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DBSQ/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125746/0

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Karla Garcia	Lead Reviewer	10/01/2021		James Kenney	
Jing Lin	Reviewer	10/01/2021		Muhammad Shahabuddin	

Through Maryna Eichelberger, Ph.D.
Division Director, DBSQ/OCBQ

Applicant: Janssen Biotech, Inc. (Janssen)

Subject: Review of Analytical Methods used for CARVYKTI Drug Substance (DS) and Drug Product (DP) Lot Release

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of CARVYKTI and the associated analytic method validations or qualifications, were reviewed:

1. Sterility (Karla Garcia)
2. Mycoplasma (Karla Garcia)
3. Endotoxin (Karla Garcia)
4. (b) (4) Purity Determination of CAR-T cells (Jing Lin)

Conclusion: The analytical methods and their validations and/or qualifications reviewed for the CARVYKTI DS and DP were found to be adequate for their intended use.

Documents Reviewed

Information in sections of the original BLA (STN125746) and IND18080 submission that describe control of DS and DP (3.2.S.4 and 3.2.P.5, respectively), including descriptions of DS and DP specifications, analytical procedures of DS and DP and validation of these analytical procedures were reviewed. Additional information in amendments specified by each reviewer were also reviewed.

Background:

On March 31, 2021, Janssen submitted a rolling BLA, STN 125746/0 for CARVYKTI, for the treatment of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody. CARVYKTI consists of autologous T cells that have been genetically modified ex vivo to express a chimeric antigen receptor (CAR) referred to as LCAR-B38M. The target antigen of the CAR is B-cell maturation antigen (BCMA), which is expressed on malignant plasma cells. The CAR is comprised of two complementary (b) (4)-derived single domain antibodies (sdAbs) that recognize human BCMA (CD269) and are (b) (4) from CD137 (4-1BB) and human CD3 zeta cytoplasmic domain. The CARVYKTI DP is formulated in a chemically defined freezing medium ((b) (4)) containing 5% DMSO. The target dose for patients weighing 100.0 kg or below is 0.75×10^6 CAR+ viable T cells. The DP is formulated for the target dose using an approximately 70 mL fill volume in a single (b) (4) freezing bag or 30 mL fill volume in a single (b) (4) freezing bag.

DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriately described, validated and suitable for the intended purposes. The following facilities perform the methods reviewed:

1. Janssen Vaccines, (b) (4)
2. (b) (4)
3. Janssen Biologics (b) (4)
4. Janssen Pharmaceuticals Inc. ((b) (4) USA)
5. Janssen Biotech, Inc. (b) (4) (R&D and QC)

The following analytical methods used for DS and DP release were reviewed:

1. Sterility

Sterility of (b) (4) Drug Product (DP) is determined using different tests as described below.

1.2 Sterility Test for DP

Method description

The sponsor uses the (b) (4) microbial detection system as a (b) (4) to determine sterility of the DP. The method complies with the (b) (4) method of (b) (4) where sample is (b) (4)

The original submission for (b) (4) sterility only provided a summary of validation results, therefore on May 18, 2021, CBER sent Janssen an information request (IR) requesting their complete validation report. Response to this IR was received on May 25, 2021 (Amendment 125746/0.8) and CBER determined it to be acceptable.

Method Qualification

Janssen performed a validation study of their (b) (4) sterility system at the (b) (4) sites covering limit of detection, specificity, suitability, robustness and ruggedness in accordance with (b) (4) as well as a comparability study with the (b) (4) sterility method. The validation and comparability studies were performed using the (b) (4) human T cell line. Upon consultation with the product office, the non-adherent human (b) (4) T cell line used as representative mock cellular product for validation of (b) (4) was found acceptable. In addition, both sites performed a method suitability test in the presence of CARVYKTI DP to ensure the method is suitable for the intended purpose.

The (b) (4) validation was performed using (b) (4)

Limit of Detection (LOD)

The LOD was assessed by (b) (4)

[Redacted]

[Redacted] LOD was

achieved at the (b) (4) which was found acceptable.

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 by (b) (4)

[Redacted]

Ruggedness is the degree of reproducibility when the same samples are tested under a variety of normal test conditions. This was assessed during the LOD study to address analyst variability and reproducibility between (b) (4) different analysts. The tests performed using different times of inoculation and different analysts during the LOD test demonstrated acceptable robustness and ruggedness of the (b) (4) sterility test method.

Specificity

Specificity is the ability of the method to recover a wide variety of microorganisms. Janssen evaluated specificity using samples (b) (4) indicator microorganisms and environmental isolates shown in Table 1. Specificity was confirmed by detection and confirmation of each challenge microorganism.

Method Suitability Assay

Janssen performed a method suitability test (B&F qualification) using three DP lots (i.e., (b) (4)) at (b) (4) , to demonstrate the product does not inhibit bacterial and fungal growth. The test was performed using all (b) (4) microorganisms mentioned in Table 1.

