



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
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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 Addendum 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

This is the final DMPQ review memo; No more addendum reviews will follow.

I recommend approval of this application. At the ((b) (4)) and the Kite Pharma, Inc. El Segundo, CA 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 axicabtagene ciloleucel. 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 based on the completed development /qualification data and experience.

A PLI at the Contract Testing Facility, (b) (4) was waived on 26 Sep 2017.

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1. Amendments related to Review

- 125643/0.47 received 08 Aug 2017 to Information request sent 24 July 2017
- 125643/0.63 received 20 Sep 2017 to Information request sent 13 Sep 2017
- 125643/0.68 received 27 Sep 2017 to Information request sent 22 Sep 2017

2. Regulatory History

My primary review was completed and approved on 09/26/17. The following information request was sent to the Firm:

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:

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.

Memo Format

For reference, I left the original sections from the Primary Review that were related to the IRs. My original Review Assessment / Comments are provided at the end of review sections in a double lined box with the related Information requests (IRs). The IRs that were pending from the primary review were left in bolded text. A summary of the firm's response to that IR will immediately follow in italicized text. My assessment of the response will immediately follow in a double lined box.

3. Processing Equipment Overview (DP and DS)

<Begin original text from Primary Memo>

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



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 is 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)

* 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)

All equipment is cleaned, maintained, and calibrated, as appropriate, per 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 per 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

<End original text from Primary Memo>

Kite's Response

1. Table 1 provides the list of equipment (the equipment ID numbers, room numbers, and associated qualification numbers) used for the manufacture and storage of (b) (4) Vector. Highlighted cells reflect corrected and/or updated information for applicable equipment.

Table 1. List of equipment used in manufacturing process of (b) (4)

(b) (4)

2. Installation and Operational Qualification (IQ/OQ) protocols are executed for each of the (b) (4) units. Each unit has met the established acceptance criteria outlined in the protocol. Attached summary report (EQT-1027 QP-0372) provides an example of IQ/OQ assessments for one of the (b) (4) units.

From EQT-1027-QP-0372 Summary of IQ/OQ is as follows:

Installation Qualification included verification of:

- System Documentation
- Component Identification
- Software Identification
- Component Installation
- Utilities
- Fabrication
- Instrument Calibration

Operational Qualification included verification of:

- Standard Operating Procedure
- General Operations and Screen Navigation
- Alarm and Interlock Testing
- Traceability Testing
- Process Recipe Configuration
- (b) (4) Protocol Minimum and Maximum Operational Range Functionality
- (b) (4) Protocol Minimum and Maximum Operational Range Functionality
- (b) (4) Protocol Minimum and Maximum Operational Range Functionality
- Test Instrumentation Calibration

Review Comment/ Assessment: The equipment table has been revised to reflect the most current and accurate equipment used in the RVV process; the use of this equipment was observed during the PLI at the facility (b) (4) . The IQ/OQ of the (b) (4) appears standard for off-the-shelf (b) (4) machine. Kite states that each unit was qualified individually. No objectionable findings noted.

4. Kite Pharma Facility TCF03

<Begin original text from Primary Memo>

(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. Per Kite, as production needs arise, the 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.**

<End original text from Primary Memo>

Kite Response:

The commercial manufacturing facility for axicabtagene ciloleucel ((b) (4)) consists of approximately (b) (4) of office, laboratory, manufacturing and warehouse space. The facility is in a general office, warehouse and light manufacturing zone. The facility, utility, manufacturing areas, and QC laboratory commissioning, qualification and validation activities have been completed with the exception of (b) (4) of the manufacturing suites. There are a total of (b) (4) manufacturing suites within (b) (4) and Suites (b) (4) have completed the necessary qualifications to become operational and are used for the manufacturing of axicabtagene ciloleucel. The (b) (4) additional suites located within (b) (4) (suites (b) (4)) are fully constructed and will be operational as product demand requires, and will be qualified per Kite SOP-0587. Facility and equipment CTD chapter, first paragraph (3.2.A.1, Section 1.1.1) has been updated to reflect this update.

