DEPARTMENT OF HEALTH & HUMAN SERVICES

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: File BL STN 125646/0 for CTL019 suspension for intravenous infusion

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Through: CDR Qiao Bobo, PhD, Branch Chief, OCBQ/DMPQ/MRBII

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Subject: **Review Memo (BLA):** [Novartis Pharmaceuticals Corporation, License # 1244]. Original BLA to get licensure for Tisagenlecleucel-T (CTL019) indicated for the treatment of pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL). The drug product is manufactured at Novartis facility in Morris Plains, NJ.

Due Date: October 3, 2017

RECOMMENDATION

Recommend approval with the concurrence of the product office.

SUMMARY

CBER received this electronic submission on February 3, 2017. Novartis Pharmaceuticals Corporation (Novartis) submitted this Biologics License Application (BLA) to provide information to support the US market authorization of Tisagenlecleucel-T (CTL019) indicated for the treatment of pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblsatic leukemia (ALL).

CTL019 is an adoptive cancer immunocellular therapy that involves the reprogramming of autologous T cells with a transgene using a lentiviral vector. The transgene encodes a chimeric antigen receptor (CAR) that allows these T cells to specifically target and destroy CD19 positive B cells in an antigen dependent, but major histocompatibility complex (MHC) independent manner.

CTL019 final product is cryopreserved in (b) (4) freezing bags, as a single-dose cell suspension, which is thawed prior to infusion. CTL019 is formulated in a defined cryopreservation medium containing Plasma-Lyte A for Injection, Dextrose and Sodium Chloride for Injection, Human Serum Albumin, Dextran 40 in Dextrose for Injection and Cryoserv® solution (containing DMSO as cryopreservation agent). The product is indicated for the treatment of pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblatic leukemia (ALL). The target dose is 0.2-5.0 x 10^6 transduced viable T cells/kg (patients ≤ 50kg), and 0.1-2.5 x 10^8 transduced viable T cells for patients > 50kg.

The viral vector drug substance is manufactured at (b) (4), (a CMO for Novartis), and viral vector drug product is filled at (b) (4), (a contractor for (b) (4). The final CAR-T cell product CTL019 is manufactured and filled and stored at Novartis Morris Plains Facility in NJ, USA.

The final cellular product has been given the INN name tisagenlecleucel and the USAN name tisagenlecleucel-T. It has the internal Novartis product code CTL019, which will be used throughout this memo.

As part of review process of this original BLA (STN 125646/0), CBER conducted Pre-License Inspections (PLI) at Novartis Morris Plains Facility [FEI # 3010353512] from 03-7 April 2017 for the manufacturing of the CTL019 drug product; and at (b) (4) and at (b) (4) for the manufacturing of the lentiviral vector. All inspections resulted in deficiencies as documented in the respective 483 observations. The inspectional findings are documented in the respective Establishment Inspectional Report (EIR) for each facility. In addition, the responses to the 483 observations are documented in separate memos.

CATEGORICAL EXCLUSION FROM ENVIRONMENTAL ASSESSMENT

Novartis Pharmaceuticals Corporation is claiming a categorical exclusion under 21 CFR 25.31 (c) from the need to prepare an environmental assessment, as they consider CTL019 final product does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

They explained that T cells are terminally differentiated cells and are unable to proliferate or survive outside of the human body unless they are in highly controlled, tissue culture conditions (i.e. presence of specific cytokines or defined cell culture medium). They added that this is in line with FDA's guidance which considers that for purposes of 21 CFR 25.31(c) that Recombinant Viral or Microbial Products (GTVVs) consisting of genetically modified human cells to be substances that "*occur naturally in the environment*" because these cells have stringent nutritional requirements for survival and replication and are therefore not viable in the environment, and are degraded into naturally occurring substances.[Reference FDA Guidance for Industry "Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products (GTVVs)"]

In addition, Novartis stated that, to the best of their knowledge, no extraordinary circumstances exist, which may significantly affect the quality of the human environment.

INTRODUCTION

The production of CL019 involves the following facilities. In this review memo I will cover the description of the facilities, equipment, and manufacturing operations for the cell drug substance and drug product performed at the Novartis Cell & Gene Therapies Facility (CGT) located at 220 East Hanover Avenue, Morris Plains, NJ, USA. The manufacturing operations of the viral vector will be reviewed in a separate memo (Reviewer – Joan Johnson).

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
Novartis Pharmaceuticals Corporation (NPC) – Legal entity Cell & Gene Therapies Facility (CGT), 220 East Hanover Avenue, Morris Plains, NJ 07950 USA FEI# 3010353512 DUNS# 078640106				
Cell Substance and Cell Product: • Manufacture of CTL019 DS and DP • Quality Control and Stability Testing of CTL019 DS and DP. • Quality Control of vector product (functional test of expressed transgene and MOI assay) • Testing and release of vector as incoming material	Inspection	Yes	Yes	The facility was acquired by Novartis from Dendreon in December 2012. The current Pre-license Inspection is the first inspection of the Novartis CGT facility
(b) (4)				
(b) (4)	Inspection	Yes	Yes	(b) (4) No FDA Inspection History Last routine GMP inspection in 2016 by MHRA per type C briefing book.

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
(b) (4)				
Vector Product: • Sterilization and Concentration • Final filling, storage and labeling • Quality control (b) (4)	Inspection	Yes	Yes	(b) (4) Previous Inspections: -2016 CDER surveillance, 483 issued (VAI) -2014 DMPQ PLI for (b) (4) 483 issued (VAI) -2016 MHRA Pharmacovigilance Inspection per type C briefing book
(b) (4)				
• Release of vector batches for use in CTL019 manufacture • CMO oversight of (b) (4)	Not Required	No	Yes	Last inspected in 2015 by CDER surveillance (NAI)
(b) (4)				
• Manufacture and Quality Control of (b) (4) Master Cell Bank (MCB)	Not Required	No	Yes	Not established
(b) (4)				
• Manufacture and Quality Control of (b) (4) Working Cell Bank (WCB) derived from the MCB • Quality Control (b) (4) testing of vector substance and vector product	Not Required	No	Yes	Previous Inspections: -2016 Team Bio, 483 issued (VAI) -2015 MHRA, routine GMP per type C briefing book
(b) (4)				
• Quality Control (ID test) of the vector product for Novartis CGT incoming material testing	Not Required	No	Yes	No inspection history

NOVARTIS MORRIS PLAINS FACILITY (CGT)

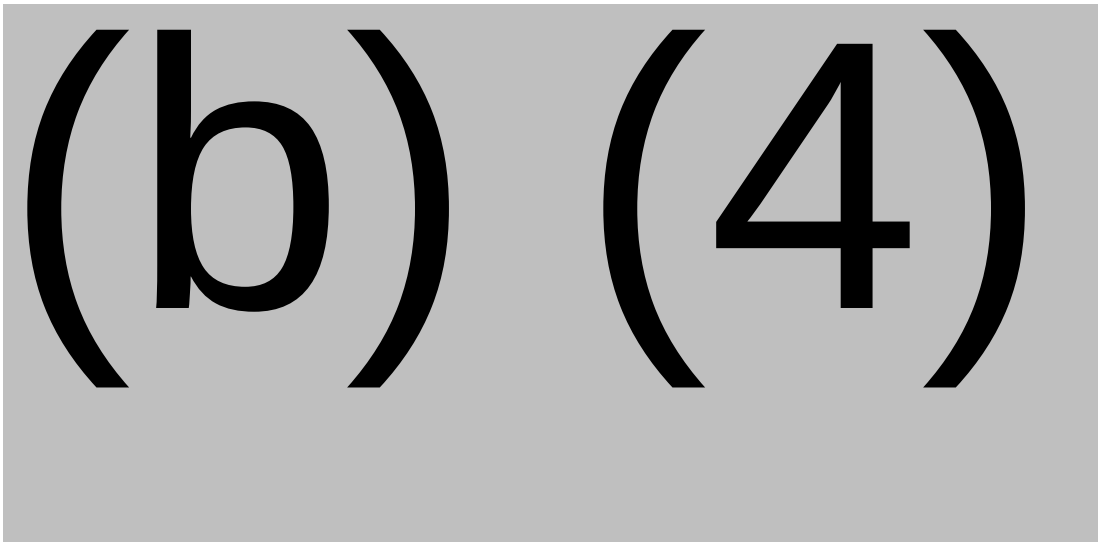
The Novartis Cell and Gene Therapies manufacturing facility is housed in a (b) (4) building of approximately (b) (4) square feet (b) (4) and Novartis is the sole occupant of the facility.

The facility (including some equipment) was acquired from Dendreon in December 2012. The CGT facility consists of cGMP manufacturing and support spaces, Quality Control (QC) and developmental laboratories, Quality Assurance (QA), Regulatory Affairs, Warehouse, Mechanical, Administrative areas, and Training areas to support the facility activities; it also includes common areas (e.g., restrooms, break-rooms, etc.). The CGT facility is designed to accommodate the concurrent manufacture of multiple lots of CTL019 and related autologous clinical products.

The CGT facility is designed in a modular format based on multiple equivalent workstations (WS) organized into modules and surrounded by support areas as shown in the following schematic diagram. The facility includes (b) (4)

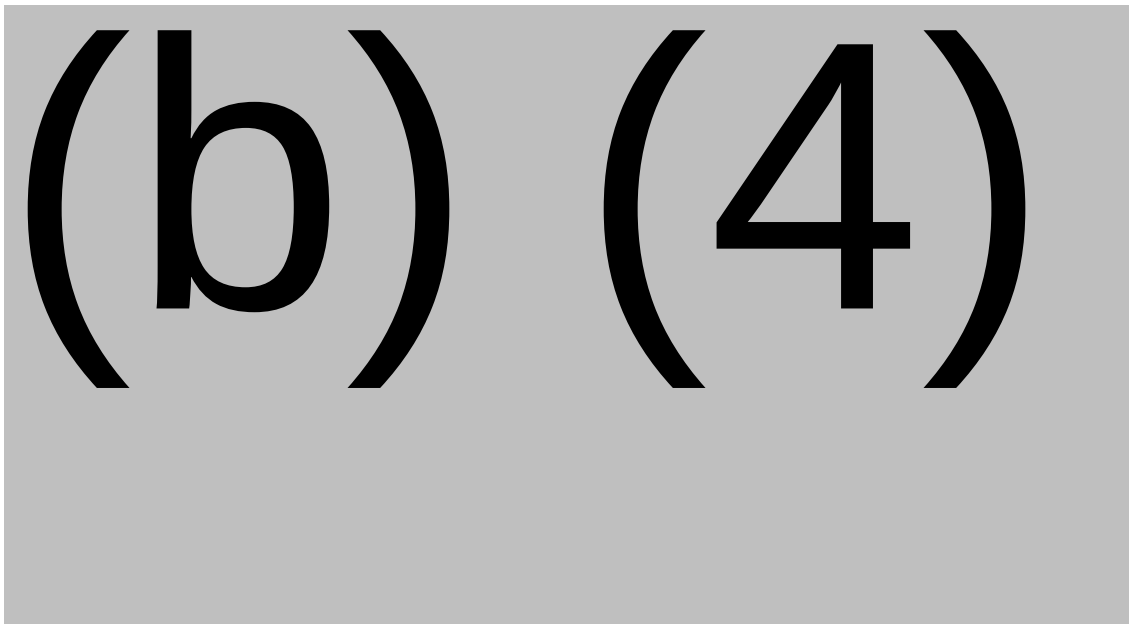
(b) (4)

Each manufacturing suite consists of (b) (4) cleanroom modules, and each module consists of a (b) (4) The cleanroom suites are surrounded by the (b) (4) corridors. Each manufacturing suite is serviced by a (b) (4) Please refer to the schematic diagram below:



Novartis reported that they have qualified (b) (4) manufacturing suites (Modules (b) (4) for GxP manufacturing operations, and the other (b) (4) suites (Modules (b) (4) are currently used for developmental work, and will be qualified prior to use for commercial manufacturing.

