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

**To:** DATS 659853
STN BLA 125646/0
tisagenlecleucel (CTL019), Kymriah™

**From**: Joan Johnson, CMC/Facility Reviewer, CBER/OCBQ/DMPQ/MRB1

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

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Debra Vause, DMPQ RPM, CBER/OCBQ/DMPQ/ARB
Xiaobin (Victor) Lu, CMC Chair, CBER/OTAT/DCGT/GTB
Randa Melhem, PhD, Reviewer, CBER/OCBQ/DMPQ/MRB2

**Subject**: DMPQ Primary Review Memo for Biologics License Application 125646/0 filed per 21CFR601.2 for tisagenlecleucel (CTL019), Kymriah™.
This review memo focuses on vector substance and vector product manufactured at (b) (4) . respectively.

**Indication:** Treatment of pediatric and young adult patients with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL)

**Applicant** Novartis Pharmaceuticals Corporation (License # 1244)

**Facility:**

1. Vector Substance manufacturer:
   (b) (4)
2. Vector Product manufacturer:
   (b) (4)
3. CTL019 Cell Substance and Cell Product manufacturer:
   Novartis Pharmaceuticals Corporation, 220 East Hanover Avenue,
   Morris Plains, NJ 07950 USA,
   FEI # 3010353512, DUNS# 078640106

**Action Recommendation:** Approval Recommended

**Due Date**: October 3, 2017

## Review Summary

Novartis Pharmaceuticals Corporation (Novartis) submitted a BLA STN 125646/0 for licensure of tisagenlecleucel, commonly described as chimeric antigen receptor (CAR) T cells against CD19. Novartis's internal product code is CTL019 and the proposed trade name is Kymriah™. The product is an autologous T cell product derived from a patient leukapheresis, genetically modified using lentiviral transgene vector, selectively expanded in culture and formulated as a final single-dose cell suspension for infusion. Tisagenlecleucel is indicated for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL).

The purified lentiviral vector bulk substance and sterile filtered /concentrated vector product are manufactured at (b) (4), respectively. The qualification, validation and control programs associated with product, facility, equipment, process, container closure and shipping activities at both manufacturing sites were reviewed and appeared to be adequate for the GMP manufacture of CTL019 vector substance and vector product for further use as a critical component in the final cell product manufacturing process at Novartis NJ facility.

DMPQ performed a PLI (Pre-License Inspection) at both the (b) (4) facility initiated on (b) (4). The PLI was classified as VAI (Voluntary Action Indicated) based on the firms commitment to timely implement corrective actions to address deficiencies identified during the PLI.

## Items Submitted and Reviewed:

| | |
|---|---|
| 1.1.2 | Form FDA 356h |
| 1.2 | Cover Letter |
| 1.11.1 | Quality Information Amendment |
| 1.12 | Environmental Analysis |
| 2.2 | Introduction |
| 2.3 | Quality Overall Summary-introduction |
| 2.3.S | Drug Substance –vector |
| 2.3.A | Appendices—(b) (4) |
| 3.2.S | Vector DS and DP (all sections under CTL019 murine HIV-1 Vector) |
| 3.2.A.1 | Appendices (all sections under CTL019 murine HIV-1 Vector) |
| 3.2.A.2 | Adventitious Agents (under DMPQ purview) |
| 3.2.R | Reginal Information (under DMPQ purview) |

## Review Memo Format and Table of Contents

I have provided a summary of information provided in the submission that is under DMPQ purview as outlined in SOPP 8401.4. In general, my Review Assessment / Comments are provided at the end of review sections in a lined box. Any information requests (IRs) related to review are included in **bolded** text. The firm's response to that IR or a response summary will immediately follow in *italicized text*. My review and assessment of the IR response and subject topic will follow in the lined box.

## Table of Contents

## Regulatory History

The following IRs was requested upon initial review of the BLA on March 7, 2017 prior to filing:

***For*** (b) (4) ***Facility***

1. Please provide environmental monitoring performance qualification (EMPQ) summary report including dynamic monitoring data and sampling locations for the (b) (4) where manufacturing processes occur. Please provide EM data summary (including BSCs) during the manufacturing of the process validation lots for the vector substance.
2. Please provide the most recent requalification of the HVAC system for AHU Unit (b) (4) and clarify if ventilation is accomplished by single pass or recirculated air, and justify your response.
3. Please confirm that (b) (4) area is not utilized for CTL019 vector substance manufacturing and provide your segregation procedure or program and associated study or risk assessment for cross-contamination prevention.
4. Please provide the qualification summary report for the following equipment to demonstrate the functionality and suitability for their use during the vector substance manufacturing process.
    - Wave Mixer
    - Orbital shaker
    - Biological Safety Cabinet
    - Centrifuge
    - (b) (4)
5. Please provide summary report of disinfectant efficacy study for cleaning agents and disinfectants used for routine equipment and production room cleaning at the vector substance manufacturing facility.
6. Please provide validation summary report for the VHP treatment of the manufacturing suite during product change over.
7. Please provide aseptic process validation summary report for the open manipulations performed in biologic safety cabinets.
8. Please provide shipping validation /qualification summary report including supporting data for the vector substance shipped from (b) (4) for final processing and fill

***For*** (b) (4) ***Facility***

9. For the filling isolator, please provide summary report of the following:
    - IQ, OQ and PQ (most recent requalification if applicable) including EM monitoring frequency, criteria and sampling points.
    - Smoke studies performed including acceptance criteria and results.
    - Validation study for the cleaning and decontamination of the isolator.
    - Sterilization of the isolator and consumables s such as tubing, (b) (4) membrane, stoppers and glass vials used inside the isolator.
10. Please provide EM data summary during the manufacturing of the process validation lots for the vector product and the most recent aseptic process validation (media fill) lots.