Review Comment/ Assessment: Submission has been updated accurately. The Firm is aware that additional suites will be approved via subsequent filings. No objectionable findings

5. Warehouse Operations

<Begin original text from Primary Memo>

Warehouse operations 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 per 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.**

<End original text from Primary Memo>

Kite Response:

All materials used in the manufacturing of axicabtagene ciloleucel are provided by approved suppliers and qualified for use per approved procedures. Kite Pharma’s supplier qualification program is risk- based and defines the requirements for selection, qualification/approval and monitoring of external providers of materials and services. Controls such as audit of suppliers and release of material based on certificate of analysis and/or testing have been established.

Upon successful completion of Normal level testing for (b) (4) unique supplier lots, testing on incoming material is performed at a reduced level. Requalification at Normal level testing will be performed (b) (4) . Table 2 summarizes the Normal Level and Reduced Level testing parameters for all excipients, media preparation reagents, reagents and buffers. Upon completion of sampling, inspection, testing and verification of acceptable test results, materials are released to manufacturing per established procedure.

Note: In addition to the test requirements in Table 2, all GMP Materials received at Kite receive a General Quality Inspection per SOP-0408-QC3, which includes:

- *Verification that the material information aligns with supplier documentation and Kite specification.*
- *Verification that material was placed in the correct storage location.*
- *Verification that the material appearance matches the description.*

- *Verification that the primary package is intact.*

Table 2. Critical Raw Material Release Test Requirements

(b) (4)

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

(b) (4)

Materials Released with only Certificate of Analysis Verification

Table 3 provides a list of processing bags and single-use kits used in the process.

These materials may be released for manufacturing use upon completion of the General Quality

Inspection per SOP-0408-QC3, and Certificate of Analysis verification,

All process and product contact material in the entire process are (b) (4) by the vendor.

Sterility and endotoxin values reported on the vendor CoA's were verified during initial material qualification, and these results are also re-verified during (b) (4) re-qualification. In addition, the cell therapy final product is tested for sterility and endotoxin, and must meet release specifications.

Table 3. Materials Released with only Certificate of Analysis Verification

(b) (4)

Review Comment/ Assessment: It appears that most of the critical materials are normally tested, at minimum, for (b) (4). It appears that Kite has a reduced testing scheme established, a standard QC practice. Kite states that all process and product contact material in the entire process are (b) (4) by the vendor. For the single use items, sterility and endotoxin values are reported on the vendor CoA's were verified during initial material qualification, and these results are re-verified during (b) (4) re-qualification. In addition, the cell therapy final product is tested for sterility and endotoxin, and must meet release specifications. No objectionable findings noted.

6. (b) (4) HVAC Systems

<Begin original text from Primary Memo>

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 in the equipment yard. Each manufacturing suite is supplied with (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 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). 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

Per 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) 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) 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.**

<End original text from Primary Memo>

Kite Response:

The Environmental Monitoring alert and action limits for all the manufacturing areas used in the production of the axicabtagene ciloleucel at (b) (4) facility are summarized in Table 2.

Table 2. Summary of the alert and action limits for Environmental Monitoring for all room classifications at (b) (4)

(b) (4)

Review Comments/Assessment: Acceptance criteria is acceptable and standard. Kite appears to perform EM consistently during manufacturing activities. No objectionable findings noted.