They provided the floor plans for the facility including room classifications and functions. The following table presents an overview of these areas and their functions.



Personnel, materials, product and waste flows during the manufacturing process were briefly described in the BLA and verified during the PLI and documented in the EIR; no issues were identified with the facility flows.

In addition to the manufacturing suites, Novartis described the following manufacturing support areas: Apheresis receipt area, the apheresis staging area, the packaging and shipping area, and the training module area.

The Apheresis Receipt area is a (b) (4) area with a (b) (4) to receive incoming leukapheresis materials in shipping transport containers (Dewars under LN2). The paperwork and the shipping container are inspected and the temperature data logger information is reviewed. In addition, patient identifiers are verified to confirm they match what is entered within (b) (4) (a validated global scheduling and operation monitoring system integrated with the (b) (4) system).

The Apheresis Staging area contains (b) (4) staging workstations, each consisting of (b) (4) . The area has been designed with (b) (4) to (b) (4) of the leukapheresis material to the product corridor.

The leukapheresis material remains in the shipping transport container until Novartis personnel transfer the container to a staging workstation located in the apheresis staging area. Using a dedicated workstation for each apheresis material, the package is opened and the leukapheresis bag is inspected for visual damage and to verify all patient identifiers match the incoming paperwork. Following inspection, the leukapheresis material is either transferred into manufacturing (b) (4) or stored in a Liquid Nitrogen (LN2) freezer.

The product packaging room contains (b) (4) packaging workstations (b) (4) The area is designed with (b) (4) to allow transfer of the final product to the packaging area.

Following processing of the batch, the final product container (b) (4) the Final Product packaging room, where it is stored in an LN2 freezer awaiting disposition, packaging and shipping.

QA personnel perform final verifications prior to shipment of the final product.

The process training module, (b) (4) The training module is currently classified as (b) (4), as it is designed to allow the execution of manufacturing processes by trainees in a safe, isolated environment which allows for practicing techniques without the potential for compromising patient processes or material.

Heating, Ventilation and Air Conditioning System

Each manufacturing suite and associated product and non-product corridors are supplied with HEPA-filtered air (b) (4) circulated air) provided by dedicated air handling units. The ISO (b) manufacturing suites are designed for (b) (4) air changes per hour and the ISO (b) support areas are

designed for (b) (4) air changes per hour. Novartis provided a Floor plan diagram that listed all the AHU and the areas they support. There is a (b) (4) air handling unit (AHU) for each manufacturing suite (b) (4) work stations). (b) (4) supports Modules (b) (4) supports manufacturing Modules (b) (4). In addition, (b) (4) supplies the training module (Module (b) (4), and (b) (4) supplies the (b) (4). The controlled non-classified (CNC) leukapheresis receipt and staging area, product packaging area and QC laboratories are also supplied with HEPA filtered air provided by a pair of air handling units.

The AHUs for the manufacturing areas operate 24/7, and are connected to the emergency power system in case of power failure.

The HVAC system supplies sufficient ventilation to create a positive pressure cascade from the ISO (b) (4) manufacturing area to the ISO (b) (corridors to prevent contaminants from entering the area. The ISO (b) (4) areas are further pressurized (b) (4) areas. Pressure differentials are maintained at a minimum of (b) (4) between different ISO classifications and a minimum of (b) (4) between ISO classified and non-classified rooms.

The HVAC system maintains a (b) (4) temperature range and (b) (4) relative humidity for the modules.

> **Reviewer's comments**: In response to an information request, Novartis provided in amendment 125646/0.10 additional information about the HVAC system which is reviewed in **Q1** of the Information Request section below.

Static and Dynamic Performance Qualifications for the Modules (EMPQ)

Novartis reported that they qualified (b) (4) of the (b) (4) manufacturing modules (Modules (b) (4), and verified that the areas operate within the defined acceptable temperature / humidity range, and meet the pre-determined environmental monitoring specifications and differential pressure requirements, under static and dynamic conditions. They stated in the BLA submission "*The performance qualifications were performed over* (b) (4) *conditions, followed by a* (b) (4) *qualification*".

> **Reviewer's comments**: Novartis clarified during the PLI that the (b) (4) static monitoring was performed before the (b) (4) dynamic monitoring.

The (b) (4) dynamic EMPQ included sampling for viable and non-viables in the ISO (b) (and ISO (b) (areas at selected pre-defined locations with maximum occupancy in the modules to simulate worst case conditions. The EM sampling was performed for (b) (4) days with no additional cleaning other than the standard daily cleaning.

Novartis reported that the non-viable particulate sampling was performed to meet ISO (b) (4) requirements for non-viable particulates. Viable sampling of air and surface sites were performed to meet limits for surface and airborne viable samples listed in (b) (4) chapter (b) (4).

Novartis considered that all the BSCs (ISO (b) (4) are equivalent based on make and model and size, initial qualifications results (2010), and then recertification per (b) (4) Standards after acquisition of the facility by Novartis. As such they performed (b) (4) in each of ISO (b) (BSCs (Modules (b) (4) under static conditions; and then performed (b) (4) study in (b) (4) BSC under dynamic conditions and simulating the different manufacturing operations to demonstrate and document that the biosafety cabinets consistently maintain unidirectional laminar flow downward from the biosafety cabinet air supply with sweeping action over and away from the work surfaces, while simulating the different aseptic manufacturing steps. All results were compliant.

They added that the temperature, humidity, air exchanges, and pressure differentials were verified to meet predefined specifications. Operational set-points for the Building Automation System (BAS) and alarm limit settings for the Environmental Monitoring System were also verified and found to meet expected values.

Novartis stated that they performed EMPQ for the ISO (b) (4) areas under static conditions. The EM included temperature, humidity, differential pressure and environmental monitoring viable/non-viable monitoring as well as verification of HEPA Certifications and air exchange rates

The HVAC system and its qualification was further discussed during the PLI and documented in the EIR.

> **Reviewer's comments**: In response to an information request, Novartis provided in amendment 125646/0.10 additional information about the EMPQ which is reviewed in **Q3** of the Information Request section below.

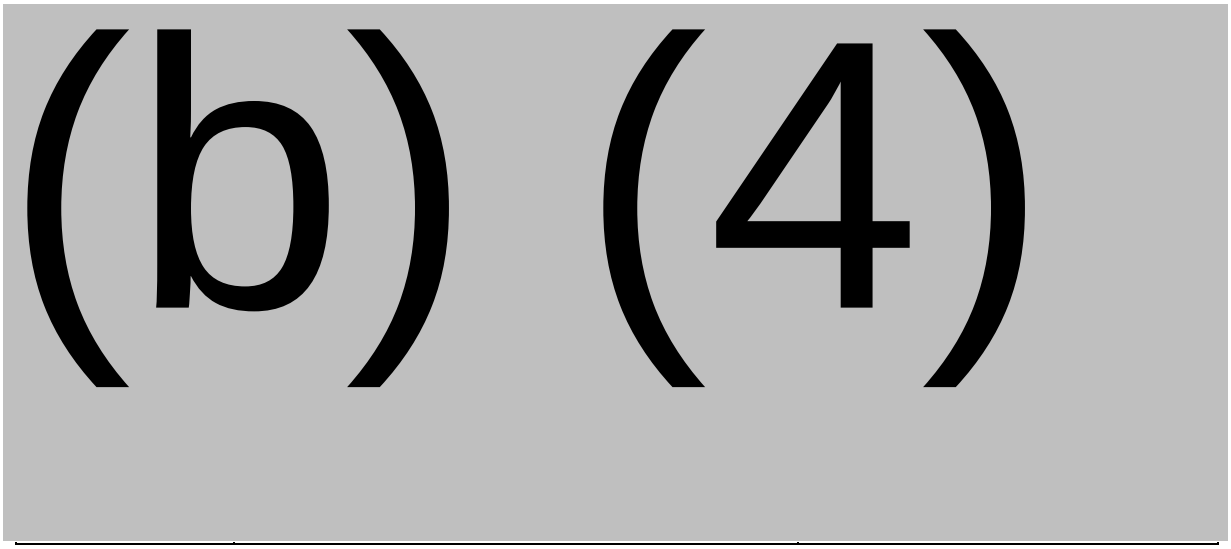
Routine Environmental Monitoring

Novartis reported that the temperature, humidity and differential pressure of the production areas are continuously monitored by the Environmental Monitoring system which alarms when there are excursions from the set parameter ranges.

In addition, their environmental monitoring program includes routine monitoring of non-viables (active air) and viables (active air and surfaces); in addition the BSC also includes passive air monitoring for viables (b) (4) the frequency depends on room classifications and manufacturing operations. Personnel monitoring is performed in the production area (aseptic manufacturing) using (b) (4) are at pre-defined steps throughout the manufacturing process per approved batch records and/or standard operating procedures. Novartis has established alert and action limits as documented in their procedure. The alert and action limits for the ISO (b) (area were discussed during the PLI and resulted in revisions to the SOPs for clarity and consistency as documented in the EIR.

Novartis provided the sampling location and monitoring frequency for the different areas as shown in the following Table:

(b) (4)



Reviewer's comments: Additional information about the environmental monitoring program was requested, and Novartis provided the information in amendment 125646/0.10reviewed in **Q4** of the information request section below.

Containment and Control of Cross Contamination

Novartis plans to perform concurrent manufacture of multiple lots of CTL019 and related autologous clinical products at the CGT facility. They explained that manufacturing operations are contained and segregated based on physical as well as procedural controls including facility design, manufacturing operations in different BSCs and work stations, cleaning and environmental monitoring; personnel training; patient screening and batch segregation, labeling and maintaining chain of identity and controls on incoming materials.

- All patients are pre-screened for blood borne pathogens based on individual country requirements as a pre-requisite for acceptance into the program
- The overall design of the facility (work stations, modules and suites) and HVAC system (b) (4) as well as the (b) (4) facility flows prevent contaminations and mix ups.
- Only (b) (4) workstation at a given time, and all aseptic manipulations are confined to the BSC within a workstation. All supplies that come in contact with the production lot are sterile, single use and disposable. Product transported or handled outside the workstation is placed into a secondary container.

