

**CBER CMC BLA Review Memorandum**

**BLA STN 125785**

**Casgevvy**  
**Exagamglogene autotemcel (exa-cel)**

**Reviewers**

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**Brian Stultz, CMC Reviewer OTP/OGT/DGT1/GTB3**  
**Zhaohui Ye, CMC Reviewer OTP/OGT/DGT2/GTIB**

1. **BLA#:** STN 125785

2. **APPLICANT NAME AND LICENSE NUMBER**

Vertex Pharmaceuticals Incorporated; License # 2279

3. **PRODUCT NAME/PRODUCT TYPE**

Non-Proprietary/Proper/USAN: Exagamglogene autotemcel (exa-cel)

Proprietary Name: Casgevy

Company codename: CTX001

UNII Code: S53L777GM8

NDC Code: 51167-290-01

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

a. Pharmacological category: Autologous Genome Edited Hematopoietic Stem Cell-Based Gene Therapy

b. Dosage form: Suspension for infusion

c. Strength/Potency:  $>3 \times 10^6$  cells/mL

d. Route of administration: Intravenous infusion

e. Indication: Treatment of transfusion-dependent  $\beta$ -thalassemia (TDT) in patients 12 years of age and older

5. **MAJOR MILESTONES**

Initial IND Submission (BB-IND 18143)	April 27, 2018
IND allowed to proceed	October 10, 2018
Orphan Drug Designation granted	May 11, 2020
Regenerative Medicine Advanced Therapy Designation granted	May 05, 2020
Pre-BLA Meeting	August 9, 2022
BLA Submission	March 31, 2023
First Committee Meeting	April 21, 2023
Filing Meeting	May 11, 2023
BLA Filed	May 30, 2023
Mid-Cycle Meeting	September 28, 2023
External Late-Cycle Meeting	December 18, 2023
PDUFA action due date	March 31, 2024

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Anna Kwilas, CMC Reviewer/Chair OTP/OGT/DGT2/GTB5	exa-cel: Comparability, Specifications, Stability
Jessica Chery, CMC Reviewer OTP/OGT/DGT2/GTB5	exa-cel: Control of Materials, Analytical Methods

Elena Gubina, CMC Reviewer OTP/OGT/DGT1/GTB3	Cas9
Eric Levenson, CMC Reviewer OTP/OGT/DGT1/GTB2	Cas9/gRNA/extra-cel: (b) (4) Analytical Methods
Brian Stultz, CMC Reviewer OTP/OGT/DGT1/GTB3	SPY101 gRNA
Zhaohui Ye, CMC Reviewer OTP/OGT/DGT2/GTIB	extra-cel: Process Validation

## 7. CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Komudi Singh, Bioinformatics Reviewer CBER/OTP/OCTHT	SPY101 gRNA (b) (4) & extra-cel On-Target Editing Frequency assay	Yes
Tianjiao Dai, Statistics Reviewer CBER/OBPV/DB	Extra-cel comparability	Yes

## 8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments
02/24/2023	2	CMC Module 3
03/03/2023	3	Response to CMC IR#1
03/10/2023	4	Response to CMC IR#2
03/17/2023	5	Response to CMC IR#2
03/27/2023	7	Response to CMC IR#3
3/31/2023	8	Labeling update
04/7/2023	9	Labeling update
05/22/2023	20	Response to CMC IR#4
07/26/2023	37	Stability data update
08/04/2023	38	Response to CMC IR#6
08/30/2023	43	Response to CMC IR#6
09/15/2023	49	Response to CMC IR#7
9/15/2023	50	Labeling update
10/4/2023	60	Labeling update
10/6/2023	61	Response to CMC IR#8
10/20/2023	64	Labeling update
10/30/2023	66	Response to CMC IR#9
11/13/2023	69	Response to CMC IR#10
11/15/2023	70	Labeling update
11/21/2023	72	Response to CMC IR#11
11/29/2023	73	Response to CMC IR#12

12/1/2023	74	Response to CMC IR#13
12/18/2023	79	Labeling update
1/3/2024	87	Response to CMC PMCs
1/5/2024	88	Labeling update
1/8/2024	89	Resubmission of response to CMC IR#5
		Labeling update
		Labeling update

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Reviewer/Status
BB-MF- (b) (4)	(b) (4)	(b) (4)	Yes	Used by multiple licensed products
BBMF- (b) (4)	(b) (4)	(b) (4)	Yes	Used by multiple licensed products
BB-MF- (b) (4)	(b) (4)	(b) (4)	Yes	Used by multiple licensed products
BB-MF- (b) (4)	(b) (4)	(b) (4)	Yes	Archana Devi Siddam (CBER/OTP/OCT HT/DCT1/CTB1): Adequate to support the intended use
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	Mercy Quagraine (CBER/OTP/OCT HT/DCT1/CTB1): No issues identified.
MF-(b) (4)	(b) (4)	Mycoplasma testing	Yes	Hyesuk Kong (CBER/OCBQ/DB SQC/LMIVTS): Adequate to support the intended use

MF-(b) (4)	(b) (4)	(b) (4)	Yes	Iain Farrance (CBER/OTP/OCT HT/DCT1/CTB1): Adequate to support the intended use
MF-(b) (4)	(b) (4)	(b) (4)	Yes	Guo-Chiuan Hung (CBER/OTP/OGT/ DGT1/GTB3): No issues identified
MF-(b) (4)	(b) (4)	(b) (4)	Yes	Elena Gubina (CBER/OTP/DGT1 /GTB3): Suitable for commercial manufacturing
MF-(b) (4)	(b) (4)	20mL (b) (4) Vial	Yes	Relevant sections reviewed by Jessica Chery & Anna Kwilas and found to be acceptable
STN-(b) (4)	(b) (4)	(b) (4)	Yes	Used by multiple licensed products
STN-(b) (4)	(b) (4)	(b) (4)	Yes	Licensed product

## 10. REVIEWER SUMMARY AND RECOMMENDATION

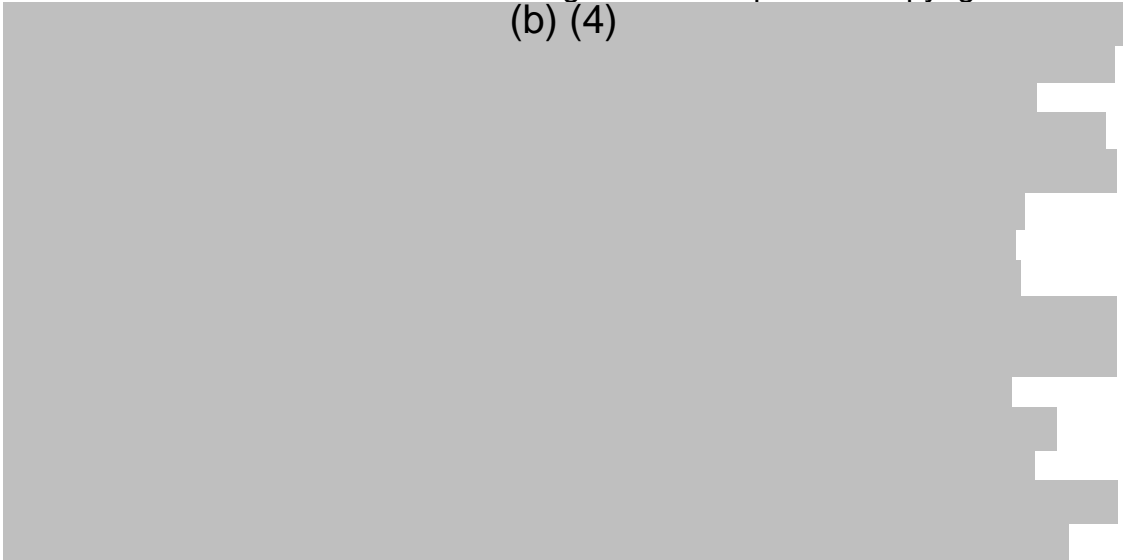
### A. EXECUTIVE SUMMARY

The CMC review team concludes that the manufacturing process, test methods and control measures for exagamglogene autotemcel (exa-cel, Casgevy) are capable of yielding autologous products with consistent quality attributes deemed acceptable for commercial manufacturing under this BLA.

Exa-cel is an autologous cell-based gene therapy product intended to treat patients 12 years of age or older with transfusion-dependent  $\beta$ -thalassemia (TDT). Exa-cel consists of a CD34+ cell enriched population, containing

hematopoietic stem and progenitor cells (HSPCs) genome edited at the GATA1 binding site of the BCL11A gene using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology composed of CRISPR associated protein 9 (Cas9) and the SPY101 single guide RNA (sgRNA). The SPY101 sgRNA targets the Cas9 to make a DNA double stranded break in the GATA1 transcription factor binding site in the erythroid specific enhancer region of the BCL11A gene. This cleavage results in insertions and deletions (indels) in the GATA1 transcription factor binding site in the erythroid specific enhancer region of the BCL11A gene, which are generated during nonhomologous end joining mediated repair of the cut site. These indels disrupt GATA1 binding thus reducing BCL11A expression. BCL11A is a master regulator of the switch between fetal hemoglobin (HbF) and adult hemoglobin (HbA) during fetal/neonatal development through its negative regulation of  $\gamma$ -globin expression (HbF contains 2  $\alpha$ -globin and 2  $\gamma$ -globin subunits while HbA contains 2  $\alpha$ -globin and 2  $\beta$ -globin subunits). Reduced BCL11A expression alleviates the BCL11A-mediated block of  $\gamma$ -globin expression resulting in increased HbF production in erythroid cells. The proposed exa-cel mechanism of action is that following engraftment, the edited HSPCs will differentiate into red blood cells (RBCs) that express HbF. Increased HbF expression is designed to correct the lack of beta-globin expression and coincident HbA in erythroid cells of patients with TDT. Reactivation of HbF increases the total Hb levels in TDT patients and has the potential to reduce or eliminate the need for RBC transfusions. HbF is known to be therapeutic in individuals with TDT who also experience hereditary persistence of HbF. Thus, upregulation of HbF is predicted to lessen the symptoms of TDT following engraftment of exa-cel. The clinical benefits of one-time exa-cel treatment are expected to last for the patient's lifetime. However, given the relatively short length of clinical follow up [subjects were followed for a median (min, max) duration of 20.4 (2.1, 48.1) months], at this time, the long-term clinical course is unknown.

The Cas9 used in exa-cel manufacturing is from *Streptococcus pyogenes* and  
(b) (4)



(b) (4)

The SPY101 sgRNA used in exa-cel manufacturing is a 100 base pair (bp) synthetic oligonucleotide with methylated 2' ribosyl hydroxyl groups and thiolated phosphate linkages incorporated at both terminal ends to inhibit degradation by nucleases. (b) (4)

To manufacture exa-cel, autologous CD34+ cells obtained by apheresis are collected from each TDT patient following mobilization with granulocyte-colony stimulating factor (G-CSF) and plerixafor. Only plerixafor is used for mobilization in the case of sickle cell disease (SCD). Up to (b) (4) collections can be made per mobilization cycle. The apheresis material is then shipped to one of (b) (4) drug product (DP) manufacturing facilities: (b) (4)

. To manufacture the

(b) (4)

Exa-cel DP is supplied as a frozen suspension of cells for intravenous infusion. The minimum dose is  $3.0 \times 10^6$  CD34+ cells/kg patient weight. However, other than the samples taken for lot release testing and retain samples, each patient receives the entire DP manufactured. Additionally, multiple exa-cel lots may be needed to meet the minimum patient dose. In this case, each lot is manufactured from a separate mobilization cycle. Exa-cel is shipped frozen in a vapor phase liquid nitrogen shipper to the administration site once the minimum dose has been obtained and patient administration has been scheduled. The DP vial(s) that make up an exa-cel lot are contained within a single carton and all lots (cartons) needed to meet patient dose are contained within the shipper. Following receipt at the administration site, exa-cel is stored in vapor phase liquid nitrogen ((b) (4)) until the scheduled treatment time, when it is thawed, passed through an 18 µm filter and infused within (b) (4). Patients receive exa-cel after myeloablative conditioning.

Manufacturing process consistency is assured through 1) raw material, component, and reagent qualification programs, 2) in-process monitoring, 3) in-process control testing, and 4) lot release and stability testing. Raw materials derived from animals and humans are appropriately controlled to ensure the absence of microbial contaminants and adventitious agents. Lot release test methods are suitably validated or verified, and product specifications are adequate to ensure product quality and consistency with DP used in the clinical study. Manufacturing processes have been adequately validated and continuous process verification is in place. Because of the autologous nature of the product, Chain of Identity/Chain of Custody (COI/COC) is established at the collection site and maintained through the manufacturing process and administration by conducting label checks at specified times throughout the process.

## **B. RECOMMENDATION**

### **I. APPROVAL**

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of exagamglogene autotemcel (exa-cel, Casgevy). The CMC review team has concluded that the manufacturing processes, along with associated test methods and control measures, are capable of yielding a product with consistent quality characteristics. This information along with the post-marketing commitments listed below satisfy 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. Based on the information provided in the BLA submission and the information gathered during the pre-license inspections of the (b) (4)

facilities, the CMC review team recommends approval of this BLA.



CBER Lot release:

Exa-cel has been deemed exempt from CBER lot release testing or protocol review.

Post-Marketing Commitments (PMCs):

1. Vertex Pharmaceuticals, Inc., commits to perform a supplemental shipping validation study of exa-cel assessing the quality attributes including (b) (4) and (b) (4)-transportation samples using the (b) (4) commercial shippers. The final validation study report will be submitted as a Postmarketing Commitment-Final Study Report by May 31, 2024.

Final Report Submission: May 31, 2024

2. Vertex Pharmaceuticals, Inc., commits to perform a supplemental (b) (4) hold time stability study in which additional data are obtained to support the current hold time proven acceptable ranges, including the cumulative proven acceptable hold time. The final validation study report will be submitted as a Postmarketing Commitment-Final Study Report by December 31, 2024.