7. KTE-C19 Media Simulations

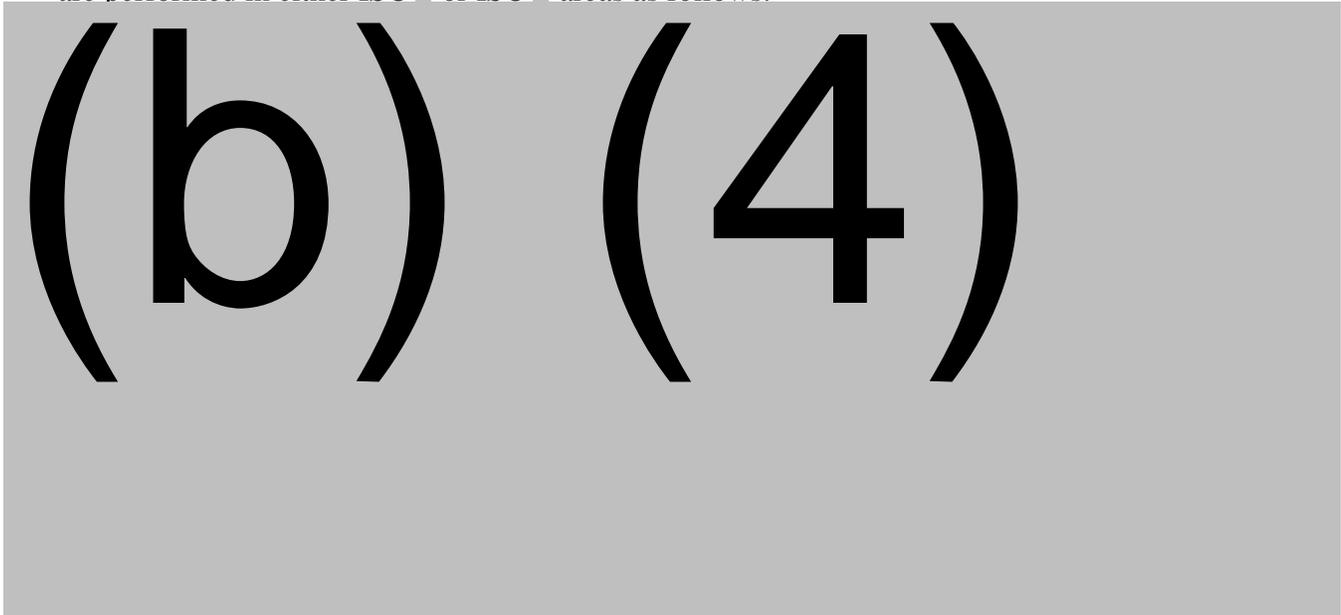
<Begin original text from Primary Memo>

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 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	(b)	(4)
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. Per 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) 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. Per 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:



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 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 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:



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. Kite considered the numbers and types of aseptic manipulations 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)

(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 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 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.**

<End original text from Primary Memo>

Kite Response:

- 1. The (b) (4) BSCs in suite (b) (4) and the (b) (4) BSC in Suite (b) (4) were selected randomly and no risk assessment was performed. As described in Section 3.2.A.1.4.3, Aseptic Process Validation, the BSCs used in the workstations in Room (b) (4) and Room (b) (4) are identical, and each had an I/OQ performed. All other equipment in each workstation, including a (b) (4) is likewise identical and organized in an identical manner within each workstation. Since each workstation is of the same layout and size, and the workstations in suite (b) (4) and the (b) (4) in Suite (b) (4) are distributed evenly throughout the suites, a Risk Assessment was deemed unnecessary to determine which BSCs to include in the APV.*

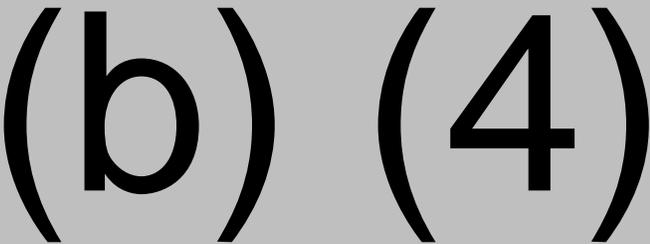
2. The BSCs used for AOQ are selected based on work station availability according to the production schedule. Since workstations are considered identical, AOQs can be performed in any work station. It is anticipated that other BSCs would be used for AOQ, due to the number of staff requiring qualification and requalification (b) (4)

Review Assessment/ Comments: To support their approach to aseptic process simulation studies, in a pre-BLA meeting package in April 2016, Kite highlighted some differences in aseptic processing conditions between conventional filling operations and the KTE- C19 process as follows:

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

Kite proposed that the differences in aseptic operating characteristics and testing approach of the KTE-C19 process as outlined above warranted a different perspective regarding the design and focus of process simulations as part of aseptic process validation. As an example, the (b) (4) facility design includes (b) (4) identical work stations and the KTE-C19 aseptic process is performed (b) (4) 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.