To prevent mix-ups, patient batch segregation, chain of identity and contamination control begins at the Apheresis Center and continues until the infusion of the product into the patient at the infusion site. Labels (leukapheresis, in-process, QC samples and Final product) are generated from validated electronic systems and verified by QA prior to release for use. The label includes the product code, barcode (chain of identity number), to maintain the chain of identity and traceability of the product through the entire manufacturing operation. Barcode scanning is performed throughout the process and the Chain of Identity/ Batch number on the barcode label is electronically verified to match what is required on the batch specific bill of

materials. A bill of materials is established within the (b) (4)

Microbial contamination is minimized by having all (b) (4)

The facility is designed with (b) (4)

The transfer of materials to and from the workstations is (b) (4)

Reviewer's comments: In response to an information request, Novartis provided in amendment 125646/0.10 additional information about segregation policy and the procedures in place to maintain the chain of identity of the different lots. The information is reviewed in **Q7 & Q8** of the Information Request section below.

Multi-Product manufacturing

Novartis reported that before introduction of a new product into the facility a comprehensive risk analysis would be performed to control the risks associated with the new product on the other products, the facility, personnel and the environment. In addition, for each new product manufactured in the facility, an identity test must be in place which allows the discrimination of the product from other products in the facility.

Computer Systems

Novartis provided a brief overview of main Computer Systems used to manage GMP operations and QC Lab testing. The computer systems and different software packages used at the Morris Plains site were discussed during the PLI and documented in the EIR.

- (b) (4)

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- **Laboratory Information Management System (LIMS)**

LIMS is used at the Morris Plains facility to support GMP requirements by providing full sample tracking with each sample assigned a unique LIMS ID number, full audit trail and sample scheduling for environmental monitoring, in-process and final product testing. The system manages the sampling plan, including printing of sample vial labels with each label containing a bar code with a unique identification number which is traceable to the batch number ensuring patient chain of identity. It also collects test results and performs calculations in support of testing and production. The system is also capable of handling multiple products and country specific samples, testing and specifications.

- (b) (4)

1 Page determined to be not relesable: (b)(4)

Reviewer's comments: In response to an information request, Novartis provided in amendment 125646/0.10 additional information about the (b) (4) system which is reviewed in **Q9** of the Information Request section below.

Manufacturing Capacity and Scheduling

Novartis Morris Plains facility manages the manufacturing operations and the scheduling of the different manufacturing steps of the different batches by utilizing (b) (4) (scheduling) and the (b) (4) systems (managing the equipment availability). The duration of a CTL019 batch manufacturing process is scheduled up to (b) (4). The approved capacity for production is entered into the scheduling system by the supply chain planner. When the batch is confirmed within the scheduling system, the supply chain planner performs a feasibility check on the routing of the batch to ensure equipment resource capacity is available. Once a batch is confirmed in the scheduling system, the batch becomes a process order scheduled in (b) (4). The maximum number of batches that can be processed per production module is therefore limited by the available equipment for the entirety of the manufacturing duration of that batch (b) (4) days).

Reviewer's comments: In response to an information request, Novartis provided in amendment 125646/0.10 additional information about the facilities manufacturing capacity which is reviewed in **Q10** of the Information Request section below.

Facility Cleaning

Novartis reported that the manufacturing areas including floors, exterior equipment and furniture surfaces, walls, ceilings and shelves, are cleaned at regular intervals according to their zone classification. They added that the cleaning methods (including those of spills in the production areas), cleaning and sanitization agents, concentration of agents, are described in SOPs. They also reported that they have validated the effectiveness of the disinfectants and cleaning agents used at the facility. The facility cleaning was discussed during the PLI and deemed acceptable.

Reviewer's comments: Additional information about cleaning/sanitization was requested, and Novartis provided the information in amendment 125646/0.10 and reviewed in **Q5** (Disinfectant Effectiveness Studies) of the Information Request section below.

Utilities

Novartis provided a brief overview of the water systems, carbon dioxide system and liquid nitrogen system used in the processing of CTL019 at the Morris Plains site. The systems were reviewed in more detail during the inspection and documented in the EIR.

- **Water Systems**

Novartis has (b) (4) water systems in the facility for non-product uses. In addition, Sterile Water for Injection is (b) (4) and used in the cleaning solutions for the ISO (b) (4) production areas.

- The High Purity Water (HPW) System is used to produce, store and distribute HPW for cleaning solutions in the ISO (b) (4) areas. The system is a (b) (4)

distribution system consisting of (b) (4), and has a capacity of (b) (4). The distribution loop is continuously monitored for (b) (4).

- The Deionized Water System supplies water for HVAC Humidification. It is a (b) (4) distribution system consisting of (b) (4) with a storage tank and (b) (4) distribution loop that distributes deionized water to all humidifiers. The distribution loop is continuously monitored for conductivity.

- **Carbon Dioxide (CO_2) System**

Carbon dioxide is distributed to the CO_2 incubators and CO_2 mixer/bioreactor systems in each manufacturing module. The system was reviewed in more detail during the inspection and documented in the EIR.

The CO_2 is stored in a (b) (4) CO_2 which is sufficient to supply the respective equipment for at least (b) (4) weeks.

In addition to the (b) (4), the CO_2 distribution system includes a regulator that controls CO_2 distribution pressure to the equipment. The CO_2 is (b) (4) includes a pressure regulator to control the final supply pressure to the CO_2 incubators and CO_2 mixer/bioreactor systems.

- **Liquid Nitrogen (LN2) System**

The Liquid Nitrogen Storage and Distribution System provides constant and uninterrupted supply of Medical Grade LN2 to controlled rate freezers (step-down freezers) and LN2 storage freezers in various rooms. In addition, it provides LN2 for filling the Dewars used for shipping of the final product. The LN2 system consists of a (b) (4), a control manifold and associated rigid vacuum jacketed piping for distribution of liquid nitrogen to the respective equipment. It is monitored by the Building Automation System at predetermined high and low levels. The system was reviewed in more detail during the PLI and documented in the EIR.

Equipment

Novartis provided the following list of equipment and their usage in the processing of CTL019.

Equipment	Usage
Autologous Blood Recovery System	(b) (4)
Bag Rotator	
Balance / Scale (inside the BSC)	
Biological Safety Cabinet	
Bioreactor	

Equipment	Usage
Cell Processing System	(b) (4)
Centrifuge (Refrigerated)	
Conical Tube Magnetic Bead Separator	
Controlled-Rate Freezer	
Flatbed Bag Magnetic Bead Separation System	
Thawing Device	

Novartis reported that they have established a comprehensive equipment qualification program at the Novartis Morris Plains manufacturing facility which includes installation, operational and performance qualification activities, based on international GMPs and Novartis standards. They added that a risk based approach was utilized for the qualification of new and existing equipment/systems. They stated that qualification data demonstrated that the equipment is acceptable for use, and that the final reports archived in the Novartis Morris Plains facility. They added that qualification information would be provided upon request. The qualification of the equipment was reviewed in more detail during the PLI and documented in the EIR.

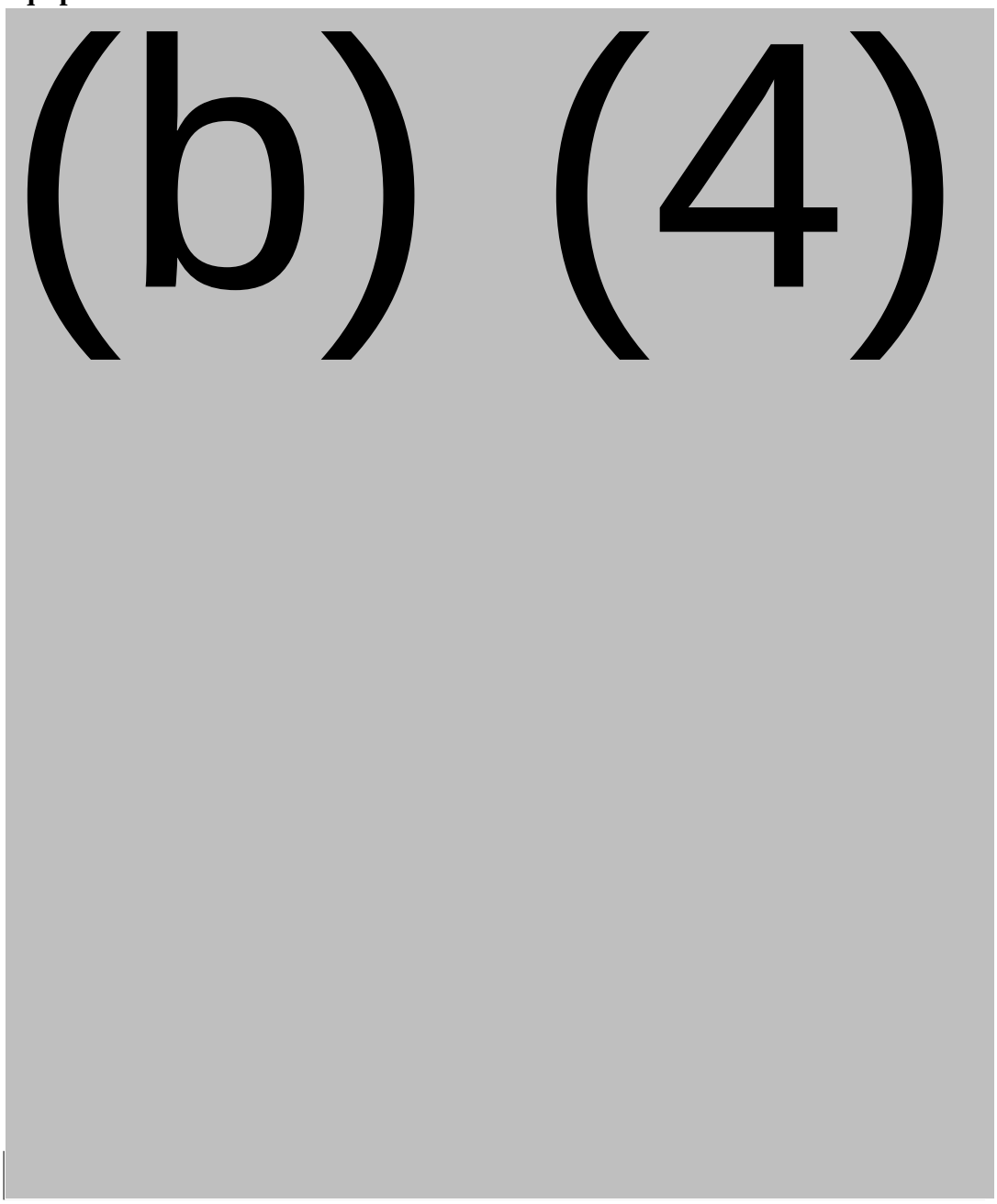
Reviewer's comments: Additional information about the qualification of equipment was requested, and Novartis provided the information in amendment 125646/0.10 reviewed in **Q5** of the information request section below.

