



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
Building 71, G112
Silver Spring, MD 20993-0002

To: DATS: 649735

STN BLA 125643/0
KTE-C19, axicabtagene ciloleucel, YESCARTA™

From: CDR Donald Ertel, Regulatory Officer, OCBQ / DMPQ / MRB1

Through: Carolyn Renshaw, Branch Chief, OCBQ / DMPQ / MRB1

CC: Mark Davidson, RPM, OTAT/DRPM/RPMBI
Mike Havert, Chair, OTAT/DCGT/GTB

Subject: DMPQ Primary Review for Original Biologics License Application filed per 21 CFR 601.2 for KTE-CD19 (autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor)

Applicant: Kite Pharma, Inc. (License Number #2064)

Facility

1. Kite Pharma, Inc. ((b) (4)) 2355 Utah Avenue, El Segundo, California, 90245, FEI# 3012583739
2. ((b) (4))

ADD: 29 Nov 2017 (internal Target for 10/30/17)

Conclusion and Recommendation

Overall conclusions and recommendation will be made in my Final Addendum Review Memo.

The following information request is being sent to the Firm to be assessed in my addendum review memo:

1. Reference equipment at ((b) (4)) used for the manufacture and storage of ((b) (4)). Please confirm the accuracy of the Equipment ID numbers, Room numbers, and associated qualification numbers in the following table (in particular, the autoclave and ((b) (4)) tank) provided in the submission:

(b) (4)

2. Reference the revised 3.2.A.1, Facilities and Equipment, sent in an amendment (rec'd 06/26/17): Section 1.1.1 Overview [first paragraph] has not been updated to reflect the current qualification status of the manufacturing suites. Please provide an updated document in an amendment to the application.
3. In reference to the Kite (b) (4) facility, please provide a summary of the alert and action limits for Environmental Monitoring that you have established for all room classifications.
4. In reference to APV at (b) (4) Facility:
 - a. How did you select the (b) (4) (Suite (b) (4) BSCs and the (b) (4) BSC (Suite (b) (4) for use in your Aseptic Processing Validation? Was a risk assessment performed to identify the specific BSCs used in the initial studies? If so, please provide the risk assessment.
 - b. Do you plan to include the use of the other BSCs in subsequent AOQs? If so, please provide your general plan. If not, please provide a justification.
5. Reference your qualification of the Kite Final Product Shipper (for axicabtagene ciloleucel): Was physical testing such as drop and vibration testing performed as part of your qualification study?
6. In reference to (b) (4) EM program, please provide the Environmental Monitoring Limits for non-viable Particulate and viable Airborne and Surface sampling for Grade (b) (4) areas (i.e. BSCs)
7. In reference to (b) (4) purified water system program, please provide the action and alert limits that established for the (b) (4) testing for Bioburden, Endotoxin, Conductivity, pH, and Total Organic Carbon.
8. Please provide a list of all product components (i.e. culture flasks, pump tubing, filters, etc.) used the processing of (b) (4).
 - a. Please indicate whether the component is received already sterilized by supplier or sterilized at (b) (4)
 - b. Please state whether Extractable/Leachable studies have been completed for the component.

9. Please provide a summary of the qualification (IQ/OQ/PQ) of the autoclave used to sterilize product contact components used in the processing of (b) (4).
10. Please provide a summary of the Aseptic Processing Simulation Validation Study for aseptic processing of (b) (4) performed at (b) (4)
11. Please provide a summary of the Container Closure Integrity Testing qualification for the (b) (4)

Secondary Information requests (also to be evaluated in my addendum review):

1. In reference to (b) (4) EM program, please describe the in-process environmental monitoring that is performed during the (b) (4) (in (b) (4)) in (b) (4) in Room (b) (4) Please provide the acceptance criteria.
2. Please provide a representative IQ/OQ Summary Report for the (b) (4) Units.
3. Reference manufacturing of axicabtagene ciloleucel at Kite: In table format, please provide a list of the all critical components (i.e. processing bags, final container bag) and raw materials (i.e. excipients and viral vector) and the incoming testing performed by Kite on each material or component for release to manufacturing. If only a Certificate of Analysis evaluation is performed, please provide your justification.
4. In reference to production at Kite: please provide an overview of how you have verified that you will be able to produce at full capacity (i.e. all BSCs in use at the same time in (b) (4) Production suites) without compromising product quality or safety.
 - a. Please confirm that all BSCs in Suites (b) (4) are qualified for use in commercial manufacturing.
5. In reference to (b) (4) WFI system:
 - a. How many drops does the system have?
 - b. How often is the WFI system tested for Bioburden, Endotoxin, Conductivity, pH, and Total Organic Carbon?
 - c. Please provide the acceptance criteria for Bioburden, Endotoxin, Conductivity, pH, and Total Organic Carbon.

Review Memo Format and Table of Contents

I have provided a summary of information provided in the submission that is under DMPQ purview as outlined in SOPP 8401.4: My review included evaluation of parts or the entirety of the following sections:

- 3.2.A.1 Air Handler Zoning
- 3.2.A.1 Apheresis and Finished Product Flow diagram
- 3.2.A.1 COI-COC Tracking diagrams
- 3.2.A.1 Facilities and Equipment
- 3.2.A.1 Floor Plan Block diagram
- 3.2.A.1 Gowning Flow diagram

- 3.2.A.1 Production Personnel Flow diagram
- 3.2.A.1 QR-0800, Aseptic Process Validation of KTE-C19 CLP Manufacturing Process –
(b) (4)
- 3.2.A.1 Raw Material Flow diagram
- 3.2.A.1 Room classification and Pressurization diagram
- 3.2.A.1 (b) (4) Product Specific Facility and Equipment Report
- 3.2.A.1 Sample Testing Flow diagram
- 3.2.A.1 SOP-0418, Apheresis Center and Treatment Site Qualification
- 3.2.A.1 SOP-0450, Commercial Apheresis Center Verification, Collection and Packaging
- 3.2.A.1 SOP-0488, Commercial Treatment Site Final Product Handling
- 3.2.A.1 Utilities - Floor Plan
- 3.2.A.1 Utilities - Roof Plan
- 3.2.A.1 VAP-0004, Chain of Identity, Chain of Custody System and Axicabtagene
Ciloleucel Manufacturing Process Integration Performance Qualification
(b) (4)-CC- 00048)
- 3.2.A.1 VAP-0006, Chain of Identity, Chain of Custody System and Axicabtagene
Ciloleucel Manufacturing Process Integration Performance Qualification
(b) (4)-CC- 00048)
- 3.2.A.1 VAR-0013 – Chain of Identity and Chain of Custody Validation Report
- 3.2.A.1 VMP-0007, Validation Master Plan
- 3.2.A.1 VMP-0018, Validation Master Plan -Integrated Enterprise Systems: Patient Chain
of Identity and Chain of Custody Validation
- 3.2.A.1 VP-0022, Aseptic Process Validation of KTE-C19 CLP Manufacturing Process -
(b) (4)
- 3.2.A.1 Warehouse diagram
- 3.2.A.1 Waste Flow diagram
- 3.2.P.1 Description and Composition of the Drug Product
- 3.2.P.2 Pharmaceutical Development- Container Closure System
- 3.2.P.2 Pharmaceutical Development- Drug Product
- 3.2.P.2 Pharmaceutical Development- Formulation
- 3.2.P.2 Microbiological Attributes
- 3.2.P.3.1 Manufacturer
- 3.2.P.3.2 Batch Formula
- 3.2.P.3.3 Description of Manufacturing Process and Process Controls
- 3.2.P.3.4 Controls of Critical Steps and Intermediates
- 3.2.P.3.5 Process Validation and/or Evaluation
- 3.2.P.4.1 Specification
- 3.2.P.4.4 Justification of Specifications
- 3.2.P.5.1 Specification
- 3.2.P.5.4 Batch Analyses
- 3.2.P.5.6 JOS-15-004, Justification of Specifications
- 3.2.P.5.6 Justification of Specification
- 3.2.P.7 CoA - (b) (4) (Container Closure System)
- 3.2.P.7 Container Closure System
- 3.2.P.8.1 Stability Summary and Conclusion
- 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

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1. Amendments related to Review

- 1256453/0.6 received 20 Apr 2017 to Information request sent 06 Apr 2017
- 125643/0.31 received 26 Jun 2017 (Response to discussion at the Kite PLI to include Aseptic Process Validation Data for Suite (b) (4))

2. Regulatory History

The agency received the BLA in eCTD format on 02 Dec 2016 as rolling BLA. I was assigned as a CMC reviewer on 08 Dec 2016. The application was appropriately filed per 21 CFR 601.2

The following DMF were referenced:

- (b) (4)

Review Assessment / Comments: I did not need to nor did I perform a documented review of the mentioned DMFs. I did a cursory review (undocumented) of BB-MF (b) (4) its contains high level facility and equipment information that is generically relevant to the production of the vector. Kite included relevant (b) (4) Facility and Equipment information in their amendment 125643/0.6, which was sufficient for my primary review.

3. Environmental Assessment

Kite is claiming an exemption from the requirement for preparing an environmental assessment for this BLA for axicabtagene ciloleucel, based upon 21 CFR 25.31(c) which allows a categorical exclusion for an action on an application for marketing approval, for marketing a biologic product for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Kite states that they are not aware of any extraordinary circumstances that would require the preparation of an environmental assessment. Per the Agency advice received during the pre-BLA meeting held on 31 Oct 2016, Kite provided a risk assessment for the following:

- Potential release of the retroviral vector
- Viability and degradation of YESCARTA in the natural environment

YESCARTA will be administered in hospitals, institutions and/or specialized clinics. At the hospitals/institutions/specialized clinics, used YESCARTA bags will be disposed of according to the biologic waste management procedures. No unused product will be disposed of in the sewer system.