Kite Pharma relied upon FDA's *Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing (2004)*, and considered most of the guidance document to be directly applicable for the KTE-C19 process and operations, and that their practices meet those requirements. However, Kite determined that there are sections within the Guidance, specifically Appendix 3, *Processing Prior to Filling and Sealing Operations*, which they felt needed further interpretation to most effectively be applied to the KTE-C19 aseptic process due to its (b) (4) nature. Therefore, Kite proposed the aseptic control strategy described in the next table, which provides a step by step explanation of how Kite Pharma plans to address specific APG guidance requirements associated with Appendix 3, and provides a design and focus of process simulation as part of the process validation and is, per Kite, aligned with FDA aseptic guideline principles.

Item	Guidance Recommendation	Kite Pharma Approach/Rationale
1	When a product is processed aseptically from the early stages, the product and all components or other additions are rendered sterile prior to entering the manufacturing process. It is critical that all transfers, transports, and storage stages be carefully controlled at each step of the process to maintain sterility of the product. In some cases, bulk drug substances or products should be tested for sterility.	
2	Procedures (e.g., aseptic connection) that expose a product or product contact surfaces should be performed under unidirectional airflow in a Class 100 (ISO 5) environment.	
3	The environment of the room surrounding the Class 100 (ISO 5) environment should be Class 10,000 (ISO 7) or better.	
4	Microbiological and airborne particle monitoring should be performed during operations.	
5	Microbial surface monitoring should be performed at the end of operations, but prior to cleaning.	
6	Personnel monitoring should be performed in association with operations.	
7	Process simulation studies covering the steps preceding filling and	

Item	Guidance Recommendation	Kite Pharma Approach/Rationale
	sealing should be designed to incorporate all conditions, product manipulations, and interventions that could impact on the sterility of the product.	<div style="font-size: 48pt; font-weight: bold;">(b) (4)</div>
8	The process simulation, from the early process steps, should demonstrate that process controls are adequate to protect the product during manufacturing.	
9	These studies should incorporate all product manipulations, additions, and procedures involving exposure of product contact surfaces to the environment.	
10	The studies should include worst-case conditions such as maximum duration of open operations and maximum number of participating operators.	
11	Process simulations do not need to	

Item	Guidance Recommendation	Kite Pharma Approach/Rationale
	mimic total manufacturing time if the manipulations that occur during manufacturing are adequately represented.	<div style="font-size: 48pt; font-weight: bold;">(b) (4)</div>
12	Process simulation studies for the formulation stage should be performed at least twice per year.	
13	In situations where results of final sterility testing are not available before the product is administered, additional controls and testing should be considered. For example, additional sterility tests can be performed at intermediate stages of manufacture, such as after the last manipulation of the product prior to harvest. Other tests that may indicate microbial contamination, such as microscopic examination, Gram stain (or other bacterial and fungal stain), and endotoxin testing should be performed and meet acceptance criteria prior to product release.	

As Kite performed their APV as originally proposed as part of the initial qualification of the process, equipment, and facility at (b) (4). The design of the APV included all process steps and will be performed using operators that have been qualified through our AOQ. Three APV lots were performed to qualify Manufacturing Suite (b) (4) Manufacturing Suite (b) (4) was qualified with one APV run in on BSC. Kite considers all workstations to be identical utilizing the same equipment. The APV were conducted through a pre-approved protocol and documented per a KTE-C19 APV Batch Record.

For the Aseptic Operator Qualification (AOQ), Kite includes both classroom and lab-based hands-on training, followed by qualification on a process simulation (as discussed in the prior table). The operator qualification process simulation has been designed to include all types of aseptic and closed manipulations used in the KTE-C19 process; performed over an approximately (b) (4) period. 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 staff member must successfully perform individual AOQ three consecutive times using media incubated and held as described in the APG with no detectable

contamination observed to be considered qualified to perform the process. Any failure of any individual exercise over the three AOQ runs performed would constitute a failure of the qualification and require the operator to start the qualification process over. The execution of each AOQ is performed and documented per an AOQ Batch Record. All Kite manufacturing personnel are qualified through this process.