In response to information request, Novartis provided in amendment 125646/0.10 (**Q15**) the following report: *MI7008911A, Description of Commercial pedALL Manufacturing Process* (approved 18 Nov 2016), which includes list of equipment and their uses in the various manufacturing steps and reproduced below:

Equipment usage per process step

(b) (4)

Equipment List



Equipment Cleaning

Novartis reported that all product contact equipment is single use and disposable. They added that the cleaning and sanitization of non-product contact equipment are described in the respective equipment procedures and include cleaning methods, cleaning agents (volume and concentration), and frequency of cleaning.

Reviewer's comments: Additional information about the qualification of equipment was requested, and Novartis provided the information in amendment 125646/0.10 reviewed in **Q5** of the information request section below.

Container Closure

CTL019 final product is stored at ≤ -120°C in (b) (4) freezing bags supplied by (b) (4). The cell bags include two sizes: (b) (4) is used for final product volumes of 10 – 30mL of cell suspension, and the (b) (4) bags are used for final product volumes of 30 – (b) (4) cell suspension. The (b) (4) freezing bags are made from (b) (4) and have two hermetically sealed spike ports and one (b) (4) inlet tube sealed on the bag on one end and separated on the other end with a Y-connector into (b) (4) tubes, each ended with a female luer-lock cap. The fluid path is sterile and non-pyrogenic. Shown below are pictures of the (b) (4) cryopreservation bags.

Novartis reported that for every received shipment of cryobags bags, they visually inspect and accept on the Certificate of Analysis/Conformity provided by the supplier (sterilization, sterility and material).

They provided the tests performed to accept a shipment of the cryobags:

(b) (4)

The (b) (4) Freezing Bags are 510(k) cleared (b) (4) . I looked up the 510(k) clearance submission and reviews of the submission, and the device was cleared as being substantially equivalent to marketed devices with regards to biocompatibility and container integrity when frozen/thawed in liquid nitrogen. Also the sterilization, sterility assurance labeling, endotoxin testing and non-pyrogenicity labeling statements were satisfactory to the reviewer of the device.

Novartis reported that the cryobags were sterilized at (b) (4) , and put on an accelerated aging study, then evaluated for changes or degradation by the vendor. Results of the aging studies showed that there was some minor discoloration of (b) (4) luer components; however, there were no changes in physical properties. They added that the sterilization facility is (b) (4) inspected by FDA and EU authorities, and that the (b) (4) cycle is (b) (4) qualified according to ISO (b) (4).

They added that The (b) (4) bags have been tested by the vendor for resistance to chemicals routinely used in cryopreservation and stem cell research. (b) (4) testing showed that the (b) (4) bag is resistant to (b) (4) . They performed extractables/leachables studies (purview of the product office).

Novartis also reported that Container Closure Integrity Testing (CCIT) was performed by (b) (4) to demonstrate integrity under worst case conditions: normal long term storage, (b) (4) They added that the cryobags are (b) (4) inspected by the vendor for leaks.

In addition to studies performed by the vendor, Novartis performed their in-house CCIT validation using the (b) (4) technique (b) (4) in conjunction with the shipping validation of the frozen bags containing (b) (4) The (b) (4) filled bags were (b) (4) stored in liquid nitrogen for up to nine months (T_0, T_{3mon} T_{9mon}) to demonstrate the integrity of the bag for the duration of the final product shelf life of nine months.

The T_0 CCIT study was performed as part of the shipping validation where (b) (4) samples (of each presentation) in the dewar shippers representing minimum and maximum loads were transported by ground and air for a duration of over (b) (4). The frozen filled bags were then thawed and tested for container closure integrity using the (b) (4) test.

Novartis provided the results for the CCIT performed on (b) (4) bags and (b) (4) bags (as one of the (b) (4) bags was damaged during shipping). They added that one (b) (4) filled bag (b) (4) and one (b) (4) filled bag (b) (4) were used as positive controls for (b) (4) method.

They provided a summary of the results as shown below, indicating that (b) (4) bags are integral during storage and shipping conditions, and thus they are suitable as primary packaging containers for CTL019 drug product.

(b) (4)

Novartis also reported that they performed CCIT as part of stability studies of (b) (4) final product batches (b) (4) manufactured from healthy donor leukapheresis material using the (b) (4) pathway to demonstrate suitability of the final container for long term storage at ≤ -120°C. The final product was formulated, packaged into (b) (4) bags and (b) (4), cryopreserved and stored at ≤ -120 °C. The bags were tested for CCIT and sterility at T=0 and T=6months, and the results met the acceptance criteria (sterile product).

In addition, they evaluated CCIT of three final product batches manufactured from patient material (b) (4) which were packaged in (b) (4) bags and (b) (4). The bags were tested for CCIT and sterility at T=6 months, and the results met the acceptance criteria (sterile product).

All the material tested exhibited no growth during sterility testing at the end of the storage period indicating that the container remained integral and can maintain the sterility of the final product.

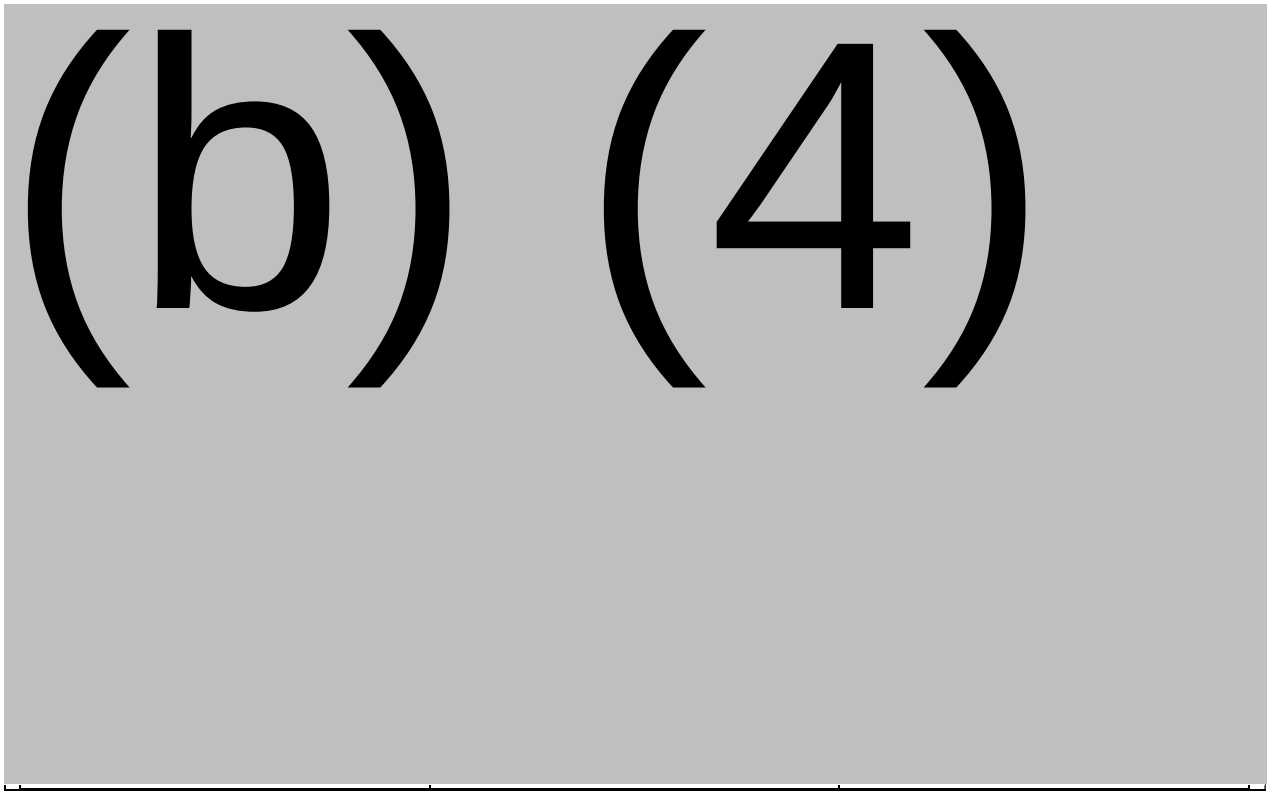
> **Reviewer comment**: Novartis did not provide the CCIT validation reports in the submission. The container closure integrity testing protocols and reports were reviewed during the inspection and no issues were identified as described in the EIR.

PROCESS OVERVIEW

The manufacturing process is a continuous process with no holding steps beginning at thawing of leukapheresis material (from a single patient collected at leukapheresis center) received frozen at Morris Plains facility → processing steps → concluding with DP formulation in a cryopreservation medium → freezing and storage in LN2 freezer pending packaging and shipping to the clinical site.

The T cells (from the leukapheresis material obtained from the patient to be treated) are processed ex vivo using a lentivirus vector coding the "CAR" into a single CTL019 final product batch. The number of final product bags filled depends on the achieved CAR+ T cell yield, from 1 to 3 bags each containing a single dose.

There are (b) (4) pathways used for the manufacturing of the clinical batches (PPQ batches) depending on the incoming leukapheresis material. Below is a general flow. Detailed information about the manufacturing process and validation is presented in the product review memo.



PROCESS VALIDATION

Novartis described the process validation protocol and provided summaries of the following process validation studies:

- Manufacturing process validation
  - Process Design
  - Process Performance Qualification (PPQ)
  - Continued Process verification (CPV)
- Aseptic process validation (APV)
  - Aseptic CTL019 manufacturing process steps
  - Holding media studies – Shelf life of the aseptically prepared media
  - Aseptic Media preparation
- Shipping validation (of the leukapheresis starting material and final product)

Manufacturing Process Validation

- (b) (4)

5 Pages determined to be not relesable: (b)(4)

(b) (4)

Reviewer's comments: In response to an information request, Novartis provided in amendment 125646/0.10 Novartis provided the APV reports for the CTL019 manufacturing process and the ancillary media preparation, as well as the validation of the media holds during manufacturing operations. The information is reviewed in the **Q13 & Q14** of the Information Request section below.

Shipping validation

The shipping validation includes the shipping of the frozen leukapheresis material from the apheresis sites to the Morris Plains facility, and the shipping of the frozen CTL019 final product from the Morris Plains facility to the infusion sites. The aim of the studies is to demonstrate that the cryopreserved leukapheresis material and final product bags (b) (4) can be maintained at ≤ -120 °C for at least (b) (4), and that the integrity of the bags is maintained during shipping.

- **Leukapheresis material preparation**

The patient leukapheresis material is collected into cryobag(s) and sentinel vials, and cryopreserved using a controlled rate freezer by the apheresis sites. Each bag is placed into a secondary container and loaded into a cryogenic dry shipper charged with liquid nitrogen, provided by a contract supplier. The cryovials are sealed together in a plastic overwrap bag with absorbent sheets, and then sealed in a Tyvek bag. Each shipping container load contain at least one cryobag and one cryovial and up to a maximum of four cryobags and three cryovials. The loaded shipping container is transported by courier to the Novartis Morris Plains facility, where the information is verified and logged in the system, and the leukapheresis material is then stored in LN2 vapor freezer until use.