YESCARTA is an engineered autologous chimeric antigen receptor (CAR) T-cell immunotherapy for the treatment of B-cell malignancies. Autologous T cells are genetically modified/transduced *ex vivo* by a replication-incompetent retroviral vector (b) (4) Vector) to express anti-CD19 chimeric antigen receptors (CAR) on the cell surface, and can target malignant B cells expressing CD19 antigens. YESCARTA is also a personalized medicine as the product is unique to each patient, being produced from leukapheresis material obtained from the individual patient. CD19 is a 95 kilodalton (kDa) transmembrane protein selectively expressed in both normal and malignant B cells (reference provided), but not in multipotent hematopoietic stem cells, or plasma cells (reference provided).

CAR-expressing T cells are generated through a process called retroviral vector-mediated transduction, whereby a replication-incompetent retroviral vector encoding the CAR transgene integrates the CAR construct into the T-cell chromosome. Replication incompetent retroviral vectors have been used for more than a decade in the design of diverse engineered T-cell products, and their clinical safety profile has demonstrated an absence of genotoxic events (references provided).

The CAR construct used for YESCARTA comprises the following domains:

1. An anti-human CD19 single-chain variable region fragment (scFv)
2. The partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28, a lymphocyte co-stimulatory receptor that plays an important role in optimizing T-cell survival and function
3. The cytoplasmic portion, including the signaling domain, of human CD3 ζ , a component of the T- cell receptor complex (reference provided).

Kite notes that the (b) (4) Vector is replication-incompetent, and is not applied *in vivo* as an advanced therapeutic product. The (b) (4) Vector is employed *ex vivo* to modify the patient's own T cells and is a starting material for the manufacturing of YESCARTA. Finally, the genetically modified autologous T cells in YESCARTA do not contain (b) (4). Retroviral vector lots are tested for (b) (4) including (b) (4) to release for use in the YESCARTA manufacturing process.

Inactivation/Clearance of Retroviral Vector in YESCARTA Manufacturing Process:

(b) (4)

[Redacted]

[Redacted]

2 Pages Determined to be Not Releasable: (b)(4)

Risks Associated with the Potential Release of YESCARTA to the environment

There is negligible risk to the environment from release of YESCARTA. Anti-CD19 CAR T cells in YESCARTA, like natural human T cells, will not survive in the environment. The continuous survival of human cells outside the human body requires a combination of well-defined culture media that maintains pH and osmolality, and controlled environmental conditions (e.g., temperature, humidity, CO₂) that does not exist in nature. Anti-CD19 CAR T cells will be destroyed outside the host when exposed to common environmental elements, such as low or high pH, high temperatures (>50°C), aqueous solution (e.g., water, solvent), or desiccant. In addition, anti-CD19 CAR T cells should be rapidly destroyed by standard means of disinfection or household cleaning solutions (e.g., bleach, soap, alcohol containing cleaning solutions).

Shedding

According to Kite, no known mechanisms to enable shedding of (b) (4) Vector from YESCARTA exist. (b) (4) Vector is replication incompetent and not produced in human T cells, and human T cells do not contain the required viral elements to mobilize (b) (4) Vector.

Retroviral particles that have not entered and transduced the T cells are removed during the manufacturing process and (b) (4) (reference provided). Therefore, it is considered that there is a negligible, if not zero, number of cell-free retroviral vector particles infused into the patient.

Anti-CD19 CAR T cells present in YESCARTA are not considered true excreta since they, like normal T cells, do not shed spontaneously via saliva, urine, or feces into the environment (reference provided).

Patient Samples

According to Kite, YESCARTA contains either no or negligibly low levels of free viral vector. Any potential remaining viral vector particles in the product would be inhibited/inactivated by the complement component of human serum after administration to the patient (references provided).

Patient samples such as blood, bone marrow or lymph node biopsies may contain anti-CD19 CAR T cells, but the latter are not pathogenic, do not replicate and do not survive outside the patient.

Theoretically, if anti-CD19 CAR T cell membrane integrity is challenged and any gamma-retroviral components that have not incorporated into the host chromosome are released into an aqueous environment, such as waste water, abundant with heterotrophic microorganisms and organic particles, it can be assumed that the gamma-retroviral components will be either degraded by microorganisms or quickly adsorbed onto particles (reference provided).

Accidental injection

In the event that the YESCARTA is transmitted through accidental injection to a healthcare professional or caregiver, the immune system or complement component of the recipient would eliminate the injected cells. A local reaction or allergic reaction may occur but such reactions are expected to be transient and can be treated with commonly available medications. Thus no lasting negative consequences are expected in the event that an accidental injection occurs.

Viability and Degradation of YESCARTA in the Natural Environment

Once (b) (4) Vector is integrated into the T cell chromosome, it becomes an integral part of the T cells for the lifetime of the transduced cell. However, T cells transduced with (b) (4) Vector do not persist for an extended period within the patient treated with YESCARTA. Evidence to date shows that after infusion of YESCARTA anti-CD19 CAR T cell levels in the peripheral circulation peaked at 7-14 days, and decreased within 1 to 3 months.

The survival of human blood cells ex-vivo requires a complex combination of special media, temperature and O₂/CO₂. The environmental conditions outside the host (body) are substantially different and not appropriate for its survival (temperature, pH, UV, biophysical and biochemical conditions). T cells, both naturally occurring and those transduced with (b) (4) Vector, cannot survive outside of the body and have a finite life span after infusion into the patient.

Administration of YESCARTA to the patient is accomplished in a closed system without exposure to the clinical staff performing the procedure. The final cell product should not contain infectious viral particles. Even if a very low number of infectious viral particles would be present, the vector is replication-incompetent and could only integrate once, therefore no further spreading is possible. YESCARTA is provided to patients in a volume of approximately 68 mL, ensuring that any theoretical viral vector particles would be rapidly diluted into the patient's bloodstream and inactivated/cleared from circulation by the complement component of human serum (references provided).

Both T cells and any potential residual retroviral vector particles within YESCARTA are susceptible to common methods of inactivation applied to microbial agents, and to many virucidal disinfectants, including (b) (4)

Using the (b) (4) virus ((b) (4) as an example of a lab-derived murine gamma-retrovirus, (b) (4) and colleagues demonstrated a reduced infectivity of (b) (4) (reference provided).

Risk Mitigation

YESCARTA contains engineered autologous human T cells and therefore, healthcare professionals will employ universal precautions for the prevention of transmission of blood-borne infections as outlined by the Center for Disease Control and Prevention (references provided). Established procedures for handling live human cells will be followed per the local institutional policies and processes.

Furthermore, all personnel involved in handling or administration of YESCARTA will be appropriately trained. All healthcare professionals involved in the administration will adhere to safe practices to avoid any release of the product into the environment. Work surfaces and material potentially in contact with YESCARTA will be decontaminated with (b) (4), according to hospital/facility hygiene procedures. In case of spillage, a spillage kit containing absorbing lining and an adequate disinfectant such as (b) (4) will be available during receipt and administration of the product. Once YESCARTA is administered to the patient, the IV bag along with the IV tubing and any other components that have been in contact with the product before and during administration will be disposed of according to the hospital biohazard waste procedures. The patient's room after use will be cleaned using standard hospital cleaning and disinfection procedures such as a (b) (4) or any other method indicated as routine cleaning and disinfection agent.

Review Assessment / Comments: Kite has provided an in-depth risk assessment, with 28 scientific references. Kite has concluded:

1. There is no likelihood of YESCARTA or (b) (4) Vector becoming persistent and invasive in natural habitats.
2. (b) (4) Vector particles are not expected to be present in YESCARTA, and therefore provide no environmental risk associated with the product.
3. There is no selective advantage or disadvantage conferred to T cells by retroviral vector transduction. Once infused, the transduced T cells do not possess any antigen-independent selective growth advantage in vivo since their half-life time is similar to or lower than that of non-transduced T cells.
4. There is no known or predicted potential for gene transfer from (b) (4) Vector to other species in the event of an accidental release to the environment.
5. There is no known or predicted potential for gene transfer from YESCARTA. Administration of YESCARTA is performed within a clinical setting under aseptic conditions. Transmission to other species is improbable. In the event of accidental injection of the autologous medicinal product to an allogeneic, non-target human subject, the cells would be recognized as major histocompatibility complex (MHC) mismatched and thus cleared by the immune system of the individual.
6. There is no known or predicted potential immediate and/or delayed environmental impact of the direct and indirect interactions between (b) (4) Vector and non-target organisms.
7. There are no known or predicted possible immediate and/or delayed effects on the health of persons working with, coming into contact with, or being in the vicinity of either YESCARTA or accidental release of (b) (4) Vector.

8. There are no known or predicted immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from either accidental consumption of YESCARTA or release of (b) (4) Vector.

According to our *Guidance for Industry, Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products, March 2015*, it appears that YESCARTA and the (b) (4) retroviral vector would qualify as “naturally occurring in the environment” per Section IV, *How Do You Decide Whether an EA Is Needed?*, B. Licensing Applications, sections 2. I agree with Kite’s conclusions, and concur with their request for CE. The Product Office Chair is in agreement with the request for CE, as well.

4. Drug Substance Overview

(b) (4)

5. Drug Product Overview

Manufactured at Kite Pharma, Inc. in El Segundo, CA, YESCARTA™, an engineered autologous chimeric antigen receptor (CAR) T cell immunotherapy, is indicated for the treatment of adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant (ASCT).

Autologous T cells are genetically modified/transduced ex vivo by a replication-incompetent retroviral vector ((b) (4) Vector) to express anti-CD19 CAR on the cell surface, and can target malignant B cells expressing CD19 antigens. YESCARTA is also a personalized medicine as the product is unique to each patient, being produced from leukapheresis material obtained from the individual patient.

CD19 is a 95 kilodalton (kDa) transmembrane protein selectively expressed in both normal and malignant B cells, but not in multipotent hematopoietic stem cells, or plasma cells. CAR-expressing T cells are generated through a process called retroviral vector-mediated transduction, whereby a replication-incompetent retroviral vector encoding the CAR transgene integrates the CAR construct into the T-cell chromosome. The CAR construct used for YESCARTA comprises the following domains:

1. An anti-human CD19 single-chain variable region fragment (scFv)
2. The partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28, a lymphocyte co-stimulatory receptor that plays an important role in optimizing T-cell survival and function
3. The cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T- cell receptor complex.

