptance Ranges

(b) (4)

Table 99. Critical In-Process Controls (CIPCs) and Acceptance Ranges

(b) (4)

Table 100. Processing Time Limits for the Diluent Manufacturing Process

Process Time Limit Description	Time Limit
Time limit from commencement of Diluent solution preparation to completion of aseptic filtration (b) (4) .	(b) (4)

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

Process validation and evaluation of the Diluent manufacturing process was conducted on PPQ lot to confirm process consistency and control to reliably meet established Diluent acceptance criteria. The validation of the Diluent manufacturing process is comprised of a Process Performance Qualification (PPQ) protocol performed at commercial manufacturing scale, Diluent release testing as well as supporting studies executed for Drug Product, such as filter validation and media fills, and the approach to shipping validation, that are also applicable to the Diluent.

Table 101. PPQ Process Performance

(b) (4)

(b) (4)

(b) (4) [Redacted]

Additional PPQ Sampling

In addition to performing routine sampling and release testing, additional in-process Diluent vial samples were collected from the (b) (4) [Redacted] of the filling process to verify the routine sampling plan and to demonstrate consistency of the filling process as evidenced by those product quality attributes.

(b) (4) [Redacted] Process Intermediate Testing

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

Reviewer's assessment: The Diluent manufacturing validation was performed on the Diluent PPQ lot. All manufacturing process parameters were met. The Diluent PPQ lot was successfully processed and met the proposed commercial Diluent specifications.

3.2.P Diluent.4 Control of Excipients

The Diluent excipients (raw materials) and corresponding (b) (4) QC Release Codes are listed in following table. The excipient manufacturers quote meeting various Pharmacopoeial grades. Upon receipt at (b) (4), testing is performed to certain Pharmacopoeial specifications only, typically USP or Ph Eur, and sometimes the more stringent of these tests also meets other Pharmacopoeial tests.

Table 102. Control of Diluent Excipients

Excipients	Manufacturer	(b) (4) QC Release Code
(b) (4) P188 (Poloxamer 188, Pluronic (b) (4)), (b) (4)	(b) (4)	A801
Sodium Chloride, (b) (4)	(b) (4)	A075
(b) (4)	(b) (4)	A321
(b) (4)	(b) (4)	A020
Water for Injection, (b) (4)	(b) (4)	A480
Water for Injection, (b) (4)	(b) (4)	A152

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

3.2.P Diluent.5 Control of Diluent

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

Table 103. Product Diluent Test Methods, Specifications and Justification

Assay	Test Site and Method number	Acceptance Criteria	Justification
<i>Physiochemical</i>			
Appearance (Visual Inspection)	Spark Therapeutics, Inc. QC028	Clear and colorless solution, free of visible particles	Expected result based on scientific knowledge and regulatory requirement
pH	Spark Therapeutics, Inc. QC020	7.3 (b) (4)	Demonstrated suitability throughout product development
(b) (4)	Spark Therapeutics, Inc. QC019	(b) (4)	Demonstrated suitability throughout product development
Concentration of Pluronic	(b) (4)	(b) (4)	Tolerance intervals based on historical data
Particulate Matter	(b) (4)	(b) (4)	Regulatory requirements
Extractable Volume	(b) (4)	(b) (4)	Regulatory requirements
<i>Safety</i>			
Sterility	(b) (4)	No growth	Regulatory requirements
Endotoxin	(b) (4)	(b) (4)	Regulatory guidance

Reviewer's comment:

Table 105 includes the revised acceptance criteria for pH, (b) (4), and the specifications for particulate matter testing. Please refer to the reviewer comments made under Section 3.2.P.5.2.3. Note, Data provided in BLA 3.2.P.5.6.1 in the submission that summarizes the approach to setting acceptance criteria for the diluent; the updated Particulate Matter testing is listed under 3.2.P.5.1 Specifications (Diluent).

The units reported for endotoxin testing have been revised from EU/ml to IU/ml considering DBSQC's IR (Amendment #55, received on 12/05/2017), informing the applicant that CBER has discontinued the U.S. Reference Standard Endotoxin (EU) roughly five years ago, and the only Reference Standard Endotoxin available now is the International Standard (IU). Since the EU and IU are equal units, and the EU standard is no longer available or used, so IU should be used from now on.

The justification provided for specification set for concentration of Pluronic is the tolerance intervals based on historical data (as described under Section) which does not include any diluent batches made at (b) (4).

The BLA submission contains data for a single batch of diluent (b) (4) which meets all acceptance criteria (Section 3.2.P.5.4).