Once qualified, staff are approved to perform aseptic operations within the facility unless a de-qualification event has occurred. These events include:

- failure to maintain gowning certification as detected through personnel monitoring program
- failure to comply with proper aseptic technique during operations
- any investigation which identified operator aseptic error through root cause determination.

Requalification is possible after successful re-completion of the aseptic operator qualification training. Kite will perform aseptic operator requalification (b) (4) per year for every operator. The requalification will require the successful execution of the formulation portion of the AOQ process simulation. Kite justifies this requalification interval and approach since operators will be routinely performing KTE-C19 aseptic operations with their performance being monitored through the EM program and individual batch test results; as well as, the simulation itself being performed on the highest risk open operation. In the event of a failure, an operator would be required to undergo the full AOQ to be requalified to perform the KTE-C19 process. Aseptic Operator requalification will be scheduled in a manner to ensure the qualifications occur over the course of the year in the facility.

I can find no deficiencies or irrational logic in Kite's justification and approach to aseptic process validation. All APV runs were valid with no deviations reported. It appears that their strategy provides evidence of a controlled aseptic processing environment. The strategy also includes control elements including:

- facility and equipment design, qualification, maintenance, and cleaning
 - This includes BSC (b) (4) certification
- supplier management of critical materials including sterile components
- personnel, material, and air flows
- gowning requirements and associated personnel monitoring
- environmental monitoring of manufacturing operations

From our pre-license inspection, we found evidence of commercial-ready facility and equipment, the same production suite configuration (i.e. HVAC supply, and process flows), and the identical workstation design. The risk of an APV study being negatively impacted based on the use of a different BSC in the facility appears low, and requiring more APVs to qualify the facility would appear to be non-value added. Kite states that additional APV would be required in the future if changes to the process, equipment, or facility warrant; or in the case of an investigation it is deemed necessary. The design of Kite's AOQ program appears adequate to support evidence of continuing aseptic processing environment. In addition, each patient dose will be tested for (b) (4) endotoxin, and sterility as part of batch release. Aseptic operations are performed in the

ISO ^{(b) (4)} area and include (b) (4)

Open manipulations are limited to a few steps in the process. Closed operations are performed in the ISO ^{(b) (4)} area and include (b) (4). Kite has reported no sterility failures to date. No objections noted.

3. *Kite has employed a multifaceted approach to ensure product quality and safety, while demonstrating the ability to manufacture at high capacity utilization for suites (b) (4). The following elements are part of this approach:*

- *Full qualification of manufacturing suite and equipment, including static and dynamic Environmental Monitoring Performance Qualification (EMPQ)*
- *(b) (4) training of the manufacturing Cell Therapy Specialists:*
 - *Instructor led trainings and on the job hands on training*
 - *Knowledge assessments*
 - *Aseptic Operator Qualification (AOQ) consisting of 3 media simulation runs*
 - *Demonstration of a successful end-to-end healthy donor lot production prior to executing a patient run*
 - *Similar training programs have been designed for support functions including Quality Assurance and Quality Control*
- *Up to 100% capacity utilization of suite ^{(b) (4)} (all BSCs in use), with concurrent manufacturing in (b) (4) comprising of clinical patient runs, healthy donor runs and AOQs*
- *Ongoing routine and lot related environmental monitoring, in-process and final product testing, and Quality System metrics review*

Based on all the elements listed above, Kite has demonstrated that the facility design, engineering controls, training and testing are sufficient to ensure that there is no impact to product quality and safety as we ramp up to full capacity. The verification of this state of control is a continuous process that is based on Kite's Quality System metrics monitoring, media simulations (AOQs), in-process and routine environmental monitoring trending.

a) *All BSCs and manufacturing equipment for (b) (4) were qualified prior to release of each suite for GMP production.*

Kite Capacity Ramp Up:

Kite initiated GMP manufacturing operations in (b) (4), with the qualification and release of Suite ^{(b) (4)} for process validation lots. Subsequently, in (b) (4), Kite began manufacturing clinical patient lots in suite ^{(b) (4)}. In anticipation of commercial demand, Suite ^{(b) (4)} was qualified and released for GMP use in (b) (4). All BSCs and manufacturing equipment were qualified prior to release of each suite for GMP production.