- **CTL019 final product**

The CTL019 final product is cryopreserved in a controlled rate freezer and stored in LN2 vapor freezer until product release and shipment. Once released and cleared for shipment, the final product is removed from the LN2 freezer and placed into a secondary container and loaded into a cryogenic dry shipper charged with liquid nitrogen, provided by a contract supplier. Each shipping container load can contain one to three cryobags. The shipping container is picked up and transported by courier to the patient transfusion site.

The shipping validation studies were performed using (b) (4)

1 Page determined to be not relesable: (b)(4)

- (b) (4)

The shipping validation study results met the following acceptance criteria: all of the shipping containers maintained temperatures ≤ -120°C for a minimum of (b) (4) Novartis reported that the highest temperature observed was -135.2°C.

> **Reviewer's comments**: Novartis did not discuss the deviation in the submitted material and did not submit the validation reports. However, the shipping validation was reviewed during the inspection and no issues were identified as documented in the EIR.

INFORMATION REQUEST

Additional information was requested by email on February 27, 2017, and Novartis submitted their responses on March 30, 2017 in amendment 125646/0/10 and reviewed below.

CBER comments are in ***bold italics*** followed the Baxalta responses in plain lettering.

All responses are acceptable.

HVAC/Environmental Monitoring

1. ***Please list the AHUs (air handling units) at the Novartis Morris Plains manufacturing facility, and the respective suites/modules and ancillary areas they service, and the most recent requalification report(s). Please also list whether the ventilation is accomplished by single pass or recirculated air, and justify your response.***

   Novartis provided a list of AHUs used for the production modules and ancillary areas as presented in the following Table, and stated that the rooms are supplied with @ (b) (4) air.

   (b) (4)

   Novartis provided the 2016 Annual USMB HEPA Certification Summary (30 Mar 2016), where they reported the results of the HEPA Certification for modules (b) (4) and the associated areas including corridors, Dispensary and staging areas. In addition they provided data for the training module (b) (4), and modules (b) (4) – currently not qualified for production) and other (b) (4) areas.

   - The certification is performed every (b) (4) and includes airflow (CFM), and air changes per hour (acceptance criterion (b) (4) and all results met the acceptance criteria.
   - In addition, they presented the room to room pressurization- Modules (b) (4), corridors, Dispensary, Training Module and various vestibules and staging areas, and all the reported differential pressures met the acceptance criteria for the respective areas.

- They also tested for HEPA filter leakage and differential pressure across the HEPA surface, and there were no leaks detected (b) (4), and the HEPA filter differential pressure (b) (4) in .w.g., thus meeting the specifications.
- Non-viable particles were also monitored in Modules (b) (4), corridors, Dispensary, Training Module and various vestibules and staging areas, and all the results were way below the acceptance criteria for the room classification.

Response is acceptable, as the AHUs provide sufficient ventilation for the respective rooms to meet their classifications, ACH and differential pressure between the different areas.

2. ***You reported the cleanroom environmental monitoring performance qualification (EMPQ) was successfully performed under static and dynamic conditions for Modules*** (b) (4) ***. Please clarify if these are the only modules that will be used for the production of CTL019.***

   Novartis confirmed that Modules (b) (4) are the only modules qualified at this time for manufacturing of CTL019 and media preparation.

Response is acceptable.

3. ***Please provide the protocol and summary report (s) for dynamic environmental monitoring performance qualification studies. Please include a description of activities performed during dynamic operations and indicate whether 'worst case' conditions were assessed.***

   Novartis stated that the environmental monitoring was qualified under static conditions (b) (4) and dynamic conditions (b) (4) for modules (b) (4), under worst case conditions with maximum number of personnel and equipment being utilized during dynamic monitoring. They clarified that the dynamic EMPQ was performed during manufacturing processes using the APV batch records (all aseptic manipulations were completed in (b) (4) of personnel due to the length of the process) to simulate worst case conditions.

   They submitted the qualification protocols and reports as listed in the following Table and reviewed below:

Module	Protocol #	Report #
Module (b)	*USMB.468.VD, Cleanroom Performance Qualification Protocol for Module* (b) *under Dynamic and Static Conditions* May 2015 (approved 27 May 2015)	*USMB.496.VD, Cleanroom Performance Qualification Report for Module* (b) *under Dynamic and Static Conditions* (approved 19 Jun 2015)
	USMB.754.VD, Addendum to USMB.468.VD, Cleanroom Performance Qualification Protocol for Module (b) *under Dynamic Conditions* (approved 09 Aug 2016)	*USMB.817.VD, Cleanroom Performance Qualification Report for Module* (b) *under Dynamic Conditions, Addendum to USMB.754.VD, September 201*6 (approved 30 Nov 2016)
Module (b)	*USMB.433.VD, Cleanroom Performance Qualification Protocol for Module* (b) *under*	*USMB.464.VD, Cleanroom Performance Qualification Report for Module* (b) *under*

Module	Protocol #	Report #
	Dynamic and Static Conditions March 2015(approved 01 Apr 2015)	*Dynamic and Static Conditions, April 2015* (approved 17 Apr 2015)
Module (b)	*USMB.199.VD, Cleanroom Performance Qualification Protocol for Module* (b), *Dynamic Conditions* (approved 09 May 2014)	*USMB.256.VD, Cleanroom Performance Qualification Final Report for Module* (b), *Dynamic Conditions* (approved 02 Jul 2014)
Module (b)	*USMB.289.VD, Cleanroom Performance Qualification Protocol for Module* (b), *Dynamic Conditions* (approved 28 Aug 2014)	*USMB.305.VD, Cleanroom Performance Qualification Final Report for Module* (b) (4) *Dynamic Conditions* (approved 22 Oct 2014)

The (b) (4) static EM was performed to demonstrate that the equipped areas can maintain the defined acceptable temperature/ humidity range and meets the environmental monitoring specifications.

The (b) (4) dynamic monitoring was performed under worst case conditions for each module: operation of all (b) (4) workstations and the process equipment simultaneously.

- EM sampling was performed on each day
- Standard/routine cleaning was performed following the manufacturing operations
- EM samples collected: Non-viable counts; Active air viable counts, surface viables, and personnel monitoring.

For Module (b) (used for ancillary media preparation), the APV for media preparation was performed during the EMPQ to create dynamic activity with the maximum number of personnel in the module.

The qualification of module (b) (4) included the gown-in rooms, incubator rooms, workstation rooms, equipment vestibules, and gown-out rooms for the respective modules.

Novartis provided the Action level for the different samples collected and the results for the modules as summarized in the following Tables:

(b) (4)

1 Page determined to be not relesable: (b)(4)

- (b) (4)

(b) (4)

Reviewer's comments: I reviewed the environmental qualification and routine EM trending reports during the PLI. There were a lot of revisions regarding the EM program: having (b) (4) in the BSCs, the frequency of monitoring personnel after manufacturing operations, and the acceptance criteria for the viables (air and surface) in ISO (b) (area which are discussed in the EIR, and the 483 response memo. The level of EM excursions was low indicating that the manufacturing areas are in a state of control.

Response is acceptable.

4. ***You reported that the environmental monitoring program included surface, air viable and air nonviable particulates. Please describe the environmental monitoring program, including diagrams depicting sampling locations (with justification) and frequency of sampling as well as the acceptance criteria for the different area classifications. Please provide a comparison of environmental monitoring performed during qualification activities, routine dynamic environmental monitoring, and static environmental monitoring. Please provide the environmental monitoring report documenting the results of environmental monitoring during the manufacturing of the conformance lots and the aseptic process simulation lots.***

Novartis provided *SOP-7018088* which describes the EM program followed during the manufacturing of the conformance lots and aseptic process validation. They also provided *SOP-7017439* and *WP-7004615* which describe the current EM program.
In addition they submitted the EM reports *QRA5135-1A_EM* and *QRA5135-2A_EM* (sampling locations), and the forms used for documenting sampling during the EM qualifications.

- *SOP-7018088, BiopharmOps Morris Plains Routine Environmental Monitoring* (v5.0, effective 04 Jan 2016) (Withdrawn/ Retired).
- *SOP-7017439, Cell & Gene Therapies Morris Plains BSC Qualification/Requalification Environmental Monitoring Report Form* (ISO 5) (v11.0, effective 05 Jan 2017)
- *WP-7004615, Cell & Gene Therapies Morris Plains BSC Qualification/Requalification Environmental Monitoring Report Form (ISO 5)* (v4.0, effective 14 Feb 2017)
- *QRA5135-1A_EM, Selection of EM sites in BSC (ISO 5) during CTL019 aseptic Processing* (approved 15 Dec 2014)
- *QRA5135-2A_EM, Selection of EM Sites in ISO 7 and ISO 8 Manufacturing Areas* (approved 30 Sep 2016).
- *FRM-7053726, Cell & Gene Therapies Morris Plains BSC Qualification/Requalification Environmental Monitoring Report Form (ISO 5)* (v4.0, effective 12 Dec 2016)
- *FRM-7053734, Cell & Gene Therapies Morris Plains Environmental Monitoring Report Form for Modules (ISO 7) Qualification/Re-Qualification (Static), (v4.0, effective 12 Dec 2016)*
- *FRM-7053735, Cell & Gene Therapies Morris Plains Environmental Monitoring Report Form for Modules (ISO 7) Qualification/Re-Qualification (Dynamic)* (v4.0, effective 12 Dec 2016).

Novartis stated that the EM results collected during aseptic manufacturing for the conformance lots met the acceptance criteria with no Alert or Action limit excursions.

(b) (4)

Novartis provided the following two reports where they stated that the EM results collected during APV for the CTL019 process (Module (b) (4) and the media preparation process (Module (b) (4) met the acceptance criteria with no Alert or Action limit excursions.

- *PVR5135-5A, Ancillary Media Process APV Report Module 8 July 2016* (approved 29 Sep 2016)

The culture media preparation aseptic process simulation was validated by three TSB runs in Module 8. The APV was executed according to the approved APV batch records and approved protocol *PVP5135-7A* described previously in this memo.

The APV included the worst-case activities and conditions possible during routine operation including (b) (4) operators and routine/inherent and non - routine/corrective interventions.

(b) (4)

- *PVR5135-8A, CTL019 Manufacturing Process APV Report* (approved 21 Oct 2016).

The CTL019 aseptic process simulation was validated by (b) (4) . As described previously in this memo, the APV was executed with minimal hold times (all operations performed in (b) (4) as per the approved Aseptic Process Validation batch records and the approved protocol (PVP5135-8A). The APV included the worst-case activities and conditions possible during routine operation including (b) (4) operators and routine/inherent and non - routine/corrective interventions.

(b) (4)

Reviewer's comments: Novartis stated that the EM collected during the manufacturing of the conformance lots met the acceptance criteria. I reviewed the trending reports for environmental monitoring during the first three quarters of 2016 (conformance lots manufactured February to May 2016), and noted excursions in personnel monitoring that were not investigated. The issue was discussed during the inspection and resulted in a 483 observation. Novartis described in their response to the 483-observation the CAPAs they put in-place to address the observation. Their response was acceptable and it was reviewed in the 483 response review memo. The EM program was discussed during the inspection and documented in the EIR.

Response is acceptable.