Following anti-CD19 CAR T cell engagement with CD19 expressing target cells, the CD3ζ domain activates a downstream signaling cascade that leads to T-cell activation, proliferation, secretion of cytokines and acquisition of effector functions, such as cytotoxicity. The intracellular signaling domain of CD28 provides a critical co-stimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function including survival and proliferation, and to increase production of specific cytokines including interleukin 2 (IL- 2). In addition to their direct cytolytic anti- tumor effect, activated T cells can amplify the anti-tumor response indirectly by recruiting and activating additional antitumor immune cells.

One infusion bag (1dose) of YESCARTA™ which contains a suspension of anti-CD19 CAR T cells in approximately 68 mL (including 5% DMSO and 2.5% human albumin) for a target dose of 2×10^6 anti-CD19 CAR T cells/kg body weight (range: (b) (4) cells/kg), with a maximum of 2×10^8 anti-CD19 CAR T cells

6. Process Overview (DP and DS)

a. Drug Substance [Retroviral Vector] (b) (4)

(b) (4)

(b) (4)

b. Drug Product [Axicabtagene ciloleucel, YESCARTA™]

At Kite Pharma, Inc., the manufacture of axicabtagene ciloleucel is a (b) (4) process, and does (b) (4). However, Kite, for sake of organizing the submission, has defined the following:

- Drug Substance – axicabtagene ciloleucel (apheresis receipt (b) (4))
- Drug Product – axicabtagene ciloleucel (formulation to shipment)

All operations are performed in (b) (4) an ISO (b) (4) BSC within the ISO (b) (4) environment of the manufacturing suite. The manufacturing process is outlined as follows:

(b) (4)

(b) (4)

7. Overall Manufacturing and Testing Facilities

The facilities involved in the manufacture and testing of YESCARTA and (b) (4) are listed below along with a short description of their manufacturing responsibilities and an indication if an inspection was performed.

Facility	Process	Comments
Kite Pharma, Inc. (b) (4) 2355 Utah Avenue El Segundo, California, 90245 3012583739	<ul style="list-style-type: none">• Manufacture, control, and storage of KTE-C19 Final Product (axicabtagene ciloleucel)• All KTE-C19 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	Inspection performed 12 -16 June 2017

(b) (4)

(b) (4)

8. Processing Equipment Overview (DP and DS)

a. Drug Substance [Retroviral Vector (b) (4)]

(b) (4)

b. Drug Product [Axicabtagene ciloleucel, YESCARTA™]

All product-contact components used in the manufacture of KTE-C19 (i.e. tubing sets and (b) (4) bags) are (b) (4) , and received sterile and ready to use. All equipment are listed in the (b) (4) Facility Validation Master Plan (VMP-0007) and were subject to user requirement specification (URS), installation qualification (IQ), operational qualification (OQ), and/or performance qualification (PQ). Major Equipment used in the manufacture of Axicabtagene Ciloleucel is:

(b) (4)

(b) (4)

* Components of each workstation in a Manufacturing Suite

** (b) (4) equipment and associated single-use kits are manufactured by (b) (4) and have been cleared for marketing by the US FDA as a Class II medical device per 510(k) number (b) (4)

The key qualification requirements that were assessed for major equipment were as follows:

(b) (4)

(b) (4)

All equipment is cleaned, maintained, and calibrated, as appropriate, according to approved written procedures and documented by trained personnel.

The BSCs

The qualification of the BSCs was evaluated during the PLI of the Kite facility. EMPQ studies were completed for the ISO^{(b) (4)} BSCs according to the following acceptance criteria:

(b) (4)

Air flow visualization Studies were performed for each BSC in the manufacturing; some smoke studies were evaluated during the PLI, no 483 observations were made.

The (b) (4) Freezer (b) (4)

(b) (4) PQ was also evaluated during the PLI. (b) (4) PQ was performed in (b) (4)

The (b) (4) PQ results showed that the (b) (4) profile steps met specifications during freezing process of each PQ run, as follows:

- (b) (4)

The performance of the (b) (4) Processing Unit was challenged as part of the overall Process Validation.

Review Comment/ Assessment: Kite and (b) (4) report performance of IQ/OQ of all equipment. Based on knowledge gained from the Pre-license inspection at (b) (4) Equipment ID numbers may be discrepant in the referenced table.

The following information request was sent to the Firm:

- 1. Reference equipment used for the manufacture and storage of (b) (4) : Please confirm the accuracy of the Equipment ID numbers, Room numbers, and associated qualification numbers in the following table (in particular, the autoclave and (b) (4) tank) provided in the submission: [Table provided in Recommendations Sections of this memo]**
- 2. Please provide a representative IQ/OQ Summary Report for the (b) (4) Units**

9. Kite Pharma Facility (b) (4)

a. (b) (4) Overview

The commercial manufacturing facility, (b) (4), for axicabtagene ciloleucel (KTE-C19) consists of approximately (b) (4) of office, laboratory, manufacturing, and warehouse space. The facility is located in a general office, warehouse, and light manufacturing zone. The facility, utility, manufacturing area, and QC laboratory commissioning, qualification and validation activities have been completed, with the exception that (b) (4) manufacturing suites (Rooms (b) (4)) are not currently used for manufacture of KTE-C19. According to Kite, as production needs arise, the (b) (4) other manufacturing suites will undergo equipment and environmental qualification and have aseptic process validation (APV) performed prior to commencement of production therein. The commissioning, qualification, and validation process for the facility is governed by an approved Facility Validation Master Plan (VMP-0007) managed by Kite personnel.

Review Comments/Assessment: In the original submission and pre-BLA meeting, Kite proposed the approval of Suite (b) (4) for the initiation of commercial manufacturing. Based on my discussion with the Firm during the pre-license inspection, Kite is proposing the use of (b) (4) for the initiation of commercial manufacturing. Accordingly, Kite sent an updated 3.2.A.1, Facilities and Equipment, and associated APV documents to include the additional APV data for Suite (b) (4). So actually, (b) (4) suites have been qualified for manufacturing use. Per my discussion with the Firm during our PLI, the Firm understands that they will need to supplement their application with supporting qualification data to gain approval for the use of suites (b) (4).

The following IR was sent to the Firm:

- 1. Reference the revised 3.2.A.1, Facilities and Equipment, sent in an amendment (rec'd 06/26/17): Section 1.1.1 Overview [first paragraph] has not been updated to reflect the current qualification status of the manufacturing suites. Please provide an updated document in an amendment to the application.**

The facility also features a qualified CO2 storage and distribution system for (b) (4)

(b) (4) A qualified reverse osmosis/deionized (RO/DI) purified water generation and distribution system supplies water for facility cleaning and the QC Laboratory.

All product contact surfaces used in the manufacture of KTE-C19 are (b) (4) components and all process equipment (such as biosafety cabinets [BSCs], (b) (4) freezers) and analytical instrumentation are controlled to established operational parameters. Major process equipment was selected to be identical to that used in clinical manufacturing.

The (b) (4) facility is currently a manufacturing facility dedicated to the production of KTE-C19 and clinical products that use the same retroviral vector, (b) (4) Vector.

The facility design includes a manufacturing area with (b) (4)

All areas of the production facility have controlled access. Entry into the production area requires (b) (4)

(b) (4) is required prior to operator entry into the ISO (b) (4) biosafety cabinets. All manufacturing suites use unidirectional material pass-throughs. Together, the facility design and procedures ensure that all personnel and material flow is unidirectional through the manufacturing suites.

The (b) (4) facility features laboratory space and equipment to perform in-process, release, and stability testing associated with the manufacture and control of KTE-C19 and related clinical products. The facility has warehouse space for receipt of incoming raw materials, including apheresis material, as well as systems and procedures for outgoing shipments of finished product. Administrative space for staff offices, document retention, and meetings is also available.

Only authorized individuals are allowed access to the manufacturing suites, the GMP warehouse, and ancillary areas via controlled-access cards. (b) (4) includes the following functional areas (identified by associated room number) used in the manufacture and control of KTE-C19:

- (b) (4)

(b) (4)

Kite provided the following floorplans and diagrams in the submission:

- Floor Plan Block Diagram
- Apheresis and Finished Product Flow Diagram
- Production Personnel Flow Diagram
- Gowning Flow Diagram
- Raw Material Flow Diagram
- Sample Testing Flow Diagram
- Waste Flow Diagram
- Warehouse Diagram
- Room Pressurization Diagram
- Air Handler Zoning
- Utilities – Floor Plan
- Utilities – Roof Plan

Review Assessment / Comments: Standard approach to facility design and flow appears evident. The diagrams appear to correspond with the description in the application. No tortuous paths are evident, no objectionable findings noted.

During the PLI, I audited the Flow patterns for waste, product, people and materials in the Production area; discussions with Kent Detweiler, Senior Manager, Manufacturing. Kites policy for proper flow in designated areas is outlined in SOP-0259-MF3, Rev1, Flow of Personnel Materials, Product, and Waste. Proper flow of personnel, material, product, and waste is maintained to ensure the cleanliness and integrity of the clean room. Each element (personnel, materials, equipment, etc.) follows specific flow directions. Flows are generally unidirectional through the manufacturing suite (i.e. in at one side, and exit at distal end of the manufacturing suite). Material can move (b) (4) between (b) (4) in Room (b) (4). Pass-throughs are used to move smaller items (i.e. materials, equipment, components) in out and out of the manufacturing areas. These pass-throughs are not supplied with their own air supply, but are balanced with existing room air through controlled opening via interlocked doors. The Facility appeared to be adequately designed to allow for compliance of the flow policy. Flow diagrams in

the SOP correlate to those provided in the BLA. Facility schematics are accurate to the actual layout of the facility. No objectionable findings were noted.