Final Report Submission: December 31, 2024

**II. COMPLETE RESPONSE (CR)**

Not applicable

**III. SIGNATURE BLOCK**

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Anna Kwilas, CMC Reviewer, Chair OTP/OGT/DGT2/GTB5	Concur	
Jessica Chery, CMC Reviewer OTP/OGT/DGT2/GTB5	Concur	
Elena Gubina, CMC Reviewer OTP/OGT/DGT1/GTB3 (Andrew Byrnes, Division Director DGT1)	Concur	
Eric Levenson, CMC Reviewer OTP/OGT/DGT1/GTB2	Concur	

<b>Reviewer/Title/Affiliation</b>	<b>Concurrence</b>	<b>Signature and Date</b>
Brian Stultz, CMC Reviewer OTP/OGT/DGT1/GTB3	Concur	
Zhaohui Ye, CMC Reviewer OTP/OGT/DGT2/GTIB	Concur	
Kimberly Schultz, Division Director, OTP/OGT/DGT2	Concur	
Denise Gavin, Office Director, OTP/OGT	Concur	

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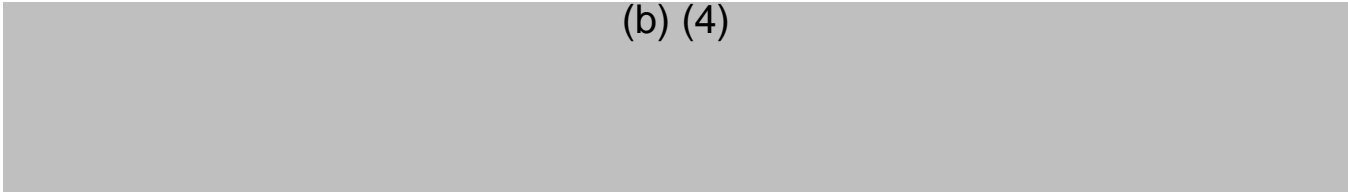
**Table of Tables**

(b) (4)

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



(b) (4)



## Module 3

### 3.2.S DRUG SUBSTANCE (CAS9)

*Reviewed by EG*

(b) (4)

(b) (4)

(b) (4)

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

### 3.2.P DRUG PRODUCT (Exa-cel)

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

Exa-cel DP consists of autologous CD34+ cells genome edited using CRISPR-Cas9, suspended in (b) (4) cryopreservation solution containing 5% DMSO at  $4-13 \times 10^6$  cells/mL. Exa-cel is supplied as a suspension for intravenous infusion in 20 mL (b) (4) vials. Each vial may contain 1.5 - 20mL of exa-cel. Exa-cel is administered as a single dose by intravenous infusion consisting of a minimum of  $3 \times 10^6$  cells per kg of patient weight. A single lot of DP may consist of up to 9 vials and a single dose may be composed of more than one DP lot.

#### 3.2.P.2 Pharmaceutical Development

##### 3.2.P.2.1 Components of the Drug Product

###### 3.2.P.2.1.1 Drug Substance

The exa-cel DS consists of autologous CD34+ cells genome edited using CRISPR-Cas9 to inhibit GATA1 transcription factor binding at the erythroid-specific enhancer region of the BCL11A gene.

###### 3.2.P.2.1.2 Excipients

(b) (4) containing 5% DMSO ( (b) (4) ).

##### 3.2.P.2.2 Drug Product

###### 3.2.P.2.2.1 Formulation Development

*Reviewed by ZY*

Exa-cel DP consists of autologous CD34+ HSPC) modified by CRISPR-Cas9 mediated genome editing. Each lot is formulated at a target concentration of (b) (4) suspended in (b) (4) cryopreservation medium containing 5% DMSO. Multiple DP lots may be combined to provide a subject dose of at least 3 million CD34+ viable cells per kg subject weight.

#### Difference Between Clinical and Commercial Formulations

The commercial formulation of exa-cel remains the same as that of clinical development, with the exception of DP fill volume per vial. During clinical development, the DP fill volume was updated from a range of (b) (4) to 1.5mL – 20mL. This change was supported by cell viability testing, and further supported by DP stability studies in **3.2.P.8 Stability**.

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

(b) (4)

(b) (4)

#### In-Use Stability Studies

*Reviewed by AK*

Exa-cel DP is stored in liquid nitrogen ( $\leq -135^{\circ}\text{C}$ ) until it is ready for administration. The DP vial is then thawed in a water bath at  $37^{\circ}\text{C}$ . While several vials could be used to constitute a complete dose, each vial is thawed individually for administration. Once thawed, exa-cel is infused within 20 minutes of completion of thawing and is handled at room temperature (RT). Vertex also proposes an upper limit of (b) (4) minutes based on clinical experience. A DP post-thaw hold study was conducted to demonstrate the in-use stability when the product is handled according to this procedure (**Table 89**).

The study consisted of (b) (4) healthy donor lots at the concentration of (b) (4) cells/mL frozen in  $\text{LN}_2$ , using a (b) (4) sample design. (b) (4) arms were tested:

(b) (4)

(b) (4)

(b) (4)

**Reviewer Comment:** There is a significant drop in (b) (4) when thawed DP is stored at 37°C for (b) (4). No significant differences for all attributes for DP held at (b) (4) for (b) (4), which supports the proposed NOR and PAR values of exa-cel in-use time of 20 minutes and (b) (4) minutes, respectively. Note, in response to CMC IR#8, dated September 29, 2023, Vertex confirmed that this in-use study was performed using materials intended for use during exa-cel administration. Specifically, exa-cel was withdrawn from the vial with the adaptor using the syringe and 18µm filter and then the exa-cel DP was passed through an IV set prior to testing.

### 3.2.P.2.2.2 Overages

There are no overages used in exa-cel.

### 3.2.P.2.2.3 Physicochemical and Biological Properties

The biological properties and physiochemical properties that are important to the performance of the exa-cel drug product are described in **3.2.S.3 Characterization** and **3.2.P.2.1 Components of the Drug Product**.

### 3.2.P.2.3 Manufacturing Process Development

*Reviewed by ZY*

#### Scale Down Model

To support process characterization studies, Vertex built a representative Scale Down Model (SDM). The rationale for this SDM includes the relative scarcity of CD34+ cells and the frequent need for multiple parallel conditions to be tested in the studies.

**Reviewer Comment:** The justification for using a qualified SDM is acceptable.

To establish that the SDM manufacturing was representative of At-Scale manufacturing, a study using was conducted comparing the DP manufactured with SDM against the DP manufactured At-Scale. The scale-dependent factors include (b) (4)

as shown in **Table 90**:

(b) (4)

**Reviewer Comment:** Vertex's identification of scale dependent factors is acceptable, as starting material, electroporation assembly (i.e., (b) (4)), and (b) (4) are the ones most likely to differ between at-scale and SDM.

Additional notes on the SDM:

- The (b) (4) CD34+ cells used in SDM were processed on Prodigy following the manufacturing protocols then immediately frozen at (b) (4) cells/mL in (b) (4) according to the Cryopreservation protocols.

**Reviewer Comment:** It is reasonable to evaluate the suitability of using (b) (4) CD34+ cells. Going through CD34+ enrichment on Prodigy for each process characterization study can be considered an undue burden.

- There have been electroporation assembly changes throughout the clinical development, due to the electroporator manufacturer (MaxCyte)'s product updates and discontinuation of older models. Additional comparability studies between (b) (4) and (b) (4) is reviewed in Development History.

**Reviewer Comment:** Some of the process characterization studies have been performed in earlier stage before the current GMP (b) (4) assembly was available from MaxCyte. The suitability of using (b) (4) in at-scale production in these analyses is supported by the comparability study between (b) (4) and (b) (4).

- Different (b) (4) were used in SDM process development studies. However, in each study that a process parameter was evaluated, consistent (b) (4) was used in comparing different values of that specific parameter. In certain cases, more than (b) (4) was used in evaluating a process parameter (e.g., in study of (b) (4) were used, with each one of them having (b) (4) conditions).

**Reviewer Comment:** Evidently, the SDM study design and process characterization study design have changed/evolved throughout product development, and are not consistent between individual experiments particularly in terms of (b) (4). However, there are sufficient data to support the different sizes of the model.

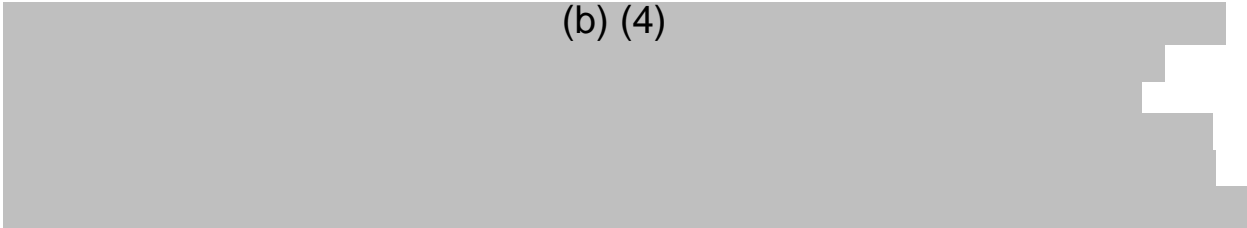
#### Effect of Starting Material on Exa-cel CQAs

Effect of the Starting Material ((b) (4) enriched CD34+ cells) is summarized in **Table 91** and **Figure 21**.



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

(b) (4)

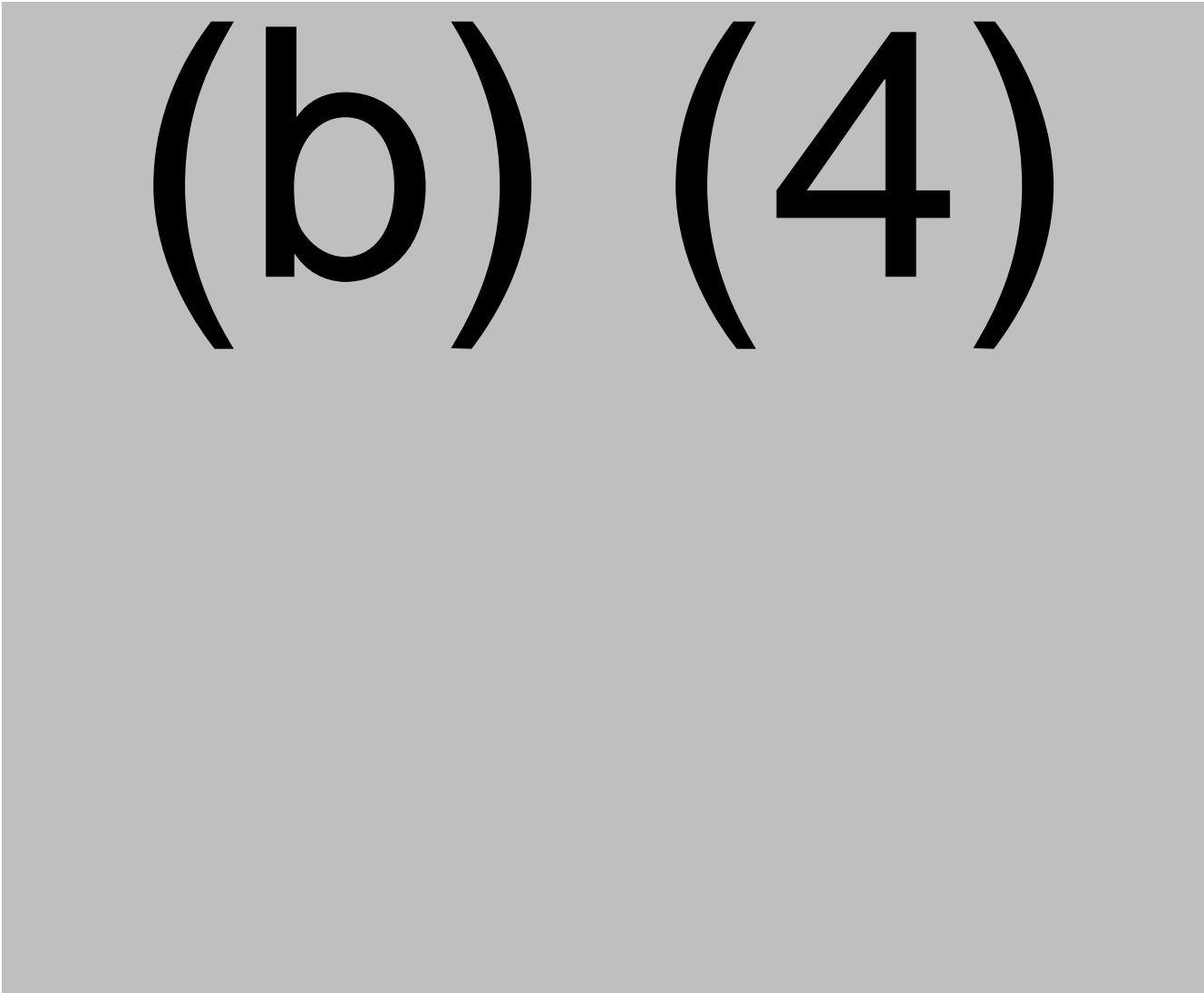


## Exa-cel Manufacturing Process Development History

### Overview of Manufacturing Process Development

The exa-cel manufacturing process was established at the (b) (4) laboratories. Clinical manufacture of exa-cel initiated at (b) (4), and then transferred to (b) (4) and (b) (4). The same overall manufacturing process has been used throughout pre-clinical and clinical development, but some process changes and optimizations steps have been introduced as presented in **Table 92** and reviewed in this section.

(b) (4)



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

(b) (4)

## Manufacturing Process Development – Characterization and Control Strategy

Exa-cel manufacturing process and control strategy was developed based on initial process development studies and process characterization studies. Initial product and process risk assessments were conducted using Quality Target Product Profile (QTPP), which is used as a basis for Critical Quality Attribute (CQA) development (**Table 99**).

**Table 99. Exa-cel Quality Target Product Profile (QTPP) and Its Link to the Associated CQAs**

<b>QTPP</b>	<b>Exa-cel</b> (autologous product of ex vivo edited CD34+ cells)	<b>Relevant CQAs</b>
<b>Safety and Efficacy</b>	Safe and efficacious	Identity, CD34 Purity, Quality/content (Viable Cell Concentration), Quality/content (Viability), Microbial contaminants (Sterility, Mycoplasma, Endotoxin)
<b>Dosage form</b>	Sterile cell suspension in vial(s)	Appearance, Quality/content (Viable Cell Concentration)
<b>Administration</b>	Intravenous injection	Identity
<b>Dosing frequency</b>	Single treatment (could be multiple lots)	Quality/content (Viable Cell Concentration)
<b>Potency/ Dose range</b>	NLT $3 \times 10^6$ CD34+ cells/ kg patient	CD34 Purity, Potency (On-Target Editing Frequency) <sup>(b) (4)</sup> , Potency <sup>(b) (4)</sup> Quality/content (Viability)
<b>Packaging/ Shelf life</b>	Primary: Vial At least <sup>(b) (4)</sup> months shelf life, stored NMT -135°C	Appearance, Identity, Quality/content (Viable Cell Concentration), Quality/content (Viability)

## Process Parameter Criticality and Proven Acceptable Range Determination

Material and process risk assessments were then carried out to determine high and medium risk parameters affecting CQAs that were then selected for further process characterization studies. The process characterization results were used to classify the process parameters using a statistical approach. CQAs and select quality attributes (e.g., yields) were monitored, and parameters for each unit operation that significantly impact CQAs were identified. Generally, a p-value being <0.05 is used to determine the statistical significance. When there is a statistically significant difference, Vertex used a calculation of Effect Size based on mean (i.e., differences between mean values of treatment groups divided by standard deviation of a control group) to evaluate the practical significance of the process parameter. In general, Vertex considers a process parameter critical if the Effect Size % Mean is <sup>(b) (4)</sup>.

