DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

CBER REGULATORY REVIEW MEMORANDUM

Date 24 March, 2021

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Office of Compliance and Biologics Quality (OCBQ)
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Food and Drug Administration (FDA)

To Biological License application (BLA) Submission Tracking Number 125736/0

Subject Review of Endotoxin, (b) (4) Sterility and (b) (4) Mycoplasma Test Method Validations for ABECMA® (idecabtagene vicleucel), also known as ide-cel, bb2121

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Applicant Celgene Corporation (Celgene)

Product ABECMA® (idecabtagene vicleucel), also known as ide-cel, bb2121

Biological License Application Submission Tracking Number (STN) 125736/0

Submission Received by CBER 27 July, 2020

Review Completed 24 March, 2021

Material Reviewed
Method qualifications for the bacterial endotoxin test (BET) and method validations for the (b) (4) sterility test and the (b) (4) using (b) (4) for the detection of mycoplasma were reviewed. In addition, information request responses received 11 January of 2021 and 01, 11, and 12 March of 2021 were also reviewed.

Executive Summary
After a thorough review of this BLA, this reviewer finds the BET method was qualified in accordance with (b) (4) and the (b) (4) sterility test method was validated in

accordance with (b) (4), by demonstrating these methods are suitable under the actual conditions of use. However, more information is required to complete review of the (b) (4)-based mycoplasma test method using (b) (4). CBER is requesting a comparability study between the mycoplasma (b) (4) and (b) (4) methods to show the sensitivity of the alternate method is equal to or greater than that of the (b) (4) method for ABECMA®.

Background

On 27 July 2020, Celgene submitted this BLA for ABECMA® (idecabtagene vicleucel), also known as ide-cel, bb2121, for the treatment of adult patients with relapsed or refractory multiple myeloma after at least three prior therapies.

ABECMA® is a B-cell maturation antigen (BCMA) second generation chimeric antigen receptor (CAR) T cell therapy. It binds to BCMA on the surface of multiple myeloma cells leading to CAR T cell growth, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells. The cell therapy is intended for patients with prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody. ABECMA® is provided as a single dose for infusion containing a suspension of CAR-positive T cells in one or more infusion bags. The target dose is 450 x 10^6 CAR-positive T cells within a range of (b) (4) x 10^6 CAR-positive T cells.

The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and suitable under the actual conditions of use. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released per their product's licensed test method specifications. In addition, DBSQC has subject matter expertise in mycoplasma method qualification, and other test methods. Therefore, this review will focus on the validation of the (b) (4) system for sterility and (b) (4) using (b) (4) for mycoplasma testing, to determine if the product matrix is suitable for testing using the intended methods and if these methods provide respective sterility and mycoplasma assurance equal to or greater than the (b) (4) methods. In addition, the qualification of bacterial endotoxin test method will be reviewed to ensure it is suitable for the intended use.

Review

(b) (4) BET Method Qualification

(b) (4) BET utilizes (b) (4) methodology measures (b) (4)

(b) (4)

Celgene qualified their (b) (4) BET by testing three batches (batch numbers: (b) (4)) in triplicate to demonstrate their method is suitable under the actual conditions of use in accordance with (b) (4) . The MVD was calculated to be (b) (4) by dividing the (b) (4) by the (b) (4) .