Additionally during the PLI, I audited the room pressurization scheme in the Manufacturing areas at (b) (4). According to Kite, sufficient DP exists to prevent contamination of cleanrooms and clean zones from adjacent areas of lower cleanliness. A DP of at least (b) (4) is maintained between areas of same classification and (b) (4) between areas of different classification. DP between adjacent rooms of different cleanliness is specified, controlled, and monitored; these DPs are defined in an attachment to the SOP-0497-EF3. The specifications appear adequate for the intended room use.. I compared these against their DP diagram and found no discrepancies.

(b) (4)

(b) (4) are used for receiving, inspection, dispositioning (quarantine, release, or reject), inventory tracking, kitting/replenishment, lot/expiry tracking.

For each item received at (b) (4) a visual and physical inspection is performed to determine if there are any signs of damage or evidence of broken seals, tampering, or gross contamination. Accepted materials are transferred to the receiving area. All materials used for the GMP manufacturing process are inspected, tested, dispositioned, and labeled prior to use per an approved procedure, by trained personnel. The (b) (4) Vector and apheresis material require special handling and are received, inspected, and dispositioned in accordance with approved procedures. Materials are kept in temperature-controlled storage locations according to the item specifications and manufacturer's recommendations.

Review Assessment / Comments: The system for control of incoming material was evaluated during inspection. See the following excerpt from the EIR:

SOP-0231 describes the process for receiving, inspecting, and storing GMP materials at (b) (4). Materials Management (MM) maintains the GMP Warehouse and GMP material segregation controls. MM receives and performs general receiving inspection incoming GMP materials. Receipt transactions are performed in (b) (4). Materials are automatically placed into quarantined status prior to QC inspection and release.

The general receiving inspection is an inspection of the outer incoming material containers. MM creates and applies status-less labels to material's secondary or tertiary containers. Materials are stored in the temperature controlled warehouse. Materials are transferred to the raw materials general inspection room with completed Material Packet to initiate Quality Control sampling and testing according to the materials specification.

If the material contains a temperature data logger (i.e. apheresis product), MM stops the data logger. Data Loggers data records are attached as part of the Material Packet. If the material data went out of range, QA would be notified. Temperature sensitive materials are placed in the appropriate temperature storage location as defined in the Specification. Status-less labeling of temperature sensitive material is performed after the material has been placed in the appropriate storage condition. If a material is unacceptable as determined by the general receiving inspection, Supplier Quality Management is notified. Receiving LN2 Shipper. SOP -0231 also

includes specific and detailed instructions for receiving the Apheresis Shipper and (b) (4) Shipper and (their critical transport containers for the shipment of apheresis starting material and final product respectively)

Kite has the following material disposition designations:

- *Hold: material is pending further evaluation by QA regarding its final disposition.*
- *Quarantine: material has been accepted by Materials Management but is pending review, inspection, and/or QA disposition*
- *Rejected: material is not eligible for use in production.*
- *Released: material is eligible for GMP use.*

For release of material, QA reviews, for completion, accuracy, and compliance, the Material Packet (MP), this may include the following documents:

- *Goods Receipt Slip*
- *Copy of the packing slip*
- *Copy of the specification*
- *Certificate documents, as required by the specification*
- *Inspection/testing results, as required by the specification*
- *Temperature records- for temperature sensitive material, ensure that temperature requirements are met and material is stored at the correct temperature.*

QA updates the status in (b) (4) . Partial releases of lots are acceptable per their SOP, as well. Kite employs a specific detailed SOP (0344-QA3) for the receiving and accessioning of Leukapheresis Material (starting material). The SOP includes steps for:

- *Chain of Custody events*
- *Use of Lot Traveler report:*
- *Handling of the Temperature monitoring device*

Receipt of the leukapheresis occurs in (b) (4) , with a second verification by QA personnel.

Primary review of the Chain of Custody / Chain of Identity system was assumed by the Product Office. I deferred review of this system to the Product Office.

The following information request was sent to the Firm:

- 1. In table format, please provide a list of the all critical components (i.e. bags) and raw materials (i.e. excipients and viral vector) and the incoming testing performed by Kite on each material or component for release to manufacturing. If only a Certificate of Analysis evaluation is performed, please provide your justification.**

Facility Validation

The commissioning and qualification of (b) (4) was performed in accordance with Kite's qualification program requirements. A Facility Validation Master Plan (VMP-0007) provided an overall roadmap through a documented process that demonstrated that the equipment, systems, and utilities were installed, operating, and performing per their intended requirements, and were therefore capable of reliably manufacturing products that meet their predetermined quality attributes. The commissioning and validation activities are described below.

Commissioning

A commissioning plan outlined the commissioning activities required to support the overall facility readiness. These activities were planned, executed, and approved to verify that the construction, installation, start-up, and turnover of all GMP facility systems were safe and fit for their intended use. All documents supporting facility start-up were controlled, with appropriate reviews and approvals. During the commissioning phase of the project, utilities underwent physical inspections, documentation reviews, operational testing, and performance testing. Enhanced Commissioning (EC) was performed for the HVAC system and building monitoring system (BMS). The EC protocols included predefined acceptance criteria and were approved by QA prior to execution.

User Requirement Specification

Systems, instruments and equipment procured and installed at (b) (4) were selected as off-the-shelf items to align with user requirements. Utilities such as the LN2, CO2, air-handling units (AHUs) and purified water systems were designed, fabricated, and installed according to URS. IQ verified and documented that all aspects of direct impact systems (facility, utility, or equipment) that can affect product quality were installed in accordance with approved specifications and user requirements. OQ verified and documented that all aspects of direct impact systems (facility, utility, or equipment) that can affect product quality were operating as intended throughout all anticipated ranges. Once the results of the OQ execution were reviewed and approved, the execution of the approved PQ was able to commence. PQ verified and documented that all aspects of direct impact systems (facility, utility, or equipment) that can affect product quality performed as intended and met predetermined acceptance criteria. A family approach or grouping strategy was adopted for the PQ of equipment that were identical (make and model) and that successfully met the same operational qualification acceptance criteria. PQs were performed in accordance to preapproved protocols.

Periodic Review and Requalification

Periodic system reviews are conducted to ensure that the process, product, systems, and facility remains in a qualified state. The evaluation considers the impact of cumulative changes, historical performance, and alignment of the existing validation with current standards and regulatory guidelines. A determination as to the need to perform requalification or supplemental validation will be assessed as part of the periodic review.

b. (b) (4) Contamination Control

Kite has implemented a risk-based control strategy to establish and maintain a controlled aseptic processing environment for the manufacture of KTE-C19 at (b) (4). The strategy includes a combination of discrete design, operational, and testing control elements including:

- Vendor qualification and management programs for suppliers of critical materials and sterile components
- Facility and equipment design, qualification, maintenance and cleaning programs
- Validation of the aseptic manufacturing process, including associated equipment and materials
- Implementation of appropriate product storage conditions and final container closure integrity assessments
- Quality system elements including batch disposition, change control, deviation management, corrective-action preventive action (CAPA) plans, and management review

In addition to the above controls, each dose of KTE-C19 is tested for endotoxin and sterility as part of the batch release process.

Personnel Monitoring

Personnel monitoring is performed on a lot-by-lot basis, and trends are examined on a periodic basis. Specifically, personnel operating in ISO (b)(4) are monitored at defined critical steps throughout operations. In addition, QC maintains a database of personnel monitored, excursions, and identification of microbial isolates.

Gowning Strategy and Qualification

Personnel are required to don appropriate garments and equipment for personal protection and hygiene per approved procedures. According to Kite, the level of gowning is equivalent to the required level of microbial and particulate control for the manufacturing process. Personnel flow is controlled and access to manufacturing areas is restricted to designated personnel and badge controlled.

The locker rooms are CNC and contain scrubs for clean room suites. Personnel don the scrubs prior to entering the ISO (b)(4) gowning room. Kite illustrated Facility gowning flow in the Gowning Flow Diagram and the stages are summarized below.

- First-stage gowning is required for all ISO (b)(4) areas and is donned upon entering an interlocking ISO (b)(4) gowning room. Personnel wear (b) (4)
- Second-stage gowning is required for all ISO (b)(4) areas and is donned upon entering an interlocking ISO (b)(4) gowning room. Second-stage gowning consists of a (b) (4). All gowning for the ISO (b)(4) area is sterile. Upon leaving the ISO (b)(4) rooms, personnel exit through an interlocking degowning room.
- Third-stage gowning is required in the ISO (b)(4) BSC. Operators don (b) (4)

(b) (4) for processing.

Aseptic Gowning Qualification includes training on the required procedures, (b) (4) initial gowning qualification tests, and personnel monitoring. Personnel must complete all requirements listed below before being granted access into the ISO (b) (4) and ISO (b) (4) production area.

1. Standard Operating Procedure (SOP) Training, including SOPs covering: 1) Personnel Protective Equipment, 2) Flow of Personnel, Materials, Product, and Waste, 3) Aseptic Gowning Qualification, and 4) Personnel Gowning and Degowning in the Clean Room
2. Aseptic gowning classroom training
3. At least 1 gowning practice with a qualified trainer prior to the qualification testing
4. While being escorted by qualified personnel, perform (b) (4) consecutive initial gowning qualification tests.

Once the individual passes (b) (4) consecutive aseptic gowning plating events, they are considered qualified in aseptic gowning.

Review Assessment / Comment: Standards practices for prevention of cross-contamination and bioburden control appear to be in place. No objectionable finding noted.

Facility Cleaning and Disinfection

Cleaning of the (b) (4) GMP facility is performed per an approved procedure that describes the cleaning for ISO-classified cleanrooms and CNC spaces, including the QC labs, warehouse, and locker rooms. The cleaning regimen consists of a (b) (4) cleaning program as follows:

Area
Horizontal surfaces
Floors
Walls/Windows
Ceilings
Commonly touched areas (e.g., door handles)
Biosafety Cabinets
Equipment exteriors
Pass-throughs

(b) (4)

In areas where product processing occurs, additional cleaning is required between specified unit operations and patient lots. The rationale for cleaning frequencies takes into account the risk of product exposure to the environment and personnel and the type of manufacturing performed in the space. The facility design, adjacent room classifications, and surfaces that can serve as a vehicle for microbial ingress were also considered.

