Food & Drug Administration
Silver Spring, MD 20993

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To The file: STN 125773/0

From Seth Schulte, M.S.
Laboratory of Microbiology, *In-Vivo* Testing and Standards (LMIVTS)
Division of Biological Standards and Quality Control (DBSQC)

Through Maryna Eichelberger, Ph.D., Director, DBSQC
Simleen Kaur, M.S., Acting Chief, LMIVTS

Applicant Iovance Biotherapeutics, Inc. (Iovance)

Subject Biologics License Application (BLA): Review of endotoxin, sterility, and mycoplasma analytical methods used for Lifileucel (AMTAGVI)

Recommendation: Approval

Executive Summary

The endotoxin, sterility, and mycoplasma analytical methods used for testing and release of AMTAGVI and the associated analytic method qualifications or validations were reviewed. The assays were adequately described and shown to be suitable for their intended purpose.

Conclusion

The analytical methods and their qualifications or validations reviewed for AMTAGVI drug product were found to be adequate for their intended use.

Documents Reviewed

Information in sections of the original submission that describe control of drug product (DP) (3.2.P.5), including descriptions of DP specifications, analytical procedures of DP, and qualification or validation of these analytical procedures were reviewed. In addition, responses to CBER's Information Requests (IRs) received on June 20, 2023 (Amendment #12), July 25, 2023 (Amendment #22), August 16, 2023 (Amendment #27), and September 6, 2023 (Amendment #37) were also reviewed as mentioned below.

Background

On March 27, 2023, Iovance submitted this BLA for AMTAGVI, a preparation of autologous, non-genetically modified tumor-infiltrating lymphocytes (TIL) for the treatment of adult patients with unresectable or metastatic melanoma previously

treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

AMTAGVI is composed primarily of (b) (4) lymphocytes obtained from resected tumor material and expanded ex vivo in the presence of cytokine interleukin-2, anti-CD3 antibody, and (b) (4) feeder cells. One dose of AMTAGVI contains (b) (4) total viable cells in a total volume of (b) (4)

AMTAGVI is administered following a nonmyeloablative lymphodepletion (NMA-LD) preparative regimen utilizing cyclophosphamide and fludarabine. Three to 24 hours after TIL infusion, aldesleukin is administered at 600,000 IU/kg every eight hours for up to six doses to support activation and expansion of the infused lymphocytes. Patients receive a single course of TIL treatment regimen.

Due to the continuous 22-day manufacturing process from tumor resection to final formulation, there is no drug substance, and all release testing is performed on the final formulated DP.

1. Endotoxin Method

Introduction

Endotoxin testing for AMTAGVI DP is performed at (b) (4) (b) (4) Iovance Cell Therapy Center (iCTC) facilities in Philadelphia, PA. Specification of (b) (4) must be met for release of AMTAGVI.

Method

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

The (b) (4) The method is described in more detail below together with the tests performed to determine suitability of the test method for its intended use.

The original qualification report for endotoxin contained a proposal for testing the DP (b) (4) and lacked sufficient information to complete the review. Therefore, IRs were sent requesting endotoxin testing be performed on the (b) (4) DP (b) (4) (b) (4) and missing information for the method qualification. Reponses were received on June 20, 2023 (Amendment #12), July 25, 2023 (Amendment #22), and August 16, 2023 (Amendment #27) which were found acceptable and explained below.

(b) (4) Qualification for DP
(b) (4) qualified their (b) (4) method for DP to determine if the method is suitable under the actual conditions of use. The test was performed using (b) (4) lots of DP (b) (4) The (b) (4) of DP was calculated to be (b) (4) by (b) (4) (b) (4)

AMTAGVI DP was tested for (b) (4) (b) (4)
Additional method verification testing was performed at (b) (4) (b) (4) As a result, (b) (4) testing (b) (4) was selected for DP (acceptance criterion is (b) (4)

iCTC qualified their (b) (4) method for DP to determine if the method is suitable under the actual conditions of use. The test was performed using (b) (4) lots of DP (b) (4) The (b) (4) of DP was calculated to be (b) (4) as described under (b) (4) qualification study above.

AMTAGVI DP was tested for (b) (4)
Additional method verification testing was performed at (b) (4) of (b) (4) (b) (4) As a result, (b) (4) testing (b) (4) was selected for DP (acceptance criterion is (b) (4)

The (b) (4) results for all DP samples found during the method verification testing were all within the release specification of (b) (4) and were found acceptable.

Conclusion
The method suitability tests were performed and compliant with (b) (4) and the test results indicate there is no product interference from DP test samples, thus indicating the (b) (4) test method is appropriate under the actual conditions of use.