11. For equipment qualification, please provide summary report of IQ, OQ and PQ for all GMP critical equipment used in the vector product manufacturing process both in Building (b) (4) and Building (b) (4).
12. Please provide summary report of disinfectant efficacy study for cleaning agents and disinfectants used for routine equipment and production room cleaning at the vector product manufacturing facility.
13. Please provide a complete list of all other products handled in manufacturing Building (b) (4) and how they are segregated from the CTL019 vector product.
14. Please provide a summary report of the most recent Aseptic Process Validation runs (media fills).
15. Please provide shipping validation/qualification summary report including supporting data and worst case conditions for the vector product shipped from (b) (4) to Novartis NJ plant for manufacturing of CTL019 cell product.

Amendment 13 was received on April 7, 2017 as response to the IRs listed above. Review of the response is provided in the respective sections below for each facility in a lined box.

**Environmental Assessment**

Novartis is requesting a categorical exclusion for an Environmental Assessment as required under 21 CFR 25.31(c) because CTL019 is an autologous T cell product genetically modified with a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). The final product is not viable in the environment and is degraded into naturally occurring substances. The potential for release in the environment of the lentiviral construct is considered negligible due to the low probability of free viral particle carry over in the final drug product.

Novartis attests that the drug substance and drug product are manufactured according to current local environmental legislations and no extraordinary circumstances exist, which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

Based on the information submitted and the nature of the product, I am in agreement with the categorical exclusion.

**Facility Table**

| Manufacturer Name/Location | Manufacturing/Testing Activities |
|---|---|
| (b) (4) | (b) (4) |
| (b) (4) | (b) (4) |
| **Novartis Pharmaceuticals Corporation/US**<br>220 East Hanover Avenue,<br>Morris Plains, NJ 07950 USA,<br>FEI # 3010353512 | Cell Substance and Cell Product:<br>Manufacture of CTL019 DS and DP<br>Quality Control and Stability Testing of CTL019 DS and DP.<br>Quality Control of vector product (functional test of expressed transgene and MOI assay)<br>Testing and release of vector as incoming material |

The CTL019 (murine) HIV-1 vector (CTL019 vector) is manufactured for Novartis under contract by (b) (4) who produces the (b) (4) subsequently undergoes further aseptic processing and filling to yield final filled vector product at (b) (4).

Novartis has quality oversight of (b) (4) via third party quality agreement established in 2014 and ensures that (b) (4) oversight of the contract filling operations at (b) (4) are in agreement with Novartis requirements. In addition, Quality control of vector product (functional test of expressed transgene and MOI assay), testing and release of vector product as incoming material are performed by Novartis NJ facility. Release of vector product batches for use in CTL019 manufacture at Novartis NJ facility and quality oversight of (b) (4) is performed by Novartis Basel site in Switzerland.

There are no CTL019 manufacturing activities conducted at the Novartis Basel Switzerland site.

**Product Background**

CTL019 is an adoptive cancer immune-cellular 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 is made up of autologous T cells derived from a patient leukapheresis and selectively expanded in culture. The manufacturing process is continuous from receipt of leukapheresis to cryopreservation. The final product is cryopreserved and stored in vapor phase liquid nitrogen at ≤ -120$^0$C. The final container is (b) (4) freezing bag (510K cleared under (b) (4) in two sizes: (b) (4) for volumes 10-30 mL and (b) (4) for volumes 30-(b) (4). The proposed shelf life is 9 months.

The composition of the final filled vector product is described in the table below:

| (b) (4) | |
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**Manufacturing Process Overview**

**Note: This review memo covers only the vector substance and vector product aspect of the manufacturing process.**

The CTL019 (murine) HIV-1 lentiviral vector (CTL019 vector) is manufactured under contract by (b) (4)

The firm stated that the vector substance and vector product manufacturing process utilizes single use disposable item for all product contact equipment and in-process components. No equipment cleaning validation is required at both the (b) (4).

The CTL019 cell product manufacturing process at the Novartis NJ facility is continuous without any intermediates and drug substance holding steps. The overall duration of the manufacturing process takes up to (b) (4) and consists of (b) (4) main phases:

- Leukapheresis material thawing and washing, T-cell enrichment, T cells activation and first vector transduction (b) (4)
- Second vector transduction, cell expansion in static and (b) (4) , cell harvest, formulation and cryopreservation ((b) (4)

The CTL019 cell manufacturing process is reviewed by DMPQ reviewer (R. Melhem) in a separate review memo.

**A. <u>Vector Substance Facility-</u>**(b) (4)

(b) (4)
(b) (4)

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**B. Vector Product Facility at** (b) (4)

(b) (4)

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