Equipment Qualifications

5. You reported that a "comprehensive equipment qualification program has been established at the Novartis Morris Plains manufacturing facility which includes installation, operational, and performance qualification activities."

Please describe and provide the qualification reports or detailed summaries for the following equipment to demonstrate the functionality and suitability for their use during

the manufacturing of CTL019. Also please provide the validation of the cleaning procedure and the routine cleaning/sanitization procedure of the following equipment (if applicable).

- ***a. Thawing device (leukopheresis bags)***
- ***b. Bag rotator***
- ***c. Centrifuge (refrigerated)***
- ***d. Closed automated cell separation system***
- ***e. Conical Tube Magnetic Bead Separator***
- ***f. Flatbed Bag Magnetic Bead Separation System***
- ***g. CO_2 incubators***
- ***h. Autologous Blood Recovery System***
- ***i. Rocking bioreactor***
- ***j. Controlled rate freezer***
- ***k. LN2 freezer***
- ***l. Biosafety cabinet***

Novartis reported that all product contact equipment is disposable, and that the cleaning of the non-product contact equipment was developed based on validated disinfectant effectiveness studies performed at the Morris Plains facility (*VR5135A-1*), reviewed below. They also described the general cleaning procedure used for the outer surfaces of the equipment (*SOP-7018161*).

Novartis stated that the equipment is grouped (e.g. BSCs, incubators, etc…) and the qualification of each member of the group follows the same approach. They provided during the PLI, the number of equipment for each group which is documented in the EIR. For each type of equipment, they listed the document number and provided the summary qualification report and the specific cleaning procedure for a representative piece of equipment of each group as listed in the following Table and reviewed below:

Equipment	**Qualification Report**	**Cleaning SOP**
Thawing device (leukapheresis bags)	*USMB.372.VD, Installation and Operational Qualification Report for the* (b) (4) (approved 23 Feb 2015)	*SOP-7018267, Operation, Cleaning and Maintenance of* (b) (4) *Thawing Device at the* (b) (4) *Morris Plains Site* (v2.0, effective 02 Apr 2014)
Bag rotator	*USMB.472.VD, Installation and Operational Report for* (b) (4) (approved 19 Oct 2015)	*SOP-7018263, Operation and Maintenance of* (b) (4) (v1.0, effective 29 Nov 2013)
Centrifuge (refrigerated)	*USMB.352.VD, Installation and Operational Qualification Report for the* (b) (4) (approved 03 Feb 2015)	*SOP-7018262, Operation, Cleaning and Maintenance of* (b) (4) *at the BiopharmOps Morris Plains Site* (v3.0, effective 09 Feb 2016)
Closed automated cell separation system (b) (4)	*USMB.686.VD, Installation and Operational Qualification Report for the* (b) (4) (approved 14 July 2016)	*SOP-7019400, Operation, Cleaning and Maintenance of the* (b) (4) *at the BiopharmOps Morris Plains Site* (v2.0, effective 15 Jun 2015)

Equipment	Qualification Report	Cleaning SOP
Conical Tube Magnetic Bead Separator (b) (4)	*USMB.392.VD, Installation and Operational Qualification Report for the* (b) (4) approved 07 May 15)	*SOP-7018265, Operation and Maintenance of* (b) (4) (v2.0, effective 24 Sep 2015)
Flatbed Bag Magnetic Bead Separation System (b) (4)	*USMB.404.VD, Installation and Operational Qualification Report for the* (b) (4) (approved 03 Jun 2015)	*SOP-7018264, Operation and Maintenance of* (b) (4) (v1.0, effective 19 Nov 2013)
CO_2 incubators*	*QVD-52596, Installation and Operational Qualification Report for the* (b) (4) (approved 19 Nov 2010)	*SOP-7018428, Operation and Maintenance of Incubators at the Cell and Gene Therapies Morris Plains Site (v.4.0, effective 04 Jan 2017)*
Autologous Blood Recovery System (b) (4)	*USMB.359.VD, Installation and Operational Qualification Report for the* (b) (4) (approved 12 Feb 2015)	*SOP-7018260, Operation, Cleaning, Maintenance, Calibration of the* (b) (4) *at BiopharmOps Morris Plains* (v2.0, effective 15 Apr 2015)
Rocking bioreactor/ CO2 Mixer	*USMB.362.VD, Installation and Operational Qualification Report for the* (b) (4) (approved 17 Apr 2015) *USMB.363.VD, Installation and Operational Qualification Report for the* (b) (4) (approved 15 Apr 2015)	*SOP-7018266, Operation and Cleaning of the Bioreactor System at the Cell and Gene Therapies Morris Plains Site* (v6.0, effective 06 Dec 2016)
Controlled rate freezer	*USMB.542.VD, Installation and Operational Qualification Report for the* (b) (4) (approved 29 Oct 2015)	*SOP-7024802, Operation and Cleaning of the* (b) (4) *at the Cell& Gene Therapies Unit Morris Plains Site* (v3.0, effective 08 Sep 216)
LN2 freezer	*USMB.809.VD, Installation and Operational Qualification Report for the* (b) (4) (approved 19 Oct 2016)	*SOP-7020732, Cell& Gene Therapies Unit Morris Plains Operations, Cleaning and Routine Maintenance of Product Retain LN2 Freezers* (v2.0, approved 03 Mar 2017) *SOP-7017450, Cell and Gene Therapies Morris Plains Operation, Cleaning and Routine Maintenance of LN2 Freezers* (v2.0, approved 02 Mar 2017)
Biosafety cabinet*	*QVD-52266, Installation and Operational Qualification Report for the* (b) (4) (approved 11 Jun 2010)	*SOP-7017618, Operation, Cleaning and Routine Maintenance of Biological Safety Cabinets at Cell and Gene Therapies Morris Plains* (v5.0, approved 14 Nov 2016)
* The qualification reports provided were the initial reports (2010) performed prior to the purchase of the facility by Novartis. The most recent qualification reports were requested and reviewed during the PLI and documented in the EIR.		

21 Pages determined to be not relesable: (b)(4)

(b) (4)

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(b) (4)

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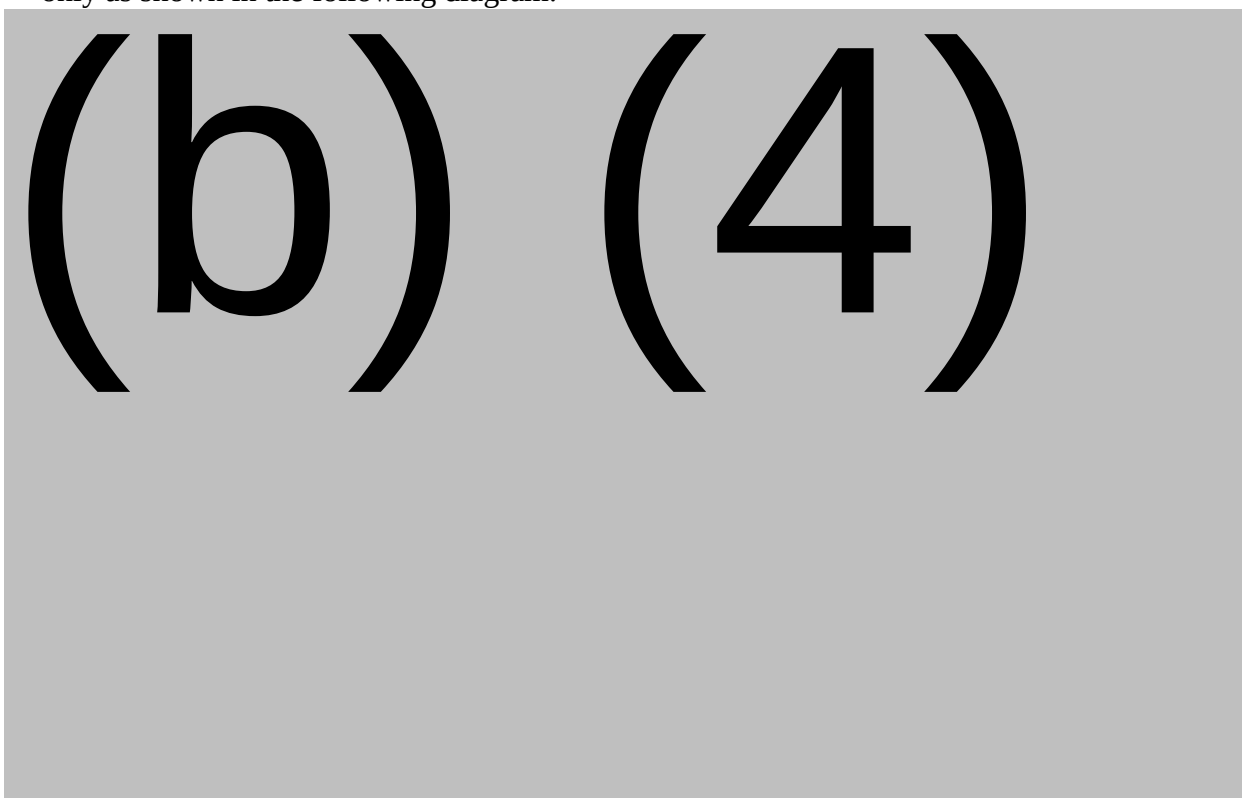
(b) (4) .

6. ***Please list the number of modules and work stations at the Morris Plains facilities, and their respective uses.***

   Novartis explained that the Morris Plains facility has (b) (4) modules each with (b) (4) work stations. Modules (b) (4) have a (b) (4) configuration, and module (b) (is used for training only as shown in the following diagram.



Response is acceptable.

Segregation/ Chain of Identity

7. ***You stated that you would be manufacturing both licensed and IND products in the facility. Please provide your segregation policy between the licensed and unlicensed products, and provide studies and/or risk assessments to support your segregation program.***

Novartis reported that "*the commercial and clinical manufacturing processes utilize the same materials, vector and production methodology*", and that each batch is segregated by workstation with sufficient controls in place to prevent cross contamination of batches (from different patients) and sample mix-up. As such, they considered that segregation of clinical and commercial manufacturing is not needed as it poses minimal risk.

They added that they performed a risk assessment, and mitigated the identified risk associated with the clinical and commercial production of CTL019 (DLBCL and pALL) at the facility. They provided the risk assessment report reviewed below:

- *USMB.394.TD, CTL019 Commercial and Clinical Product Cross- Contamination and Segregation Quality Risk Assessment* (approved 14 Oct 2016).

  Novartis reported that their manufacturing strategy is that the Morris Plains facility will be used "*to manufacture both clinical and commercial CTL019 product for the global markets with the potential for additional, unique cell and gene therapy products*".

  The risk assessment was performed by a cross-functional team to identify and mitigate risks associated with the multiple batch manufacturing. They employed the Failure Mode and Effect Analysis (FMEA) methodology by evaluating the following failure mode areas: Personnel, Equipment, Materials, Method, and Environment.

  The FMEA evaluated risk of cross-contamination of clinical and commercial patient materials as well as product segregation and sample mix-ups.