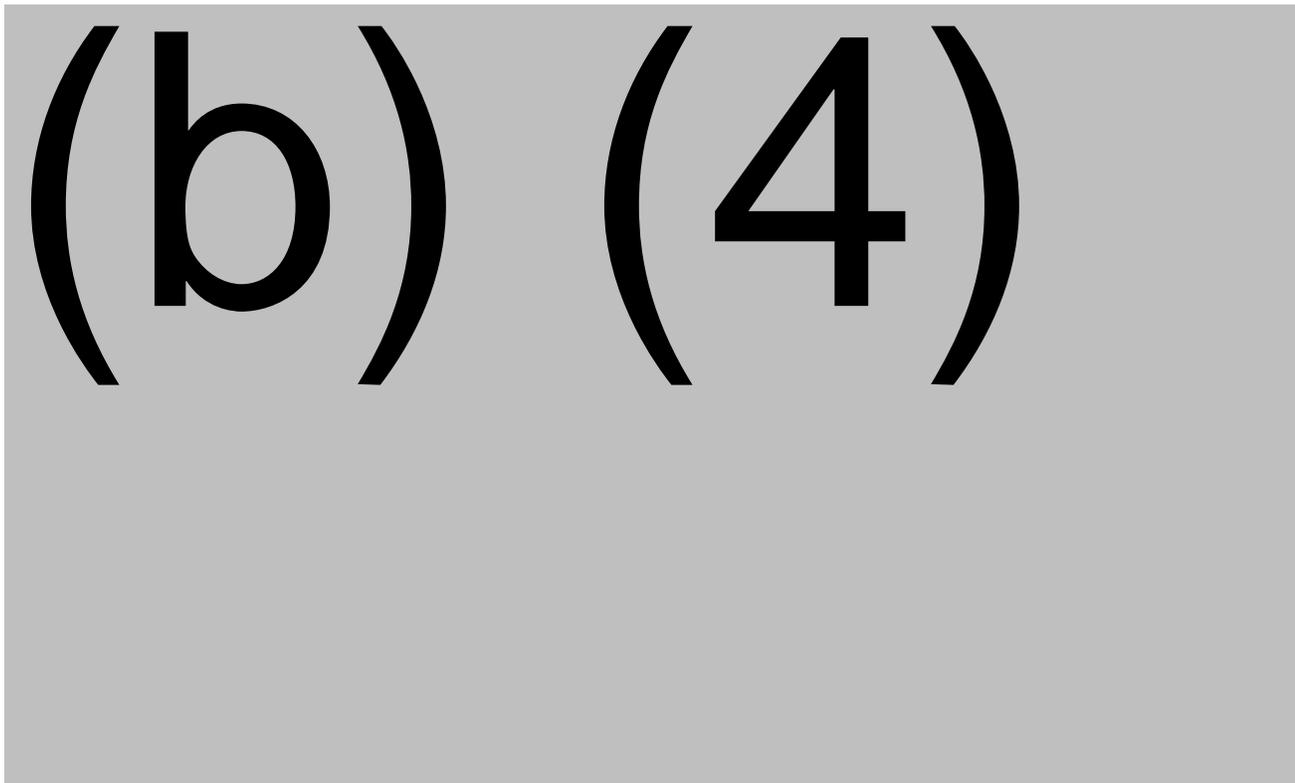
Kite also performed static and dynamic EMPQ of each suite demonstrating that the

manufacturing suites can be maintained in a state of control through all conditions. The dynamic monitoring took into consideration activities performed at each workstation with a maximum number of (b) (4) people in each suite. The data showed that the manufacturing suite was maintained in a state of control during this worst-case challenge to the environment. In a table in the amendment, Kite provided a summary of the EMPQ dynamic results for Suite (b) (4)

Kite has also implemented a very robust training program for all the new Cell Therapy Specialists, which consists of class room training, hands on training, and knowledge assessments to ensure that trainees have a comprehensive understanding of the entire manufacturing process. The training includes overview of the science behind the process, along with in depth review of aseptic techniques. Each Cell Therapy specialist must also complete three media simulation runs and one healthy donor end to end production run prior to executing patient runs.