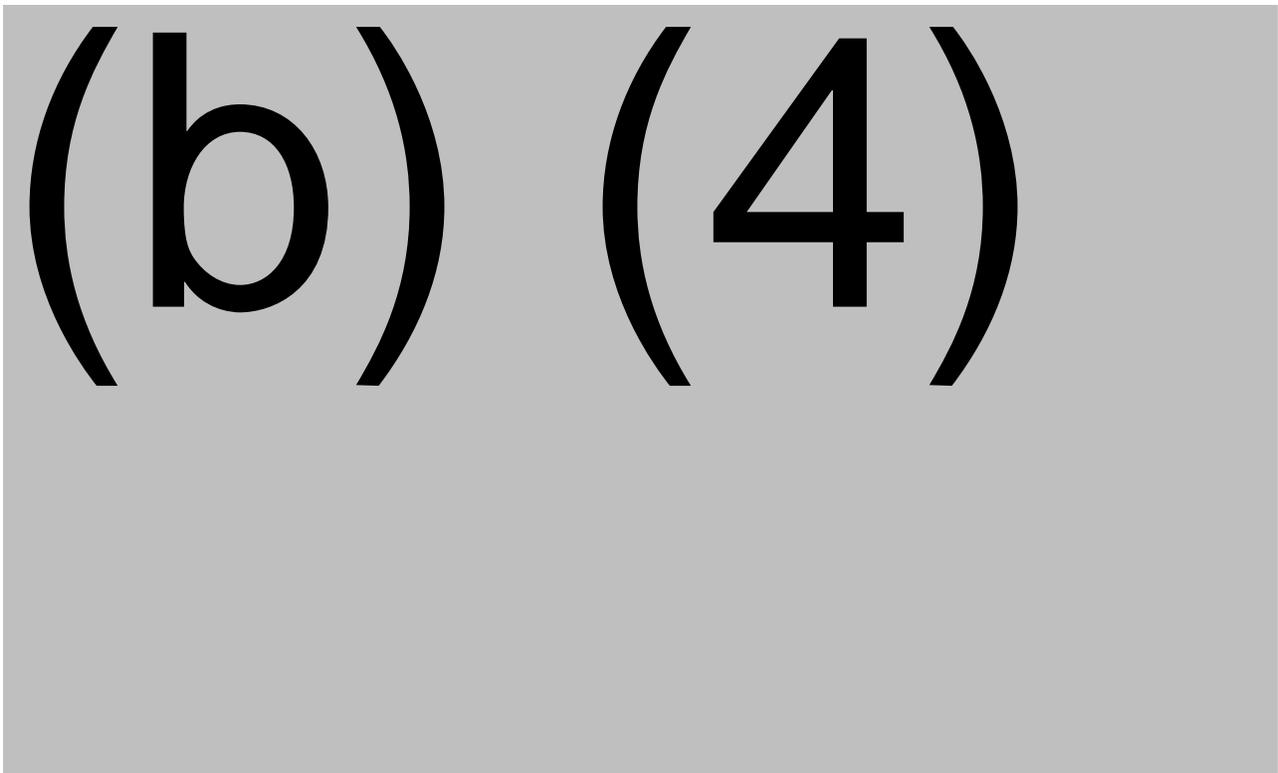
(b) (4)

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Comparability Study

Janssen performed a comparability study between (b) (4) and the (b) (4) method. (b) (4) used (b) (4) T cells for testing, with the (b) (4) microorganisms and media/incubation conditions listed in Table 1 below:

Table 1: Microorganism, Media and Incubation Conditions used in Validation and Comparability Studies

The content of Table 1 is completely redacted. The table area is filled with a solid grey color, and the large text '(b) (4)' is superimposed in the center of this area in a large, bold, black font.

(b) (4)

(b) (4)

Conclusion

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 determined to be suitable for its intended use.

2. Mycoplasma

The mycoplasma tests for (b) (4) DP are different, as described below.

(b) (4)

(b) (4)

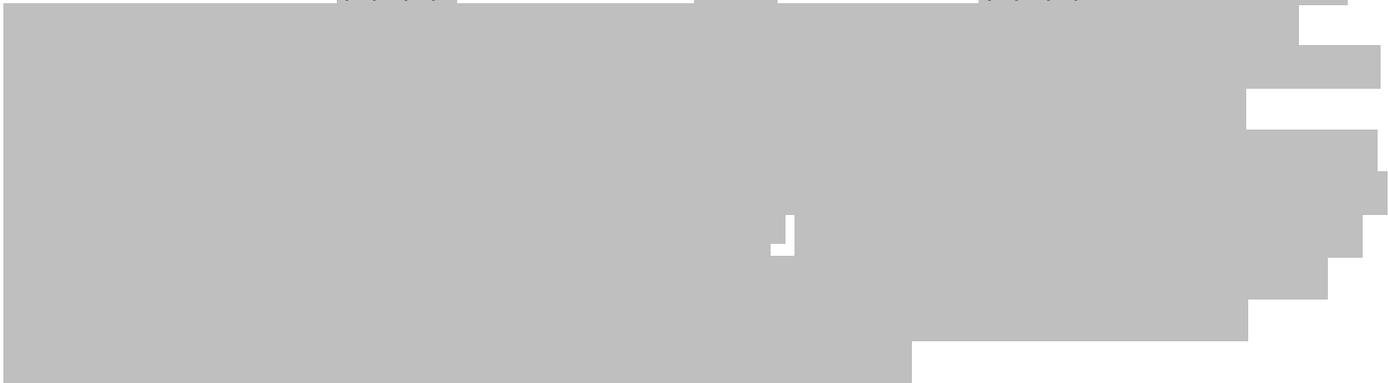


2.2 (b) (4)