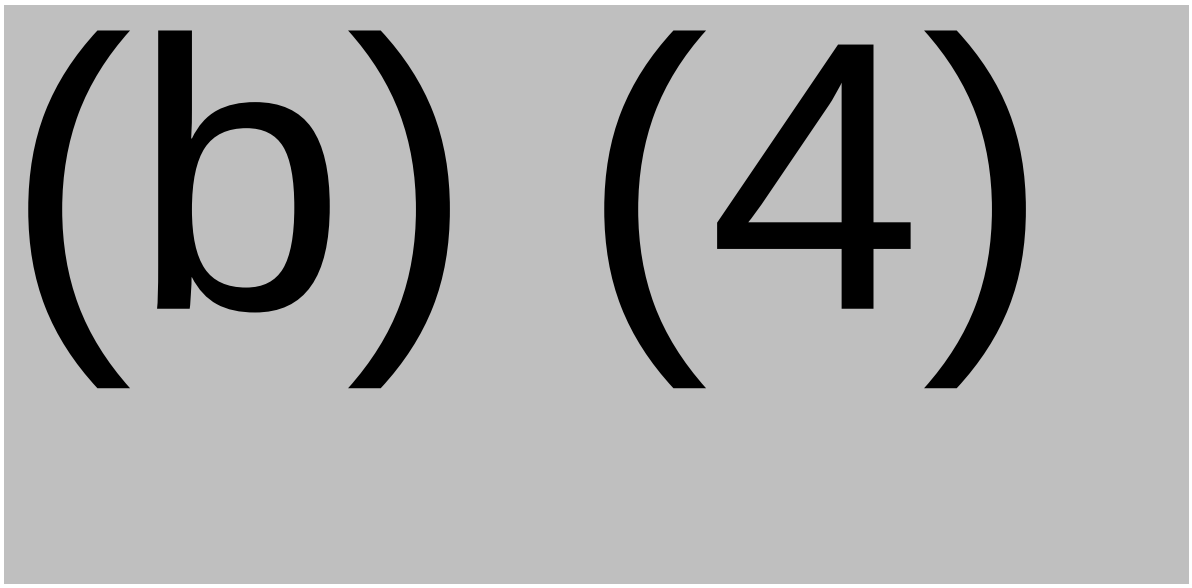
A suitability test for interfering factors was performed on spent media samples at (b) (4) dilutions, where the spike recoveries for positive product control were between (b) (4) , which were within the (b) (4) acceptance criteria. A sample testing dilution of (b) (4) was selected, and all test qualification parameters were compliant with the requirements in (b) (4) . The bacterial endotoxin sample test results analyzed during the method suitability test for interfering factors were less than the lowest point on the achieved standard curve, providing results (b) (4) , which were within the release specification of (b) (4) .

After review of the information submitted in this BLA, this reviewer finds Celgene's (b) (4) BET test method was qualified and performed in accordance with (b) (4) , demonstrating it is suitable under the actual conditions of use.

(b) (4) Sterility Test Validation
(b) (4)

Celgene performed a detailed validation study for (b) (4) sterility system for ABECMA® that covered limit of detection (LOD), specificity, robustness and ruggedness in accordance with (b) (4) as well as comparability study with (b) (4) sterility method. Repeatability results were determined from LOD and ruggedness experiments. Throughout the validation, tests for each organism were performed in triplicate.

(b) (4)



Specificity

Specificity is the ability of the method to detect a variety of microorganisms. Celgene evaluated specificity using samples volumes of (b) (4) . Microorganisms listed in Table 1 were tested at an inoculum concentration of (b) (4) . Specificity was confirmed by performing microbial identification and confirming the organism identified matched that of the corresponding organism inoculated. The ABECMA® product matrix did not interfere with the growth and detection of the (b) (4) microorganisms tested indicating the (b) (4) test method demonstrates acceptable specificity.

Limit of Detection (LOD)

The LOD was assessed by demonstrating the lowest concentration of microorganisms that could be detected form the sample matrix, as the test specification is 'no growth detected/observed'. Celgene performed their LOD test using (b) (4) inoculum

concentrations (i.e., (b) (4)) of the microorganisms listed in Table 1. Undiluted samples ((b) (4) were tested at each inoculum concentration, in triplicate, for each microorganism. LOD was also tested for the (b) (4) sterility test method ((b) (4)). The LOD acceptance criteria was detection of all (b) (4) organisms in at least one replicate at the (b) (4) inoculum concentration will establish the LOD for this assay.