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

The analytical assays used for diluent testing are similar to that used for testing of Drug Substance, or Drug Product, and are described (and reviewed) under the sections as described in the table above. The related validation/qualification study is reviewed under Section 3.2.S.4.2 of this review memo, unless noted as reviewed by DBSQC.

Reviewer's comment: Note, the change in specification for particulate matter from (b) (4) as listed in the table above to (b) (4) as agreed with the applicant. Please refer to the Diluent test methods and specification in Section 3.2.P.5.1, and to the corresponding reviewer comments made under Section 3.2.P.5.2.3.

For concentration of Pluronic; Method Validation Report - SPK-02-01; the (b) (4) used for Diluent testing is similar to that used for Drug Substance and Drug Product except that the Diluent does not require any sample preparation ((b) (4)) before (b) (4) analysis. Additional details under Section 3.2.S.4.2.24 of this review memo.

Sterility

Testing of the diluent by membrane filtration sterility test is performed in accordance with (b) (4)

Validation: Refer to DBSQC review. DBSQC reviewer has identified no issues.

Endotoxin

Validation: Refer to DBSQC review. DBSQC reviewer has identified no issues.

Batch Analyses

Table 104. Diluent Summary Information

Lot #	Fill Date	Batch Use	# Vials	Container Closure	Fill Volume	Fill Site #
(b) (4)	19Dec2016	PPQ	(b) (4)	2 mL (b) (4) gray, (b) (4) 13 mm stopper, (b) (4) 13 mm, 6-bridge, matte (b) (4) white, Flip-Off seal	1.7 mL	(b) (4) Building (b) (4)

Table 105. 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)	(b) (4)
(b) (4)	Spark Therapeutics, Inc.	QC019	(b) (4)	(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)

3.2.P Diluent.7 Container Closure System

The container closure system is the same as described for DP with one exception. For the diluent the matte top button is white and for DP it is green.

Component sterilization, container closure extractables and leachables, and container closure integrity were the same as for the DP.

3.2.P Diluent.8 Stability

3.2.P Diluent.8.1.1 Overview of Studies Performed

Three lots of Diluent have been placed on stability as shown in Table 106. Diluent Stability Studies. The primary stability data consist of one lot of diluent stored in the intended commercial container closures (2.0 mL (b) (4) vials with Chlorobutyl stoppers) – lot (b) (4). The same stability protocol was also used for one of the supporting stability studies. Six months of stability data (Amendment #38 received November 2, 2017) are available for lot (b) (4). All available data demonstrate diluent stability across all available time points.

Two supporting stability studies are available for diluent. One clinical diluent lot, manufactured and tested at CHOP, lot (b) (4), was stored in 2.0 mL polypropylene cryovials. Lot (b) (4) was placed on stability at (b) (4) for (b) (4). All specifications were met throughout the (b) (4) study.

Additionally, an engineering lot of diluent, manufactured at (b) (4) and tested at Spark, lot (b) (4), has been placed on stability. The stability protocol for (b) (4) is shown

in the Table 107. Diluent Stability Protocols – Primary and Supporting Stability Studies (Lots (b) (4)). Twelve months of stability data (Amendment #38 received November 2, 2017) are available for lot (b) (4) at (b) (4) different stability conditions ((b) (4)).

The proposed commercial stability specification for voretigene neparvovec-rzyl diluent is provided in Table 108. Diluent Drug Product Shelf-life Specification.

Table 106. Diluent Stability Studies

Batch #	Manufacturing Date	Manufacturing Site	Storage Conditions	Available Data (Months)	Package Configurations
(b) (4)	December 2016	(b) (4)	(b) (4)	6 6 6	2.0 mL (b) (4) Vial, Chlorobutyl Stopper
	November 2015	(b) (4)		12 12 12	2.0 mL (b) (4) Vial, Chlorobutyl Stopper
	May 2007	CHOP		(b) (4)	(b) (4) Polypropylene Cryovial

Table 107. Diluent Stability Protocols – Primary and Supporting Stability Studies (Lots (b) (4))

Study	Time Intervals (Months)				
	0 ¹	6 ³	12	18	(b) (4)
(b) (4)	A,B,C ²	A	A,B,C ²	A	(b) (4)
	A,B,C ²	A	A,B	NP	
	A,B,C ²	A	A,B	NP	

A = Appearance, pH, (b) (4) , Pluronic content; B = Particulate Matter; C = Sterility
 NP = No testing performed at this time point

¹ Release data will be used for the t=0 time point.

² In lieu of Sterility testing for all time points after t=0, CCIT may be performed.

³ An additional test point at 3 months was performed for (b) (4) using the testing scheme prescribed for the 6 month timepoint.