Kite uses qualified disinfectants in rotation, including the use of a sporicidal agent on a (b) (4) basis. The preparation of the solutions as well as the method of cleaning are described in an approved procedure and documented in associated checklists by trained personnel. The disinfectants currently qualified for use in (b) (4) are:

(b) (4)

Biohazardous Waste Management and Spill Handling

Kite illustrated the flow of waste through (b) (4) in the Waste Flow Diagram. All employees who handle biological waste are trained regarding the proper segregation, handling, packaging, labeling, storage, and treatment of biological and biohazardous waste, including the following:

- (b) (4)

Biohazardous waste spills are cleaned using (b) (4) with a minimum of (b) (4) contact time.

Retroviral Vector Spill Containment and Cleaning

Manufacturing within the (b) (4) facility is conducted using a (b) (4) retroviral vector (b) (4) Vector) encoding an anti-CD19 CAR. The (b) (4) Vector is (b) (4) prior to use in manufacturing, the vector is transported throughout the facility in (b) (4). In the event of a spill, the staff follows approved procedures to contain, disinfect, and clear the vector from the area.

Review Comments/ assessment: Cleaning and disinfection practices appear to be adequate for their intended use. No objectionable finding noted.

c. (b) (4) HVAC Systems

HVAC systems serving the cleanrooms, labs, warehouse, administrative, offices, and support spaces include the following:

- Air handlers
- Rooftop packaged unit
- Exhaust fans
- Chillers
- Gas-fired boilers
- Chilled water and hot water pumps

Air handlers and exhaust fans are located on the roof. The chillers, boilers, pumps, and associated hydronic equipment are located in the equipment yard. Each manufacturing suite is supplied with a (b) (4) and pressure cascades are in place for product protection. All the manufacturing suites and media preparation rooms are classified as ISO (b) (4) through dynamic testing. The ISO (b) (4) manufacturing suites and ISO (b) (4) manufacturing corridor, gowning, kitting, de-gown, and janitor rooms all meet the requisite minimum numbers of air exchanges per hour based on their classification.

All the manufacturing rooms are temperature controlled at (b) (4) and the thermostat is located in the return air duct. Relative humidity is also continuously monitored but not controlled.

The AHUs serving the manufacturing rooms have a (b) (4) pre-filter section, chilled-water cooling coil, hot-water heating coil, and (b) (4) final filter section. Terminal HEPA filters in the rooms are either (b) (4) and have an efficiency rating of (b) (4)

Air-Handling Units in (b) (4) are as follows:

(b) (4)

The building monitoring system (BMS) controls the building environment and air quality to achieve temperature, relative humidity, and differential pressures that support a clean room environment.

ISO Classification, Differential Pressure, and Airflow

Kite illustrated the classifications of rooms in (b) (4) in the Floor Plan Block Diagram and their associated differential air pressures in the Room Pressurization Diagram. The HVAC systems provide a room pressurization cascade with appropriate pressure differentials, minimizing the potential for contamination, cross-contamination, and product migration. Pressure differential of at least (b) (4) is maintained between adjacent areas of different classification and pressure differential of at least (b) (4) is maintained between adjacent areas of the same classification for containment and to protect from cross-contamination.

The facility design includes airlocks with cascading pressures for gowning and material transfer rooms into the manufacturing suites. Interlocking pass-through windows are used for flow of kits, QC samples and final product. The media preparation room has an additional material pass-through for the (b) (4) materials. The pass-through located between the (b) (4) is used to transfer QC samples. Airlock doors are electronically interlocked to allow only one door to open at a time with emergency abort buttons and door status lights. (b) (4) product is introduced to the product within the ISO^(b) BSCs within the (b) (4).

Environmental Control and Monitoring

According to Kite, PQs of the manufacturing areas were performed under preapproved protocols which included assessments in both static and dynamic conditions. PQs of clean rooms were performed to assess bioburden risks in the non-aseptic and the aseptic areas as well as to confirm area classifications.

Environmental monitoring includes continuous monitoring and control of the HVAC system, quantification of particulates in specified areas of the facility, and assessment of microbiological bioburden in all controlled areas, including ISO^(b) BSCs. Results from environmental monitoring are compiled on a regular basis and analyzed for any trends that may require attention or modification to existing facilities components or procedures.

Environmental Sampling Locations

Environmental sampling locations with the highest microbiological risk to the product and process are a critical part of the environmental monitoring system. Evaluation of optimal sample selection locations includes:

- Sites near areas where product or product contact surfaces are exposed
- Sites where activity may spread contamination (e.g. frequently touched surfaces)
- Sites representing difficult-to-clean areas
- Other surface types (i.e. walls, floors, equipment, doors, etc.) representing potential contamination sources

The sampling sites for environmental monitoring at the (b) (4) facility were selected to maximize the potential for detection of product contaminants that can adversely impact the integrity of the aseptic manufacturing process for KTE-C19.

Air Monitoring for Non-viable and Viable Particulates

Non-viable airborne particulates are monitored (b) (4). Active sampling for viable airborne particulates is performed using either a (b) (4) (b) (4). Passive sampling for viable airborne particulates are routinely used to qualitatively assess the aseptic environment. Non-viable and viable air monitoring is performed during manufacturing in the ISO (b) (4) environment.

Surface Monitoring

Surface monitoring is performed in the ISO (b) (4) ISO (b) (4) and ISO (b) (4) areas using (b) (4). The surface monitoring of ISO (b) (4) environments includes surfaces that directly contact sterile parts or products and is conducted after completion of operations and prior to cleaning of the BSC surfaces.

Action/alert limits/levels

The alert levels and action levels for the environmental monitoring system are established as per the FDA Aseptic Processing Guideline and (b) (4). Trending analysis is performed and results are reviewed on a regular basis.

Review Comments/Assessment: The following IRs were sent to the Firm:

1. In reference to the Kite (b) (4) facility, please provide a summary of the alert and action limits for Environmental Monitoring that you have established for all room classifications.

d. (b) (4) Utilities

Carbon Dioxide System

CO₂ is required for (b) (4) in the manufacturing areas (Rooms (b) (4)), the QC labs, and other support spaces. It is supplied as (b) (4) grade from an on-site (b) (4) located outside the building. A vaporizer delivers CO₂ gas to the point of use in (b) (4).

Liquid Nitrogen System

Liquid nitrogen is required for (b) (4) and in Cry-Packaging (Room (b) (4)). It is supplied as (b) (4) grade from an on-site (b) (4) located outside the building. Distribution piping is (b) (4), with the required check valves, relief valves, and cryo-vent assembly. Oxygen depletion monitoring and alarms are provided.

Purified Water System

Water from the (b) (4) utility system is (b) (4) grade Purified Water and is used for facility cleaning and QC lab water supply. Purified water is not used in any product processing steps or on product contact surfaces. The water is produced by reverse osmosis and deionization. It is supplied from a (b) (4) system located in the mechanical equipment room and the distribution loop includes the cleaning supply closet located in the ISO (b) (4) corridor. The system is monitored for microbial and chemical contaminants. The Building Management System (BMS) controls and monitors hot and chilled water equipment status.

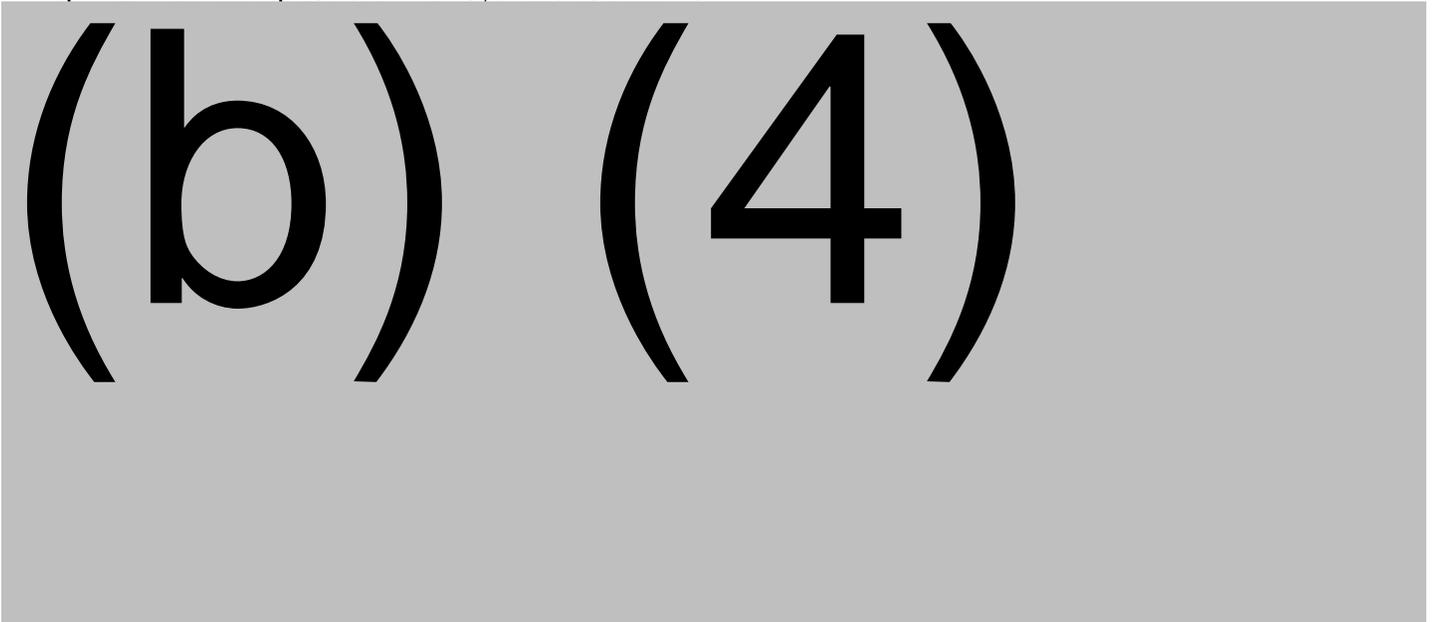
Review Assessment / Comments: The purified water system is not used for buffer or product preparation. No objectionable findings noted.

