



CBER REGULATORY REVIEW MEMORANDUM

Date 19 September, 2017

From Hyesuk Kong, Ph. D
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Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To Biologics License Application Submission Tracking Number # 125643/0

Subject BLA: Review of Sterility, Mycoplasma, and Endotoxin Test Method Qualifications;
and (b) (4) Sterility and (b) (4) Mycoplasma Test
Method Validations for Yescarta (axicabtagene ciloleucel, KTE-C19)

Through James L. Kenney, D.Sc., Acting Director, DBSQC/OCBQ/CBER/FDA

Applicant Kite Pharma, Inc. (Kite)

Product Yescarta™ (axicabtagene ciloleucel, KTE-C19)

Biologics License Application (BLA) Submission Tracking Number (STN) 125643/0

Submission Received by CBER 31 March, 2017

Review Completed 19 September, 2017

Material Reviewed

Method qualifications for: 1) sterility; 2) mycoplasma; and 3) (b) (4) endotoxin test (b) (4); and method validations for 1) (b) (4) sterility test and 2) (b) (4) for the detection of mycoplasma.

Executive Summary

After a thorough review of this BLA, this reviewer finds Kite's (b) (4) sterility test method and (b) (4) mycoplasma test method using (b) (4) performed on the Yescarta^M drug product (DP) were validated in accordance with (b) (4), respectively, by demonstrating the tested product matrixes are suitable for these intended test methods. Kite demonstrated these test methods provide assurance of tested matrix safety and purity that is equal to, or better, than the assurance of the current compendial methods. Also, sterility and mycoplasma using (b) (4) method (b) (4) endotoxin (b) (4) DP test methods were qualified in accordance with (b) (4)

(b) (4) respectively, by demonstrating these matrixes are suitable for the intended test methods.

Background

On 31 March, 2017, Kite submitted this BLA for Yescarta™ (axicabtagene ciloleucel, KTE-C19) for the treatment of adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma who are ineligible for autologous stem cell transplant.

Yescarta™, axicabtagene ciloleucel is a novel autologous, immunotherapy, which involves a patient's own T-cells with a transgene encoded chimeric antigen receptor (CAR) to target CD19, an antigen expressed on the cell surface of B cell lymphomas and leukemas. The autologous CD3+T cells are transduced with a replication-deficient retroviral vector (b) (4) Vector) and contain signaling domains: CD28 and CD3 zeta (ζ). The activation domains include the cytoplasmic portion of CD28 linked to cytoplasmic portion of the terminal CD3-zeta element. The CD3-zeta domain activates the downstream signaling cascade leading to T cell activation, proliferation and acquisition of effector functions. The CD28 signaling element provides a co stimulatory signal deployed through antigen recognition rather than separate interaction with co stimulatory molecules. Upon binding to CD-19 expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of transduced T cells.

Yescarta™ is available as a cell suspension for intravenous infusion. Each single infusion bag of Yescarta™ contains a suspension of anti-CD19 CAR T cells in approximately 68 mL for a target dose of autologous T cells of 2×10^6 anti-CD19 CAR T cells/kg body weight (range: (b) (4) cells/kg), with a maximum of 2×10^8 anti-CD19 CAR T cells supplied in a cryostorage infusion bag. To ensure that viable live autologous cells are administered to the patient, the Yescarta™ bag is stored in the vapor phase of liquid nitrogen and must remain frozen until the patient is ready for treatment, and supplied in a liquid nitrogen dry shipper.

The (b) (4) Vector is manufactured at (b) (4) and is tested for (b) (4)

The KTE-C19, axicabtagene ciloleucel final product is manufactured by Kite, CA, USA. The manufacturing process is a (b) (4) process, as the transition from axicabtagene ciloleucel drug substance (DS) to DP (b) (4). The axicabtagene ciloleucel DP is tested for (b) (4) sterility, mycoplasma using (b) (4) endotoxin. These methods were originally validated at Kite's clinical manufacturing site (b) (4) for testing of clinical lots and were subsequently transferred to its commercial manufacturing site (b) (4) for testing of commercial lots.

The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews endotoxin release specifications to ensure they reflect process capability and are regulatory compliant. These review activities support DBSQC's lot-release mission: the confirmatory testing of submitted product samples; review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. In addition, DBSQC has subject matter expertise in mycoplasma method qualification, antimicrobial effectiveness and other test methods. Therefore, this review will focus on the validation of the (b) (4) system for sterility and (b) (4) for mycoplasma testing for DP, to determine if the product matrix is suitable for testing using the intended methods and if these methods provide assurance equal to or greater than the compendial methods. In addition, the qualification of (b) (4)

vector to ensure the matrix is suitable for the intended test method.

Review

(b) (4) Vector

(b) (4) [Redacted]
(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

(b) (4)

(b) (4)

Axicabtagene ciloleucel (KTE-C19) Drug Product

(b) (4) Method Qualification for axicabtagene ciloleucel (KTE-C19) DP
Kite qualified their (b) (4) method on three lots (i.e., lots: (b) (4)
of KTE-C19 DP matrix in (b) (4) at (b) (4) to demonstrate their axicabtagene ciloleucel DP matrix is
suitable for the intended test method in accordance with (b) (4)

(b) (4)

(b) (4)

(b) (4)

4 Pages determined to be non-releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

Conclusion

After a thorough review of the information submitted in this BLA, this reviewer finds Kite's (b) (4) sterility and the (b) (4) mycoplasma test method performed on DP were validated in accordance with (b) (4), respectively, by demonstrating the tested product matrix is suitable for these intended test methods. Kite demonstrated these test methods provide assurance of tested matrix safety and purity that is equal to, or better, than the assurance of the current compendial methods. Also, the sterility, mycoplasma using (b) (4), and (b) (4) endotoxin (b) (4) DP) test methods were qualified in accordance with (b) (4) respectively, by demonstrating these matrixes are suitable for the intended test methods. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.