**Reviewer Comment:** The process parameters selected by Vertex for process characterization (**Table 103**) are reasonable. In terms of process parameter criticality determination, there is no standard on criticality determination using effect size analysis or any other statistical analysis alone, but it is common in scientific disciplines for an effect size of 10%-30% to be considered as having small effect (e.g., Cohen, *Statistical power analysis for the behavioral sciences*. 1988). Vertex's approach is of acceptable risk, considering both CPPs and nCPPs evaluated in the characterization study are monitored and controlled through defined normal operating ranges (NORs) and proven acceptable ranges (PARs) in commercial exa-cel manufacture.

To establish PAR, Vertex stated that they conducted Edge of Failure analysis for each process parameter and its impacted CQA(s) (except the cell-based assays: (b) (4) ) to generate simulations using the Simulator function in the JMP profiler report, spanning the experimental range of the design. Simulations were generated with N = (b) (4) . Parameter ranges were restricted as necessary to result in a (b) (4) parts per million (PPM) failure rate. The resulting ranges, together with historical manufacturing experience and SME judgment, constitute the PAR for each parameter.

**Reviewer Comment:** The biological relevance of the statistical edge of failure analysis is not well supported. The proposed PARs, however, apparently aligned with either the studied ranges or historical manufacturing experience. Review of the parameter ranges was also based on the experimental results from the characterization studies and/or historical manufacturing data.

#### DP Quality Attribute Acceptance Criteria and Limits Used in Process Characterization Studies

The CQA acceptance criteria and limits used in the process characterization studies to monitor process parameters' effects on these exa-cel CQAs are shown in **Table 100**.

**Table 100. Acceptance Criteria and Limits for Assessment of Material Attribute and Process Parameters**

Exa-cel Attributes	Acceptance Criteria or Limits
CD34 Purity	(b) (4)
Product-related substances ( (b) (4) )	Follow historical experience
Potency (On-Target Editing Frequency (b) (4) )	(b) (4)
Potency (b) (4)	(b) (4) per viable cell
Potency (b) (4)	Follow historical experience
Potency (b) (4)	(b) (4)
Quality/content (Viable Cell Concentration)	(b) (4)
Quality/content (Viability)	(b) (4)

**Reviewer Comment:** Safety related attributes (sterility, mycoplasma, endotoxin) are not assessed in process characterization studies, which is acceptable. The acceptance limits used in the studies are the same as the proposed DP release specifications in the original submission. Even though the DP release acceptance ranges for several tests

*have since been updated during the BLA review, the changes did not have a negative impact on the conclusions of characterization studies, because in experiments that evaluated these attributes, the passing results are still within the new ranges.*

Material Risk Assessment - (b) (4)

(b) (4)


(b) (4)

(b) (4)

(b) (4)

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

(b) (4)



#### Control Strategy Based on Outcome of the Process Characterization Study

The results of the process characterization studies were used to classify the process parameters and define the DP manufacturing process control strategy. The process parameter control ranges and their categorization are shown in **Table 104**. In-process



controls (IPCs) and their acceptance criteria are summarized in **3.2.S.2.4 Controls of Critical Steps and Intermediates**.

(b) (4)

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## Comparability

### *Reviewed by AK and TD*

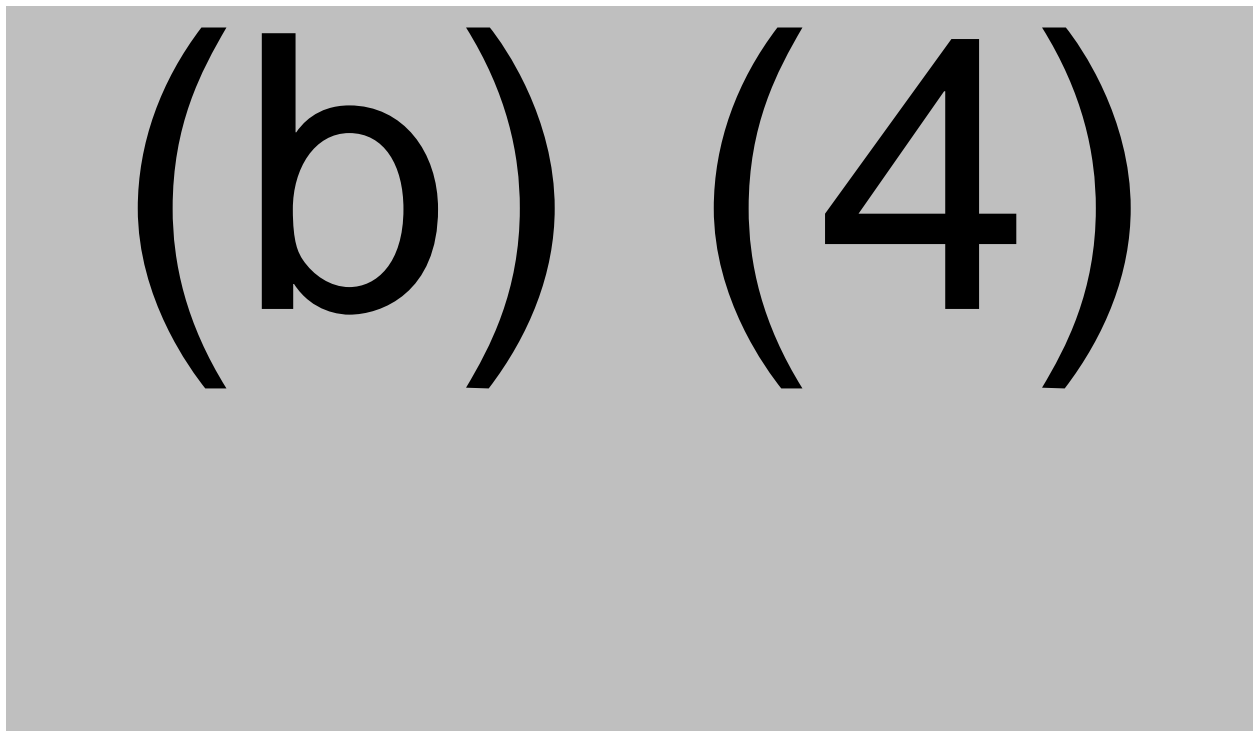
During clinical development, exa-cel was manufactured at (b) (4). The manufacturing process was originally developed at (b) (4) (reference site) and (b) (4) was added as a manufacturing site following initial Technology Transfer (TT) of the exa-cel manufacturing process and analytical method transfer to (b) (4). (b) (4) was introduced as the commercial manufacturing site (along with (b) (4)) following a TT from (b) (4) (b) (4). To support comparability two pairs of comparability studies were performed as described in Comparability Reports: COMPR-58127, COMPR-58681. The study design is based on (b) (4) runs: execution of (b) (4) runs between the reference site (b) (4) and either (b) (4) or (b) (4) (test site) to mitigate the impact of donor-to-donor variability.

Both Healthy Donor (HD) and patient material was used to perform the (b) (4) run studies. For each (b) (4) run, the material from a single donor (b) (4), either HD or patient, was (b) (4). Each contract development manufacturing organization (CDMO) site processed the (b) (4) within a similar time frame and processed the (b) (4) using the same manufacturing procedures. A total of (b) (4) runs were executed with (b) (4) considered successful for comparability between (b) (4) and (b) (4). A total of (b) (4) runs with (b) (4) considered successful were executed for the comparability between (b) (4) and (b) (4).

**Reviewer Comment:** *In CMC IR#8, dated September 29, 2023, Vertex was asked to provide data supporting the combination of HD and patient material for this analysis. In Amendment 69, Vertex provided a comparative analysis of the release data obtained from healthy donor (N=(b) (4)) and patient lots (N=(b) (4)) manufactured at (b) (4) (combined total N=(b) (4)). The distributions of HD and patient data for On-Target Editing Frequency (%) and Cell Viability (%) were highly overlapped. While the means and standard deviations of CD34 Purity (%) were statistically significantly different for HD and patient lots ((b) (4), respectively), the absolute difference between the means was not meaningful since the total range of the data was narrow ((b) (4), respectively). Thus, it was determined to be acceptable to combine these data for the comparability assessment.*

To assess commercial comparability of the sites, 90% confidence intervals for mean site differences were calculated from the (b) (4) run differences per donor (i.e., paired t-test) for the following attributes: (b) (4) and compared with pre-specified Equivalence Acceptance Criteria (EACs). Comparability between sites is demonstrated if, for each attribute, the 90% confidence interval for the mean difference between sites is fully contained within  $\pm$  EAC.

When a (b) (4) run approach provides an estimate of the difference between sites that is not affected by variation among donors, the mean of these per-donor differences provides a characterization of the difference between manufacturing sites that is not conflated with donor-to-donor variability. While the impact of donor-to-donor differences is neutralized, experimental variability and sample size (the number of donors employed) must still be taken into account. This is accomplished by calculating a 90% confidence interval to surround the mean difference using the following equation:



*Reviewer Comment: For (b) (4) and (b) (4), the 90% CI were evaluated against pre-specified EAC, but for (b) (4), the 90% CI were also interpreted directly in terms of centering and width in the context of subject matter expertise in biological, scientific, and process knowledge.*

In addition to meeting the aforementioned comparability acceptance criteria, the following criteria must also be met:

- All DP lots were required to meet current lot release criteria.
- The residuals meet the specified limit and the rest of characterizations tests follow historical trends.
- For (b) (4) ratios the mean difference between sites is not statistically significant, with  $p < 0.05$ , with the additional requirement that (b) (4) satisfies release criteria ( (b) (4) only).
- For (b) (4) for the diseased patient DP, the DP must pass the set specification release criteria and overall follow historical trends ( (b) (4) only).

- Any results that don't meet the target limits or are not consistent with historical trends may be considered comparable based on further scientific evaluation of the data.

The initial comparability study between (b) (4) and (b) (4) employed the following attributes: (b) (4)

(b) (4) were used to generate the EACs. The decision to add (b) (4) and (b) (4) was made at a later date, after additional lots had been manufactured at (b) (4) had been assessed for these attributes: (b) (4) (N= (b) (4)) and (b) (4) (N= (b) (4)). **Table 105** summarizes the resulting EACs for all (b) (4) parameters calculated according to the methodology described above.

(b) (4)

**Reviewer Comment:** All 90% confidence intervals fell well within the EAC supporting comparability between (b) (4) and (b) (4).

The (b) (4) comparability assessment was originally based on EACs generated from (b) (4) data, HD and clinical, combined. **Table 107** summarizes the EACs for all (b) (4) parameters derived from data from the combined reference dataset ( (b) (4) ).

(b) (4)

**Table 108** summarizes the 90% confidence intervals for the (b) (4) successfully completed (b) (4) runs comparing to the pre-established (b) (4) EACs.

(b) (4)

**Reviewer Comment:** It was determined that the use of both (b) (4) data to set the EACs for the (b) (4) comparability assessment was not strictly appropriate. However, given that exa-cel manufactured at (b) (4) was shown to be comparable and the use of the combined dataset resulted in tighter EACs, this was determined to be acceptable. Furthermore, all 90% confidence intervals fell well within the EAC supporting comparability between (b) (4).

**Reviewer Comment:** For the (b) (4) comparability assessment, the EAC is defined based on historical data where donor variability was included into the SD calculation. Also, the estimated upper limit of 90%CI of the sample SD,  $\sigma'$ , is used in the (b) (4). Thus, the EAC ended up as more than (b) (4) times of the sample SD. Although this  $\sigma'$  accounts for associated with the observed sample variance, the power, operating characteristics, and performance of such EAC was unclear. Vertex was asked to address this in CMC IR#8, dated September 29, 2023. In Amendment 61, Vertex provided a revised EAC calculation using a (b) (4) based on the number of (b) (4) runs performed and using the standard deviations based on the (b) (4) -run data only (**Table 109**).

(b) (4)

The 90% confidence intervals for mean site differences between (b) (4) still demonstrated comparability versus the narrower equivalence margins. The 90% confidence intervals for mean site differences between (b) (4) demonstrated comparability versus the narrower equivalence margins for (b) (4) but not for (b) (4) and (b) (4).

However, given the sample size and the scale of the raw data, comparability can still be considered established. Particularly, given that the observed differences are considered not biologically meaningful.

Vertex also provided additional justification for using the UCL of the SD, arguing that the UCL will get close enough to the SD as the reference sample size  $n$  goes larger. Though the operating characteristic of this approach is still not completely clear and the use of the UCL in the EAC is not considered ideal, it is acceptable given the data provided.

**Overall Reviewer Assessment:** Based on the analyses performed, comparability of exa-cel manufactured at (b) (4) for the proposed critical attributes can be considered established from a statistical perspective.

### 3.2.P.2.4 Container Closure System

*Reviewed by JC*

The primary container closure used for exa-cel DP is 20 mL (b) (4) Vials (vial) from (b) (4).

#### Container Closure Integrity Testing

According to Vertex, (b) (4) formulation cryoprotectant manufactured at the exa-cel DP manufacturing (b) (4) site in (b) (4) using the intended commercial manufacturing process was used to perform container closure integrity (CCI) studies. The (b) (4) was filled into the DP Container Closure system (b) (4) Vials) and stored at NMT -135°C in liquid nitrogen vapor phase. Vertex reports two CCI studies were done with (b) (4) and (b) (4) test methods.

CCI Testing With (b) (4)

(b) (4)

(b) (4)

(b) (4)

**Reviewer Comment:** The data indicates there is little change in (b) (4) in the (b) (4) vials up to 3 months of storage and 20ml vials up (1.5mL and 20mL fill) to 3 months of storage. The lots vials did not impact the analysis as they fill volume was bracketed with other study samples. Defer to DMPQ review memo for additional analysis.

CCI Testing With (b) (4)

(b) (4)

**Reviewer Comment:** The data indicates (b) (4) was unable to enter the vials after long-term storage, supporting integrity of the (b) (4) vials container closure system. Defer to DMPQ review memo for additional analysis.



**Extractable and Leachable Studies**

Vertex states that (b) (4), the manufacturer of the (b) (4) Vials, performed a leachable simulation study and results of that study were determined acceptable for low-risk for exa-cel. In addition, Vertex performed extractable and leachable studies on the 20mL vials container closure system to support commercial licensure (**Table 111**, **Table 112**). According to Vertex, study conditions were chosen based on (b) (4) and (b) (4).

**Table 111. Extraction Studies for Drug Product Container Closure**

Container Closure Components	Compounds	Extraction Solvent	Analytical Method
(b) (4)			
(b) (4)			

**Table 112. Leachables Study Conditions for Drug Product Container Closure**

Container Closure System	Storage Condition	Analytical Method
(b) (4)		
(b) (4)		

**Table 113. Leachables Study Results of Container Closure System With (b) (4) Cryoprotectant**

Leachables	Amount (µg/mL)	Analytical Method
(b) (4)		

(b) (4)

Vertex provided a rationale for the leachables study conditions. (b) (4)

Overall, the leachables study conditions are intended to represent worst-case scenario.

