DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

CBER REGULATORY REVIEW MEMORANDUM

Date 25 July, 2017

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Food and Drug Administration (FDA)

To Biologics License Application: Submission Tracking Number # 125646/0

Subject BLA: Review of Bioburden, Endotoxin, Compendial Sterility Method Qualifications; and (b) (4) Sterility and (b) (4) Mycoplasma Test Method Validations for KYMRIAH (tisagenlecleucel-T, CT019)

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

Applicant Novartis Pharmaceutical (Novartis)

Product KYMRIAH™ (tisagenlecleucel-T, CT019)

Biologics License Application (BLA) Submission Tracking Number (STN) 125646/0

Submission Received by CBER 02 February, 2017

Review Completed 25 July, 2017

Material Reviewed
Method qualifications for: 1) Bioburden; 2) Endotoxin; and 3) Compendial Sterility; and method validations for: 1) (b) (4) sterility test; and 2) (b) (4) for the detection of mycoplasma. In addition, the responses to CBER's Information Request (IRs) received 23 March, 20 and 21 April, 24 and 30 May and 19 July of 2017 were also reviewed.

Executive Summary

After a thorough review of this BLA, and the responses to CBER's IRs, this reviewer finds Novartis' (b) (4) sterility test method performed on the KYMRIAH™ drug product and the (b) (4)-based mycoplasma test method performed on (b) (4) drug product were validated in accordance with (b) (4), respectively, by demonstrating the tested product matrixes are suitable for these intended test methods. Novartis 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, bioburden ((b) (4) sterility (b) (4) and endotoxin (b) (4) drug product) test methods were qualified in accordance with (b) (4) respectively, by demonstrating these matrixes are suitable for the intended test methods.

However, there were deficiencies found in validation of mycoplasma test method performed on vector (b) (4). Novartis committed to revalidate the (b) (4) mycoplasma test method for vector (b) (4) and submit a response by the second quarter of 2018, as stated in their IR response dated 19 July, 2017.

Background

On 2 February, 2017, Novartis submitted a BLA for KYMRIAH™ (tisagenlecleucel-T, CT019) for treatment of pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL).

Tisagenlecleucel-T is a novel autologous, immunocellular cancer therapy, which involves reprogramming patient's own T-cells with a transgene encoded chimeric antigen receptor (CAR) to identity and eliminate CD-19 expressing malignant cells. The CAR is comprised of a murine single-chain antibody fragment, which CD19 is fused to intracellular signaling domains from 4-1BB and CD3-zeta. The CD3-zeta component is critical for initiating T-cell activation and antitumor activity, while 4-1BB enhances expansion and persistence of T-cells. 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.

Tisagenlecleucel-T was granted a breakthrough therapy designation on April 7, 2016. Novartis submitted a rare pediatric disease designation for ALL to Office of Orphan Products Development (OOPD) on December 15, 2016.

The CTL019 vector is manufactured for Novartis under contract by (b) (4) produces the bulk purified lentiviral vector (vector substance), which is tested for (b) (4) testing. The (b) (4) by (b) (4). The vector substance subsequently undergoes further aseptic processing and filling to yield final filled vector product at (b) (4). The vector product is tested for (b) (4).

The CTL019 final product is manufactured by Novartis. The manufacturing process is continuous without any intermediates and consists of T-cell enrichment, activation, followed by vector transduction, cell expansion, harvest, formulation and cryopreservation. The CTL019 (b) (4) is tested for mycoplasma and final product is tested for sterility and bacterial endotoxin.

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 release specifications for endotoxin testing to ensure they reflect process capability and meet regulatory compliance. 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 (for drug product) and (b) (4) using (b) (4) for mycoplasma testing (for (b) (4) CTL019 (b) (4) drug product), to determine if the product matrixes are suitable for testing using the intended methods and if these methods provide sterility or mycoplasma assurance equal to or greater than the (b) (4) methods. In addition, the qualification of bioburden, (b) (4) sterility and bacterial endotoxin test methods performed on the (b) (4) to ensure the matrix is suitable for the intended test method.

Review

CTL019 Vector Substance and Vector Product

(b) (4)

(b) (4)

(b) (4)

1 page determined to be not releasble: (b)(4)

(b) (4) .

