CBER CMC BLA Review Memorandum

BLA STN 125703/0

KTE-X19, Autologous chimeric antigen receptor (CAR) T cell product Tecartus®

CDR Donald Ertel, CMC Reviewer, OCBQ / DMPQ / MRB1

1. BLA#: STN 125703/0

2. APPPLICANT NAME AND LICENSE NUMBER
Kite Pharma, Inc. (License Number #2064)

3. PRODUCT NAME/PRODUCT TYPE

Non-proprietary/Proper/USAN:	brexucabtagene autoleucel
Proprietary name:	TECARTUS
Company codename:	KTE-X19

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

brexucabtagene autoleucel consists of autologous T cells that have been genetically modified ex vivo to express a chimeric antigen receptor (CAR) to target CD19 on the cell surface of malignant B cells. The active substance of brexucabtagene autoleucel is composed of a patient's T cells that has undergone ex vivo T cell activation, gene transfer by replication-deficient retroviral vector (b) (4) Vector), and expansion. These transduced T cells are then formulated in a cryopreservation medium suitable for infusion. brexucabtagene autoleucel is supplied cryopreserved at a temperature of ≤ -150°C in cryostorage bags."

Each bag of brexucabtagene autoleucel is filled to deliver a dose of (b) (4) anti-CD19 CAR T cells/kg of patient weight (maximum allowable dose: 2.0×10^8 anti-CD19 CAR T cells based on patient weight ≥ 100kg) in a nominal volume of 68mL.

5. MAJOR MILESTONES
Refer to RPM

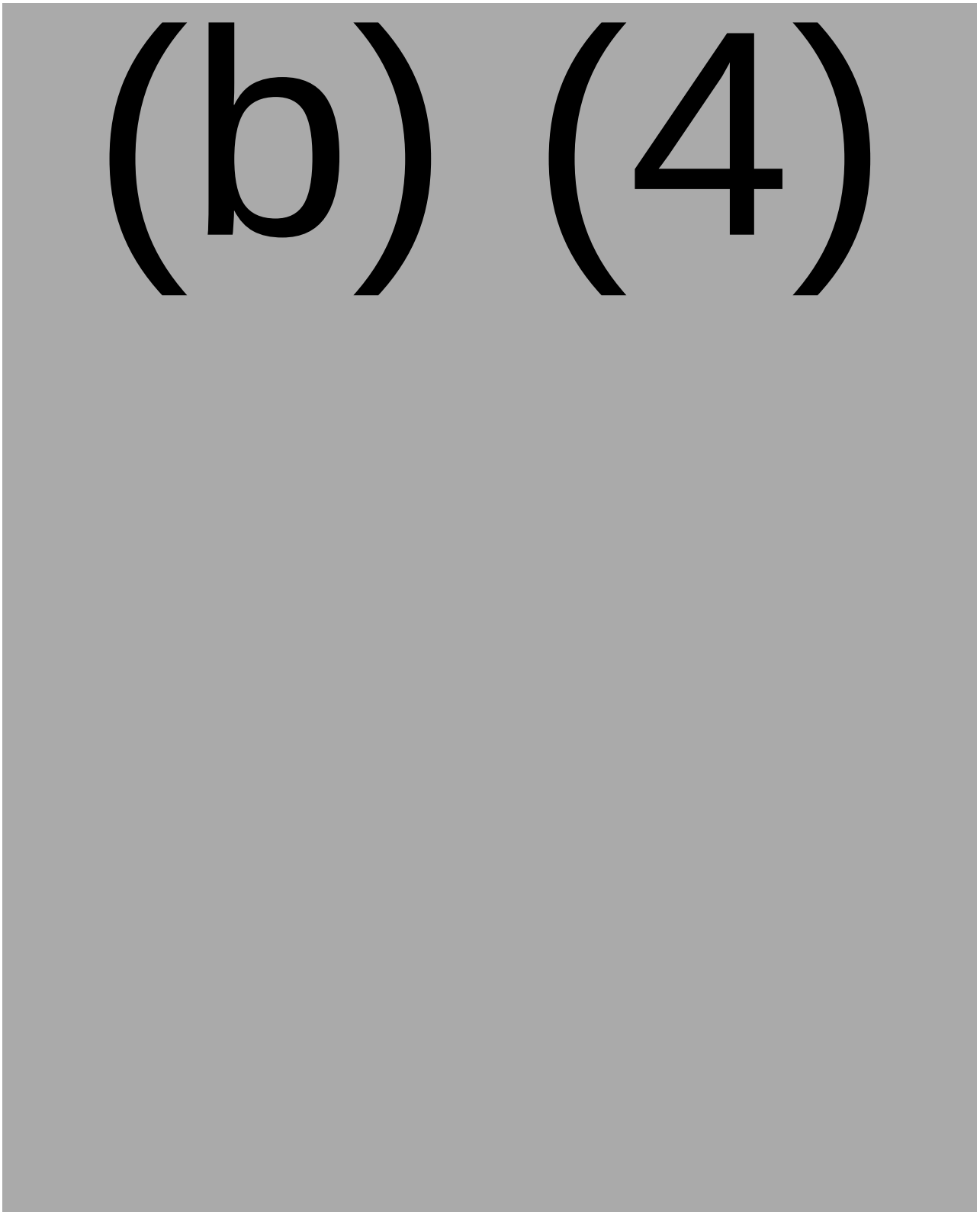
6. CMC/QUALITY REVIEW TEAM
Refer to RPM

7. INTER-CENTER CONSULTS REQUESTED
Refer to RPM

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
11 Dec 2019	125703/0	reviewed
22 Jan 2020	125703/0.8	IR sent 14 Jan; reviewed
29 Jan 2020	125703/0.10	IR sent 24 Jan; reviewed
11 Mar 2020	125703/0.28	IR sent 26 Jan; reviewed

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



Review Assessment/ Comments: According to amendment 125703/0.10, Kite states that (b) (4) cross-references the (b) (4), tubing sets and

buffer within the individual Reagent Master Files, therefore only LOAs to the Reagent Master Files were provided to Kite. All the performance data provided within the reagent Master File are derived from use with the (b) (4) .

I and Dr. Price concurred that LoA for the Master File for the overall (b) (4) not needed since we had access to the MFs for the (b) (4) (b) (4) and enough data has been provided in the application on validation of the (b) (4) steps and instrumentation. No further scrutiny is required.

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

At the Kite Pharma, Inc. (b) (4) facilities, the qualification, validation, and control activities as related to facility, equipment, and container closure appear to be adequate for the drug substance and drug product (respectively) manufacturing of brexucabtagene autoleucel. From my purview of the original application, there appears to be no evidence that the identity, strength, safety, quality, and purity of the product produced in the facilities would be adversely impacted as based on the completed development /qualification data and experience.

Supply including manufacturing and facility of (b) (4) Vector remain unchanged as previously approved by CBER for Yescarta (reference STN 125643/0).

B. RECOMMENDATION

I. APPROVAL

I recommend approval of this application.

- Drug Substance and Drug Product manufacturing facilities are as follows:

Kite Pharma, Inc.
1800 Stewart Street
Santa Monica, CA 90404
FEI: 3014007584

(b) (4)

One Inspectional Recommendation:

Note: CBER understands that the recommendation may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

1. Verify that procedures and requirements for the operation, maintenance, and calibrations of the (b) (4) have been established and compliance is supported.