Vertex calculated the Analytical Evaluation Threshold (AET) for organic compounds using dose (NLT  $3 \times 10^6$  CD34+ cells per kg of patient body weight), volume of drug product (1.5-20 mL) with CD34+ concentration between  $4\text{--}13 \times 10^6$  cells/mL. A max volume of (b) (4) was used to calculate AET to represent the worst-case scenario, according to Vertex, even though historically the maximum volume administered was (b) (4). 5µg/day was used for the threshold of toxicological concern (TTC) because exa-cel is only administered once in a subject's life.

**Reviewer Comment:** According to the 2018 FDA guidance “M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk” 5 µg/day total daily intake of mutagenic impurities or compounds is an acceptable TTC for a marketed product with >10 years to lifetime for duration of treatment. This limit applies to all routes of administration per the guidance. The use of published TTC is acceptable.

Using the dose, volume, TTC, an AET of (b) (4) was calculated for organic leachables and (b) (4) AET for organic extractables. From the extractables study, Vertex reports detection of compounds with AET greater than (b) (4) as well as trace elements.

**Reviewer Comment:** The concentration of leachables reported from the leachables study are below published TTC for mutagenicity (b) (4), sensitization (b) (4), and toxicity (b) (4). This is acceptable. In response to CMC IR#6, dated July 21, 2023, in Amendment 38, Vertex clarified the source of the compounds and elements detected at AET greater than (b) (4) as well as trace elements. According to Vertex, the extraction study (performed with empty vials and stoppers with solvents (b) (4)) was done to generate a library of compounds to use for identification of compounds detected in the leachables study. Therefore, the extraction study data included more compounds than the simulation study performed with (b) (4) solution. Vertex considers data from the simulation study more representative of compounds that could potentially leach into the DP. Vertex performed toxicological

assessment on these compounds and has concluded that compounds above AET value of (b) (4) from simulation study are low risk for toxicity per ICH Q3D guidelines. This is sufficient.

#### Leachables Study With Drug Product at Proposed Storage Conditions

Vertex performed an aged placebo leachables study of the DP in the container closure system. Vials were filled with DP and stored at -135°C for 7-8 months (aged placebo), reflective of the real time storage conditions. From this study Vertex identified (b) (4) at levels greater than (b) (4) and (b) (4). According to Vertex's toxicology assessment (b) (4) is not a risk to patients because it is not mutagenic in-silico or in-vitro and is not a sensitizer.

**Reviewer Comment:** This is sufficient.

### **3.2.P.2.5 Microbiological Attributes**

Exa-cel is comprised of living cells and is manufactured under aseptic conditions. Sterility is maintained by using verified, pre-sterilized raw materials and components, and maintaining appropriate aseptic controls during manufacturing and packaging. The container-closure and excipients are verified to be sterile before use. The vials are sterilized by (b) (4) by the vendor and are pyrogen-free. DP lot release testing includes (b) (4) sterility, mycoplasma, and endotoxin testing with samples that are aseptically obtained during filling of the final container. Container closure integrity testing, including (b) (4), demonstrated that the vial remains integral following representative filling, freezing, shipping, and thawing conditions.

### **3.2.P.2.6 Compatibility**

Exa-cel is supplied in one or more 20 mL vials for direct infusion to the patient and is not reconstituted or diluted prior to use. Each vial is thawed, withdrawn through a 18µm filter using a syringe and administered directly to the patient within 20 min of thaw. The infusion sets used for exa-cel delivery are provided by the administration sites based on commonly sourced materials. Please see **Section 3.2.P.2.2.1 Formulation Development** for in-use stability studies for details on the study performed to support compatibility of exa-cel with the intended administration procedures and materials.

#### **Overall Reviewer's Assessment of Section 3.2.P.2:**

*The information provided in section 3.2.P.2 is suitable.*

### **3.2.P.3 Manufacture**

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

The exa-cel DP is manufactured and tested at the sites listed in **Table 114**.

**Table 114. Drug Product Manufacturers and Testing Facilities**

Name and Address of Manufacturer/Testing Facility	FDA Identification No.	Operation/Responsibility
(b) (4)	(4)	Manufacturing, labeling, packaging, storage
		Release and stability testing (except potency, sterility, and mycoplasma),
		Manufacturing, labeling, release and stability testing (except potency, sterility, mycoplasma), packaging, storage
		Release testing (mycoplasma)
		Release testing (mycoplasma)
		Release and stability testing (sterility)
		Release and stability testing (on-target editing)
		Release and stability testing ( (b) (4) Only)
		Release testing (mycoplasma)
		Release and stability testing (sterility)
		Release and stability testing ( (b) (4) Only)

### 3.2.P.3.2 Batch Formula

The exa-cel batch formula is outlined in **Table 115**. The entire volume of exa-cel (b) (4) is processed into DP, which consists of the cells resuspended in cryopreservation solution. Each batch of DP may be packaged in up to nine 20-mL (b) (4) vials, depending on the total number of cells present. Lot volume and the number of vials filled is dependent on the number of cells processed from one mobilization cycle.

**Table 115. Drug Product Batch Formula**

Component	Function	Amount per Batch
CRISPR-Cas9-mediated gene-edited autologous CD34+ cells	DS	(b) (4)
(b) (4)	Excipient	(b) (4)

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

*Reviewed by ZY*

Exa-cel manufacturing is an uninterrupted process from drug substance to drug product. Please see **3.2.S.2.2 Description of Manufacturing Process** for description and review of manufacturing process.

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

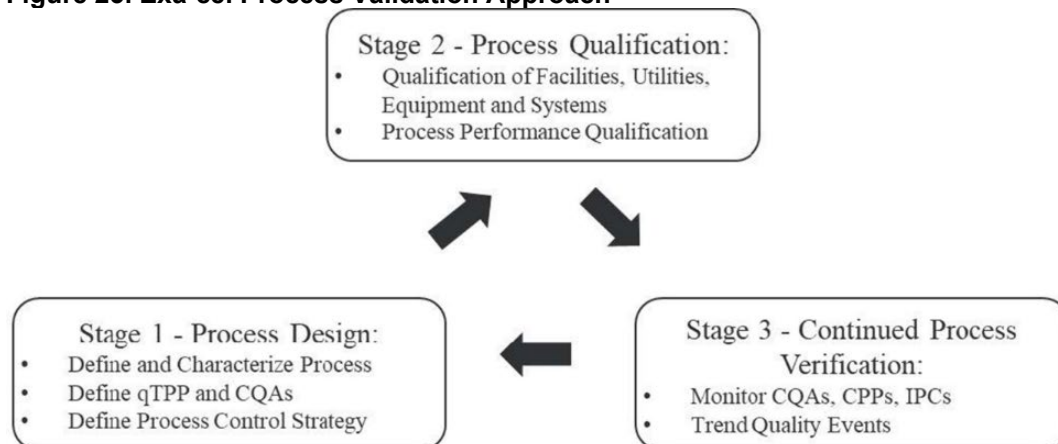
Exa-cel manufacturing is an uninterrupted process from drug substance to drug product. Please see **3.2.S.2.4 Controls of Critical Steps and Intermediates** for description and review of manufacturing process.

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

*Reviewed by ZY*

The overall exa-cel process validation approach is summarized in **Figure 23**:

**Figure 23. Exa-cel Process Validation Approach**



Stage 1 refers to the process development and characterization, which are reviewed in other sections in this BLA review. This section summarizes the stage 2 process qualification, including process performance qualification (PPQ) manufacturing runs, and stage 3 continued process verification.

Since two CDMOs are proposed to manufacture commercial exa-cel product, process validation was performed at both (b) (4) (referred to as “(b) (4)” in this section) with separate PPQ campaigns in each facility. Successful PPQ was defined by the following conditions:

- PPQ manufacturing campaigns are executed within the established Control Strategy.
- Pre-defined PPQ lots are successfully manufactured (i.e., meeting release specifications) in accordance with the approved manufacturing process and PPQ protocol to meet the acceptance criteria for CPPs and IPCs.
- Any failure to meet validation acceptance criteria was investigated as per site quality procedures and impact to validation disposition was assessed with reference to the validation protocol and documented as per protocol requirements.
- All relevant manufacturing documentation and analytical data associated with PPQ Validation lots have been reviewed and dispositioned by the Quality units of both the Sponsor and CDMO for lot release including the approved commercial product specifications.

Site process qualification summaries are provided for (b) (4) and (b) (4).

**(b) (4) Process Performance Qualification:**

(b) (4) manufacturing suites ( (b) (4) , all classified as Grade (b) (4) suites) are designated to commercial manufacturing of exa-cel at (b) (4). PPQ activities were performed in all (b) (4) suites, which share common utilities and have the same design with respect to layout, material and personnel flows, area classification and dedicated gowning areas.

*Reviewer Comment: Facility Design, Equipment and Utilities Qualification is provided in Section 3.2.A.1 Facilities and Equipment and reviewed by DMPQ. A pre-license inspection of the (b) (4) facility was conducted during (b) (4), confirming the equivalence between these (b) (4) suites. A Form FDA 483 was issued with seven CGMP deficiencies, which have been adequately addressed.*

In the process validation protocol (PVP), the proposed minimum number of PPQs is (b) (4) runs per suite, with (b) (4) being a patient run. (b) (4) lots were added proactively in case of unforeseen events for a total of (b) (4) PPQ lots ((b) (4) HD and (b) (4) clinical patient). During the execution of PPQ, deviations were encountered, resulting in (b) (4) additional batches ((b) (4) batches per suite) being processed in (b) (4) to ensure CAPA effectiveness and process reproducibility (Table 116). A total of (b) (4) lots of each of the critical components Cas9 ( (b) (4) )

(b) (4) ) and SPY101( (b) (4) ) were used in the PPQ campaign.

**Reviewer Comment:** Confirmed with reviewers of Cas9 and SPY101, that these genome-editing component lots are commercial representative, and that their use in the PPQ runs is appropriate.

**Table 116. Summary of (b) (4) Exa-cel PPQ Lots**

Lot Number	Description	Manufacturing Date	Manufacturing Suite	Cas9 (b) (4) Lot	SPY 101 (b) (4) Lot
(b) (4)					

**Reviewer Comment:** The use of Healthy Donor (HD) material together with patient apheresis in PPQ is acceptable because 1) they use the same process controls and testing, and can be considered representative of manufacturing performance; 2) limited availability of patient materials due to the rarity of the diseases. In addition, as discussed in **3.2.P.2.3 Manufacturing Process Development**, data from **Table 102** and from Amendment 20 (comparison of HD DP lots from (b) (4) mobilized using (b) (4) method) suggest that disease indication (i.e., HD, SCD, and TDT) and mobilization method do not have significant impact on exa-cel DP CQAs. Because the same manufacturing process is used to produce DP lots for both SCD and TDT patients, it is reasonable to include both SCD and TDT patient materials, together with HD material, for the PPQ study.

#### PPQ DP Release Results:

Detailed release testing results of all quality attributes for each PPQ lot are provided in the submission. A summary of the results is provided in **Table 117**:

**Table 117. DP Release Testing Results – (b) (4) PPQ Lots**

Attribute/Test	Acceptance Criteria	All Lots – Results Range (Mean ± SD; N)
Appearance	(b) (4)	(4)
CD34 Purity		
On-Target Editing Frequency		
(b) (4)		
(b) (4) (TDT)		
(b) (4) (SCD)		
(b) (4)		
Viable Cell Count		
Cell Viability		
Sterility		
Mycoplasma		
Endotoxin		

a. Lot (b) (4), (b) (6); the other TDT lot (b) (4), (b) (6) failed Viability

b. Lot (b) (4), (b) (6)

**Reviewer Comment:** (b) (4) lots met release specification. The (b) (4) lots that failed lot release are reviewed in discussion of **Table 122** in this section.

#### DP Characterization and Residuals Testing:

Additional characterization testing was performed for HD runs only and compared to historical experience (summarized in **Table 118**). Note that the historical experience data used in the PPQ analysis are combined data from the two CDMOs.

**Table 118. Summary of Characterization and Residual Testing Results for (b) (4) Exa-cel Healthy Donor PPQ Lots**

Test	Historical Experience	PPQ HD lots – Range (N)
Cas9 (b) (4)	(b) (4)	(4)
SPY101 gRNA (b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
Product related substances		
Editing Frequency in (b) (4)		
Enriched subpopulation		

a. Excluded Lot (b) (4), (b) (6), which most likely

b. Product Related Substances LOQ = (b) (4)

**Reviewer Comment:** It is acceptable to use only the HD lots for residual analysis; the sample size ( $N = (b) (4)$ ) is adequate to draw conclusions. Residual levels are mostly within historical manufacturing experience. Lot (b) (4), (b) (6) has higher-than-historical residuals in both (b) (4), but the differences are not as significant as to be a safety concern. Both Cas9 and SPY101 are within the lower



*ranges (i.e., higher purity) of historical experience. (b) (4) is a (b) (4)*

*It is variable and is donor-dependent. It is not a concern that the PPQ (b) (4) range is a slightly wider than historical experience. Overall, no concerns with characterization and residual testing.*

Process parameters in PPQ Campaign:

A summary of the IPC and CPP results for the exa-cel PPQ runs is provided in **Table 119** and **Table 120**, respectively.

(b) (4)

*Reviewer Comment: All (b) (4) lots met all the IPCs. No concerns.*

(b) (4)

(b) (4)

*Reviewer Comment: All CPPs met acceptance criteria. No concerns.*

#### Process Performance Assessed by Yield

PPQ run process performance was also assessed for yield against historical data (**Table 121**). Yields assessed include each unit operation as well as the total yield.

(b) (4)

*Reviewer Comment: PPQ manufacturing yields are within historic ranges. When the final (b) (4) PPQ lots are analyzed separately, they appear to have a relatively more consistent performance in terms of yields. No concerns.*

#### Manufacture Deviations and Resolution During (b) (4) PPQ Campaign

There were 12 deviations in the PPQ campaign classified as either Critical or Major. Three of the critical deviations that led to invalidating (b) (4) PPQ lots are summarized in **Table 122**:

**Table 122. Summary of Critical Deviations That Led to PPQ DP Lot Rejection (b) (4)**

Description	Impacted Lots	Root Cause Analysis	CAPA
(b) (4)			

Descriptions for each of the other nine major and critical deviations is also provided in the submission and have been reviewed.