All organisms inoculated at (b) (4) were detected in each replicate within (b) (4) in the (b) (4) sample. Growth was detected at the (b) (4) in at least one replicate in (b) (4) for all (b) (4) organisms tested in the (b) (4) sample. Results from inoculation at (b) (4) show growth detection in (b) (4) of replicates for the (b) (4) microorganisms, respectively. Collectively, these results established the (b) (4) sterility test method has a LOD of (b) (4) with an average-(b) (4) to detection of (b) (4) for all (b) (4) microorganisms.

Celgene's validation data support the use of the (b) (4) assay with a LOD of (b) (4) for (b) (4) organisms and at an incubation duration of (b) (4) .

Robustness and Ruggedness

Robustness is the ability of the method to remain unaffected by small, but deliberate variations in method parameters and provides an indication of method reliability. Robustness was determined using different sample volumes (i.e., (b) (4)) during the LOD test. Growth of all microorganisms were detected in (b) (4) in a (b) (4) sample volume inoculated with (b) (4) . (b) (4) sample volume showed growth within (b) (4) and a (b) (4) sample showed growth within (b) (4) . Robustness was demonstrated using different sample volumes inoculated with (b) (4) during the LOD study.

Ruggedness is the degree of test results reproducibility obtained by analysis of the same samples under a variety of normal test conditions, which was assessed during the LOD study to address analyst variability and reproducibility between (b) (4) different analysts. The tests performed using different analysts during the LOD test demonstrated acceptable robustness and ruggedness of the (b) (4) sterility test method.

Information Request and Review

The following questions were sent in an IR to the sponsor on January 11, 2021 and response was received on January 25, 2021.

a. Based on the data provided in your validation report ((b) (4) FOR bb2121 (ide-cel), CBER requests sterility testing using (b) (4) method be performed for (b) (4) using (b) (4) undiluted ide-cel product instead of your proposed for (b) (4) using (b) (4) of undiluted product.

Also, CBER does not agree with using only (b) (4) for sterility testing. The test must include:

(b) (4)

Review of the Response:
The sponsor acknowledges CBER's request related to the test duration, test volume, and medium selection using the (b) (4) method. The sponsor clarified their test method meets CBER requirements, as (b) (4) of undiluted drug product is inoculated into (b) (4), for a total test volume of (b) (4) of undiluted drug product. (b) (4) The test method is described in Method Validation Package – Method – Sterility b (b) (4). In addition, Table 1 compares CBER requirements to the Sponsor's method.

The following questions were sent in an IR to the sponsor on March 01, 2021 and response was received on March 09, 2021.

b. Based on the data provided in your validation report (Table 42 of (b) (4) system rapid microorganism detection for bb2121 (ide-cel)), CBER requests sterility testing using (b) (4) method be performed using (b) (4) undiluted ide-cel product per media bottle instead of your proposed (b) (4) of undiluted product per media bottle. Please comment.

Review of the Response:
The Sponsor acknowledges CBER's request to complete sterility testing on the (b) (4) with (b) (4) of undiluted ide-cel drug product per media bottle. The Sponsor will amend the sterility testing method for ide-cel from (b) (4) undiluted drug product per media bottle to (b) (4) undiluted drug product per media bottle.
A timeline for implementing the modified method is described below.

- All associated SOPs pertaining to the method will be updated by April 15, 2021.
- All staff will be trained on the updated method and procedures by April 29, 2021.
- All commercial batches of ide-cel will be tested using the updated method beginning on April 30, 2021.

The following questions were sent in an IR to the sponsor on March 11, 2021 and response was received on March 12, 2021.

c. Please confirm that all Celgene's commercial batches of ide-cel will be tested using the updated method, with (b) (4) of undiluted ide-cel drug product per media bottle.

Review of the Response:
The sponsor confirms that all commercial batches of ide-cel will be tested using the updated method, with (b) (4) of undiluted ide-cel drug product per media bottle. The sponsor submitted the updated method (Section 3.2.P.5.2 - Sterility) and method SOP (Method Validation Package - Method - Sterility by (b) (4)) to the BLA on March 19, 2021.