II. COMPLETE RESPONSE (CR)

N/A

III. SIGNATURE BLOCK

Title/Affiliation	Concurrence	Signature and Date
CDR Donald Ertel, Reviewer, OCBQ / DMPQ / MRB1	Concur	
Lori Peters, Team Lead, OCBQ / DMPQ / MRB1	Concur	

Review of CTD
Table of Contents

Module 2

Review Assessment/ Comments: Information and data in the introduction and Quality Overall Summary correlate with the data in Module 3.

Since there are many similarities in the processing (including shared equipment and processing areas) and formulation of Kite's approved Yescarta product (BLA STN 125643) and proposed Tecartus product (subject of this BLA), I am focusing my review on the significant differences of the two products.

No objectionable findings noted. Data is acceptable.

Module 3

Reviewer Comment: The manufacturing process for KTE-X19 is a (b) (4) So, Kite covers some data in Drug Substance sections and other data in the Drug product sections. Where applicable, Kite references the relevant section (i.e. Drug Substance Specification 3.2.S.4.1 does not contain data but references 3.2.P.5.1 for the KTE-X19 specification. Applicable references are made in my review, as well.

3.2.S DRUG SUBSTANCE

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

Deferred to Product Office CMC Reviewer

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Facility	Process	Compliance check to support approval?	Enter the location into RMS-BLA?	inspection or inspection waiver
Kite Pharma, Inc. (b) (4)	• Manufacture, control, and storage of KTE-X19 Final Product brexucabtagene autoleucel) • All KTE-X19 Final Product release testing, including identity, potency, sterility (b) (4) purity, sterility (b) (4) mycoplasma, and replication competent retrovirus (RCR) by (b) (4) testing • (b) (4) Vector release and stability testing per specifications • (b) (4) Vector lot disposition • Raw Material Testing	Yes	Yes	Waiver
Kite Pharma, Inc. 1800 Stewart Street Santa Monica, CA 90404 FEI: 3014007584 DUNS: 116931311	• Raw Material Testing	No	No	No inspection needed

(b) (4)

Facility	Process	Compliance check to support approval?	Enter the location into RMS-BLA?	inspection or inspection waiver
(b) (4)				

Review Assessment/ Comments: Inspections were waived for Kite Pharma, Inc. ((b) (4) ; Inspection waiver uploaded to EDR.

3.2.S.2.2 Description of Manufacturing Process

Review Assessment/ Comments: The Tecartus manufacturing process is essentially a (b) (4) , the majority of which is described under drug substance. Therefore, most data related to manufacturing and validation is described in Section 3.2.S.

- **Manufacturing process steps**

See process flow:

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

(b) (4)

Review Assessment/ Comments: The manufacturing process of Tecartus and approved Yescarta are similar. The significant differences in the Tecartus process is (b) (4). Kite reports full process validation- see Process validation section.

See 3.2.A.1 Facilities and Equipment for applicable process equipment differences.

- **Batch Numbering, (b) (4) and Scale Definition**

See section 3.2.P.1

- **Storage and Shipping**

The manufacturing process for KTE-X19 is a (b) (4) No DS shipment occurs for this product.

3.2.S.2.3 Control of Materials

As part of Kite's bioburden control program, Kite utilizes (b) (4)

Reviewer Assessment /Comments: Kite provided CoC/ CoAs of all their (b) (4) items such as CryoStor (b) (4) cryobags, etc. Kite provided evidence of sterility conformance of these consumables used in the product path. No objectionable findings noted. Data is acceptable.

- **Control of Raw Materials NOT of Biological Origin**

Defer to Product Office CMC Reviewer

- **Control of Raw Materials of Biological Origin**

Defer to Product Office CMC Reviewer

- **Control of Starting (i.e., Source) Material(s)**

Defer to Product Office CMC Reviewer

- **Generation of the Seed Stock and Expression Construct (e.g., vector and plasmid)**

Defer to Product Office CMC Reviewer

- **Cell Banking System - Generation, Characterization, and Testing**

Defer to Product Office CMC Reviewer

- **Master and Working Viral or Bacterial Seeds**

Defer to Product Office CMC Reviewer

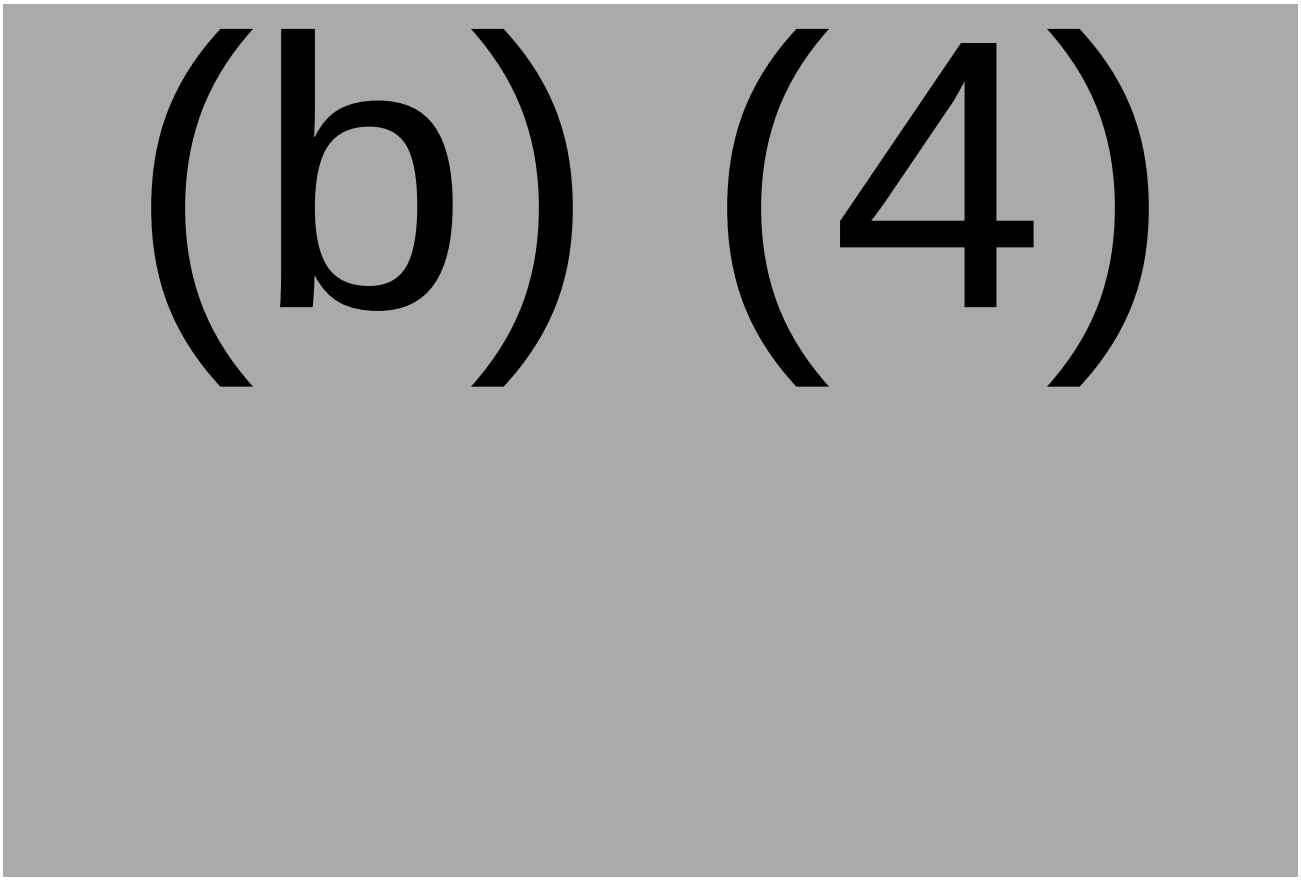
Review Assessment / Comments: This application has two DS (3.2.S) Sections; one is related to the (b) (4) Vector, which is approved by US FDA for use in Yescarta; this vector (DS) is identical for KTE-X19. There are no reported changes to the vector; I will not be reviewing DS sections designated to (b) (4) Vector. The other DS section is the KTE-X19 common section; my review will be directed to those sections as applicable to my review responsibility.