  The Risk Priority Number (RPN) is determined by (b) (4)

  Novartis reported that they have procedures in place to minimize/prevent cross contamination and mix-ups – these include single use disposable equipment, well trained and gowned personnel, environmental controls, segregation and cleaning procedures, line clearance procedures, use of an operator and a verifier, electronic label printing, label inventory and label verification through (b) (4), using barcodes and barcode readers, label reconciliation, etc... They added that the FMEA identified a medium risk for label mix-ups, and they mitigated that by implementing (b) (4) to enhance and automate label generation throughout the process for apheresis/leukapheresis (APH) and product samples. The FMEA also identified a low risk area (RPN = (b) (4), during testing of leukapheresis sentinel vials prior to manufacturing. Novartis reported that they initiated change control CR-0000015488 to add more controls to this process step.

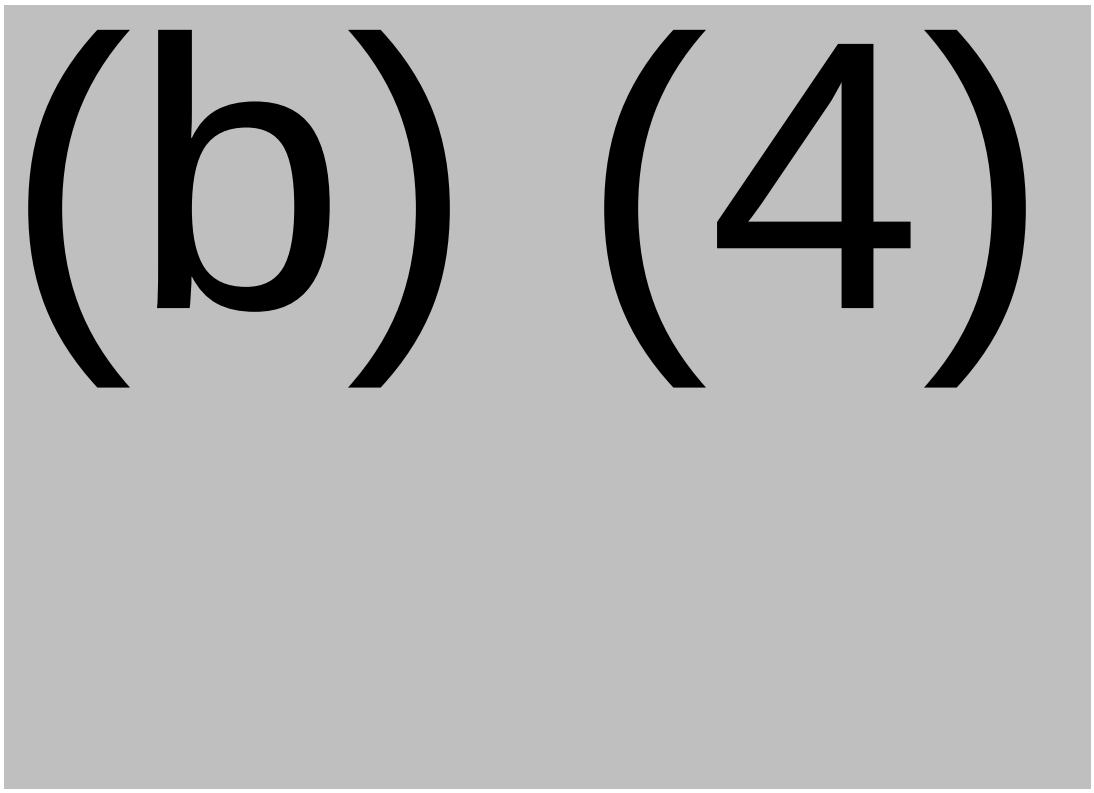
  Reviewer's comment: The manufacturing of each patient lot (whether clinical or commercial) is treated as a "new product". In addition, there is cleaning and line clearance following each manufacturing step of the process to ensure appropriate segregation. We noted during the PLI that there are some differences between the commercial and the clinical batch records and this was discussed in detail during the PLI. However, the manufacturing processes are similar and the operator and verifier for every step follow the work procedures loaded on monitors during manufacturing operations – this process is aimed to prevent mistakes. In addition, there are sufficient APH receipt stations, work stations, incubators, freezers and packaging

and labeling stations, which allows for the manufacturing operations of the various lots in separate areas.

Response is acceptable.

8. ***There will be several leukopheresis units (different patients) processed at the facility at the same time. Please describe the procedures in place, and their qualifications to maintain the chain of identity from the Apehersis center, to receipt at Morris Plains facility to different manufacturing steps (including QC testing), final product (including release testing), and then shipment to the clinic.***

Novartis reported that the chain of identity (CoI) is managed by the validated (b) (4) computer system (the validation of the system is reviewed by the product reviewer on the BLA review team). They described and provided a diagram depicting all the steps managed by the (b) (4) system from the initial patient request to the final product infusion into the patient to assure maintenance of CoI. Four key identifiers – Name, Date of Birth, DIN (Donor Identification Number), and Batch ID are linked and maintained together throughout the process:



Novartis described the procedures for initiating a product request to APH collection followed by receipt and processing at Morris Plains facility and then release of final product, packaging, labeling and shipping for infusion at the clinical site. Both manual and electronic procedures are used to maintain the Chain of Identity.

Reviewer's comment: The maintenance of the chain of identity was presented and discussed in detail during the inspection and documented in the EIR. It is also reviewed in detail in the product review memo.

Response is acceptable.

9. ***You reported that you implemented the*** (b) (4) ***system for the scheduling and monitoring of the process, and that*** (b) (4) ***is integrated with the*** (b) (4) ***system at the Morris Plains site. Please provide a detailed description of the*** (b) (4) ***system, the user requirements, and the validation studies and their results to demonstrate suitability of the*** (b) (4) ***for its intended use, and for compliance with user requirements.***

Novartis explained that the (b) (4) system is the global Pharma TechOps platform for supporting autologous therapies based on widely used standard software products, using standard functionality where possible and limiting customization to the essential requirements only. It consists of (b) (4) . They added that the system supports the supply chain process and manufacturing scheduling process of the Novartis Cell & Gene Therapies Morris Plains site and non-Novartis CMOs (Contract Manufacturing Organizations). The system is comprised of the following technologies:

- (b) (4)

The (b) (4) system maintains GxP management of the following electronic records that are critical to patient safety (PS), product quality (PQ), and data integrity (DI): the Certificate of Conformance (CoC), apheresis label and finished product label, apheresis data form, Chain of Identity.

(b) (4) User Requirements Specifications (URS) incorporates a complete assessment of GxP and ERES (Electronic Record, Electronic Signature) requirements.

The (b) (4) Link is used to capture critical patient identifiers and associate these identifiers with a unique Batch ID that is tracked throughout the Cell & Gene CTL019 logistics and manufacturing process.

They provided the following diagram to illustrate the typical "end-to-end" business process for Cell & Gene Therapy:

Novartis explained that the (b) (4) system performs different functions: traceability of the chain of identity, scheduling and tracking tool and issuance of invoices as listed below:

Process	Function
Chain of Identity	• Recording the patient identity through the automatic creation of a Unique Batch ID for traceability throughout the end-to-end process. • Association of Patient identifiers and a unique apheresis identifier (DIN) to the BatchID for secure maintenance of Chain of Identity.
Scheduling tool Scheduling tool	• Scheduling and tracking of plant appointments. • Scheduling of apheresis appointments in clinical and procurement of apheresis from the treating hospital in commercial. • Scheduling and tracking of apheresis pick-up appointments. • Scheduling and tracking of infusion delivery appointments (clinical). • Plant scheduling and monitoring including resource capacity planning.
Commercial Operations	• Invoicing upon finished product delivery

Novartis reported that the (b) (4) system supports the supply chain process and manufacturing scheduling process of the Novartis Cell & Gene Therapies Morris Plains site and non-Novartis CMOs (Contract Manufacturing Organizations).

Novartis provided Validation Report CLLCHN_VR_01_001_LTA, and stated that the validation of the system is maintained by adhering to (b) (4) operational Handbook.

- *CLLCHN_VR_01_001_LTA,* (b) (4) *Validation Report* (approved 22 Sep 2016)

They stated that the (b) (4) system was internally validated and met the international regulatory requirements. The validation included User Requirements Specifications, Functional Specifications, Design Specifications, Multiple levels of Testing – IQ, OQ, PQ, a Traceability Matrix, and assessment and monitoring of Strategic Vendors.

Reviewer's comment: The (b) (4) validation was discussed during the inspection and will be reviewed in the product review memo.

Response is acceptable.

Process Validation

10. Each patient lot is a separate manufacturing operation with several manual manipulations and incubation steps over a span of (b) (4). Have you performed capacity studies (actual or simulated) to determine the number of lots that the facility/equipment/QC and personnel can handle and sustain per day, week, etc…? Please provide a detailed description and results.

Novartis reported that they have not performed a formal capacity study. They added that the during (b) (4) months (b) (4) of clinical manufacturing, they operated (b) (4) manufacturing modules for CTL019 production and used (b) (4) module for media production, and manufactured an average (b) (4) batches per week. This is a demonstrated capacity performance of (b) (4) batches per month. They added that for (b) (4) consecutive weeks from (b) (4) (within the same 9-months period), the Morris Plains site manufactured (b) (4) batches per week, which is a demonstrated capacity performance of (b) (4) batches per month. The clinical manufacturing was performed by trained operators at the rate of (b) (4). Novartis stated that the anticipating the efficiency to increase with time.

Novartis added that since starting the clinical manufacturing operations, they qualified (b) (4) module for a total of (b) (4) manufacturing and (b) (4) media preparation module (please refer to the response to **Q6** above). They also purchased and qualified additional equipment, and increased the number of trained personnel (cell processing operators, testing technicians, and quality control, scheduling and support functions) to support an increase in flexibility of manufacturing and a capacity up to over (b) (4) batches per month.

Novartis forecast the demand for manufacturing of the drug product for commercial pALL and active clinical trials during the months after approval to be around (b) (4) per month. They consider that the clinical studies performed demonstrate that the Morris Plains facility manufacturing capability surpassed the anticipated demand.

In addition to the currently qualified modules and equipment mentioned above, the Morris Plains Facility is scheduled in 2017 to qualif (b) (4). To support the (b) (4) cleanroom capacity, additional equipment is being purchased and qualified for manufacturing, and quality testing laboratories, and warehouse and support space are planned.

Novartis stated that they actively monitor the facility operations as they relate to capacity across manufacturing, laboratory, warehouse and support functions. They added that they continuously, monitor and adjust to improve efficiency and operations; and that their Quality System ensures proper implementation and planning so that scaling up is done in a controlled way. As additional space is required, proper qualification of the environment, equipment and facilities is ensured as part of bringing these areas into service.

Response is acceptable.

11. You reported that (b) (4) successful PPQ lots were manufactured to qualify each of the (b) (4) pathway and (b) (4) pathway manufacturing processes. Please clarify which modules (and work stations) were used, and whether (b) (4) work station was assigned to (b) (4) lot through the whole manufacturing process of that lot. Please clarify, and describe the cleaning and line clearance procedure for the BSC, and whether it is performed after every step, every day, etc.