After review of the information submitted in this BLA, this reviewer recommends the approval of (b) (4) Sterility Test method, as the method was validated in accordance with (b) (4) and was found to be suitable for its intended use.

(b) (4) Mycoplasma Test Validation
The mycoplasma test is performed in accordance with (b) (4), except the detection of mycoplasma is performed via (b) (4). (b) (4) . The (b) (4) mycoplasma test is explained in (b) (4).

The proposed (b) (4) assay includes several steps: (b) (4)

The test was performed on three lots of ABECMA® (i.e., (b) (4)) using (b) (4) mycoplasma species (i.e., (b) (4)).
The following parameters, specificity, intermediate precision, LOD, accuracy, intermediate precision, and robustness was preformed according to (b) (4) However, a comparability study with (b) (4) mycoplasma method was not conducted; which is covered in the information request section of this method review.

Specificity
Specificity is the ability of the method to detect only mycoplasma and no other mycoplasma related microorganisms. The assessment of specificity for the (b) (4) was performed with (b) (4) All samples were also run as three (b) (4) replicates. All un-spiked test samples were negative for mycoplasma, where all samples spiked with (b) (4) for each mycoplasma species were positive for mycoplasma. None of the tests of the (b) (4) showed a false result, providing specificity assurance of the proposed (b) (4) method.

Intermediate Precision
Intermediate precision was validated while evaluating assay LOD, as the tests were performed by different analysts on different days using different reagent lots. The LOD results support the intermediate precision of the assay.

Detection Limit (LOD)
The LOD of the method was determined for (b) (4) different strains of mycoplasma by the (b) (4) that can be detected by (b) (4) assay in (b) (4) of test runs (positive cut-off) as per (b) (4). To determine the method limit of detection, a (b) (4) dilution series was performed for each of the (b) (4) Mycoplasma species (i.e., (b) (4)). The positive cut-off for each mycoplasma strain was determined in (b) (4) with (b) (4) replicates for each dilution giving a total of (b) (4) test results. The results obtained demonstrated the LOD for all tested mycoplasma was at (b) (4) with a recovery frequency of (b) (4). The sensitivity of this (b) (4) is obtained by (b) (4) The results of the LOD of the (b) (4) method showed all tested mycoplasma was detected at (b) (4), which meets the comparability requirements for the (b) (4) as an alternative method in the (b) (4).

Robustness
Robustness is the ability of the method to remain unaffected by small but delicate variations in methodology and provides assurance of its reliability during normal usage. Reagent was evaluated to ensure that a second lot of critical reagents used for testing would not impact assay results. All sample and control replicates had CV (b) (4), meeting the acceptance criterion of a coefficient of variation (b) (4). The (b) (4) for (b) (4) were (b) (4) respectively, meeting the acceptance criterion of (b) (4) less than (b) (4). These robustness results were acceptable.

Comparability Study
Celgene did not perform the comparability study of the (b) (4) to the mycoplasma (b) (4) method. IRs were sent to request a comparability or

equivalency study be performed to meet the requirements of (b) (4). Celgene is committed to conducting a comparability study and a final study report will be provided as a post-marketing commitment by August 31, 2021.

Information Request and Review

The following questions were sent in an IR to the sponsor on January 11, 2021 and response was received on January 25, 2021.

a. CBER expects a comparability or equivalency study be performed to ensure the alternate method is equivalent to the (b) (4) method. Please provide a detailed explanation of why equivalence of the (b) (4) to the mycoplasma (b) (4) method was not performed.