**Reviewer Comment:**

*The deviation reports (DI-22-314, DI-22-332, DI-22-333, DI-22-360, DI-22-362) for events resulting in rejection of the (b) (4) lots were reviewed by interviewing (b) (4) Quality Operations Supervisor during the (b) (4) PLI (b) (4). The review and inspection activities confirmed the descriptions submitted in the BLA. No issues identified with the investigations or the root cause analyses.*

*We do not agree with Vertex's statement that the assignable root cause for (b) (4), (b) (6) Potency OOS "was deemed non-related to the manufacturing process controls" since it is assigned to human error. Two occurrences in (b) (4) lots indicates a deficiency in process control even if it was caused by human error. However, the CAPA (CAPA-22-063 updating BPR procedures) implemented to ensure completion and verification of critical electroporation activities was evidently effective; the (b) (4) supplemental PPQ lots manufactured in (b) (4), as well as other following clinical lots to date, have not encounter such deviations. Therefore, this issue is considered resolved without negative impact on PPQ assessment.*

*The (b) (4) OOS investigation was thorough with conclusion supported by relevant hypothesis-testing. By (b) (4) for the assay, (b) (4) re-tests using (b) (4) suggested that the original OOS testing results were due to the high variability of the original process. The CAPA to (b) (4) is likely helpful in resolving the assay variability issue. Although we do not agree with Vertex's classification (based on (b) (4) re-testing results during investigation) of lots (b) (4), (b) (6) as manufacturing success, the (b) (4) supplemental PPQ runs demonstrated the consistency of (b) (4) current manufacturing control.*

*Reviewer's Assessment of (b) (4) PPQ: Although the process validation acceptance criteria did not specify the number of (consecutive) lots required to meet all release specifications and process parameters, the number of successful manufactured lots (out of (b) (4)) and the success of the final (b) (4) lots (b) (4) patient lots and (b) (4) HD lots) suggest that the process in (b) (4) is capable of consistently manufacturing exa-cel DP lots.*

### (b) (4) Process Performance Qualification:

When the process validation protocol (PVP) was prepared, (b) (4) manufacturing suites ((b) (4)), both Grade (b) (4) were designated to commercial manufacturing of exa-cel at (b) (4). PPQ activities were performed in (b) (4) suites, which share common utilities and have the same design with respect to layout, material and personnel flows, area classification and dedicated gowning areas.

*Reviewer Comment: Facility Design, Equipment and Utilities Qualification is provided in Section 3.2.A.1 Facilities and Equipment and reviewed by DMPQ. A PLI of the (b) (4) facilities including (b) (4) was conducted during (b) (4). A Form FDA 483 was issued with two CGMP deficiencies, which have been adequately addressed.*

In the PVP, the proposed minimum number of PPQs is (b) (4) runs per suite, with at least (b) (4). (b) (4) more lots were added proactively in case of unforeseen events for a total of (b) (4) PPQ lots ((b) (4)). The (b) (4) lots of Cas9 and SPY101 as used as (b) (4) were used in the (b) (4) PPQ campaign. A summary of PPQ lots is provided in **Table 123**.

**Table 123. Summary of (b) (4) Exa-cel PPQ Lots**

Lot Number	Description	Manufacturing Date	Manufacturing Suite	Cas9 (b) (4) Lot	SPY 101 (b) (4) Lot
(b) (4)					

*Reviewer Comment: During the (b) (4) PLI, we were informed that (b) (4) Grade (b) (4) suites ((b) (4)), instead of (b) (4), are dedicated to exa-cel manufacture. Given that all (b) (4) suites have the same design and equipment, and are supported by the same (b) (4) Grade (b) (4) suites and common areas, it is acceptable that PPQ runs were conducted in only (b) (4) of them.*

### PPQ DP Release Results:

Detailed release testing results of all quality attributes for each PPQ lot are provided in the submission. A summary of the results is provided in **Table 124**:

**Table 124. DP Release Testing Results – (b) (4) PPQ Lots**

Attribute/Test	Acceptance Criteria	All lots – Results Range (mean ± SD; N)
Appearance	No vial defects, translucent cell suspension, essentially free of visible foreign particles	All conform
CD34 Purity	(b) (4)	(4)
On-Target Editing Frequency		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
Viable Cell Count		
Cell Viability		
Sterility		
Mycoplasma		
Endotoxin		

a: Lot (b) (4)

b: Lot (b) (4)

**Reviewer Comment:** All PPQ lots met release specification. No concerns.

#### DP Characterization and Residuals Testing:

Additional characterization testing was performed for the (b) (4) HD runs only and compared to historical experience (summarized in **Table 125**).

**Table 125. Summary of Characterization and Residual Testing Results for (b) (4) Exa-cel Healthy Donor PPQ Lots**

Test	Historical Experience	(b) (4)	(b) (4)	(b) (4)
Cas9 (b) (4)	(b) (4)	(4)		
SPY101 gRNA (b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
Product-related substances				
Editing Frequency in (b) (4) Enriched Subpopulation				

**Reviewer Comment:** Cas9 residual level is overall higher than observed in (b) (4) PPQs, with (b) (4) lots also being outside of historical experience. Actual residual testing data from Section 3.2.P.5.5 **Characterization of Impurities** show that the majority of Cas9 residuals in these (b) (4) PPQ lots are detected in (b) (4). Together with the fact that other residual components (e.g., (b) (4)) are well within historical ranges, this suggest that the high level of Cas9 is not associated with (b) (4) procedures. It is unclear what causes the variability of residual

*intracellular Cas9 between lots/donors. However, because the PPQ range is still within the range (i.e., (b) (4)) that is determined in section 3.2.P.5.5 Characterization of Impurities as having negligible risk to patient safety, the observed residual Cas9 level is not considered as having a significant impact on PPQ acceptance.*

*(b) (4) in (b) (4), (b) (6) and (b) (4) are also slightly outside historical ranges. But these are not process-related. Overall, no concerns with PPQ characterization and residual testing.*

Process parameters in PPQ Campaign:

A summary of the IPC and CPP results for the exa-cel PPQ runs is provided in **Table 126** and **Table 127**, respectively.

(b) (4)

*Reviewer Comment: All lots met all the IPCs. No concerns.*

(b) (4)

*Reviewer Comment: All CPPs are within PV acceptance ranges. No concerns.*

Process Performance Assessed by Yield

PPQ run process performance was also assessed for yield against historical data (**Table 128**). Yields assessed include each unit operation as well as the total yield.

(b) (4)

**Reviewer Comment:** Manufacturing yields are within historic ranges (**Table 128**). No concerns.

Manufacture Deviations and Resolution During (b) (4) PPQ Campaign

There were 12 deviations in the PPQ campaign. Their descriptions were provided in the submission. These include (b) (4)

(b) (4)


None of the deviations has led to DP lot out-of-specification or manufacture failure.

**Reviewer Comment:**

The deviations have been addressed without issues, except for the (b) (4) in DP. During the BLA review, we have informed Vertex that DP vials with (b) (4) should be rejected (please see the summary below). Vertex's investigation suggested that the source of these (b) (4) is most likely single-use consumables including the (b) (4) vial. We have agreed to Vertex's general plan to continue working with suppliers to reduce/eliminate visible (b) (4) post-licensure. Considering (b) (4) generation is intrinsic to the manufacturing process prior to resolving consumable quality issue, it is acceptable not to classify these deviations as manufacture failures.

Summary and Reviewer Comment on the visible (b) (4) issue:

(b) (4)



*Reviewer's Assessment of (b) (4) PPQ: The (b) (4) PPQ runs (b) (4) patient lots and (b) (4) HD lots) were successfully manufactured and met the process validation acceptance criteria, suggesting that the process in (b) (4) is capable of consistent manufacture of exa-cel DP lots.*

### **Exa-cel Continued Process Verification**

Phase 3 of the process validation will be CPV, which includes a process monitoring plan to ensure that the exa-cel manufacturing remains consistent and controlled within the validated state throughout the product lifecycle. Process monitoring will assess for trends in process performance and quality attributes. Manufacturing trend analysis started from the first batch of PPQ runs. The initial statistics (e.g., means, upper limits and lower limits) are established using manufacturing data from the first (b) (4) batches, and re-calculated every (b) (4) batches with the statistical data being accumulative. Trends and out of limit events will be investigated. If trend investigations do not identify any deviation, the data can be used for the purpose of statistics re-calculation.



**Reviewer Comment:** The CPV plans were implemented in the (b) (4) manufacturing facilities. The plans, as well as data from the initial batches, were reviewed during the PLIs. No concerns.

### DP Shipping Validation:

(b) (4) LN2 dry shippers were qualified for exa-cel DP transport from manufacturing sites to authorized treatment centers:

(b) (4)

Studies related to DP shipping validation include the following:

### Operational Qualification Assessments:

Three reports (SD-59156, SD-59157, and SD-56370) were provided in the BLA for operational qualification assessments of the (b) (4) dry shippers. These are Vertex's assessment of the dry shipper manufacturers' Thermal Operational Qualification and Physical Operational Qualification.

(b) (4)

**Reviewer Comment:** In response to CMC IR#9, Vertex submitted in Amendment 66 (received October 30, 2023) the operational qualification report SD-56370, which was missing from the original submission. In the same response, Vertex also clarified that only the (b) (4) shippers will be used in shipping commercial exa-cel DP.

### Physical OQ:

Shippers are also tested for their ability to retain physical integrity and thermal performance against distribution hazards. (b) (4)

Performance Qualification (Transport Simulation Studies):

(b) (4)

**Reviewer Comment:** No concerns with the operational qualification assessments. Deficiencies of the DP shipping simulation study include the following:

- (b) (4) data were not provided in the BLA.
- No data on other DP CQAs pre- or post-transport to further support that the shipping conditions do not have adverse effects on product quality.
- (b) (4) shippers were used in the simulation study (based on Vertex's response to CMC IR#9); however, (b) (4) will be used for commercial products.

To address these issues, Vertex agreed to perform a supplemental shipping validation study of exa-cel assessing the quality attributes including (b) (4) for (b) (4) and (b) (4)-transportation samples using the (b) (4) commercial shippers,

*and submit the final validation study report by May 31, 2024, as a Post Marketing Commitment. With this commitment, the available data supporting temperature and container closure integrity are considered adequate for DP shipping validation.*

**Overall Reviewer's Assessment of Section 3.2.P.3.5:**

*Data and information provided are adequate to demonstrate that the proposed commercial process can consistently manufacture exa-cel at the two contract manufacturing facilities. Deficiency in DP shipping validation was identified, and is addressed through a supplemental shipping validation study as a post market commitment.*

**3.2.P.4 Control of Excipients**

*Reviewed by JC*

**3.2.P.4.1 Specifications**

Refer to Section 3.2.P.4.5 Excipients of Human or Animal Origin.

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

Refer to Section 3.2.P.4.5 Excipients of Human or Animal Origin.

**3.2.P.4.4 Justification of Specifications**

Refer to Section 3.2.P.4.5 Excipients of Human or Animal Origin.

**3.2.P.4.5 Excipients of Human or Animal Origin**

The only excipient in exa-cel DP formulation is (b) (4) which is manufactured by (b) (4) specifications are listed in Table 129.

(b) (4)

(b) (4)

**Reviewer Comment:** Vertex has provided a Letter of Authorization (LOA) from (b) (4) to cross-reference Master File (b) (4) which describes manufacturing of (b) (4). Vertex releases (b) (4) for exa-cel manufacturing based on the quality testing provided in (b) (4) COA and their incoming testing. (b) (4) COA and (b) (4) statement that product is (b) (4) are also provided to support safety of the (b) (4) from human or animal derived adventitious agents.

In response to CMC IR#6, dated July 21, 2023, in Amendment 38, Vertex provided additional information about the change in acceptance criterion for (b) (4) (extension of the range) that was made. The range for (b) (4) was changed due to introduction of (b) (4). According to Vertex, the (b) (4) was determined from qualification studies performed by the manufacturer of (b) (4). (b) (4) studies included testing of (b) (4) lots for accuracy and precision to bridge the (b) (4), as well as system suitability and calibration studies. Vertex also performed a separate study comparing (b) (4) of (b) (4) lot of (b) (4) measured by the (b) (4) and results met the criterion for (b) (4). These studies are used to bridge the (b) (4). This is sufficient. Vertex has provided summary of validation results for each of their methods. This is sufficient.

### 3.2.P.4.6 Novel Excipient

There are no novel excipients.

### 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)

*Reviewed by AK*

The final agreed upon exa-cel lot release acceptance criteria are summarized in **Table 130**.

**Table 130. Final Commercial Exa-cel Release Specifications**

Quality Attribute	Test	Method	Acceptance Criteria	Justification
General	Appearance	Visual assessment	Translucent cell suspension, essentially free of visible foreign particles	Based on observation of DP prior to freezing; will not allow release of DP with visible foreign/intrinsic particles.
Identity	CD34 expression	Flow Cytometry	Positive	Observed value equal to or above (b) (4) is considered "positive".
-	On-Target Editing Frequency	TIDE	Positive	Observed value equal to or above (b) (4) is considered "positive".
Purity	CD34 Purity	Flow Cytometry	(b) (4)	This was the lowest value observed for a DP lot used to treat a subject in the clinical trial with acceptable safety and efficacy. A one-sided criterion was deemed acceptable since the highest value observed with acceptable safety and efficacy was (b) (4).
Potency	On-Target Editing Frequency	TIDE	(b) (4)	This criterion was set at (b) (4) by Vertex because the lowest value observed for a DP lot used to treat a subject in the clinical trial with acceptable safety and efficacy was (b) (4). A one-sided criterion was deemed acceptable since the highest value observed with acceptable safety and efficacy was (b) (4).
-	(b) (4)	(b) (4)	(b) (4)	This was the lowest value observed for a DP lot used to treat a subject in the clinical trial with acceptable safety and efficacy. It was deemed acceptable not to have an upper limit as there were no identified safety concerns with expressing additional y-globin.
-	(b) (4)	(b) (4)	(b) (4)	This was the lowest value observed for a DP lot used to treat a subject in the clinical trial with acceptable safety and efficacy. It was deemed acceptable not to have an upper limit as there were no identified safety concerns with having (b) (4)
Quantity and Content	Viable Cell Count	(b) (4)	(b) (4)	This was the range of total viable cells used in the clinical trial with acceptable safety and efficacy.

Quality Attribute	Test	Method	Acceptance Criteria	Justification
-	Cell Viability	(b) (4)	(b) (4)	This was the lowest value observed for a DP lot used to treat a subject in the clinical trial with acceptable safety and efficacy. A one-sided criterion was deemed acceptable since the highest value observed with acceptable safety and efficacy was (b) (4).
Safety	Sterility	(b) (4)	Drug Product: No growth (b) (4)	Requirement
-	Mycoplasma	(b) (4)	Negative	Requirement
-	Endotoxin	(b) (4)	(b) (4)	(b) (4)

**Reviewer Comment:** In CMC IRs #8 (dated October 6, 2023), #9 (dated October 23, 2023), and #10 (dated November 7, 2023) Vertex was asked to tighten the On-Target Editing Frequency, (b) (4), Viable Cell Count, and Cell Viability acceptance criteria compared to the initially proposed criteria to better reflect clinical study and manufacturing experience. Additionally, Vertex was asked to update the criterion for (b) (4) to “(b) (4)” and add the requirement to be “(b) (4)”. Vertex provided updated acceptance criteria and justifications in Amendments 61, 66, and 69 with the final acceptable acceptance criteria being submitted in Amendment 69. All updates are reflected in **Table 130**.