3.2.S.2.4 Controls of Critical Steps and Intermediates

Kite used a risk-based approach to assess the criticality of product quality attributes and associated process parameters of KTE-X19. During process characterization, the effect of process parameters on product quality attributes was then evaluated and appropriate operational and in-process controls (IPCs) were established. As part of lifecycle management, Kite states that these risk assessments are reviewed periodically and updated as needed to ensure that the control strategy is current.

Kite has established the following IPCs for KTE-X19 manufacturing process:

Parameter	Action Limits	Classification



Impurity controls

Kite used a risk-based approach to determine the process-related impurity clearance through the KTE-X19 manufacturing process. Per Kite, the manufacturing process has redundancy in terms of (b) (4) to ensure control of impurities in the drug substance and the final product. The removal of process impurities has been characterized with process capability and confirmed during process performance qualification runs

Bioburden controls

Kite states that their overall bioburden control strategy encompasses manufacturing process design features and procedural controls that have been implemented to minimize the potential for introduction and proliferation of microbial contaminants including the following key elements:

- aseptic process validation program
- Use of (b) (4)
- (b) (4)
- environmental monitoring program
- Final Product release that includes sterility and mycoplasma testing.

Control of Intermediates

(b) (4)

(b) (4)

Review Assessment / Comments-Section 3.2.S.2.4: Evaluation of In-process controls such as (b) (4) are deferred to the CMC Product Office Reviewer. As replicated with the CBER approved Yescarta (STN 125643), since KTE-X19 is a (b) (4) process, Kite does not perform (b) (4) and sterility testing is performed at release for every unit. No objectionable findings noted.

See Evaluation of the in applicable sections:

- Contamination control risk assessment was performed to identify high risk operations and systematically close higher risk (b) (4) steps. Control of (b) (4) in the operation by (b) (4) with training and operator qualification through the aseptic process validation program (see Section 3.2.A.1).
- (b) (4) (see Section 3.2.S.2.3).
- (b) (4) (see Section 3.2.S.2.6).
- Comprehensive bioburden environmental monitoring program with action limits and comprehensive facility cleaning program (see Section 3.2.A.1).
- Final Product release that includes sterility and mycoplasma testing (see Section 3.2.P.5.1).

(b) (4)

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

(b) (4)

(b) (4)

3.2.S.3 Characterization
3.2.S.3.1 Elucidation of Structure and Other Characteristics
Deferred to Product Office CMC Reviewer

3.2.S.3.2 Impurities
Deferred to Product Office CMC Reviewer

3.2.S.4 Control of Drug Substance
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)
See Section 3.2.P.5.1

3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures
Deferred to Product Office CMC Reviewer

3.2.S.4.4 Batch Analyses
See Section 3.2.P.5.4.1 & 3.2.P.5.2

3.2.S.5 Reference Standards or Materials
Deferred to Product Office CMC Reviewer

3.2.S.6 Container Closure System
See Section 3.2.P.7

3.2.S.7 Stability
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data
3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

See Stability Summary Section 3.2.P.8

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

Each bag of KTE-X19 is filled to deliver a dose of (b) (4) anti-CD19 CAR T cells/kg of patient weight (maximum allowable dose: 2.0 x 10^8 anti-CD19 CAR T cells based on patient weight ≥ 100kg) in a nominal volume of 68mL. The batch formula is equivalent to the composition of the final product as follows:

Component	Quantity	Function
Anti-CD19 CAR T cells	(b) (4) anti-CD19 CAR T cells/kg (Maximum allowable dose: 2.0 x 10^8 anti-CD19 CAR T cells based on patient weight ≥ 100kg)	Active Ingredient
CryoStor® (b) (4)	(b) (4)	(b) (4)
Sodium Chloride, (b) (4)	(b) (4)	(b) (4)
Albumin (Human), (b) (4)	(b) (4)	(b) (4)

Review Assessment /Comments: No significant differences exist between the final formulation volumes and raw materials in the Yescarta and Tecartus product. The process is small scale, single lot output. No objectionable findings noted. Data is acceptable.

3.2.P.2 Pharmaceutical Development
3.2.P.2.1 Components of the Drug Product
Deferred to Product Office CMC Reviewer

3.2.P.2.1.1 Drug Substance
Deferred to Product Office CMC Reviewer

3.2.P.2.1.2 Excipients
Deferred to Product Office CMC Reviewer

3.2.P.2.2 Drug Product
3.2.P.2.2.1 Formulation Development
Deferred to Product Office CMC Reviewer

3.2.P.2.2.2 Overages
Deferred to Product Office CMC Reviewer

3.2.P.2.2.3 Physicochemical and Biological Properties
Deferred to Product Office CMC Reviewer

3.2.P.2.3 Manufacturing Process Development

- **Hold Times of Intermediates**

As the KTE-X19 manufacturing is a (b) (4) process, Kite states that the process

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

(b) (4)

.

(b) (4)

3.2.P.2.4 Container Closure System

The primary container closure systems intended for distribution of KTE-X19 are commercially-available cryostorage bags specifically designed for storage of blood and blood components, the (b) (4) The (b) (4) bag were previously validated and qualified for commercial use for YESCARTA.

(b) (4)

(b) (4)

Kite intends for the (b) (4) bags to be used (b) (4) for the distribution of KTE-X19 as they are for Yescarta.

The suitability of (b) (4) bags as the intended container closure systems for KTE-X19 was demonstrated through the following studies:

- Characterization Study- demonstrated that the (b) (4) bags had comparable recovery, (b) (4) values
- Stability Studies-data from long term stability studies, when product is stored under the recommended storage condition of ≤ -150°C support the suitability of (b) (4)

(b) (4) bags for distribution of KTE-X19.

- Extractables Testing-performed on (b) (4) the (b) (4) bags with and without labels.
- Container Closure Integrity Testing- performed on the (b) (4) bags as well as for the stability cryostorage (b) (4) bags. A (b) (4) test based on (b) (4) was developed and qualified specifically for use with the (b) (4) (b) (4) bags.

Reviewer Comments / Assessments: (b) (4) are fully qualified for the use with the similar product, Yescarta, both products have same formulation constituents (minor variations in volumes) both with a nominal volume of 68mL. Kite took the same approach to qualification of the bags as that they have in Yescarta application (STN 125643). Kite used (b) (4) these bags in development studies and process validation runs. The evaluation of characterization and extractables study is deferred to the Product Office CMC reviewer. CCIT is evaluated in next section 3.2.P.2.5. No objectionable findings noted. Data is acceptable.

3.2.P.2.5 Microbiological Attributes

Kite states that the current (b) (4) indicates that (b) (4) tests are preferred over (b) (4) tests, such as (b) (4), when establishing the inherent integrity of a container closure system. Therefore, a (b) (4) test based on (b) (4) was developed specifically for use with the (b) (4) cryostorage bags that make up the container closure system for KTE-X19 and for stability samples, respectively.