Mycoplasma Test for DP

Method description

Mycoplasma testing by (b) (4) is performed by (b) (4) on the DP by (b) (4)



On May 18, 2021, CBER also requested that Janssen provide a validation report that included data to demonstrate the specificity, robustness/ruggedness, and sensitivity of the test, as well as the (b) (4) values of all samples included in the suitability study. All requested data were provided in amendment 125746/0.8 and are described below.

Method Validation

(b) (4)

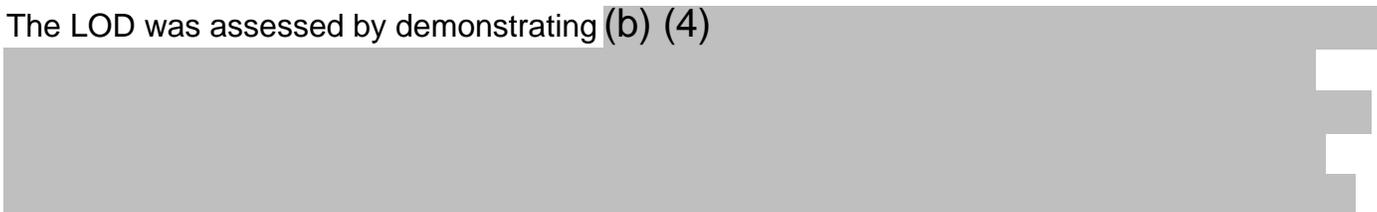


(b) (4)



Limit of Detection (LOD)

The LOD was assessed by demonstrating (b) (4)



Specificity

Specificity is the ability of the method to detect only mycoplasma and no other mycoplasma-related microorganisms. Specificity was assessed during the LOD study where no mycoplasma (b) (4) was detected in negative (b) (4) control and negative (b) (4) controls.

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.

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. The robustness was assessed during LOD where deliberate variations such deliberate change to a critical reagent of samples was assessed and CBER determined this was acceptable in accordance with (b) (4) robustness requirement.

Comparability Study

A comparability study between (b) (4) and the (b) (4) mycoplasma methods using (b) (4) T cells mentioned above at (b) (4) for all (b) (4) mycoplasma reference strains was performed. The test between (b) (4) and the (b) (4) methods was performed (b) (4). The results obtained demonstrated the (b) (4) sensitivity is equivalent to (b) (4) method for all tested mycoplasma species at (b) (4) and met the acceptance criteria for assay validity (i.e., positive and negative controls).

Conclusion

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

3. Endotoxin

Method description

Endotoxin is detected or quantitated in (b) (4) DP by (b) (4) Bacterial Test (b) (4)-BET). (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Method Qualification for DP

(b) (4) -BET was performed as described previously and Janssen qualified their (b) (4) -BET at Janssen Pharmaceuticals, (b) (4) and Janssen Pharmaceuticals, (b) (4) facilities.

In Janssen's May 18, 2021 IR response, the DP endotoxin data provided by the sponsor did not clearly indicate where testing was performed. On June 3, 2021 CBER sent a follow-up IR requesting that Janssen clarify where testing was performed and provide data from verification or comparability study to demonstrate acceptable transfer of the assay to the alternate test site. A response was received on June 14, 2021 (Amendment 125746/10) stating the release test is performed at both the (b) (4) test sites and the data submitted was determined to be acceptable.

Method suitability testing was conducted on three lots of DP at (b) (4) (i.e., (b) (4)) and three more lots at (b) (4) (i.e., (b) (4)) to demonstrate their method is suitable under the actual conditions of use in accordance with (b) (4) . The (b) (4) was calculated to be (b) (4) by (b) (4)

A suitable testing (b) (4) was determined by performing (b) (4) tests where the samples were tested at (b) (4) . All sample results showed acceptable (b) (4) (acceptance criterion is (b) (4)). Based on the results, (b) (4) testing (b) (4) was selected for release testing, which CBER finds acceptable. A method verification was performed by each testing

site using the same (b) (4) and the results of the endotoxin method verification met the acceptance criteria, indicating no product interference.

Conclusion

Janssen submitted bacterial endotoxin concentration results of several lots of (b) (4) DP. All results were within their proposed release specification of (b) (4) (1 DP bag) for DP. After review of the (b) (4)-BET test for (b) (4) DP, this reviewer concludes the test methods were performed and compliant with (b) (4).

4. (b) (4) **Purity Determination of CAR-T cells**

Method description

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