Stand-By Generator

The emergency generator (approximately (b) (4)) is a (b) (4) unit located outside the building. It includes an automatic transfer switch to maintain electrical power to all critical equipment.

e. (b) (4) Computer and Software Systems

The computerized control systems that record and archive GMP data have been verified and documented to comply with 21 CFR Part 11 requirements. Systems have been validated and, according to Kite, the depth and scope of validation depended on the complexity of the computerized system. The major computerized systems used in (b) (4) consist of both site-specific and enterprise software systems as follows:



The building monitoring system (BMS) controls the building environment and air quality to achieve temperature, relative humidity, and differential pressures that support a clean room environment. The control system architecture consists of BMS servers, central computer

workstations, control panels, a chiller interface panel, and a boiler interface panel. All control points for the air handling systems are programmable through the control system. The control system utilizes electric actuators on all control valves and dampers. The control panels are connected to back-up power supply and include uninterruptible power supply devices to maintain programmed sequences and set points upon restoring normal power. The equipment on the BMS are:

System	BMS Function	Equipment
HVAC	Controls and monitors HVAC equipment status	(b) (4)
Hot Water	Controls and monitors Hot Water equipment status	
Chilled Water	Controls and monitors Chilled Water equipment status	

The equipment monitoring system (EMS) is used to monitor operating parameters for the facility, equipment, and GMP utility systems. Equipment on the EMS are:

System	EMS Function	Equipment
GMP Utilities	Monitor, alarm, and trend	(b) (4)
Rooms	Monitor, alarm, and trend	
Equipment	Monitor, alarm, and trend	

The EMS notifies personnel of any excursions via workstation notifications, audible and visual alarms, and phone calls.

f. KTE-C19 Product Contact Components

All process and product contact material in the entire KTE-C19 process is (b) (4) by the vendor and released by Kite Quality prior to use. In addition, the single-use-systems have been categorized based on risk and high risk materials have been tested for extractables.

According to Kite, materials may be replaced with alternatives of the same type and grade following completion of appropriate testing, documentation and/or validation, as well as supplier approval and material qualification.

A risk priority number was determined for each process material based on (b) (4) steps were categorized as high risk. The high risk product contacting consumables used in the manufacture of axicabtagene ciloleucel are:

(b) (4)

g. KTE-C19 Process Validation

According to Kite, the combined knowledge from product development, process development, process characterization, and clinical manufacturing lots was used to establish the criticality of process and performance parameters and the overall commercial manufacturing control strategy. This control strategy and an understanding of process variability then led to the establishment of the PPQ strategy. Kite determined the number of PPQ runs required to qualify the axicabtagene ciloleucel process from process knowledge and statistical analysis of donor-to-donor variability in (b) (4), which is the critical product quality attribute that determines dose. Statistical analysis of data from (b) (4) available donor full-scale Good Manufacturing Practice (GMP) lots with an acceptable variability of (b) (4) and a power of (b) (4) gave a PPQ sample size of (b) (4) lots. Apheresis material from donors was collected for the PPQ campaign. Results for the (b) (4) consecutive PPQ lots are compared with the prospectively established PVAC. PVAC were generated using a tolerance interval approach with a 95% confidence interval (CI) and 95% or 99% proportion based on data obtained using at-scale lots from (b) (4) healthy donors and (b) (4) clinical subjects.

The process validation campaign includes the following individual PPQs:

- Axicabtagene ciloleucel manufacturing process, including (b) (4) as an in-process intermediate
- (b) (4)

All PPQ studies were performed using approved protocols, manufacturing procedures, and standard operating procedures. (b) (4)

(b) (4)

PPQ are as follows:

(b) (4)

2 Pages Determined to be Not Releasable: (b)(4)

(b) (4)

The Final Product Attributes conformed to Product Specifications as follows:

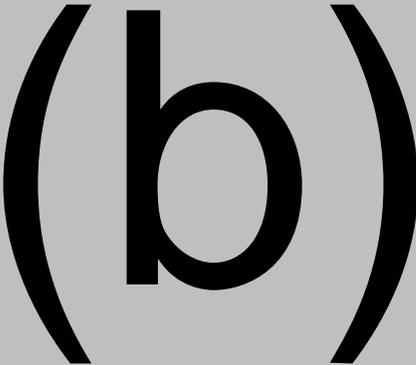
Test	Method	Method Number	Acceptance Criteria
Appearance	Visual inspection	SOP-0317-QC3	White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no visible foreign particles.
Identity	(b) (4)	TM-0009-QC3	(b) (4)
Dose	Viable cell count/Anti- CD19 CAR expression	TM-0005-QC3 TM-0001-QC3	(b) (4) anti-CD19 CAR T cells/kg (maximum allowable dose: 2×10^8 anti-CD19 CAR T cells)
Potency	Cell viability	TM-0005-QC3	(b) (4) viability
	Anti-CD19 CAR expression	TM-0001-QC3	(b) (4)
	(b) (4)	TM-0002-QC3	(b) (4)
Purity	Endotoxin	TM-0004-QC3	(b) (4)
	(b) (4)	TM-0010-QC3	(b) (4)
	Gentamicin	TM-0033-QC3	(b) (4)
Microbiological tests	Mycoplasma (b) (4) method	TM-0006-QC3	(b) (4)
	Sterility	TM-0007-QC3	No growth
Testing for Retrovirus	RCR by (b) (4)	TM-0008-QC3	(b) (4)
	RCR (b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

All PPQ lots met final product release specifications.

Review Assessment/Comments: Kite reports all parameters and acceptance criteria were met with one minor deviation. No objectionable findings noted.

h. KTE-C19 Media Simulations

Kite has relied upon and incorporated elements outlined within the US FDA’s Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing Guideline (FDA 2004) into the aseptic manufacturing control strategy for KTE-C19. Due to the nature of the manufacturing process for KTE-C19, sections within Chapter IX (Validation of Aseptic Processing and Sterilization) and Appendix 3 (Processing Prior to Filling and Sealing Operations) have been adapted by Kite in order to most effectively be applied to the aseptic process being utilized. Product lots are unique to a single patient, and a number of differences in aseptic processing conditions exist between conventional aseptic filling operations and the manufacturing process for KTE-C19, as summarized:

Item	Conventional Aseptic Filling	Aseptic Process for KTE-C19
Source material		
Aseptic Filling Line Operations		
Batch Size		
Product Conditions Post Container Closure		
Sampling for Sterility Testing		
Process Simulations (Media Fills)		

In particular, Kite notes that unlike conventional aseptic filling, every dose of KTE-C19 is tested by validated sterility and endotoxin tests prior to product release. According to Kite, the highest risks in the aseptic process for KTE-C19 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)(1)} BSC. Therefore, Kite is utilizing an aseptic control strategy that includes execution of media simulations as part of the initial aseptic process validation (APV), and also 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-C19.

The manufacturing process for KTE-C19 includes several manipulations and connections that are performed in either ISO ^{(b) (4)} or ISO ^{(b) (4)} areas as follows:

(b) (4)

Aseptic operations, when necessary, are performed in ISO ^{(b) (4)} areas and include ^{(b) (4)}

^{(b) (4)}. Closed operations are performed in ISO ^{(b) (4)} areas and include ^{(b) (4)}. All of the operations were included in the APV and representative ISO ^{(b) (4)} operations are performed as part of the AOQ program.

Aseptic process validation at ^{(b) (4)} was performed as part of the initial qualification of the manufacturing process, equipment, and facility. Prior to APV, an assessment was made of the manufacturing process, materials, containers/closures, and interventions made during routine manufacturing in order to assure that the APV would reflect the manufacturing process as it occurs in practice. Interventions (both inherent/routine and corrective) were included as an integral part of the APV. Inherent intervention included operator change out/shift change and corrective interventions included a ^{(b) (4)} error during ^{(b) (4)}, compromised equipment, and repeat sampling for sterility testing. The interventions were as follows:

(b) (4)

(b) (4)

As described in APV protocol VP-0022, the validation study included process simulations designed to encompass all KTE-C19 manufacturing steps by utilizing APV records based on the manufacturing production records. (b) (4) was used to replace apheresis starting material, buffers, media, and final formulated product. The numbers and types of aseptic manipulations were considered to be more important than duration of operations with respect to potential for contamination (for example, contamination is unlikely to be introduced during days of (b) (4)). During each APV run, KTE-C19 manufacturing process was performed, and mimicked as close as possible to the actual process. All critical steps (aseptic manipulations) and potential interventions are captured in the APV batch records MPR-0020 and MPR-0021.

During the APV runs, process interventions were performed to simulate the operational challenges and the worst case situations. The resulting samples and all the in process samples were evaluated for microbial growth after incubation.

Below are the interventions that are tested during the APV runs:

- (b) (4)

The APV is performed over a period of about (b) (4)

(b) (4)

(b) (4)

(b) (4)

Aseptic Operator Qualification

Kite's AOQ program includes both classroom and lab-based hands-on training, followed by qualification via process simulation. The operator qualification process simulation has been designed to include all types of aseptic manipulations used in the manufacturing process for KTE-C19; performed over approximately (b) (4). This represents a worst-case condition for an operator as it requires the execution of a series of operational events back to back which normally occur over the process duration, with the highest risk operation performed last.

The design of the AOQ includes individual groups of exercises performed in sequence for each AOQ run and the entire qualification period is observed for compliance to procedure, with exceptions documented. Each operator must successfully perform individual AOQ three consecutive times using media incubated and held as described in the Aseptic Processing Guideline and no detectable contamination can be observed in order to be considered qualified

to perform the process. The execution of each AOQ is performed and documented per an AOQ Batch Record.