#### Potency Assessment of Exa-cel

Prior to initiation of the exa-cel Phase 3 clinical trials, Vertex was asked to develop and implement cellular biologically relevant potency assays supporting the ability of Cas9/SPY101 editing to correct the phenotypic deficiencies observed in SCD and TDT RBCs in addition to the assays evaluating editing efficiency (b) (4) and (b) (4). Vertex chose to implement an assay evaluating (b) (4) for the SCD indication and an assay evaluating (b) (4) for the TDT indication.

When Vertex submitted BLA 125785, they proposed (b) (4) as the sole measure of exa-cel potency. To support this proposal, Vertex provided data correlating the (b) (4) readout to the (b) (4) readouts. In **Figure 24**, data from (b) (4) variably edited healthy donor lots of CD34+ HSPCs demonstrate that there is a significant correlation between (b) (4). The correlation was determined within each of the lots by

$R^2$  value ( (b) (4) ) and p value ( (b) (4) ). However, data from (b) (4) SCD patients (**Figure 25**) and (b) (4) TDT patients (**Figure 26**) showed more variability. In the disease setting, most lots continued to exhibit high correlation, while others ( (b) (4) ) did not.

(b) (4)

(b) (4)

Correlation analyses between (b) (4) and either (b) (4) were also performed using data from exa-cel clinical lots. However, again, most likely due to patient-to-patient variability correlations were not observed. These data have been excluded for brevity.

**Reviewer Comment:** While correlations between (b) (4) in the patient setting, it appears that combining (b) (4) offers equivalent product control as (b) (4). This has been concluded because the lots that did not exhibit high correlation of either (b) (4) with (b) (4) did exhibit high correlation of (b) (4) with (b) (4). Note, correlation analyses with clinical outcomes were not performed. However, given the efficacy rate of exa-cel (b) (4) it is doubtful these analyses would have provided further clarity. Thus, it is acceptable that (b) (4) be included as potency assays in the commercial exa-cel specification and that (b) (4) be excluded.



### Release of Out of Specification Commercial Product

Vertex was asked if they intended to have an expanded access protocol (EAP) or mechanism for releasing OOS commercial product in CMC IR#10, dated November 13, 2023. Vertex responded in Amendment 69 that they have no plan to submit an EAP. If they identify a need for administration of OOS commercial lots of exa-cel, submission(s) will be made following the FDA guidance on expanded access.

### **Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:**

The information provided is suitable.

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

*Reviewed by JC*

#### **Appearance**

Appearance is evaluated by visual inspection of post-thaw DP in a (b) (4) under (b) (4) conditions for both DP lot release and stability. According to Vertex, the (b) (4)

A summary of the Appearance method validation is provided in **Table 131**.

**Table 131. Appearance Analytical Method Validation**

Attribute	Acceptance Criteria
Appearance	Identical results between (b) (4) operators for the following observations: (b) (4)

This method was validated by evaluating precision of operators at both DP manufacturing facilities: (b) (4). Operator precision was assessed using DP lots (b) (4) with (b) (4) operators at (b) (4), and at (b) (4), (b) (4) lots (b) (4) vials per lot) of healthy donor DP with (b) (4) operators over (b) (4) days were used for validation. At (b) (4) facilities, each lot (b) (4) or vial (b) (4) was assessed independently by (b) (4) different operators. No particles/particulates were reported in the validation results; all lots tested are reported as practically free of particles/particulates present in the cell suspension.

**Reviewer Comment:** Vertex reports all lots tested at both facilities met acceptance criteria after visual inspection by operators; this data is used to support validated precision of the method. This method and validation relies on appropriate training of the

operators, hence it is subjective. The (b) (4) validation protocol requires operators to (b) (4) to allow them to train for the appearance method. According to (b) (4) validation report, (b) (4) and only operators trained on the protocol will be scheduled for routine appearance testing. In response to CMC IR#8, dated September 29, 2023, in Amendment 61, Vertex provided information on training used to qualify operators for appearance test for DP release and stability. This is acceptable.

### Viable Cell Count and %Viability

According to Vertex, viable cell count (VCC) and % Viability is tested (b) (4). VCC and % viability are determined using (b) (4). VCC and % viability of exa-cel DP are assessed by (b) (4)

VCC system suitability criteria are summarized in **Table 132**.

**Reviewer Comment:** In response to CMC IR#8, dated September 29, 2023 in Amendment 61, Vertex clarified that (b) (4) for the VCC and %Viability method, as used in method validation studies. This is acceptable.

**Table 132. System Suitability Criteria**

Attribute	Acceptance Criteria Proposed
VCC and %viability of DP	(b) (4)
VCC and %viability of (b) (4)	Meets the predefined criteria for VCC and %viability Repeatability: (b) (4) Intermediate Precision: (b) (4) Reproducibility: (b) (4)

Vertex has a Master Protocol (AVP-54460) for validation of Viability and Cell Count Assay to define the validation parameters for both sites (b) (4) and to ensure validation is performed the same at both sites. Cell count and viability method was validated (specificity, linearity, accuracy, precision (repeatability and intermediate), limit of quantitation (LOQ), range, robustness) using CTX001 Drug Product (DP) cells from

(b) (4) individual healthy donor lots at each manufacturing facility ( (b) (4) ). The (b) (4) was used for validation.

For validation studies, (b) (4)

Validation for (b) (4) Drug Product **Table 134** were executed using the same procedure.

Drug Product In-Process Testing

(b) (4)

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

(b) (4)

(b) (4)

#### Drug Product Lot Release

(b) (4) Individual HD lots (N=(b) (4)) were measured in (b) (4) technical replicates in the validation studies (AVP-54220, AVR-54814) at (b) (4) site ((b) (4)). (b) (4) additional DP lots were used in repeat studies due to failed parameter measurements/invalidated data (at (b) (4)). Deviations for failed runs were raised and corrective actions applied ((b) (4)).

**Table 134. Validation for DP Viability Cell Count and % Viability Method**

Validation Parameter	Validation Study	Acceptance Criteria	Result
<b>VCC</b>			
Specificity	(b) (4)		
Linearity			
Accuracy			
Precision			
Robustness (VCC and %Viability)			

Validation Parameter	Validation Study	Acceptance Criteria	Result
Range	(b) (4)		
LOQ			
%Viability			
Specificity			
Linearity			
Accuracy			
Precision			
LOQ			
Range			

(b) (4)

Variability is defined as %CV in (b) (4) protocol MVAL-0009, and %RSD in (b) (4) protocol VD/(b) (4)/PQ/0223

**Reviewer Comment:** In response to CMC IR#8, dated September 29, 2023 in Amendment 61, Vertex clarified that the LOQ for the CCV method is (b) (4) as established in the method validation studies, and that the LOQ of (b) (4) is for the (b) (4) LOQ based on the manufacturer of the (b) (4) equipment. Vertex also clarified that the LOQ of (b) (4) is included in the method validation to define that cell counts below (b) (4) acquired during validation are invalid because such values are below LOQ of the instrument. In addition, in response to CMC IR#8, dated September 29, 2023 in Amendment 61, Vertex clarified that the method was validated according to SOP/QCP/162 (not SOP/QCP/123) which is the intended commercial method. This is acceptable.

#### Reproducibility of %Viability and VCC between (b) (4)

Vertex assessed the reproducibility of the VCC and %Viability between (b) (4) using the same lot of assay control cells ( (b) (4) ) in studies separate from the validation studies (**Table 135**).

**Table 135. Reproducibility of %Viability and VCC Between (b) (4)**

Method	Data Source	Acceptance Criteria	Results (%CV)
%Viability	Repeatability ( (b) (4) )	(b) (4)	(b) (4)
	Intermediate Precision (b) (4)		
	Reproducibility (b) (4)		
VCC	Repeatability (b) (4)	(b) (4)	(b) (4)
	Intermediate Precision (b) (4)		
	Reproducibility (b) (4)		

**Reviewer Comment:** In response to CMC IR#8, dated September 29, 2023 in Amendment 61, Vertex clarified that instrument to instrument variability was evaluated in the reproducibility assessment between (b) (4) **Table 135**. Although results meet acceptance criteria for validation, the data indicates tighter validation AC can be set. In response to CMC IR#8, dated September 29, 2023 in Amendment 61, Vertex declined to update the validation AC: Vertex stated validation AC would be updated in the future if changes to the method are made. Cumulatively the validation data indicates low variability in the cell count and viability method, supporting a controlled method suitable of accurately and precisely measuring DP cell numbers and viability across test sites. Validation studies indicate the method is suitable for the intended purpose.

#### Identity and Purity: CD-34+ Expression by Flow Cytometry

The CD34 purity (%CD34 (b) (4) of viable cells) of exa-cel DP is a CQA that it used to calculate the dose of DP administered to each patient. The percentage of CD34 (b) (4) cells out of viable cells in the exa-cel DP is assessed by flow cytometry after staining



(b) (4)

Controls:

(b) (4)

For the CD34+ flow cytometry, (b) (4) samples are prepared:

(b) (4)

(b) (4)

**Table 136. Flow Cytometer Instruments**

Equipment	Manufacturer	Model	Testing Site
(b) (4)			

For validation, DP is

(b) (4)

Summaries of the samples used in the validation study are provided in

**Table 137** and Error! Reference source not found.. A summary of the validation data is provided in **Table 138**.

**Table 137. Validation Study Samples for CD34+ Flow Cytometry Method**

Sample	Purpose
(b) (4)	

**Table 138. Validation Summary of CD34+ Expression Flow Cytometry Method**

Parameter	Validation studies	Acceptance Criteria	Validation Data
Linearity	(b) (4)		
Accuracy	(b) (4)		
Precision	(b) (4)		
Range	(b) (4)		
Limit of Quantitation (LOQ)	(b) (4)		

Parameter	Validation studies	Acceptance Criteria	Validation Data
Specificity	(b) (4)	(b) (4)	(b) (4)
Robustness			

Vertex states reproducibility between (b) (4) was evaluated using (b) (4). For the assay control, precision (Repeatability and Intermediate) was evaluated with the same lot (N= (b) (4)) at both (b) (4) with (b) (4) analysts, (b) (4) days, and (b) (4) instruments (b) (4). For HD DP, (b) (4) lots were manufactured from the same starting material at both (b) (4) (b) (4) lots total). Both sites tested each lot providing duplicate results per lot. Reproducibility was assessed as (b) (4) results per lot. A summary of the reproducibility data is provided in **Table 139**.

**Table 139. CD34+ Expression Method Reproducibility Between (b) (4)**

Sample	Parameter	Acceptance Criteria	Results
VX290- AC003 (assay control)	(b) (4)	(b) (4)	(b) (4)
HD			

**Reviewer Comment:** In response to CMC IR#8, dated September 29, 2023 in Amendment 61, Vertex provided (b) (4) for all donor samples tested in the CD34+ Purity validation studies. In response to CMC IR#8, dated September 29, 2023 in Amendment 61, Vertex also clarified that robustness evaluations for different reagent lots was performed at Vertex for the CD34+ purity assay. Vertex reported that the robustness studies included (b) (4) performed with (b) (4), and evaluation of (b) (4) results for all conditions tested are reported as (b) (4). Cumulatively, validation studies indicate the method is suitable for the intended purpose.

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

Reproducibility of VCC, %Viability, CD34+ Purity Methods Between (b) (4)

As part of the assay control validation studies, Vertex evaluated reproducibility of (b) (4) by assessing comparability data from (b) (4) exa-cel DP lots manufactured from (b) (4) healthy donor material at both sites (**Table 142**). Final DP from each site was tested at both sites to assess reproducibility across sites; both sites generated results for each of the (b) (4) lots. Vertex calculated %CV of VCC, %Viability, and CD34+ purity from every lot.

**Table 142. Reproducibility of VCC, %Viability, CD34+ Purity Methods Between (b) (4)**

Parameter	VCC	%Viability	CD34 Purity
Number of HD lots	(b) (4)		
%CV	(b) (4)		

**Reviewer Comment:** The data supports acceptable reproducibility between (b) (4)

**Potency:** (b) (4)

(b) (4)

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

(b) (4)

### Identity and Potency: On-Target Editing Frequency by TIDE

The frequency of on-target editing is evaluated using a method called Tracking of Indels by Decomposition (TIDE). TIDE is defined by Vertex as a computational approach in which Sanger sequence traces from edited and unedited cells are analyzed by a decomposition algorithm that estimates the editing frequency. Vertex is using this method to determine potency and identity, which is defined at the lowest point of on-target editing frequency: (b) (4).

For Identity: positive = (b) (4)

(b) (4)

### Validation of TIDE Analysis

TIDE analysis involves comparing Sanger sequencing trace files of the DP against trace files of the unedited donor to determine total editing rate. TIDE analysis is performed by (b) (4). Validation ((b) (4)), accuracy, intermediate precision, repeatability, overall precision, linearity, and range)

of the TIDE analysis was done according to the protocol outlined in AVP-50273. Intermediate precision, repeatability, overall precision, linearity, and range were evaluated using (b) (4) from (b) (4) healthy edited and (b) (4) in (b) (4) runs (b) (4) operators performing (b) (4) runs each on multiple days). DP samples were analyzed in (b) (4).

**Reviewer Comment:** The experimental validation of the TIDE Analytical method is reviewed below. Komudi Singh, from the Bioinformatics group reviewed the TIDE software validation, including data processing and analysis on the CRISPR therapeutics analysis platform, (b) (4) used for analysis, accuracy and linearity calculations performed in (b) (4) software, and precision calculations done with ANOVA. Please refer to the Bioinformatics review memo for additional details.

#### Positive Control

Accuracy was evaluated with (b) (4)

(b) (4)

In the validation studies, the (b) (4)



(b) (4)

(b) (4)

Negative Control

(b) (4)

Drug Product

Vertex provided (b) (4) for (b) (4) Donor cell samples and corresponding edited DP lots; a (b) (4) operator (b) (4) from these samples **Table 146**.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

TIDA method validation data are summarized in **Table 148**.

**Table 148. TIDE Method Analysis Validation**

Validation Parameter	Acceptance Criteria	Results
Specificity	(b) (4)	(b) (4)
Accuracy		
(b) (4)		

Validation Parameter	Acceptance Criteria	Results
Repeatability (b) (4)	(b) (4)	(4)
Intermediate Precision (IP) (b) (4)		
Overall Precision (OP)		
Linearity		
Linear regression of reference versus measured values		
Range		

For specificity testing, (b) (4)

(b) (4)

#### TIDE Supplemental Validation Studies

Supplemental validation studies (per protocol AVP-52747) were performed to extend the range of the assay beyond (b) (4) editing efficiency (AVR-54500 report), as determined in the initial validation studies. The same acceptance criteria were applied as the initial validation studies **Table 148** except that acceptance criterion for accuracy were (b) (4) in the supplemental studies. For supplemental validation, the TIDE analysis method was validated for accuracy, intermediate precision, repeatability, overall precision, and linearity in similar fashion as the initial validation. (b) (4) runs with (b) (4) operators (b) (4) runs per operator) were performed and samples were performed in (b) (4). The same (b) (4) representing the (b) (4) and used in the initial validation studies were used to prepare the (b) (4) for the supplemental validation studies. (b) (4)

validation report (AVR-54500). Results from the supplemental validation studies were used to extend the range of the assay from (b) (4) to (b) (4) **Table 149**.