(b) (4)

.

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

(b) (4)

Review Assessment/ Comments: Evidence of completed CCIT study is provided. Kite reports (b) (4) observed in any of the test samples. The (b) (4) test is the same for all their cryostorage storage bags as originally approved. Kite reports no change to the original test method. Test results for (b) (4) appear consistent with (b) (4) bag. No objectionable findings noted, Data is acceptable.

3.2.P.2.6 Compatibility
Deferred to Product Office CMC reviewer

3.2.P.3 Manufacture
3.2.P.3.1 Manufacturer(s)
See Section 3.2.S.2.1

3.2.P.3.2 Batch Formula
See Section 3.2.P.1

3.2.P.3.3 Description of Manufacturing Process
See Section 3.2.S.2.2

3.2.P.3.4 Controls of Critical Steps and Intermediates
See Section 3.2.S.2.4.

3.2.P.3.5 Process Validation and/or Evaluation
For PV: See Section 3.2.S.2.5

- **Shipping Validation**

Shipping of cryopreserved KTE-X19 within (b) (4) container closure in (b) (4) at an internal temperature range of (i.e., ≤ -150°C) was validated for final product transportation.

Kite provided the following protocols to support Shipping Validation:

- QR-0783; OQ Summary Report: Protocol VP-112 Revision 0 "Operational Qualification of (b) (4) Shipper"
- QR-0792; PQ Summary Report: (b) (4) Shipper for KTE-C19 Final Product
- QR-1301; PQ Report for the Performance Qualification of EU Final Product (KTE-C19) Shipment in the (b) (4) Shipper ((b) (4)
- QR-1356; OQ Report: Physical Testing of the (b) (4) Shipper with Updated Final Product Cassette Rack and Cassette Inserts
- QR-1356 Appendices; Executed Protocol: Physical Testing of the (b) (4) Shipper with Updated Final Product Cassette Rack and Cassette Inserts

Review Assessment/ Comments: Since there is no change to final primary container, secondary packaging cassette, cryoshipper, or required transport temperature, Kite supported shipping of the KTE-X19 with studies performed for Yescarta. The studies were reviewed and found acceptable for Yescarta under STN 125643. No objectionable findings noted; data is acceptable and applicable for TECARTUS product.

3.2.P.4 Control of Excipients
3.2.P.4.1 Specifications
Deferred to Product Office CMC reviewer

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures
Deferred to Product Office or DBSQC CMC reviewer

3.2.P.4.4 Justification of Specifications
Deferred to Product Office CMC reviewer

3.2.P.4.5 Excipients of Human or Animal Origin
Deferred to Product Office CMC reviewer

3.2.P.4.6 Novel Excipient
Deferred to Product Office CMC reviewer

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)

Kite reports the following specification for KTE-X19:

Attribute	Test	Sample Point (Process Step)	Method	Acceptance Criteria
Appearance	Visual Appearance Inspection	Inspection and Labeling	Visual Inspection	White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no visible foreign particles
Identity	(b) (4)	Formulation	(b) (4)	(b) (4)
Dose	Viable Cell Count/Anti- CD19 CAR Expression	N/A	(b) (4)	(b) (4) anti-CD19 CAR T cells/kg (Maximum allowable dose: 2.0×10^8 anti-CD19 CAR T cells based on patient weight ≥ 100kg)
Potency	Cell Viability	(b) (4)	(b) (4)	(b) (4)
	Anti-CD19 CAR Expression	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Safety	Mycoplasma	(b) (4)	(b) (4)	Negative
	Sterility	Formulation	(b) (4)	Negative
	Endotoxin	Formulation	(b) (4)	(b) (4)
	(b) (4)	Formulation	(b) (4)	(b) (4)

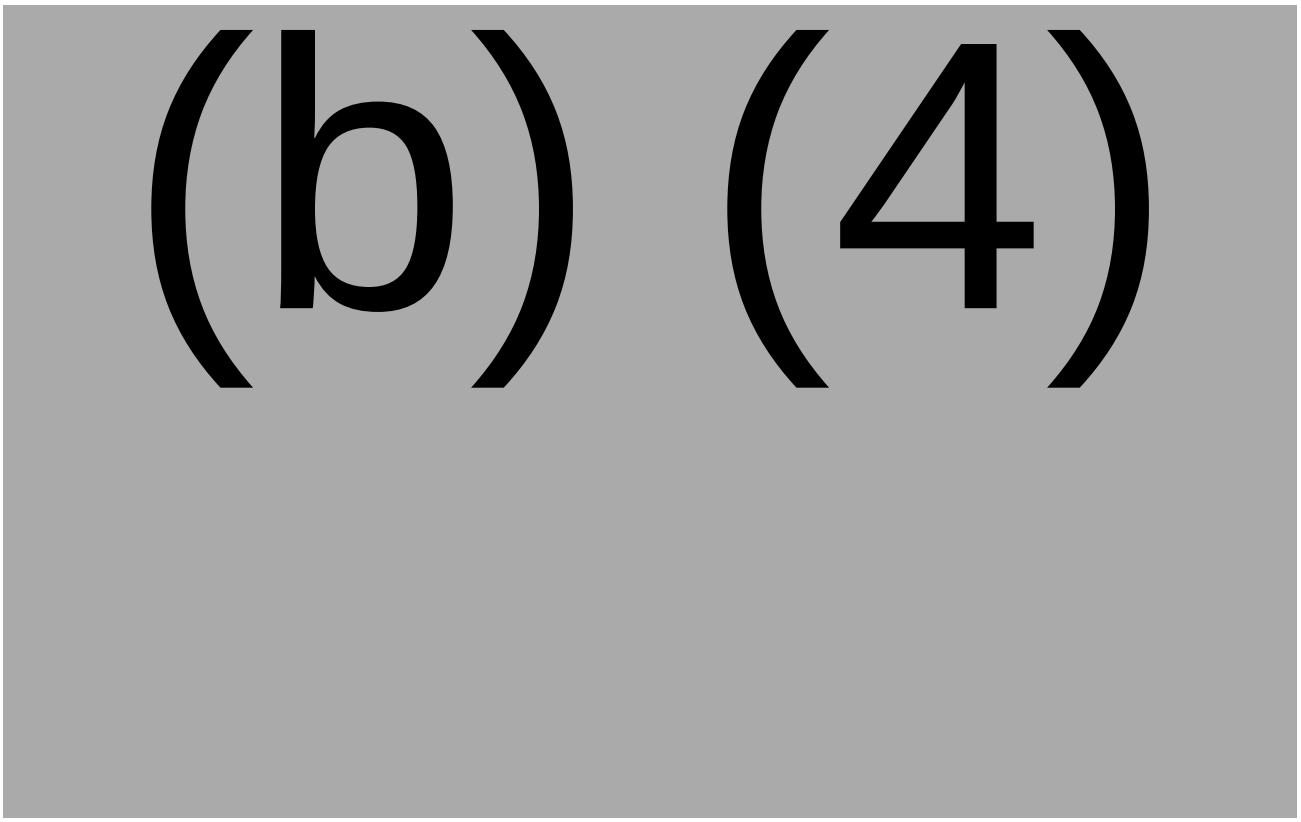
Review Assessment / Comments: With exception to potency, there are no differences between the specifications for Yescarta and Tecartus product. The safety attributes are

the same and appear acceptable. Final product is expected to be sterile. No objectionable findings noted. Data is acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures
Deferred to Product Office or DBSQC CMC reviewer

3.2.P.5.4 Batch Analyses

All KTE-X19 lots were tested against the proposed specification, and results met batch release specification acceptance criteria in prior section 3.2.P.5.1.