Kite's AOQ program includes aseptic operator requalification (b) (4) per year for every operator. The requalification requires successful execution of the formulation portion of the AOQ process simulation. This requalification interval and approach is justified because: 1) operators are routinely performing aseptic operations, with their performance monitored through the EM program and individual batch test results, and 2) the simulation of the formulation step represents the highest-risk unit operation. In the event of a requalification failure, operators are required to undergo the full AOQ in order to be requalified to perform the manufacturing process for KTE-C19. Aseptic operator requalification will be scheduled in a manner to ensure the qualifications occur multiple times over the course of a year within the facility.

Review Assessment / Comments:

No deviations were reported. Kite will be performing AOQ on an (b) (4) basis for all personnel performing the manufacturing tasks. Kite did not provide a justification for the selection of the specific BSCs used in the studies.

The following information request was sent to the Firm:

In reference to APV at (b) (4) Facility:

1. How did you select the (b) (4) (Suite (b) (4) BSCs and the (b) (4) BSC (Suite (b) (4) for use in your Aseptic Processing Validation? Was a risk assessment performed to identify the specific BSCs used in the initial studies? If so, please provide the risk assessment.
2. Do you plan to include the use of the other BSCs in subsequent AOQs? If so, please provide your general plan. If not, please provide a justification.
3. In reference to production at Kite: please provide an overview of how you have verified that you will be able to produce at full capacity (i.e. all BSC in use at the same time in (b) (4) Production suite) without compromising product quality or safety.
 - a. Please confirm that all BSCs in Suites (b) (4) are qualified for use in commercial manufacturing.

i. KTE-C19(b) (4)

(b) (4)

(b) (4)

j. KTE-C19 Container Closure

The primary container closure system intended for distribution of axicabtagene ciloleucel is a commercially-available (b) (4) cryostorage bag specifically designed for storage of blood and blood components, the (b) (4). It is FDA cleared as a Class II medical device, specifically as an “empty container for the collection and processing of blood and blood components.”

Component	Description	Supplier Name and Address	510(k) Number (Regulation/ Classification Product Code)
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(b) (4)

Kite receives the (b) (4) with an attached tubing set that is used in the aseptic filling process. Once filling is complete, the tubing is (b) (4), leaving the final filled cryostorage bag containing axicabtagene ciloleucel. Kite provided a schematic diagram of the (b) (4) cryostorage bag and a vendor certificate of analysis in the submission.

The Kite Specification for (b) (4) is as follows:

(b) (4)

(b) (4)

The suitability of the primary container closure system has been assessed with respect to extractables and leachables and container closure integrity. The (b) (4) bag has been used during the clinical development of axicabtagene ciloleucel and a (b) (4) version of this bag (model (b) (4) manufactured by the same company (b) (4)) using the same materials, has also been used in long-term and accelerated stability studies of axicabtagene ciloleucel. Compatibility of axicabtagene ciloleucel with the primary container closure system is therefore considered to be demonstrated via long-term and accelerated stability studies.

Secondary Packaging

The secondary packaging for axicabtagene ciloleucel is an aluminum cassette, designed to protect the product during storage, shipment, and handling. Information on the aluminum cassette is as follows:

Component	Description	Supplier Name and Address
(b) (4)	Aluminum Cassette Dimensions: 192 × 152 × 11 mm	(b) (4)

Kite provided a schematic Diagram of Aluminum (b) (4)

Container Closure Integrity

The primary container closure system for KTE-C19 is a cryostorage bag specifically designed for storage of blood and blood components. The (b) (4) is commercially-available and has been cleared by the US FDA under 510(k) # (b) (4) It has been used during the clinical development of KTE-C19 and a (b) (4) version (model (b) (4) manufactured by the same company using the same materials, has been used in long-term and accelerated stability studies.

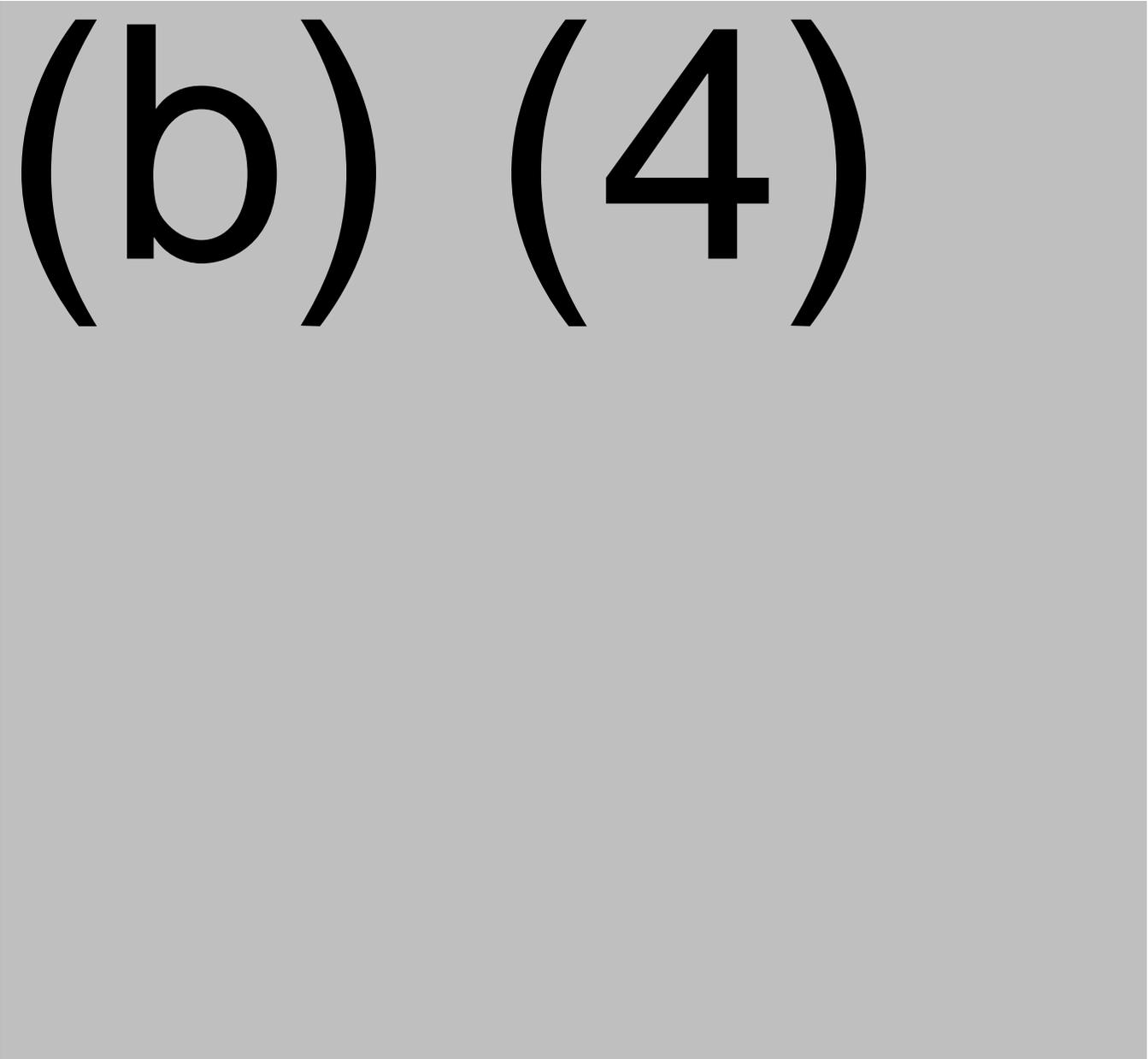
Kite states that the current (b) (4) when establishing the inherent integrity of a container closure system. Therefore, a (b) (4) was developed specifically for use with the (b) (4) cryostorage bags that make up the container closure system for KTE-C19 and for stability samples, respectively. (b) (4)

(b) (4)



Kite qualified and executed the ^{(b) (4)} method to detect ^{(b) (4)} manufacturing and closure defects using a (b) (4) to simulate a defect. Following a product life-cycle approach, ^{(b) (4)}-based container closure integrity (CCI) testing was developed, qualified, and executed, in two separate phases.

(b) (4)



(b) (4)

Review Assessment/ Comments: Evidence of completed CCIT study is provided. Kite reports no leaks observed in any of the test samples. E/L studies are deferred to Product Office. No objectionable findings noted.

k. KTE-C19 Drug Product Stability

Kite investigated the stability of KTE-C19 has been via long-term, accelerated, and stress studies conducted in accordance with (b) (4) KTE-C19 lots manufactured from healthy donor apheresis material at Kite's commercial manufacturing facility ((b) (4) have been studied in long-term stability studies. KTE-C19 lots from clinical manufacturing facilities ((b) (4)) have been studied in long-term and accelerated studies. In addition, stress testing (i.e., (b) (4)), in-use stability, stability of patient lots (i.e., from clinical-trial subjects), stability of (b) (4) and maintenance of sterility have been assessed. All lots used in these studies were manufactured using the (b) (4) manufacturing process intended for commercial use.

A formal stability program is ongoing in accordance with (b) (4) guidelines using (b) (4) lots of KTE-C19 held at recommended ($\leq -150^{\circ}\text{C}$) and/or accelerated ((b) (4)) storage conditions. (b) (4) lots in the stability program were manufactured at (b) (4) (tested at -150°C only). All stability studies used samples stored in a (b) (4) version of the primary container closure used for commercial KTE-C19 (i.e., (b) (4)). These cryostorage bags are constructed of the same materials, are made by the same manufacturer, and were selected for stability studies so that multiple time points could be evaluated for the same lot throughout shelf life. Appropriate justification for the use of the (b) (4) volume bags has been established based on consideration of material composition, dimensional analysis, and freezing profiles relative to the full-scale bags. Of the (b) (4) lots, four lots were studied out to 6 months, the other (b) (4) lots (PPQ lots (b) (4) Bags) are slated to be studied to (b) (4) . At the time of the submission, all (b) (4) lots were evaluated at the 6 month time point.

(b) (4) lots in the formal stability program were manufactured at (b) (4) using donor apheresis material.