Table 108. Diluent Drug Product Shelf-life Specification

Test	Method	Limits
Appearance	Spark / SOP.QC.028	Clear and colorless solution
pH	Spark / SOP.QC.020	7.3 (b) (4)
(b) (4)	Spark / SOP.QC.019	(b) (4)
Particulate Matter	(b) (4)	(b) (4)

Pluronic Content	(b) (4)	(b) (4)
Sterility	(b) (4) / SOP 1140	No Growth
CCIT	(b) (4)	Pass

3.2.P Diluent.8.1.2 Ongoing Stability Study

Ongoing Stability Protocol

A post-approval stability protocol is provided that tests the diluent at 0, 6, 12, 18, (b) (4) months and uses the specification as described. The specification is the same as in the previous section with the following exceptions: CCIT is not tested at any time, particulate matter is not tested at 6 and 18 months, and sterility is not tested at 6 and 18 months.

Ongoing Stability Study

In addition to reporting these ongoing stability results, Spark Therapeutics commits to the following:

- Complete the ongoing registration stability studies.
- Initiate a long-term stability study using the stability protocol provided in module 3.2.P.8.2 at least every (b) (4) .

CMC Reviewer Comments: The data tables were updated in amendment #38, received November 2, 2017, and show the diluent is stable at all time points that were tested; 6 months for the primary stability buffer lot (b) (4) , 12 months for the engineering lot (b) (4) , and (b) (4) . Lots (b) (4) were tested at (b) (4) . Lot (b) (4) was only tested at (b) (4) .

3.2.P Diluent.8.1.4 Recommended Shelf Life

Based on the available primary and supporting stability data, the shelf life of 18 months determined for the Drug Product is also supported for the Diluent. (b) (4) .

CMC Reviewer Comments: The proposal of 18 month shelf life for Diluent is acceptable.

3.2.A Appendices

3.2.A.1 Facilities and Equipment:

The Spark facility located at 3737 Market Street, Suite 1300, Philadelphia, PA will be used for commercial manufacturing of Drug Substance. Spark's manufacturing facilities and equipment were reviewed by DMPQ (please see DMPQ review for additional details).

The Drug Product and Diluent are manufactured at the (b) (4) and will be used for commercial manufacture. (b) (4) manufacturing facilities and equipment were reviewed by DMPQ (please see DMPQ review for additional details).

A Quality Technical Agreement (QTA) exists between Spark Therapeutics, Inc. (product

owner and contract giver) and (b) (4) (contracted manufacturer) which defines, establishes and documents the responsibilities of each party involved in the contract manufacturing subject to Current Good Manufacturing Practice (GMP). The agreement describes how parties share responsibilities, communicate and confirm GMP compliance. It details the manufacturing arrangement, including materials management, sampling, testing, change control, audits, sub-contracting arrangements, deviation handling, records, release, archiving, complaints and recalls.

3.2.A.2 Adventitious Agents Safety Evaluation

The voretigene neparvovec-rzyl manufacturing process is animal-free, except for the use of New Zealand sourced fetal bovine serum (FBS) during the (b) (4) steps. Additionally, no helper virus is used in the production of the Drug Substance. A detailed discussion pertaining to the control of raw materials including FBS and the HEK293 cell bank can be found in 3.2.S.2.3 Control of Materials, and to the testing for adventitious agents in bulk harvest can be found in 3.2.S.4 Control of Drug Substance.

Transmissible Spongiform Encephalopathy Agents

The voretigene neparvovec manufacturing process is animal-free, except for the use of fetal bovine serum (FBS) during the (b) (4) steps. The FBS is sourced from (b) (4), a country recognized to be free from Bovine Spongiform Encephalopathy.

Mycoplasma

(b) (4)

Bacteria and Fungi

Testing for bacteria and fungi was performed as part of the development and characterization of the HEK293 cell bank. Testing for bacteria and fungi was performed (b) (4).

Bioburden testing is performed on the (b) (4). Sterility testing is performed on the Drug Product according to (b) (4) and (b) (4).

Viral Agents

Testing for viral contaminants was performed as part of the development and characterization of the HEK293 cell bank and is performed as part of (b) (4).

Viral Clearance Studies

It is atypical for live viral vaccines or viral gene therapy vectors to conduct viral clearance studies. Typically live viral products cannot undergo orthogonal viral removal steps as the product is a viral particle. For the production of voretigene neparvovec-rzyl, the adenoviral helper genes are supplied on a plasmid. No live helper virus is used in the manufacture of voretigene neparvovec-rzyl. Therefore, Spark did not perform viral clearance studies.