Review Assessment / Comments: Except for the ECs reported in the process validation (adequately resolved), all other results met specifications including mycoplasma, sterility, and endotoxin. No objectionable findings noted. Data is acceptable.

3.2.P.5.5 Characterization of Impurities
Deferred to Product Office CMC reviewer

3.2.P.6 Reference Standards or Materials
Deferred to Product Office CMC reviewer

3.2.P.7 Container Closure System

See Section 3.2.P.2.4

3.2.P.8 Stability

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

Kite demonstrated the stability of KTE-X19 with long-term, accelerated, and stress studies. The KTE-X19 stability program utilizes final product from clinical subjects and from healthy donor lots. According to Kite, final product from clinical subjects is most representative; however, only lots from subjects who have dropped off the study are available. The number of final product bags is also limited to (b) (4) 1, (b) (4) Therefore, Kite studied only a 12-month or (b) (4)-month timepoint in these subject lots. In order to evaluate the same final product lot in multiple timepoints, several healthy donor lots were produced and filled in (b) (4) bags, which yield up to (b) (4) bags. These studies yield results for multiple timepoints in a (b) (4)-month period from the same lot. Finally, PPQ lots were evaluated in stability. These lots were produced in (b) (4) bags and hence yielded a maximum of (b) (4) bags per lot. Therefore, this ongoing study utilizes (b) (4) lots (b) (4) PPQ lots and (b) (4) post PPQ lots) to create a matrix to cover a range of (b) (4) months. Overall, (b) (4) KTE-X19 lots manufactured from clinical subjects and healthy donor apheresis material have been placed into long-term stability studies. All lots used in these studies were manufactured according to intended commercial manufacturing process. The shelf life of 12 months for KTE-X19 final product is proposed.

Summary of Stability Studies for KTE-X19 Lots:

Section	Description	Duration/Status	Available Data	Conclusion
3.2.P.8.1.1-Patient	Stability was conducted on (b) (4) KTE-X19 lots from clinical subjects stored at the ≤ -150°C.	Completed	Stability of patient material was conducted for a period of up to (b) (4) months.	Results from this study demonstrate that KTE-X19 clinical subject lots stored at the recommended storage condition remain viable and potent for at least (b) (4) months.

Section	Description	Duration/Status	Available Data	Conclusion
3.2.P.8.1.1- Long Term-HD	Long-term stability was conducted with (b) (4) KTE-X19 lots of from healthy donor material at ≤ -150°C: (b) (4) lots from healthy donor subjects and (b) (4) lots from PPQ runs from healthy donor subjects.	Long-term stability for the (b) (4) lots from health donor subjects has completed. Long-term stability of the (b) (4) lots from PPQ runs is an ongoing study for up to (b) (4) months.	Long-term stability was conducted for up to (b) (4) months for (b) (4) lots from health donor subjects. Results on (b) (4) lots from PPQ runs are available for up to (b) (4) months.	Long-term stability studies conducted on (b) (4) lots of KTE-X19 tested at time points up to (b) (4) months have demonstrated that the product remains viable and potent for at least (b) (4) months. Results on (b) (4) PPQ lots have indicated that different conditions evaluated as part of PPQ did not impact product stability up to the time point studied.
3.2.P.8.1.1- In-Use	In-use stability was conducted in two studies, and each study used (b) (4) KTE-X19 lots from healthy donor material, which was frozen and stored at ≤ -150°C, and then thawed and kept at room temperature.	Completed	Samples were stored at ≤ -150°C for 6 weeks or through (b) (4) months, and then thawed. Stability at room temperature was conducted for a period of up to 3 hours.	Results from this study demonstrated that KTE-X19 is stable at room temperature for at least 3 hours post- thaw and is suitable for routine use in clinical administration settings.
3.2.P.8.1.2- Accelerated-HD	Accelerated stability (b) (4) was conducted with (b) (4) KTE- X19 lots at the (b) (4) cells/mL dose from healthy donor material.	Completed	Accelerated stability (b) (4) was conducted for a period of (b) (4) months.	All samples of KTE-X19 tested during the accelerated stability study met protocol acceptance criteria for all parameters tested at up to (b) (4) months of storage at (b) (4), indicating stability of the product under these conditions.
3.2.P.8.1.3- Stressed-HD	Stressed stability (b) (4)) was conducted with (b) (4) KTE- X19 lot at the (b) (4) cells/mL dose from healthy donor material.	Completed	Stressed stability (b) (4) was conducted for a period of up to (b) (4).	Results from the study demonstrated that both potency by (b) (4) and anti-CD19 CAR expression declined over time during the stressed study and are, therefore, stability indicating.

HD, healthy donor

Review Assessment / Comments:

For Long Term stability, product and container appearance were tested at T0, 3,6, 9,12, (b) (4) Months. Sterility was tested at T0 and (b) (4) Months.

For Accelerated stability, product and container appearance were tested at (b) (4) Months. Only product CQAs were tested, Sterility was not tested in accelerated studies.

For stressed stability, product and container appearance were tested at (b) (4) Only product CQAs were tested, Sterility was not tested in the stressed study.

Kite reported no OOS for product & container appearance or sterility. Evaluation of other product characteristics test is deferred to the Product Office CMC reviewer. No objectionable findings noted. Data is acceptable.

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

For Post approval stability, Kite proposes (b) (4), sourced from a healthy donor and manufactured and filled. Kite will select the commercial container closure for the sterility study (b) (4) from (b) (4) approved commercial container closures: (b) (4) bags. The batch will to be placed on long term stability as described previously.

Review Assessment / Comments:
Strategy is acceptable.

3.2.A APPENDICES
3.2.A.1 Facilities and Equipment

In the application, Kite provided their comprehensive Facilities and Equipment Report.

In summary, two facilities are involved in the manufacture of KTE-X19: (b) (4) Vector contract manufacturers) and Kite Pharma, Inc. (Internal site identifier: (b) (4). The facility and equipment section for (b) (4) provides detailed information on the site including manufacturing facility description, facility overview, utilities, manufacturing process, manufacturing equipment, environmental control and monitoring, cross contamination prevention, materials management, and the quality unit. Furthermore, Aseptic process validation has been completed at (b) (4) for the vector starting material, including process simulation runs as required by globally recognized requirements/guidance.