**Table 149. TIDE Method Supplemental Validation**

Validation Parameter	Acceptance Criteria	Results
Accuracy	(b) (4)	(4)
(b) (4)		
(b) (4)		
(b) (4)		
Repeatability		
(b) (4)		
Intermediate Precision (IP)		
(b) (4)		
Overall Precision (OP)		
Linearity		
Linear regression of reference versus measured editing rate (b) (4)		
Range		

#### TIDE Validation Robustness Studies

Per AR-51013, (b) (4) robustness studies evaluating different parameters of the TIDE method ( (b) (4)

were performed using (b) (4)

**Reviewer Comment:** In response to CMC IR#8, dated September 29, 2023 in Amendment 61, Vertex provided information on the assessments done to evaluate impact of (b) (4) step in the TIDE method validation. In the IR response (received October 6, 2023) Vertex reported that during development (b) (4) on TIDE results was assessed using (b) (4). Differences in (b) (4) are reported to have had no impact on (b) (4). This is acceptable. Validation studies indicate the

method is suitable for the intended purpose. CMC defers to the bioinformatics review memo for review of suitability of the (b) (4)

### Safety: Endotoxin

Bacterial endotoxin in Exa-cel drug product is tested according to (b) (4) and (b) (4), using the (b) (4) method via (b) (4) and (b) (4).

**Reviewer Comment:** CMC differs to DBSQ review of this safety assay. DBSQ determined assay was acceptable.

### Safety: Mycoplasma

**Reviewer Comment:** MF (b) (4) held by (b) (4) was cross-referenced for DP Mycoplasma testing, but the full information required to review the assay was acquired over IR by DBSQ. CMC differs to DBSQ review of this safety assay. DBSQ determined assay was acceptable.

### Safety: Sterility

Sterility testing for exa-cel drug product (DP) is done according to (b) (4) and (b) (4) by (b) (4)

**Reviewer Comment:** CMC differs to DBSQ review of this safety assay. DBSQ determined assay was acceptable.

### Characterization Assays

**Reviewer comment:** The following assays are not used for exa-cel release, however the assays were validated to support the adequacy of the proposed potency assay. Full assay validations were provided and found to be acceptable. An abbreviated review is provided as these assays are not used for commercial release.

(b) (4)

**Reviewer Comment:** This method is further reviewed in Section 3.2.S.3.1 Elucidation of Structure and Other Characteristics.

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

(b) (4)

### 3.2.P.5.4 Batch Analyses

*Reviewed by AK*

A total of (b) (4) clinical exa-cel lots were manufactured to treat SCD: (b) (4) lots manufactured at (b) (4), (b) (4) lots manufactured at (b) (4), and (b) (4) lots manufactured at (b) (4). A total of (b) (4) clinical exa-cel lots were manufactured to treat TDT: (b) (4) lots manufactured at (b) (4), (b) (4) lots manufactured at (b) (4), and (b) (4) lots manufactured at (b) (4). All lots met the release criteria in place at the time of release and all were administered. It is important to note that multiple lots of exa-cel may be needed to meet the minimum required patient dose. For SCD, (b) (4) patients were treated, of which (b) (4) required multiple exa-cel lots to meet the minimum dose: (b) (4) patient required (b) (4) lots, (b) (4) patients required (b) (4) lots, (b) (4) patients required (b) (4) lots, and (b) (4) patients required (b) (4) lots. For TDT, (b) (4) patients were treated, of which (b) (4) required multiple exa-cel lots to meet the minimum dose: (b) (4) patient (b) (4) lots, (b) (4) patients required (b) (4) lots, and (b) (4) patients required (b) (4) lots. The observation that more lots are needed to treat SCD patients correlates with the observation that they mobilize CD34+ cells less efficiently (see Section **3.2.S.2.6 Manufacturing Process Development**).

Commercial specifications were established using available data from all (b) (4) exa-cel lots because comparability was established between (b) (4) and because no differences were observed between quality attribute values exhibited by exa-cel lots manufactured from SCD or TDT starting material. Representative CD34 Purity, On-Target Editing Frequency, and (b) (4) data are provided in **Figure 30**, **Figure 31**, and **Figure 32**, respectively (SCD lots are shown in blue; TDT lots are shown in pink).

(b) (4)

(b) (4)

Data from the following numbers of lots were used to determine the DP potency release specification described in 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s):

(b) (4)

Data were provided supporting the stability of these attributes over the testing time frame to support use of both prospective and retrospective data for setting the commercial lot release acceptance criteria.

Information on the exa-cel manufacturing failure rate was requested in CMC IR#9, dated October 23, 2023, and was received in Amendment 66. The manufacturing failure rate for all clinical lots of exa-cel was (b) (4). Of the (b) (4) clinical lots manufactured, (b) (4) lots were rejected. The failure rate was roughly consistent between indications (SCD: (b) (4); TDT: (b) (4)). However, (b) (4) did exhibit a slightly higher lot failure frequency compared to (b) (4). The reasons for lot failure are summarized below:

(b) (4)



(b) (4)

[REDACTED]

**Reviewer Comment:** *The ability to combine data across manufacturing sites, indications, and prospective and retrospective testing resulted in a robust data set for setting commercial lot release criteria. However, the fact that many patients received multiple product lots needed to be accounted for.*

*Additionally, while the manufacturing process does appear robust, there is a relatively high manufacturing failure rate for exa-cel. The main causes of this appear to be incoming starting material contamination, inability to obtain an adequate number of cells, and (b) (4) OOS. Starting material contamination may be able to be better controlled by the implementation of stricter guidelines in the commercial setting. The inability to obtain an adequate number of cells seems to be a result of the patient populations, particularly in the case of SCD, and the manufacturing process itself (e.g., (b) (4) ) and is unlikely to change much in the commercial setting. The (b) (4) OOS may result in Vertex submitting an EAP in the future. Another important thing to consider is that the observations of particulates may result in a significant increase in lot failures in the near term due to the correcting of Vertex's handling of particulate observations during exa-cel 100% visual inspection. This too may increase the number of exa-cel lots needed to meet the minimum patient dose.*

### 3.2.P.5.5 Characterization of Impurities

*Reviewed by AK*

Impurities in exa-cel are divided into two categories: (1) process-related impurities arising from the manufacturing process, primarily from residual materials used during manufacturing that are not intended to be part of the final product and (2) product-related impurities originating from the autologous starting material (cellular impurities). Assessments of exa-cel process-related impurities were performed on developmental, comparability and PPQ runs (N= (b) (4)). Evaluation of exa-cel product related impurities is described in Section **3.2.S.3.1 Elucidation of Structure and Other Characteristics**.

#### Residual Cas9

(b) (4)

#### Residual SPY101

(b) (4)

**Reviewer Comment:** Note, residual Cas9 and SPY101 RNP were not assessed. Vertex was asked to comment on this in CMC IR#10, dated November 7, 2023. In response, Vertex stated that editing is transient, taking place within (b) (4) and there is no known mechanism by which intracellular SPY101-Cas9 RNPs could be transferred from cell to cell following administration. Furthermore, any residual RNP in the (b) (4) would not be able to diffuse into cells in vivo due to its

*size and charge and would be expected to be systemically cleared quickly following dosing. Based on this information, in the event residual SPY101-Cas9 RNPs are present in the DP, there are no additional safety concerns.*



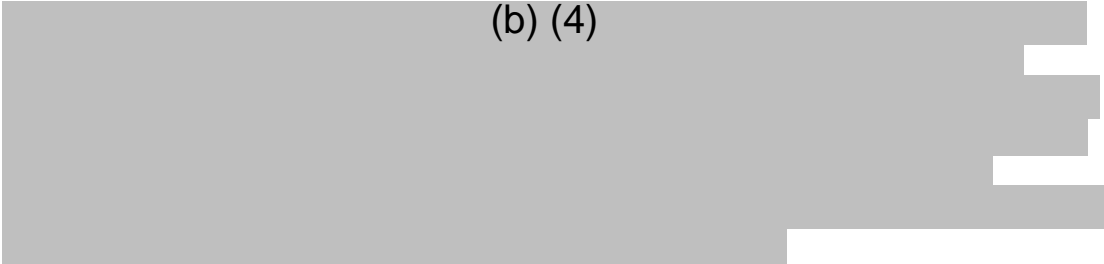
Residual (b) (4)

(b) (4)

Residual CD34 Reagent

The CliniMACS CD34 Reagent used in exa-cel manufacture is composed of (b) (4)

(b) (4)



*Reviewer Comment: Based on the data provided, there are no safety concerns regarding residual (b) (4) or CliniMACS CD34 Reagent in exa-cel. Of note, the CliniMACS CD34 Reagent used to manufacture exa-cel is the version used to purify CD34+ cells for stem cell transplants licensed under the Humanitarian Device Exemption.*

### 3.2.P.6 Reference Standards or Materials

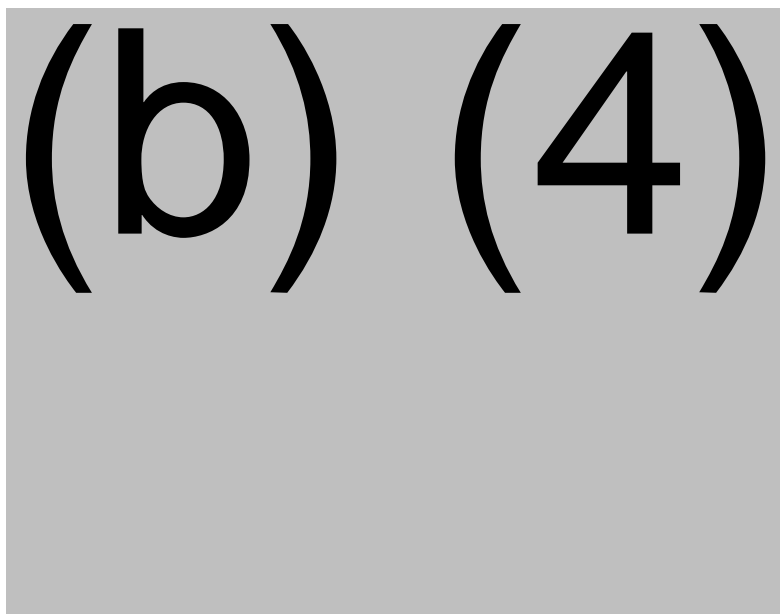
*Reviewed by JC*

There is no reference standard for exa-cel DP because it is an autologous product. The on-target editing method is compared using donor-matched unedited samples.

### 3.2.P.7 Container Closure System

*Reviewed by JC*

The container closure system for Exa-cel DP is 20mL (b) (4) (Figure 33, Table 154, Table 155) supplied by (b) (4) which holds a Master File (MF) (b) (4), which describes manufacturing and testing of the (b) (4). According to Vertex, the vials are filled using a needle designed to insert through the stopper followed by (b) (4) of the needle puncture of the stopper.



**Table 154. Exa-cel DP Primary Container Closure System**

Component	Material	Quality Documentation
20 mL vial	(b) (4)	MF (b) (4), Certificate of Conformity,
Stopper		
Top Ring (seal)		
Cap (seal)		

**Table 155.** (b) (4) **Specifications for 20mL** (b) (4) **Lot Release**

Test	Acceptance Criteria
(b) (4)	

1. According to Vertex, at a dose validated within a range of (b) (4) .

**Reviewer Comment:** Vertex has provided LOA to cross-reference MF(b) (4) for the Container Closure. This is acceptable.

### Compatibility

Please see Section **3.2.P.8 Stability** for DP compatibility and stability.

### Shipping Validation

Refer to Section **3.2.S.2.5 Process Validation and/or Evaluation** for shipment qualification studies.

### Extractables and Leachables Studies and CCI Testing for (b) (4)

Refer to Section **3.2.P.2.4 Container Closure System** for Extraction and Leachable studies, container closure integrity testing, and additional details on the DP container closure system.

### Exa-cel DP Secondary Container Closure System

Vertex states the exa-cel DP filled vials are packaged into a paperboard carton box (approximately 5.2 × 5.2 × 3 inches) with a maximum capacity of 9 vials and held upright by an insert.

**Reviewer Comment:** This is acceptable.

## 3.2.P.8 Stability

*Reviewed by AK*

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

Long-term stability under the recommended long-term storage condition ( $\leq -135^{\circ}\text{C}$ ) was evaluated for (b) (4) exa-cel lots produced at (b) (4). All ex-cel long-term stability lots were manufactured from healthy donor material using a commercially representative process and were stored in either (b) (4) 20mL (b) (4) vials. **Table 156** summarizes the long-term stability data provided. Note, in addition to the tests listed, all lots were tested for appearance at each time point in the respective stability study. Lots (b) (4) (b) (4) mL fill in (b) (4) mL (b) (4) vial) were also tested for sterility and endotoxin at the end of the stability study. Lots (b) (4) will be tested for sterility and endotoxin at the end of the stability study (b) (4) months). Lots (b) (4) were tested for sterility at 12 months and will be tested for sterility and endotoxin at the end of the stability study. All subsequent lots will be tested for sterility at 12 months and for sterility and endotoxin at the end of the stability study.

Table 156. Summary of Available Eli-cel Stability Data

Lot Number (Manufacturer)	Available Data (Months)	Packaging	Post Thaw Viable Cell Count	Cell Viability	CD34 Purity	On-Target Editing Frequency	(b) (4)	(b) (4)
(b) (4)	(b) (4) M	(b) (4) mL fill in (b) (4) mL A (b) (4) vial	X	X	X	X		
	(b) (4) M	(b) (4) mL fill in (b) (4) mL (b) (4) vial	X	X	X	X		
		5 mL fill in 20 mL (b) (4) vial	X	X	X	X		
	(b) (4) M	1.5 mL and 2.5 mL fill in 20 mL (b) (4) vial	X	X	X	X		
	18M	(b) (4) mL fill in (b) (4) mL (b) (4) vial	X	X	X	X	X	X
		5 mL fill in 20 mL (b) (4) vial	X	X	X	X	X	X
	18M	5 mL fill in 20 mL (b) (4) vial	X	X	X	X	X	X
	18M	(b) (4) mL fill in (b) (4) mL (b) (4) vial	X	X	X	X	X	X
	12M		X	X	X	X	X	X
	9M		X	X	X	X	X	X
	9M		X	X	X	X	X	X
	9M		X	X	X	X	X	X
	9M	(b) (4) mL fill in (b) (4) mL (b) (4) vial	X	X	X	X	X	X
	9M		X	X	X	X	X	X
	9M		X	X	X	X	X	X

Not only did all stability data meet the acceptance criteria in place at the time of study implementation but they also met the agreed upon commercial acceptance criteria with one exception. Lot (b) (4) On-Target Editing Efficiency started at (b) (4) and ranged from (b) (4) throughout the study. However, this is acceptable as the data still support product lot stability. Representative graphs of Viability and (b) (4) data are provided in **Figure 34** and **Figure 35**, respectively, as these attributes were shown to be stability indicating.