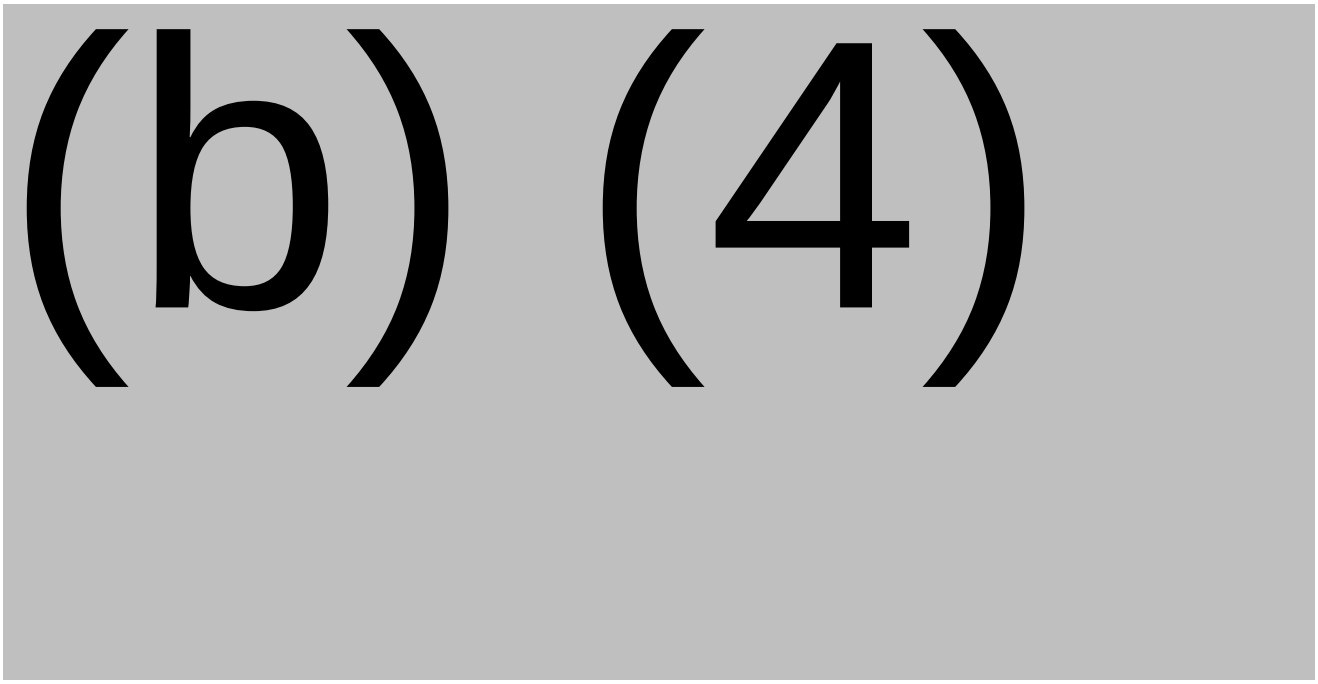
2. Sterility Method
Introduction
Sterility testing for AMTAGVI DP is performed at Iovance Cell Therapy Center (iCTC) (b) (4) facilities in Philadelphia, PA.
Specification of 'No growth' must be met for release of AMTAGVI.

Method
(b) (4) The method is described in more detail below together with the validations that were performed to determine suitability of the test method.

The original validation reports for sterility lacked sufficient information to complete the review. Therefore, IRs were sent requesting data and clarification to fulfill these deficiencies. Reponses were received on June 20, 2023 (Amendment #12), August 16, 2023 (Amendment #27), and September 6, 2023 (Amendment #37) which were found acceptable and explained below.

Sterility Test Validation for DP
iCTC performed a detailed validation study for the (b) (4)

2 pages have been determined to be not releasable: (b)(4)



Conclusion
The method suitability tests were performed and compliant with (b) (4) (b) (4) and the test results indicate there is no product inhibition of microorganism growth, thus indicating the (b) (4) sterility test method is appropriate under the actual conditions of use.

3. Mycoplasma Method
Introduction
Mycoplasma testing for AMTAGVI DP is performed at (b) (4) (b) (4) Specification of 'Not Detected' must be met for release of AMTAGVI.

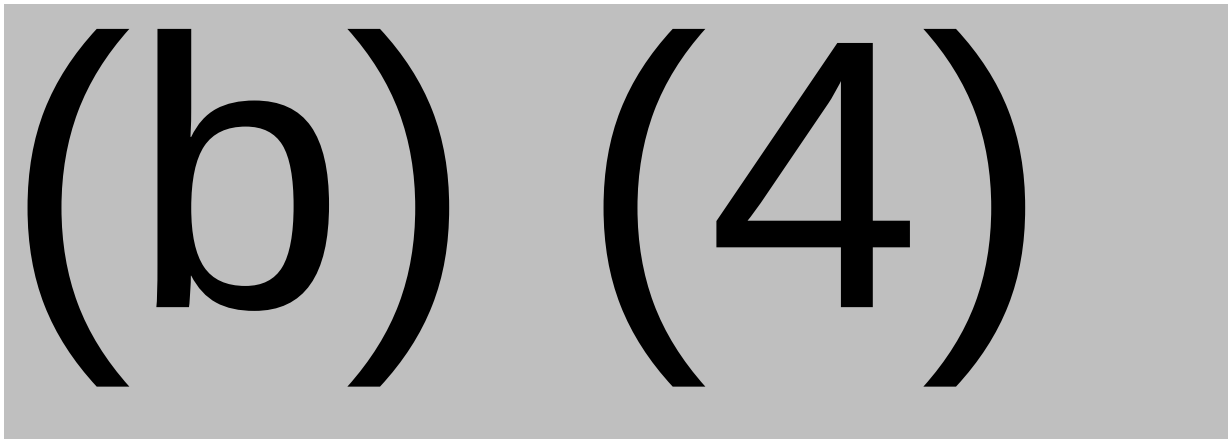
Method
The test for mycoplasma is performed in accordance with (b) (4) (b) (4) The method is described in more detail below together with the tests performed to determine the suitability of the test method for its intended use.

The original validation reports for mycoplasma lacked sufficient information to complete the review. Therefore, IRs were sent requesting data and clarification to fulfill these deficiencies. Reponses were received on June 20, 2023 (Amendment #12), August 16, 2023 (Amendment #27), and September 6, 2023 (Amendment #37)

which were found acceptable and explained below. Additionally, Drug Master File No. (b) (4) was authorized and reviewed as part of the test validation described below.

Mycoplasma Test Validation for DP

(b) (4)



Conclusion

The method validation tests were performed and compliant with (b) (4) (b) (4) and the test results indicate there is no product interference from the test sample. The (b) (4) method was demonstrated to provide assurance equal to or greater than the (b) (4) method and is appropriate under the actual conditions of use.