The Kite (b) (4) facility design includes (b) (4)
,

(b) (4)

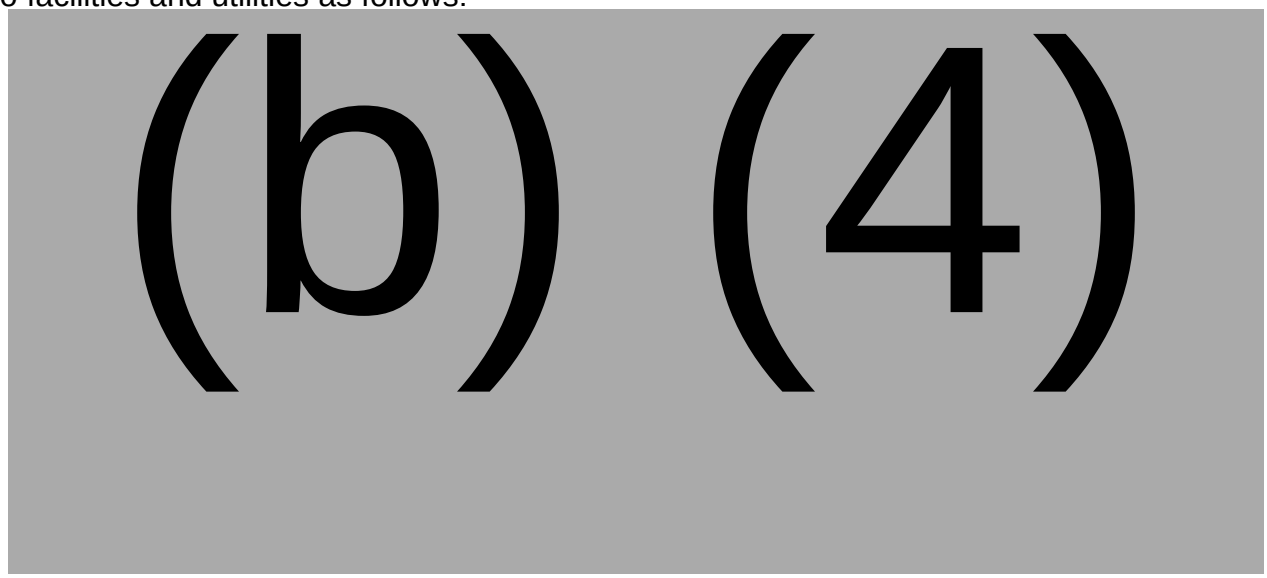
.

Kite has established aseptic control strategy that includes the following qualification activities:

- Initial qualification of the facility, equipment, and process through Aseptic Process Validation (APV)
- An Aseptic Operation Qualification (AOQ) and (b) (4) requalification program integrating media process simulations to ensure that (b) (4) aseptic process steps are appropriately challenged on a regular basis

Kite has established controls to assure the chain of identity and chain of custody of KTE-X19 throughout the entire supply chain, including patient apheresis, transit of apheresis material to (b) (4), manufacture and storage of KTE-X19 at (b) (4), and transit of final product to the treatment site. Kite has also established qualification and monitoring programs for the apheresis centers and treatment sites that assure patient identification throughout the entire process.

In amendment STN125703/0.8, Kite provided a comparison between KTE-X19 process and YESCARTA® approved process, highlighting the differences, as applicable, related to facilities and utilities as follows:



Review Assessment / Comments: Since Kite is using the same facility and most of the same equipment for manufacturing of KTE-X19 as those for Yescarta, Kite has essentially duplicated the Facility and Equipment Report from the Yescarta application and provided updates where applicable in the document. The non-updated sections of F&E report are identical to the information provided and reviewed under Yescarta; therefore, no further scrutiny is needed to support the Tecartus BLA. Nothing had changed about the Viral Vector product supply and manufacturing (identical to approved Yescarta), so no further scrutiny is needed.

As determined at filing, my F&E review concentrates on the updated (different from Yescarta application) data, which are as follows:

1. Section 2.4.3. Aseptic Process Validation - media simulation activities of the final formulation manufacturing process step using the (b) (4). See following Aseptic Process Validation section for further evaluation)
2. Section 2.3. (b) (4) Manufacturing Equipment updated with data fo (b) (4) (See following Equipment Qualification Section for further evaluation)
3. Kite also mentions under the APV section that (b) (4) workstation layouts in Suite (b) (4) were modified to include a (b) (4) (See following Facility Section for further evaluation)

- **Facility**

Kite proposes to use Room (b) (4), Room (b) (4), Room (b) (4), already CBER approved for Yescarta, for KTE-X19 processing. In this application, Kite provided room diagrams, overview of utilities, data on the environmental monitoring program, and the facility cleaning program. Kite mentions under the APV section that (b) (4) workstation layouts in Suite (b) (4) were modified to include a (b) (4)

Review Assessment / Comments: It had been established through review and inspection that all the workstations in Rooms (b) (4) are (b) (4) except for the (b) (4) workstations that have been modified/reconfigured for the inclusion of the (b) (4) system. Kite does not provide enough description of the reconfiguration in Suite (b) (4) and its effect to environment and flow.

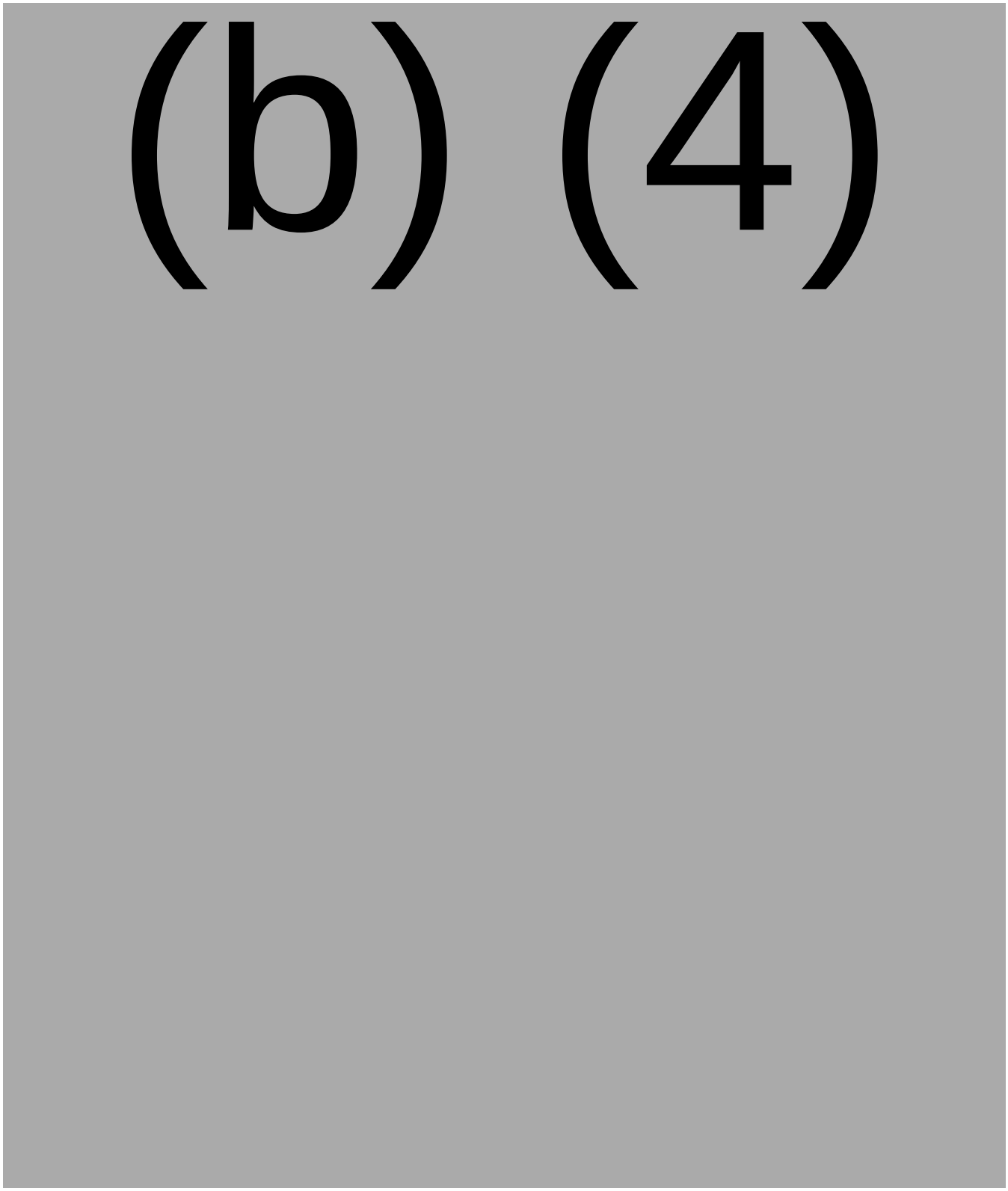
The following information request was to the Firm:

1. **Please provide a description of the modifications that were introduced to the (b) (4) workstations in Suite (b) (4) to include the (b) (4). You may provide images or diagrams to support your response.**

a. **Please identify the (b) (4) stations (station numbers).**
b. **Was environmental monitoring requalification required and/or performed to support the maintenance of your cleanroom status?**
c. **Was the flow of materials, personnel, waste, etc. impacted by the modifications?**

Kite's Response (.28)

1. *The workstation layout was reconfigured to accommodate the* (b) (4)



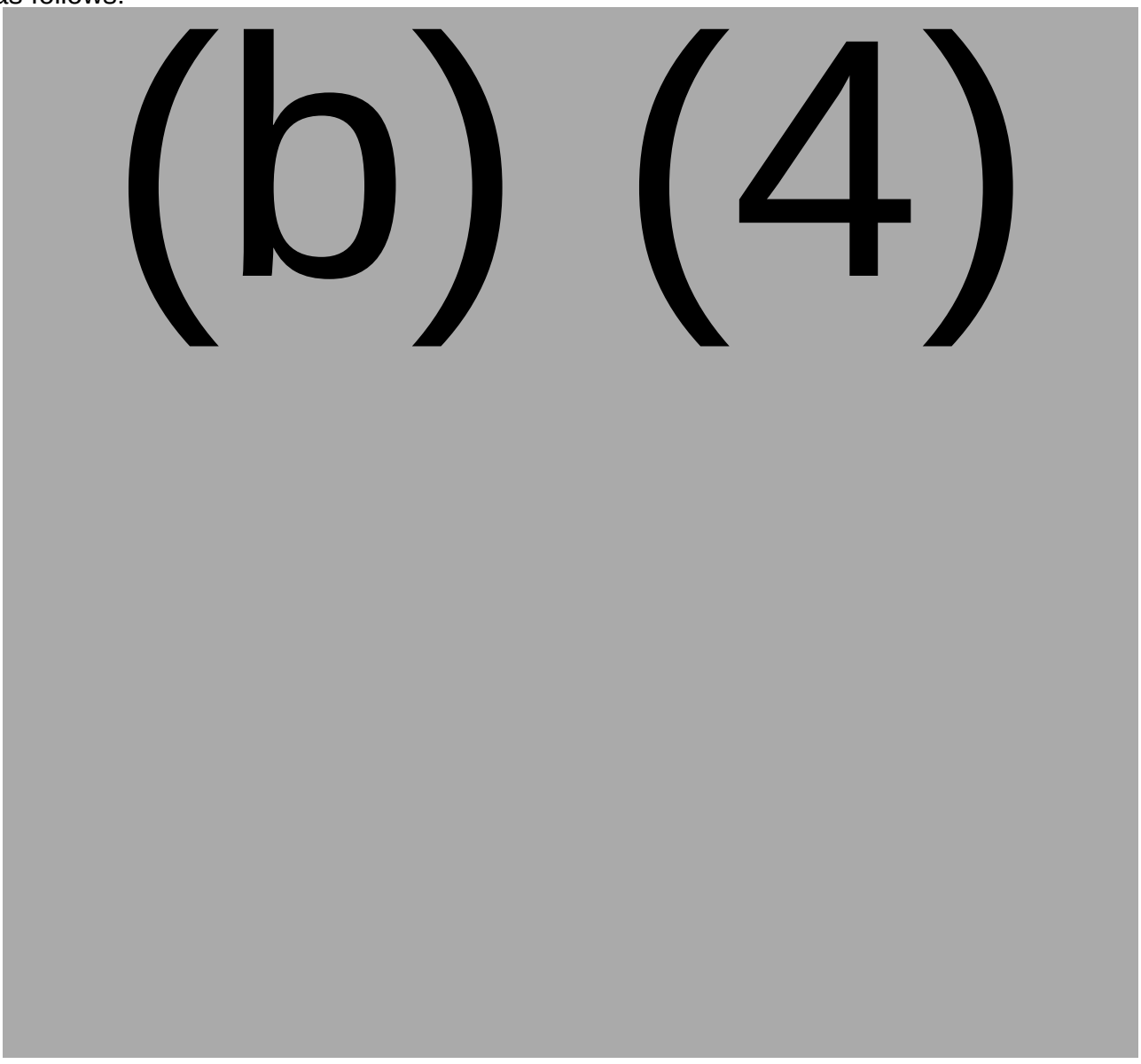
Review Assessment / Comments: Kite reports no change to the approved routine environmental monitoring program in all production rooms. There is no evidence of

negative impact of reconfiguration of the (b) (4) workstations on environment or workflow, EMPQ completed; original acceptance criteria approved by CBER under STN 125643/0 and in the introduction of Room (b) (4) under STN125643/58 (08 Mar 2019). No further scrutiny is required, data is acceptable.

- **Equipment Qualification**

Kite reports that all product-contact surfaces are (b) (4) components that are provided sterile and ready to use, and all equipment has been qualified for use in manufacturing KTE-X19.

In amendment STN125703/0.8, Kite provided a comparison between KTE-X19 process and YESCARTA® approved process, highlighting the differences related to equipment as follows:



(b) (4)

Review Assessment / Comments: All shared equipment between Yescarta and KTE-X19 as outlined in the table have been previously qualified, and that qualification data has been duplicated in this application. No further scrutiny is needed for this equipment.

Kite provided only high-level description and qualification data for the (b) (4)

The following information request was sent to Firm:

1. **Please provide a brief description of the (b) (4) and the scope of use in KTE-X19 manufacturing. You may provide images or diagrams to support your response.**

2. **Please provide a detailed description of the Installation, operational, and performance qualification, as applicable, performed for the (b) (4)**

a. **Are the cycles, parameters, etc. and configuration of the (b) (4) used as (b) (4) or have you modified or customized any system settings or configuration for use in KTE-X19 manufacturing?**
b. **Please describe the quality control (including integrity checks), calibration, and preventative maintenance procedures required for the use of the (b) (4) in KTE-X19 manufacturing.**

3. **Please provide a brief description of the (b) (4), and the scope of use in KTE-X19 manufacturing. You may provide images or diagrams to support your response.**

4. **Please provide a detailed description of the Installation, operational, and performance qualification, as applicable, performed for the (b) (4)**

a. **Are the cycles, parameters, etc. and configuration of the (b) (4) used as (b) (4) or have you modified or customized any system settings or configuration for use in KTE-X19 manufacturing?**
b. **Please describe the quality control (including integrity checks), calibration, and preventative maintenance procedures required for the use of the (b) (4) in KTE-X19 manufacturing.**

Kite Response (.28)

1. (b) (4)

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

(b) (4)

(b) (4)

(b) (4)

Review Assessment / Comments: Kite has provided evidence of comprehensive qualification and working understanding of the operation of (b) (4) No enhancements or customizations have been made to either of the off the shelf instruments, with qualification supported and/or performed by the vendor. All equipment has been challenged in the Process validation. No objectionable findings noted, data is acceptable.

The following Inspectional consideration is recommended.