Review of the Response:

The (b) (4) method used for ide-cel was validated according to (b) (4) requirements for specificity and sensitivity (limit of detection). The validation studies included (b) (4) from (b) (4) required Mycoplasma species ((b) (4) spiked into ide-cel drug product (DP) using (b) (4) certified reference standards at concentrations of (b) (4). Equivalence to the (b) (4) method was addressed in the validation by showing that (b) (4) of the (b) (4) required Mycoplasma species were detected in (b) (4) or more of the test runs. (b) (4) states that equivalence to the Mycoplasma (b) (4) method may be shown through equivalent limits of detection in terms of (b) (4) in the test sample using a certified reference standard. The (b) (4) validation for ide-cel DP release meets this requirement, as detection of (b) (4) is equivalent to or better than the (b) (4) requirement of the mycoplasma (b) (4) method. Therefore, the validated (b) (4) method has demonstrated equivalence to the mycoplasma (b) (4) method.

The following questions were sent in an IR to the sponsor on March 01, 2021 and response was received on March 09, 2021.

b. CBER has reviewed your response received January 25, 2021. CBER/FDA requires data to compare the (b) (4) method to the (b) (4) method, to provide assurance the alternate method is equal to or greater than the assurances provided by the (b) (4) method for ABECMA. Therefore, please perform a comparability study between the (b) (4) method as per (b) (4) and submit limit of detection results from both methods for further continued review.

Review of the Response:

The ABECMA mycoplasma assay submitted in the BLA was developed in 2016 prior to the start of the pivotal registration Phase 2 study (BB2121-MM-001). The use of the alternate assay was discussed as part of the Type B End of

Phase 1 meeting (meeting ID #10784). Additional validation data was provided in an amendment to IND 016664 (sequence number 0060) to address comments received by the Agency on the assay. Subsequently, the assay was used as a release test for all clinical ABECMA lots and was also included in the BLA.

A (b) (4) was selected for testing of ABECMA, since the (b) (4) time requirement of the (b) (4) method is prohibitive to short shelf-life cell therapy products. The (b) (4) validation for ide-cel drug product release met the requirement for equivalence described in (b) (4), as detection of (b) (4) in greater than (b) (4) of test samples is equivalent to or better than the (b) (4) LOD requirement of the (b) (4) method.

As requested by the Agency, the Sponsor will conduct a comparability study between the (b) (4) and the (b) (4) method that meets the requirements of (b) (4) to provide further assurance of equivalence. Due to the scope of work and time duration of the (b) (4) method, the study report will be available and provided to the agency by August 2021.

The following questions were sent in an IR to the sponsor on March 12, 2021 and response was received on March 16, 2021.

c. Please respond with the statement below as written and include the due date for when you will submit your PMC final study report. We request that you make the following post-marketing commitment:

Review of the Response:

Post-marketing commitment for BLA 125736: Celgene commits to conduct a comparability study between the mycoplasma (b) (4) and (b) (4) method as per (b) (4) to provide assurance that the alternate method is equal to or greater than the assurances provided by the (b) (4) method for ide-cel. A final study report will be provided as a post-marketing commitment by August 31, 2021. The response was found acceptable.

This reviewer recommends approval of (b) (4) mycoplasma test. Currently, the (b) (4) mycoplasma test validation provides assurance of detection of mycoplasma for ide-cel at an acceptable level of sensitivity, but additional assurance that this level of sensitivity is equal to or greater than that provided by the (b) (4) method for ide-cel still needs to be demonstrated. Celgene committed to conducting a comparability study and will submit the results for continued review as a post-marketing commitment by August 31, 2021.

Conclusion

After a thorough review of this BLA, this reviewer finds bacterial endotoxin test method was qualified in accordance with (b) (4) and the (b) (4) sterility test method was validated in accordance with (b) (4), by demonstrating these methods are suitable under the actual conditions of use. However, more information is required to complete review for their (b) (4)-based mycoplasma test method using (b) (4). CBER

is requesting a comparability study between the mycoplasma (b) (4) and (b) (4) method to provide assurance that the alternate method has equal or greater sensitivity than the (b) (4) method for ABECMA®.