Novartis stated that the assignment of modules during the manufacture of the conformance lots will not be the same for routine commercial or clinical manufacturing. They explained that during the manufacturing of PPQ lots, (b) (4) throughout the manufacturing process due to the availability of excess workstations/modules as compared to manufacturing demands. They added that for routine manufacturing, workstations are scheduled based on availability; and that the manufacturing of a lot (over (b) (4) days) can occur (b) (4) work station is used for the aseptic processing of different lots. However for the duration of the operation, the workstation is dedicated for (b) (4) is performed between for each operation by verifying that all components, labels, paperwork and waste have been removed from the workstation.

This same procedure is verified by a second operator at the time of execution. All results are documented in the appropriate sections of the associated batch record.

Novartis clarified that biological safety cabinet (BSC) undergoes cleaning before and after each use by production operations (also referred to as Process Unit (PU)). The pre-cleaning is performed using (b) (4) The post-cleaning is performed using (b) (4)

Novartis provided the list of work stations (WS) and modules used for the conformance lots as summarized in the following Table:

(b) (4)

Reviewer's comments: I discussed the line clearance process during the inspection. Novartis does not have an SOP for line clearance; however the line clearance

instructions are included in the work procedures (WP) for every day of manufacturing process of CTL019. The production operators perform the pre and post line clearance, and document in the batch record. QA performs a review of the cleaning and clearance of the work stations during their review of the batch record, and if any discrepancies are noted, a deviation and investigation will be initiated.

Response is acceptable.

12. Please specify the incubators used for the manufacturing of the conformance lots, and clarify whether lots manufactured concurrently can be incubated in the same incubator. Please explain and describe the segregation of the lots in incubators.

Novartis explained that each incubator contains only one patient lot during use, and thus no segregation of lots in individual incubators is needed.

They clarified that during the manufacture of the PPQ lots one incubator was dedicated to each lot for the different incubation steps of that lot. They added that routine manufacturing does not require that all incubation steps for one lot occur in one specific incubator, and that an incubator is not dedicated to only one lot for the duration of the incubation activities for that particular lot.

Novartis listed the incubators used for the PPQ lots as summarized in the above table (response to **Q11**).

Response is acceptable.

Aseptic process validation (APV)

13. You reported that the aseptic process validation is performed for both CTL019 manufacturing process and for the cell culture media preparation process, every (b) (4) months, in the manufacturing module. It is not clear whether you are referring to a specific module, and the number of BSCs involved in the (b) (4) monthly APV for each process (to simulate worst case conditions). Please explain and justify your response.

Novartis explained that (b) (4) APV runs (media prep or CTL019 process) were performed to qualify each module. After initial qualification, the relevant APV is performed every (b) (4) months on a (b) (4) basis, with (b) (4) module re-qualified every (b) (4) months. They justified the frequency of qualification on the identical design of the modules. They reiterated the APV is performed under worst case conditions – for the simulation of the CTL019 process, APV is performed using (b) (4) BSCs per module; and for the culture media preparation simulations, all (b) (4) BSCs are used. In addition each BSC is qualified every (b) (4) months to ensure it meets its specifications and HEPA certification.

Response is acceptable.

14. You reported that the initial APV for the CTL019 was conducted in Module (b) (, and included (b) (4) work stations (out of (b) (4) work stations) for that module as routine production of CTL019 uses up to (b) (4) BSC (each BSC in a work station). You explained

that (b) (4) ***work station (BSC with its ancillary equipment) was used to simulate the CTL019 process by using*** (b) (4) ***and the other*** (b) (4) ***work stations were used to simulate the CTL019 process using*** (b) (4) ***to create a challenge operations condition in terms of personnel movement and particulate generation during APV. Each APV run in each of the*** (b) (4) ***work stations was completed in*** (b) (4) ***of personnel due to the length of the process. You also reported that the validation process included*** (b) (4) ***validation runs:*** (b) (4) ***station on*** (b) (4) ***days.***

a. ***Please clarify if Module*** (b)(***is the only module that will be used for the production of CTL019. If other modules are used, please explain your APV strategy for qualification of those modules, and justify your response.***

Novartis clarified that modules (b) (4) are used for the production of CTL019. All these modules (b) (4) were initially qualified and validated by APV. These modules are requalified (APV) every (b) (4) months on a rotational basis as described above.

Response is acceptable.

b. ***You reported that during APV, the incubation times were*** (b) (4)***; and you added that worst case incubation times were evaluated using*** (b) (4) ***in a separate study conducted prior to this APV study, and that all results were compliant. Please provide the protocol and summary report for that study.***

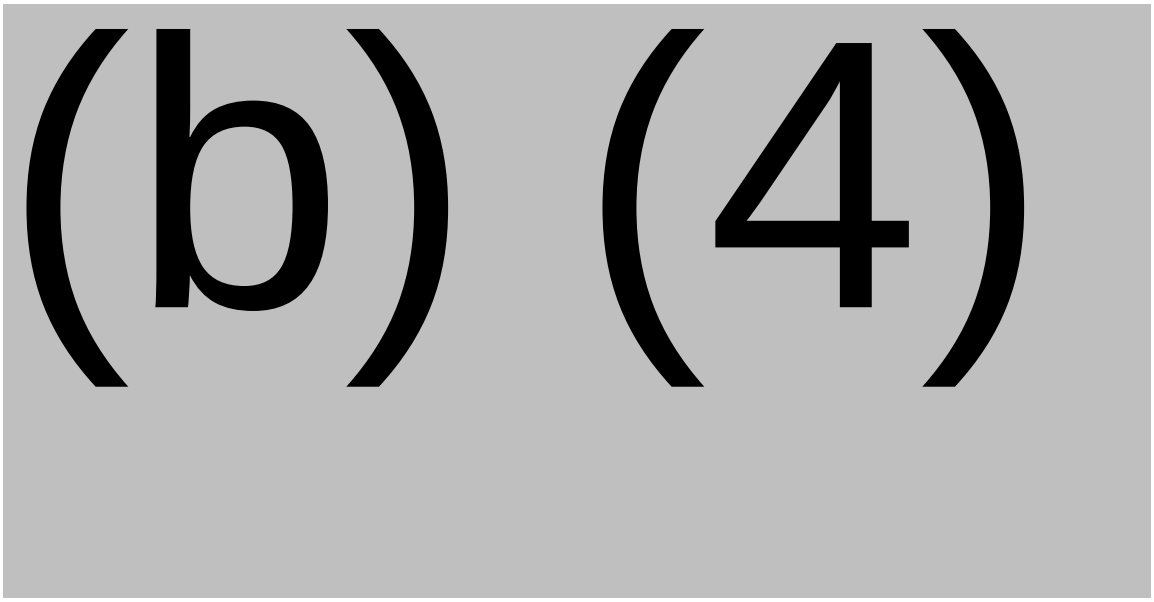
Novartis reported that the worst case media hold (APV) was evaluated according to protocol *USMB.098.TD* and documented in report *USMB.115.TD*. They stated that the incubation duration tested was (b) (4) which is worst case for the current CTL019 manufacturing process that includes (b) (4) .

They provided the protocol and report which are reviewed below:

- *USMB.098.TD, Integrity Study for non-processing times during static & perfusion culture in the CTL019 process* (approved 02 May 2014)
- *USMB.115.TD, Integrity Study Report for non-processing times during static & perfusion culture in the CTL019 process* (approved 23 Jul 2014)

The media hold studies, performed using (b) (4) as summarized in the following Table:

(b) (4)



Response is acceptable.

c. ***You reported that during APV you sampled after each step and that the final container was sampled and tested for sterility. Please clarify whether the final container (filled with*** (b) (4) ***was incubated (and assessed for absence of growth, followed by growth promotion studies), to demonstrate the validity of the aseptic process, and justify your response.***

Novartis confirmed that all final product containers filled with (b) (4) and assessed for absence of growth, followed by growth promotion testing to demonstrate the validity of the aseptic process.

Response is acceptable.

d. ***You also reported the APV for cell culture media preparation was performed in*** (b) (4) ***separate runs in*** (b) (4) ***work stations of Module*** (b) (***. Please clarify if Module*** (b) (***is the only module used for the preparation of cell culture media. If other modules are used, please explain your APV strategy for qualification of those modules, and justify your response.***

Novartis clarified that Module (b) (was also qualified and validated for the preparation of culture media. Both Module (b) (and Module (b) (were initially qualified and then validated for APV and are included in routine re-validation program (b) (4) basis every (b) (4) months) as described above.

Novartis reported in response to **Q10** that they plan to outsource culture media preparation so that they can free Module (b) (for CTL019 commercial and clinical manufacturing.

Response is acceptable.

Continued Process Verification

15. You provided in report PVP5135-6B, Continued Process Verification Plan: CTL019 Product links to several documents, however all the links go to the Reference section of the same document. Please submit the referenced documents.

Novartis provided the following reports:

- AS5135F, Specifications for Clinical Development (approved 19 Aug 2016)
- CQAP5135B, Criticality Assessment of Quality Attributes – Analysis Plan (approved 10 Oct 2016)
- *MI7008911A, Description of Commercial pedALL Manufacturing Process* (approved 18 Nov 2016), which Includes list of equipment (Table 12-1) and their uses in the various manufacturing steps (Table 122-10) of the report.
- *PCMP5135B, CTL019 Process Characterization Master Plan (PCMP)* (approved 20 June 2016)
- *PCSR5135E, CTL019 Process Characterization Summary Report* (approved 09 Dec 2016)
- *PVP5135B, Morris Plains Process Validation Master Plan 2016: CTL019 Product* (26 Apr 2016)
- *QbD1_5135B, Process risk assessment (Drug product QbD1)* (approved 10 Nov 2016)
- *SI5135, Clinical Batch Sampling Instructions* (approved 05 Jan 2017)
- *SOP 7007242, APR/PQR Process Performance Analysis* (v3.0, effective18 Mar 2014)
- *SOP-7013054, Periodic Product Quality Review* (Including Annual Product Review (APR) / Product Quality Review (PQR) (v4.0, effective 28 Sep 2016)
- *SOP-7014994, Continued Process Verification (CPV)* – withdrawn/retired
- *SOP-7015371, Process Validation Lifecycle in PharmOps* (v3.0, effective 18Apr 2016)
- *SOP-7017454, Cell & Gene Therapies Unit Morris Plains Laboratory Investigations in AQWA* (v7.0, effective 07 Nov 2016)
- *SOP-7017813, Morris Plains AQWA Deviations and CAPAs Procedure* (v 5.0, effective 16 Aug 2016)
- *SOP-7018963, Pharma Change Control in* (b) (4) – withdrwan/retired
- *SOP -7019073, BiopharmOps Morris Plains Management of GMP Document Control Storage Locations* (v3.0, effective 16 Mar 2016)
- *SOP-7027692, Global Document Management Process for GxP documents in* (b) (4) (v3.0, effective 01 Dec 2015) (Not yet fully implemented and in use at the Morris Plains Facility)

Response is acceptable.