CTL019 Drug Product (DP)

(b) (4) Mycoplasma Test Validation for DP

(b) (4) validation was performed on CTL019 (b) (4) material using a (b) Mycoplasma (b) (4) Detection Assay (refer to DMF #23784, ABI) with sample preparation using a (b) (4), in accordance with (b) (4), which specifies requirements for validation of the (b) (4) - based test as a replacement for the culture method. The validation study of the (b) (4) was performed using (b) (4) different mycoplasma reference strains (i.e., (b) (4) For the validation study, Novartis used (b) (4) of the (b) (4) sample and (b) (4) mycoplasma genomic DNA during extraction instead of viable mycoplasma. CBER found this acceptable because Novartis does not have a laboratory to culture and maintain viable mycoplasma. The mycoplasma species were obtained from (b) (4), genomic DNA was extracted and diluted to genomic copies (GC)/mL for the validation study.

The (b) (4) assay included several steps: a (b) (4)

Specificity

Specificity is the ability of the method for detection of only mycoplasma and no other mycoplasma-related microorganisms. ABI validation study (DMF #23784) evaluated closely-related species including (b) (4) species (i.e., (b) (4)) suggested by the (b) (4) for the validation of (b) (4) methods.

The assessment of specificity of the (b) (4) was performed on (b) (4) CTL019 (b) (4) material in (b) (4) tests were performed: (b) (4) CTL019 (b) (4) DNA was (b) (4) with mycoplasma DNA equivalent to (b) (4) genomic copies of the (b) (4) mycoplasma species listed above. The tests were performed to investigate interference with the test system that could produce false positive or negative readings. All (b) (4) samples were negative for mycoplasma, where all samples (b) (4) with DNA equivalent to (b) (4) genomic copies for the 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.

Limit of Detection (LOD)

The LOD was assessed by demonstrating the lowest number of genomic copies that could be detected from the CTL019 (b) (4) sample matrix. The test was performed on (b) (4) CTL019 (b) (4)

samples in (b) (4) . Novartis performed (b) (4) and (b) (4) reaction (b) (4) (as explained under specificity) using (b) (4) genomic copies for the (b) (4) mycoplasma species listed above. The results of the LOD of the (b) (4) method demonstrated the LOD for all tested mycoplasma was (b) (4) genomic copies/reaction, which met the (b) (4) LOD requirement.

Robustness and Ruggedness

The robustness of the (b) (4) was evaluated using different sample matrix volume (b) (4) instead of (b) (4) for extraction (b) (4) test and different primer volume (b) (4) primer volume) for (b) (4) reaction (b) (4) test. The test was performed using (b) (4) genomic copies of positive control provided in the (b) (4) Detection Kit. A (b) (4) test (b) (4) test) was performed on (b) (4) samples where (b) (4) genomic copies of (b) (4) different templates: (b) (4) and the (b) (4) detection kit positive control were added to the same sample preparation and tested using (b) (4) .

The results of the robustness demonstrated no changes in sensitivity of the assay despite of deliberate changes made to sample matrix volume and primer volume for the (b) (4) assay. In addition, the Tm results of (b) (4) and positive control (b) (4) demonstrated the both templates were amplified and distinguishable in the cross contamination test.

Assay ruggedness was validated while evaluating assay specificity and LOD, as the tests were performed by different analysts on (b) (4) days using (b) (4) reagent lots. The specificity and LOD results support the ruggedness of the assay.

Comparability Study

Since Novartis does not have an in-house laboratory for culturing and maintaining viable mycoplasma, they referred to comparability study between (b) (4) and (b) (4) test performed in (b) (4) validation study (DMF #23784) using (b) (4) cell culture samples. Novartis provided a risk assessment document, RA002504A: "Risk assessment on equivalency of (b) (4) to (b) (4) and sample justification" evaluating the risk of the appropriateness of (b) (4) -based assay to verify the absence of mycoplasma, as being equivalent to the (b) (4) methods (b) (4) and (b) (4) and the risk of sampling at (b) (4) . The risk assessment document was reviewed and approved by the product office; therefore, the comparability study performed by (b) (4) was found acceptable for CTL019 (b) (4) material.

(b) (4) Sterility Test Validation for Drug Product (DP)

(b) (4) validation was performed using (b) (4) media types and (b) (4) temperatures; (b) (4) for anaerobic microorganisms at (b) (4) for aerobic microorganisms a (b) (4) . Four parameters (i.e., limit of detection, robustness, ruggedness and specificity) for the validation of alternate methods, as listed in qualitative tests under (b) (4) were evaluated during the validation study using the (b) (4) indicator microorganisms (i.e., (b) (4) . Media and incubation conditions for each microorganism are listed in Table 1. Novartis performed a comparability/equivalency study with (b) (4) method while evaluating the four validation parameters mentioned above.