In preparation for launch Kite has been performing concurrent runs in (b) (4) to demonstrate sustained GMP manufacturing performance. Concurrent runs are comprised of clinical patient runs, healthy donor runs and AOQ runs, which is representative of our routine GMP operations that need to occur within the manufacturing suites. Based on the clinical demand, training of new staff with healthy donor material and aseptic operator qualification, the manufacturing suites have been running at a capacity utilization averaging (b) (4) and up to (b) (4) over the last (b) (4) months (Graph 1). Based on commercial and clinical demand at launch, Kite anticipates operating at similar capacity levels as reflected in Figure 1.

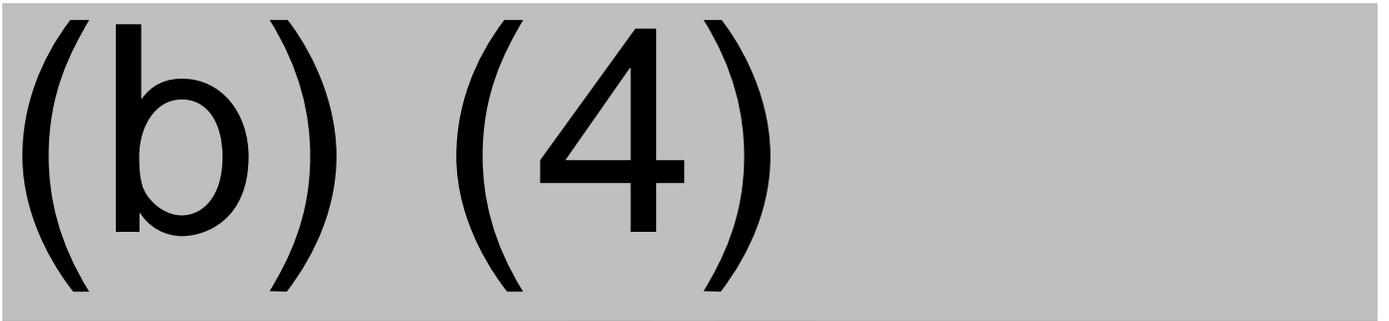
Figure 1. Suite (b) (4) Capacity Utilization



All clinical patient lots have successfully been manufactured, with no loss of chain of identify or chain of custody, and have been dispositioned for patient treatment. All other runs performed for validation, training and/or AOQ have passed their acceptance criteria, with no mix up or chain of custody failures.

To illustrate that the suites have maintained in a state of control, Table 5 summarizes the routine and in- process environmental monitoring data from (b) (4).