1. Verify that procedures and requirements for the operation, maintenance, and calibrations of the (b) (4) have been established and compliance is supported.

- **Aseptic Processing Simulations (APS)**

Kite provided the following documents in support of APS:

- PRO-19070; Aseptic Process Simulation of KTE-X19 (b) (4) Manufacturing Process from (b) (4)
- RE-20566; Validation Report for Aseptic Process Simulation of KTE-X19 (b) (4)
- REP-00224; Aseptic Process Validation of KTE-C19 CLP Manufacturing Process – (b) (4)
- VAR-0038; Media Simulation of Final Formulation Manufacturing Process Step Using (b) (4)

Kite has taken the same approach to APS as previously approved for the (b) (4) facility. As with Yescarta, Kite continues to incorporate elements outlined within the US FDA's Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing Guideline into the aseptic manufacturing control strategy for KTE-X19. Due to the nature of the manufacturing process for both Yescarta and KTE-X19, Kite adapted sections within Chapter IX (Validation of Aseptic Processing and Sterilization) and Appendix 3 (Processing Prior to Filling and Sealing Operations) in order to most effectively be applied to the aseptic process being utilized.

Product lots are unique to a single patient, and several differences in aseptic processing conditions exist between conventional aseptic filling operations and the manufacturing process for KTE-X19, as summarized:

Item	Conventional Aseptic Filling	Aseptic Process for KTE-C19
Source material	(b) (4)	
Aseptic Filling Line Operations		
Batch Size		

Item	Conventional Aseptic Filling	Aseptic Process for KTE-C19
Product Conditions Post Container Closure	(b) (4)	
Sampling for Sterility Testing		
Process Simulations (Media Fills)		

Kite notes that unlike conventional aseptic filling, as with Yescarta, every dose of KTE-X19 is tested by validated sterility and endotoxin tests prior to product release. According to Kite, the highest risks in the aseptic process for KTE-X19 (and Yescarta) are associated with individual operator aseptic process performance. This includes both execution of aseptic and closed manipulations as well as proper entry of materials and components being used in the ISO (b) (4) BSC. Therefore, Kite continues to utilize an aseptic control strategy that includes execution of media simulations as part of the initial aseptic process validation (APV), and periodically as part of the aseptic operator qualification (AOQ) program. According to Kite, this combined approach (aseptic process qualification and operator qualification) is effective in assuring microbiological control of the manufacture of KTE-X19.

Except for workstations (b) (4), Kite considers all workstations in suite (b) (4) to be identical, consisting of same equipment. All workstations are also cleaned and monitored in an identical manner. Any workstation that will be used for APV is therefore considered to be representative of all workstations in the manufacturing suite.

Per their master APS plans, since the addition of the (b) (4) fill finish step represents a change to the aseptic path and processing movements, reported in VAR-0038; Kite executed (b) (4) APV at the reconfigured (b) (4) workstations. The studies also included AOQ of the trained operators. Kite reports no change to the previously CBER approved (b) (4) performed during the runs.

Kite reported that all acceptance criteria were met. Kite reported two exceptional conditions related to minor protocol generation (typographical) errors only.

Review Assessment / Comments: Confirmation that the (b) (4) was challenged in the APV studies is needed.

The following information request was sent to the Firm:

1. Did you include the use of the (b) (4) in an APV run? If so, please provide a summary of the APS study (or identify the reference in your application). If not, please provide your justification.

a. Please identify the workstation(s) and production suite(s) where the (b) (4) is installed.

Kite's Response (.28)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Review Assessment / Comments: The APV runs were executed identically to production runs. It is evident that contamination control risk assessment was performed to identify high risk operations. The APV appears to have challenged the aseptic pathway adequately. Control of open steps in the operation continues to be maintained with performance in ISO (b) (4) with training and operator qualification through the aseptic process validation program. Inclusion of the (b) (4) steps appears to represent the worst-case scenario between all the suites and products. No objectionable findings noted; data is acceptable.

- **Chain of Custody / Chain of Identity**

As with Yescarta, the control of Chain of Custody / Chain of Identity during processing of KTE-X19 is critical for this autologous product. The COC/COI data provided sections of F&E report are identical to that of Yescarta.

Review Assessment / Comments: The COC / COI data provided in the submission outlines the verifications at a higher level but does not specify the finite low-level controls at each step of the process. CBER effectively scrutinized the COC/COI system (task execution steps) during the PLI for Yescarta (STN 125643/0).

With the following information request, I confirmed the inclusion of the "new" steps to the COC/COI system.

1. Please provide a description of the additional Chain of Custody/ Chain of Identity controls implemented with the use of the (b) (4)

Kite's Response (.28)

Each product lot is unique to a specific patient and identity is established at the time of apheresis collection for each cell order. The patient cell order is booked based on physician prescription.

The final product item number associated with KTE-X19 is integrated with the Chain of Identity (COI) and Chain of Custody (COC) and associated documentation (batch records and final product labels) are verified and issued based on the patient cell order. The control, review, tracking, and reporting of patient COI and COC is managed using a combination of procedures and integrated validated electronic systems. COC events are documented, by scanning of barcode labels and lot documentation for each step where physical movement of the patient's cells is required. COC procedures and controls are established for intake of the patient identifying information, apheresis collection, apheresis shipment to the manufacturing site, manufacturing process, shipment of the final product to the treatment site and handling of the final product up to infusion, refer to Figure 2 in section 3.2.A.1.

As part of the KTE-X19 manufacturing process, the apheresis is received, inspected and dispositioned by Quality and COC events are documented as the patient cells are removed from the shipper, placed in a designated storage location and further when the patient cells are moved into the manufacturing suite and into a designated workstation for processing. The first unit operation for the KTE-X19 manufacturing process requires the use of the (b) (4) *during processing of the patient cells. Only one patient lot is actively being processed in one workstation at a given time. At the conclusion of the operations, a COC event is documented for patient cell movement into a designated incubator as per the approved manufacturing procedures.*

The (b) (4) *is used on harvest day operations. COC events are executed for movement of cells out of the incubator and into a designated workstation to begin Harvest operations. During Harvest operations, COC events are documented for application of the Patient ID labels to the final product bags and cassettes, and further processing. Upon the conclusion of the harvest operations, COC events are documented for movement of the final product bags/cassettes out of the workstation, out of the manufacturing suite and into the visual inspection workstation.*

As part of the lot disposition process, the manufacturing COC report, inclusive of all COC events is reviewed to ensure the COC was maintained throughout the manufacturing process and movement of patient cells. The COI/COC procedures and controls are consistent for KTE-X19 and YESCARTA®.

Review Assessment / Comments: Kite provided evidence that their COC /COI system is utilized as expected, and all critical steps are accounted for. No objectionable findings note; Data is acceptable.

3.2.A.2 Adventitious Agents Safety Evaluation
Deferred to Product Office Reviewer

3.2.A.3 Novel Excipients
Deferred to Product Office CMC Reviewer

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

Kite provided the following executed batch records from the PPQ in the application:

- (b) (4)

The comprehensive unexecuted MBR, which includes all validated processing scenarios is provided, as well.

Review Assessment / Comments: The executed batch records from at least one validation lot is provided. EBRs and MBRs appear to correlate with the process validation parameters. No objectionable findings noted, data is acceptable. The batch records are the primary responsibility of the PO CMC reviewer to evaluate.

Other eCTD Modules
Module 1

A. Environmental Assessment or Claim of Categorical Exclusion
Deferred to Product Office CMC Reviewer