Kite based the evaluation of KTE-C19 on a subset of the lot release tests. (b) (4) were also monitored on stability, and T-cell phenotype was assessed in some early studies. Parameters were selected based on their potential to monitor features of the product that

may be susceptible to change or influence its quality, safety and/or efficacy. In some cases, analytical methods used in early studies were replaced with improved methods in subsequent studies (e.g., (b) (4) was replaced with (b) (4) for determination of cell viability, and the reagents used for anti-CD19 CAR expression by (b) (4) (b) (4) was changed from (b) (4) . The tests performed and methods were as follows:

Stability Test	Stability Test Method	Commercial Acceptance Criteria
Appearance	Visual	White to red, including shades of white, light yellow, and orange. Clear to opaque liquid with no visible foreign particles.
(b) (4)	(b) (4)	N/A (Report results)
(b) (4)	(b) (4)	N/A (Report results)
Cell viability	(b) (4)	(b) (4)
Anti-CD19 CAR expression	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)
(b) (4)	(b) (4)	N/A (Report results)
Sterility	(b) (4)	No growth

All stability results are tabulated against both the protocol acceptance criteria and the commercial acceptance criteria, with results based on earlier test methods noted where appropriate.

Long-term (up to 12 months at $\leq -150^{\circ}\text{C}$) and accelerated (up to (b) (4) months at (b) (4)) stability data are available from (b) (4) lots of axicabtagene ciloleucel manufactured at the commercial manufacturing facility ((b) (4)) and from (b) (4) lots manufactured at facilities used for clinical-trial production. Results from samples stored at the accelerated condition support axicabtagene ciloleucel stability during unintended temperature excursions that could occur during long-term storage. With the exception of 2 results at (b) (4) months that were slightly (b) (4) vs specification upper limit of (b) (4), all long-term stability results met the commercial specification. Axicabtagene ciloleucel produced at the commercial and clinical facilities demonstrate similar stability profiles.

Stress testing has confirmed the ability of tests used in the stability program, particularly cell viability and potency by (b) (4), to be stability indicating. In-use stability testing has confirmed that thawed axicabtagene ciloleucel is stable for at least 3 hours at room temperature. While most stability studies utilized axicabtagene ciloleucel manufactured from donor apheresis material, patient-derived product has also confirmed stability for up to 6 months when stored at $\leq -150^{\circ}\text{C}$. Axicabtagene ciloleucel that has been (b) (4) step has been shown to be stable, and the full-scale container closure system has been confirmed to maintain sterility.

For Post approval stability, Kite proposes (b) (4) per year, sourced from a healthy donor and manufactured and filled into (b) (4) bags at (b) (4) to be placed on stability as follows:

Storage Condition	Study Type	Time Points (months)
≤ -150°C	Long-term	Lot Release 1, 0 2, 3, 6, 12, (b) (4)

Testing at each interval will include Appearance, Cell viability, Anti-CD-19 CAR expression, Potency (same acceptance as in the ongoing studies) plus Container Appearance (Sealed bag with sealed connections and no visible leaks or cracks)

Kite Pharma commits to extend the expiry only after satisfactory stability data have been obtained per the above protocol and with appropriate regulatory notification.

In addition to the stability studies in the (b) (4) bags, a separate stability program will be performed to affirm that the full-scale cryostorage bags used for commercial doses provide suitable protection from microbial contamination. (b) (4) of donor-derived axicabtagene ciloleucel, filled into the commercial container closure ((b) (4)) will be placed on stability (b) (4). For these studies, appearance will be monitored and sterility testing will be performed at the end of the currently approved expiration period.

Stability testing will continue until data for at least (b) (4) independent axicabtagene ciloleucel patient doses are gathered for up to (b) (4).

Review Assessment/ Comments: Kite is proposing an expiry of 12 months for axicabtagene ciloleucel when stored at the recommended storage condition of ≤ -150°C. However, Kite has reported results up to six months only for batches produced at (b) (4). Kite reports no sterility OOS to date. No objectionable findings noted. I defer the review of the Drug substance / product characteristics to the Product Office Specialists.

I. KTE-C19 Shipping Validation

Vapor Phase Liquid-Nitrogen Shipper

Packaging and Shipping

Frozen finished product is transferred to the Cryo-Packaging Room and prepared for shipment per approved procedures. These procedures describe the process of receiving, releasing, and preparing the vapor-phase LN2 shipper and packaging and shipping final product from Kite. All outbound frozen finished product is shipped from the shipping area in (b) (4) vapor-phase LN2 shipping containers.

A vapor phase liquid-nitrogen (LN2) shipping container is used to ship axicabtagene ciloleucel to the treatment site. A brief description, including model number and supplier, is as follows:

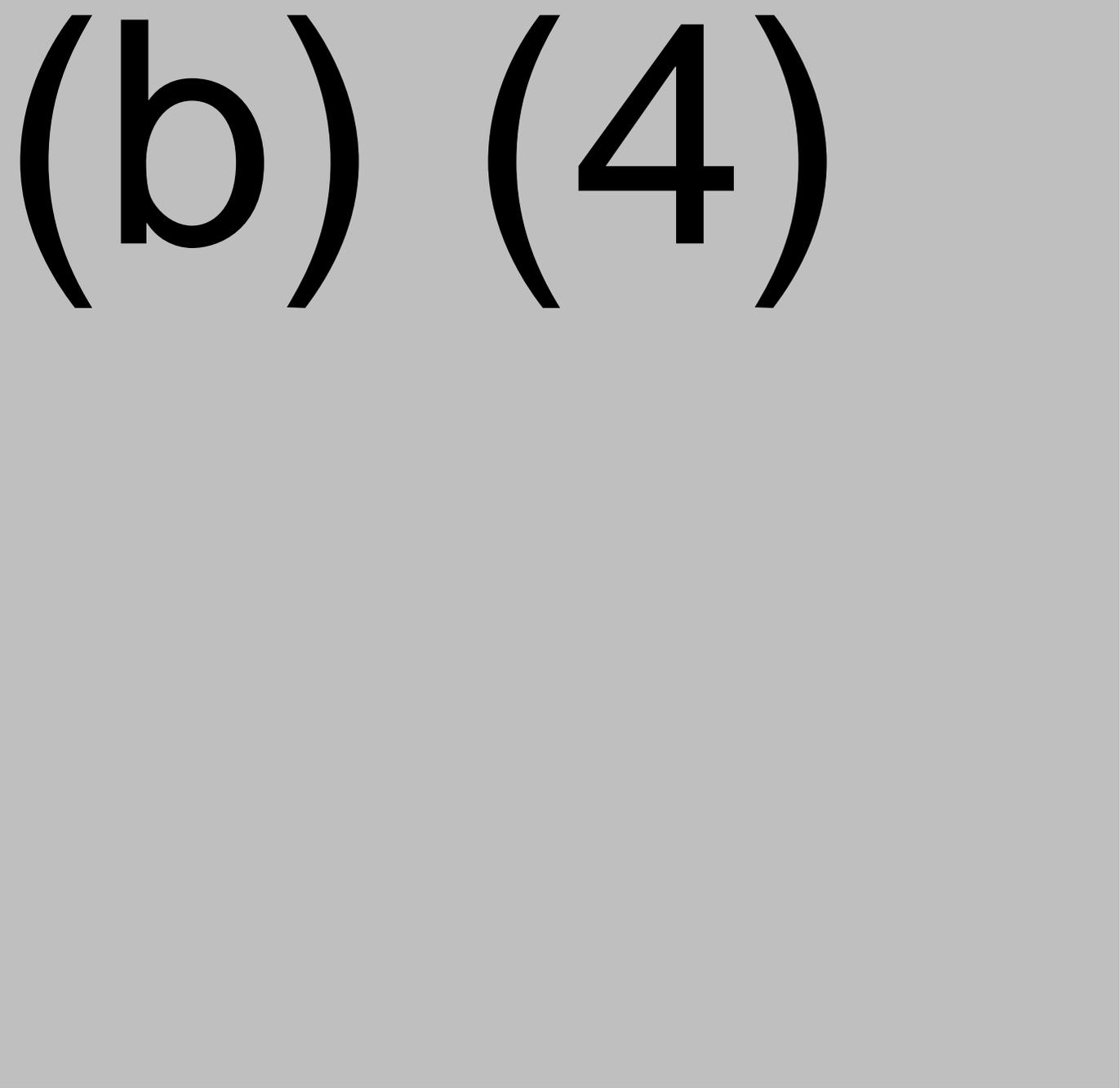
Component	Description	Supplier Name and Address
(b) (4)	Vapor Phase liquid-nitrogen shipper composed of a protective plastic outer container that incorporates pressure release valves, and an inner metal dewar	(b) (4)

Kite provided a schematic Diagram of the exploded assembly of the shipping container, the final packaging configuration is the vapor phase LN2 shipper including an aluminum cassette containing axicabtagene ciloleucel final product in the (b) (4) bag.

For Shipping validation, Kite included (b) (4)

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(b) (4)

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(b) (4)

According to the data provided in the submission, all 3 shipments met the acceptance criterion of maintaining internal temperature $\leq -150^{\circ}\text{C}$ during transit. Furthermore, following shipment, the axicabtagene ciloleucel contained in all 3 shipments met the protocol acceptance criteria (and proposed commercial specifications) for cell viability and potency by (b) (4), and the results were comparable to corresponding control samples held in a freezer in Santa Monica, CA.

Review Assessment/ Comments: It appears that temperature extremes were challenged and maximum transports times were established. According to Kite, in commercial practice, a temperature monitoring device will be included in each shipment of axicabtagene ciloleucel, so any temperature excursions can be noted and evaluated. This appears to be a good practice allowing for continuous verification. Kite does not mention if physical testing such drop and vibration exposure were performed as part of the shipper qualification.

The following information request is being sent to the Firm:

1. Reference your qualification of the Kite Final Product Shipper (for axicabtagene ciloleucel): Was physical testing such as drop and vibration testing performed as part of your qualification study?

10. (b) (4) Facility

(b) (4)

20 Pages Determined to be Not Releasable: (b)(4)

(b) (4)

11. Inspection Considerations

Note: Line items below are hyperlinked to the applicable section of this review memo, as applicable.

- None