(b) (4)

Data from a single lot of exa-cel ( (b) (4) ) stored at the (b) (4) storage condition of (b) (4) were also provided and met all acceptance criteria in place at the time of study implementation and agreed upon commercial acceptance criteria.

Additional (b) (4) end-point stability data from (b) (4) SCD and (b) (4) TDT patient lots were also provided. The age of these lots ranged from 12- (b) (4) months. The data from these lots also met all acceptance criteria in place at the time of study implementation and agreed upon commercial acceptance criteria. These data also exhibited no trends in reduced stability over the time frames tested.

**Reviewer Comment:** *The data provided clearly supported the stability of exa-cel under the intended storage conditions. Based on the data provided, exa-cel was granted a shelf life of 18 months when stored at the intended long-term storage condition of  $\leq -135^{\circ}\text{C}$ . This was due to the fact that the (b) (4) month data lacked potency assessment.*

*Of note, the volume range for exa-cel in a single vial is 1.5 – 20mL. (b) (4) of exa-cel ( (b) (4) ) was assessed for stability at the low end of this volume range. Since the data on this lot included assessments of potency and supported stability, Vertex was allowed to maintain this volume range. Additional long-term stability data at the low end of the volume range will be obtained as part of the post-approval stability plan.*



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

Vertex commits to continue monitoring the ongoing stability studies according to the stability protocols provided in Section **3.2.P.8.1 Stability Summary and Conclusion** and **3.2.P.8.3 Stability Data**. Furthermore, post-approval, Vertex commits to perform (b) (4) stability study per (b) (4) at (b) (4) active manufacturing site. This study will include at least one healthy donor lot of exa-cel manufactured using the commercial manufacturing process, (b) (4) fill volume in a (b) (4) vial, stored at the long-term storage condition of  $\leq 135^{\circ}\text{C}$ . These lots will be tested as indicated in **Table 157**.

**Table 157. Stability Protocol for Exa-cel Healthy Donor Lots in Vapor Phase Liquid Nitrogen ( $\leq -135^{\circ}\text{C}$ )**

Timepoint (Months)						
0	3	6	9	12	18	(b) (4)
Viable Cell Count, % Viability, CD34 Purity, (b) (4)						
Sterility, (b) (4)				Sterility, (b) (4)		Sterility, (b) (4)

In response to CMC IR#9, dated Vertex also committed to perform a (b) (4) stability study on (b) (4) healthy donor exa-cel lots with a fill volume of 1.5 mL in 20 mL (b) (4) vials, to support stability data generated for low volume lots. This study will also be conducted as per the design provided in **Table 157**.

*Reviewer Comment: The proposed post-approval stability studies are acceptable.*

## 3.2.A APPENDICES

### 3.2.A.1 Facilities and Equipment

*Reviewed by DMPQ. Please see DMPQ review for details.*

Pre-license inspections of the (b) (4) facilities were performed in support of approval of BLA 125785. Please see Establishment Inspection Reports for additional details.

### 3.2.A.2 Adventitious Agents Safety Evaluation

Information in this section is integrated into sections **3.2.S.2.3 Control of Materials-Cas9**, **3.2.S.2.3 Control of Materials – SPY101**, and **3.2.S.2.3 Control of Materials**.

### Viral Clearance Studies

Viral clearance studies were not performed on (b) (4) the exa-cel DP.

*Reviewer Comment: This is acceptable.*

**3.2.A.3 Novel Excipients**

Not Applicable

**3.2.R Regional Information (USA)****Executed Batch Records**

*Reviewed by ZY*

The submission includes unexecuted and executed batch records for exa-cel at (b) (4) and (b) (4). Unexecuted batch records include:

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

Executed batch records from (b) (4) PPQ Lot (b) (4), (b) (6) (SCD patient lot) and (b) (4) PPQ Lot (b) (4) (SCD patient lot) are also provided.

*Reviewer Comment: Although the batch records from (b) (4) and (b) (4) use different templates, the instructions outlined in them are consistent with Vertex's exa-cel manufacturing control strategy. No concerns.*

**Method Validation Package**

Refer to Section **3.2.P.4.2** and **3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures** for details on exa-cel lot release and characterization method validation.

**Comparability Protocols**

Not applicable

## Other eCTD Modules

### Module 1

#### Environmental Assessment or Claim of Categorical Exclusion

Vertex claims a categorical exclusion under 21 CFR 25.31(c) from the need to prepare an environmental assessment. Vertex is not aware of any extraordinary circumstances that would require the preparation of an environmental assessment.

Exa-cel is composed of human CD34+ cells genetically modified with CRISPR/Cas9. No viral vector is involved in the manufacture of exa-cel. FDA generally considers products that consist of genetically modified human cells to be eligible for the naturally occurring categorical exclusion [21 CFR 25.31(c)] because these cells have stringent nutritional requirements for survival and therefore are not viable in the environment.

*Reviewer Comment: The categorical exclusion claim is acceptable. No FONSI review required.*

#### Reference Product Designation Request

Vertex claimed a reference product exclusivity period of 12 years from the date of approval of this BLA. According to Vertex, approval of this BLA will constitute “first licensure” for exa-cel and there are no licensed biological products that are structurally related to exa-cel for which Vertex or one of its affiliates, licensors, predecessors in interest, or related entities are the current or previous license holders.

*Reviewer Comment: The proposed reference product exclusivity period of 12 years is acceptable.*

#### Labeling Review

##### Full Prescribing Information (PI):

The following sections of the PI were reviewed: Section 2 (Dose and Administration), Section 3 (Dosage Forms and Strengths), Section 11 (Description), Section 12 (Clinical Pharmacology – Mechanism of Action) and Section 16 (How supplied / storage and handling). The PI provides a detailed and correct description of exa-cel and its mechanism of action. The PI also carefully and correctly describes the receipt and preparation procedures for exa-cel.

*Reviewer Comment: There were multiple interactions with Vertex during review of the PI where Vertex was asked to clarify multiple details on the description, receipt and administration preparation procedures of exa-cel. Vertex agreed to make the requested changes and the changes were found to be adequate.*

### Carton and Container Label:

Examples of the exa-cel syringe (**Figure 36**), vial (**Figure 37**), an carton (**Figure 38** and **Figure 39**) labels as well as the Lot information Sheet (**Figure 40**) are provided below. All labels contain the required text.

**Reviewer Comment:** Review of the labels was performed in conjunction with Hosna Keyvan. The initial labels provided complied with 21 CFR 610.60-62 However, the statements regarding the number of CD34+ cells/mL, the number of vials in a carton, use of an in-line filter or infusion pump, and that the cells are genetically modified needed to be included on the bag label. In Amendment 79 Vertex provided updated vial and carton labels incorporating these requested additions as well as the syringe label and Lot Information Sheet. The updated vial and carton labels as well as the syringe label and Lot Information Sheet are acceptable from a CMC perspective.

**Figure 36. Exa-cel Syringe Label**

exagamglogene autotemcel casgevy™	
Patient ID:	V0000000
First Name:	XXXXXXXXXXXXXXXX
Last Name:	XXXXXXXXXXXXXXXX
Patient DOB:	YYYY-MM-DD
COI ID:	0000000000
LOT:	000000000000
DIN 1:	000000000000
DIN 2:	000000000000
DIN 3:	000000000000

1644-1537-1538-00

**Figure 37. Exa-cel Vial Label**

1698-1537-1538-00

This is placeholder part number

NDC 51167-290-01

exagamglogene autotemcel  
casgevy™

4-13 × 10<sup>6</sup> CD34<sup>+</sup> cells/mL

suspension for IV infusion

U.S. License #: 0000

Patient ID: V0000000

First Name: XXXXXXXX

Last Name: XXXXXXXX

Patient DOB: YYYY-MM-DD

COI ID: 0000000000

LOT: 000000000000

EXP: YYYY-MM-DD

Note: "x" is an internal reference number

**For autologous and intravenous use only**

1.5 to 20 mL per vial

**Dosage:** See prescribing information and Lot Information Sheet (inside shipper)

Manufactured for:  
Vertex Pharmaceuticals, 50 Northern Ave, Boston, MA 02210

Figure 38. Exa-cel Carton

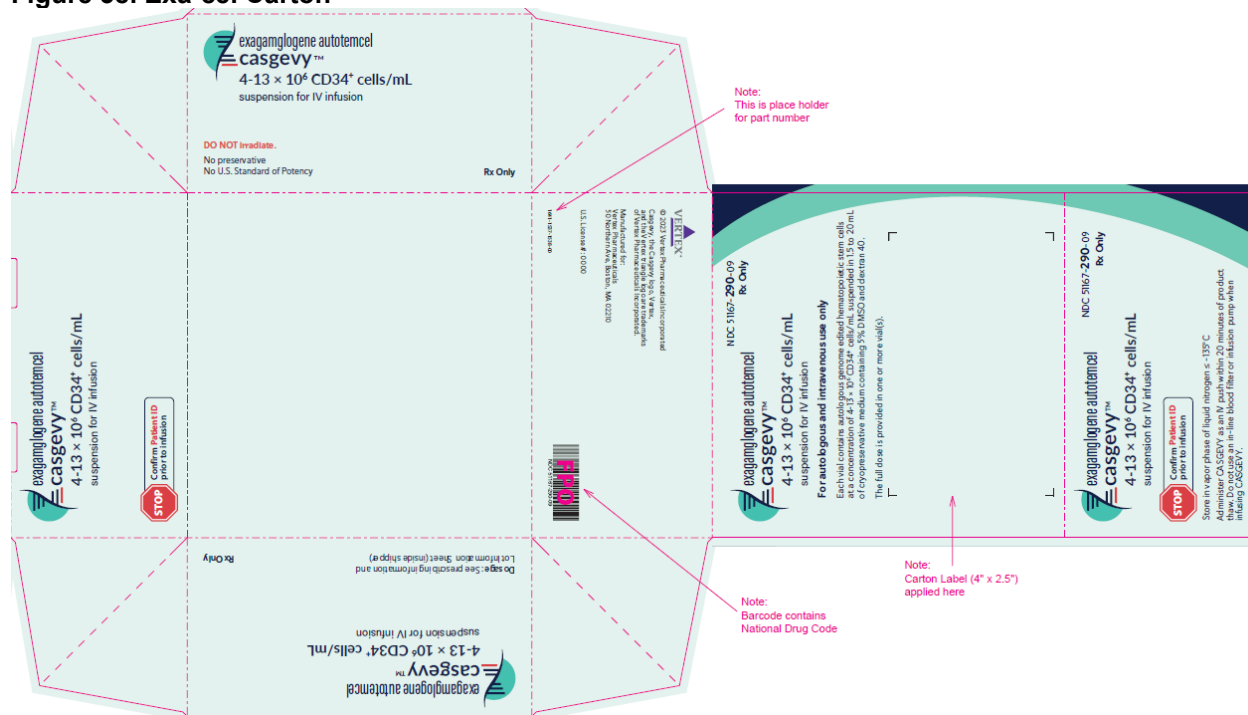


Figure 39. Exa-cel Patient Specific Carton Label


Patient ID: V0000000  
 First Name: XXXXXXXXXXXXXXXXXXXX  
 Last Name: XXXXXXXXXXXXXXXXXXXX  
 Patient DOB: YYYY-MM-DD  
 COI ID: 0000000000  
 LOT: 000000000000  
 EXP: YYYY-MM-DD  
 DIN 1: 000000000000  
 DIN 2: 000000000000  
 DIN 3: 000000000000  
 Number of vials: X

DIN 1:  
 W0123 45 678900 8 1  
 DIN 2:  
 W0123 45 678900 8 1  
 DIN 3:  
 W0123 45 678900 8 1

NOTE: DIN 2 and DIN 3 are only printed if additional Apheresis collections are required. If no additional cycles are required N/A will be printed.  
 "X" is a Placeholder for the amount of vials  
 All Artwork is Variable Printing and will be printed online at the time of labeling

Encoded element is the Apheresis collection DIN, flag characters and check digits if applicable for the 1st collection cycle.  
 Encoded element is the Apheresis collection DIN, flag characters and check digits if applicable for the 2nd collection cycle. NOTE: DIN 2 and DIN 3 are only printed if additional Apheresis collections are required.  
 Encoded element is the Apheresis collection DIN, flag characters and check digits if applicable for the 3rd collection cycle. NOTE: DIN 2 and DIN 3 are only printed if additional Apheresis collections are required.

Figure 40. Exa-cel Lot Information Sheet

 exagamglogene autotemcel  
**casgevy™**  
4-13 × 10<sup>6</sup> CD34<sup>+</sup> cells/mL  
suspension for IV infusion

### Lot Information Sheet

<b>1. Name of the medicinal product</b>	CASGEVY 4-13 × 10 <sup>6</sup> CD34 <sup>+</sup> cells/mL suspension for intravenous infusion exagamglogene autotemcel (CD34 <sup>+</sup> cells)
<b>2. Statement of active substance(s)</b>	This medicine is an autologous genome edited hematopoietic stem cell based gene therapy. Each vial contains 4-13 × 10 <sup>6</sup> CD34 <sup>+</sup> cells/mL suspended in 1.5 – 20 mL of cryopreservative medium. This medicine contains cells of human origin.
<b>3. Contents by weight, by volume or by unit, and dose of the medicinal product</b>	

Information on supplied lot(s):

Lot Number	DIN (List all collections)	Number of Vials	Total Volume (mL)	Concentration (x10 <sup>6</sup> CD34 <sup>+</sup> cells/mL)	Total CD34 <sup>+</sup> cells (x10 <sup>6</sup> )	Total Dose (x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg)
<b>TOTAL:</b>						

Syringe label(s) are provided within this packet.

<b>4. Method and route(s) of administration</b>	Read the product information before use. For autologous use only. For intravenous use only.
<b>5. Other special warning(s), if necessary</b>	Save this document and have it available when preparing for administration of CASGEVY.
<b>6. Special storage conditions</b>	Store vials in carton at -135 °C (-211 °F) until ready for thaw and administration. When the dose consists of multiple vials, thaw and administer one vial at a time. Once thawed do not re-freeze.
<b>7. Expiry date and other batch specific information</b>	EXP:
<b>8. Special precautions for disposal of unused medicinal products or waste materials derived from such medicinal products, if appropriate</b>	This medicine contains human cells. Unused medicine or waste material must be disposed of in compliance with the local biosafety guidelines on handling of waste of human-derived material.
<b>9. Patient ID</b>	Patient ID:
<b>10. Name and address of the marketing authorization holder</b>	Vertex Pharmaceuticals Incorporated 50 Northern Avenue Boston, MA 02210
<b>11. National Drug Code(s)</b>	NDC 51167-290-09

0000-0000-0000-00  
↑  
This is a placeholder for part number



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## Module 5

### Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

*Reviewed by JC*

(b) (4)

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