Table 5. Routine and Lot Related Environmental Monitoring ((b) (4)) *



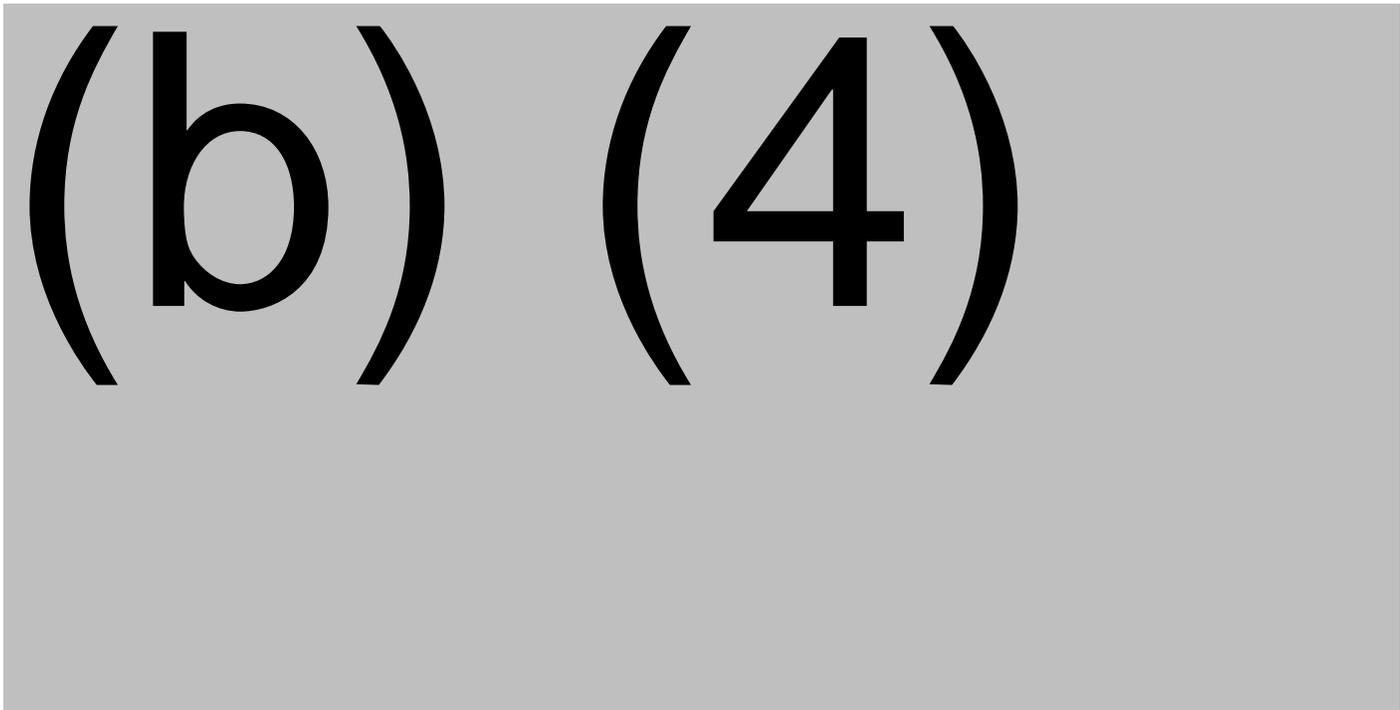
(b) (4) – First Clinical Subject Lot Manufactured at (b) (4)

The success of these activities demonstrates the ability of Kite to manufacture at a high capacity utilization and still maintain product quality and safety.

Commercial Scale-up and Future Capacity Planning



Figure 2. Kite Commercial Scale-Up Activities



Review Comments/Assessment: Although Kite has not performed an official validation study, Kite appears to have been closely evaluating their ability to manufacture commercially at increased to maximum capacity based in the data they provided. It is evident that Kite has a plan outlined to perform (b) (4) by the expected approval date. I have no objections.

8. KTE-C19 Shipping Validation

<Begin original text from Primary Memo>

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	(b) (4)

Component	Description	Supplier Name and Address
	release valves, and an inner metal dewar	

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)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

Per 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. Per 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?**

<End original text from Primary Memo>

Kite Response:

Protocol QP-1168 and the associated report QR-1168 demonstrated through (b) (4) testing that the final product packaging configuration provided sufficient protection to the final product bags inside.

(b) (4) (sequences 3, 4, and 6) tests were performed on the final product packaging configuration. The testing demonstrated that all (b) (4) product bags (maximum load of (b) (4) in each of (b) (4) shippers) within the successful packaging configuration remained unbroken during testing and did not show signs of leaking following thawing.

<i>Test Performed</i>	<i>Number of Final Product Bags Tested</i>	<i>Number of Acceptable Final Product Bags Following Testing</i>
(b) (4)		

Review Comments/Assessment: Kite provided evidence of a complete shipping study incorporating (b) (4) standards. I have no objections.

22 Pages Determined to Be Not Releasable: (b)(4)