(b) (4)

Limit of Detection (LOD)

The LOD was assessed by demonstrating the lowest number of microorganisms that could be recovered from the sample matrix. Novartis used commercially prepared (b) (4) microorganisms from (b) (4) . Each (b) (4) contains approximately (b) (4) CFUs per/mL. Each microorganism was serially diluted to (b) (4) for the LOD study. Because of the limited availability of product, Novartis used only (b) (4) microorganisms (b) (4) for the LOD study. With CBER's experience and confidence in (b) (4) system and its performance as an alternate sterility test method, this LOD study using only (b) (4) microorganisms was found acceptable under this extenuating circumstance.

A (b) (4) sample of final product was inoculated into an (b) (4) (Table 1) for (b) (4) days. Positive results determined by detection on the (b) (4) System were confirmed and identified via representative microorganism growth on agar medium from each positive sample bottle. The lowest LOD microorganism results obtained by both methods are listed in Table 2 below.

(b) (4)

The 95% confidence intervals overlapped between (b) (4) and (b) (4) methods, which is indicative of non-inferiority. Overall, Novartis demonstrated the (b) (4) method was better than or equivalent to (b) (4) test method in detecting the tested microorganism in the CTL019 DP.

Specificity

Specificity is the ability of the method to recover a variety of microorganisms. Novartis evaluated specificity using (b) (4) of (b) (4) microorganisms (mentioned above). (b) (4) tests were performed: 1) using (b) (4) of the final product using (b) (4) method; and 2) as an (b) (4) test using (b) (4) samples using (b) (4) and (b) (4) methods. Because of the limited availability of product, Novartis

could not expand their specificity tests to include more than (b) (4) microorganisms (listed in Table 1). CBER found this acceptable under this extenuating circumstance, based on our experience and confidence in (b) (4) system and its performance as an alternate sterility test method.

The statistical analysis of (b) (4) chi-square results of the tests demonstrates the specificity and equivalency of (b) (4) system to the (b) (4) method.

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 product volumes/concentration of the product as mentioned in LOD and specificity studies.

Ruggedness is the degree of test result reproducibility obtained by analysis of the same samples under variety of normal test conditions which was assessed during the LOD and specificity studies. A statistical chi-square analysis of these tests performed using different lots of product and media (b) (4) methods) and different analysts provided (b) (4) results in LOD and specificity results demonstrated that robustness and ruggedness of (b) (4) System.

(b) (4) Method Qualification for CTL019 DP

Novartis qualified their (b) (4) method for CTL019 DP to verify their product matrix was suitable for the intended test method in accordance with (b) (4)

Novartis performed a suitable test dilution test on (b) (4) lot of DP (i.e., lot number (b) (4) at (b) (4) dilution. Based on the results, Novartis selected a test sample dilution of (b) (4) for DP release testing. The MVD was calculated to be (b) (4)

The inhibition/enhancement test was performed on (b) (4) lots of DP (i.e., lot numbers: (b) (4) . The samples tested at (b) (4) showed no inhibition or enhancement, as their (b) (4) recoveries for the PPC were between (b) (4) which were within the acceptance criteria of (b) (4)

After review of (b) (4) method qualification results, this reviewer concludes this method was qualified in accordance with (b) (4) Novartis submitted the bacterial endotoxin results for several CTL019 DP lots, which met the endotoxin test specification of (b) (4) . CBER finds the proposed specification acceptable.

Conclusions

After a thorough review of the information submitted in this BLA and Novartis's commitment to revalidate the (b) (4) mycoplasma test method for vector substance (see Novartis's IR response dated 19 July, 2017), this reviewer finds Novartis' (b) (4) sterility test method performed on the KYMRIAH™ drug product and the (b) (4) mycoplasma test method performed on (b) (4) drug product were validated in accordance with (b) (4) , respectively, by demonstrating the tested product matrixes are suitable for these intended test methods. Novartis 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,

bioburden (b) (4) sterility (b) (4) and endotoxin (for (b) (4) drug product) 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; except for their mycoplasma test method performed on (b) (4) .