3.2.A.3 Shedding Studies

Shedding (Section 2.7.2 Summary of Clinical Pharmacology Studies):

The shedding of AAV2-hRPE65v2 vector DNA sequences was evaluated in blood and tear samples from subjects in the three clinical studies (Study 101, Study 102, and Study 301). Shedding was reported for each clinical sample as the number of genome copies of AAV2-hRPE65v2 vector in a qPCR reaction at the time points evaluated (if < 10 copies of AAV2-hRPE65v2 per reaction, then samples were scored negative). The Phase 1 vector shedding results are provided as supportive analyses as the qPCR assay used for analyzing the clinical samples was not validated, and the dose and regimen in the Phase 1 study was different than that in Phase 3 (as noted below). Phase 3 samples were batched for analysis by Subject ID and then by Sample Type (*i.e.*, tear, blood, etc.).

Reviewer's comments: The study design is appropriate.

Results summary: In the Phase 1 study, there appeared to be a dose-dependent increase in the percentage of subjects with positive vector shedding results. The majority of the positive results were non-quantitative (positive but below the level of quantitation). Because minimal shedding was detected in blood during the initial Phase 1 studies, it is unlikely that vector DNA would be detectable in bodily fluids such as urine or feces.

Table 109. Overall Summary of Vector Shedding Data- Phase 1

Category	Study 101 (N=12)	Study 102 (N=11)	Total (N=12)
Subjects with Any Positive Samples	7 (58%)	8 (73%)	10 (83%)
Subjects with Only Positive Tear Samples	5 (42%)	3 (27%)	4 (33%)
Subjects with Only Positive Peripheral Blood Samples ^a	1 (8%)	1 (9%)	1 (8%)
Subjects with Both Positive Tear and Peripheral Blood Samples ^a	1 (8%)	4 (36%)	5 (42%)

^a Peripheral blood samples include positive results for serum and / or peripheral blood mononuclear cells (PBMCs)

Table 110. Overall Summary of Vector Shedding Data- Phase 3

Category	Original Intervention (N = 20)	Control / Intervention (N = 9)	Total (N = 29)
Subjects with Any Positive Samples	9 (45%)	5 (56%)	14
Subjects with Only Positive Tear Samples	7 (35%)	4 (44%)	11
Subjects with Only Positive Serum Samples ^a	1 (5%)	0	1 (3%)
Subjects with Both Positive Tear and Serum	1 (5%)	1 (11%)	2 (7%)

^a No whole blood samples were positive for AAV2-hRPE65v2 vector DNA.

Reviewer's comments:

The data from Phase 1 and Phase 3 is consistent and supports applicant's conclusion that transient shedding occurred in tear samples of some (~ 30-40%) subjects, mostly 1-3 days after sub-retinal injection of AAV2-hRPE65v2. Extended shedding was noted in two subjects, one until 14 days post treatment, and another that showed shedding until a day past injection in the second eye (shedding for >14 days). In each shedding study, the applicant has reported the number of vector genomes in the PCR reaction but not in the total (clinical) sample. The applicant has not analyzed/discussed whether shedding of vector genomes in tears could mean that intact vector particles are also shed; in that case, it is assumed that the shed material is intact.

In this section, applicant has not discussed the transmission risks due to viral vector shedding. However, in the reviewer's assessment, transmission risk due to shedding of AAV2-hRPE65v2 in tears would be negligible considering the following:

- *shedding data (low transient shedding in tears)*
- *vector characteristics (replication defective vector)*
- *the known biology of AAV serotype 2 [AAV2 is not a disease-causing virus (not a pathogen) in humans, and*
- *the high prevalence of antibodies in humans against AAV2, with estimates of up to 80% being seropositive [Grim and Kay, Curr Gene Ther. (2003) 4: 281-304; Boutin et al., Hum Gene Ther. (2010) 6: 704-712]; which would be protective against an AAV infection.*

3.2.R Regional Information (U.S.A.)

Executed Batch Records:

Executed batch records of Drug Substance lot #(b) (4) (including the (b) (4) sub-lots (b) (4)) were included in the BLA. The information contained in the batch records are summarized throughout the BLA in the form of tables and graphs. Executed batch records confirm the data used in the tables and graphs.

Drug product batch record of (b) (4) (manufactured on 08 Nov 2016) was submitted, with a Certificate of Conformance signed by (b) (4). Diluent batch record (b) (4) (manufactured on 16 Dec 2016) was submitted, with a Certificate of Conformance signed by (b) (4).

The device compatibility study reports (TR2016-046 and TR2016-049) were included in the submission under this section and address the stability and recovery of voretigene neparvovec vector using injection cannulas that are commercially available FDA Class I devices and EMA CE mark devices for ophthalmic use. The information is reviewed under [3.2.P.2.6](#) Compatibility.