



DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125787

From:

Reviewer	Role	Date finalized	Stamp	Laboratory/Lab Chief	Stamp
Tao Pan Ph.D.	Lead Reviewer	11/14/2023		Kenneth S. Phillips, Ph.D.	
M. Nahid Parvin, Ph.D.	Reviewer	11/03/2023		Muhammad Shahabuddin, Ph.D.	
Hyesuk Kong, Ph.D.	Reviewer	11/06/2023		James L. Kenney, D.Sc.	

Through Maryna Eichelberger, Ph.D.
Division Director, DBSQC

Applicant: Vertex Pharmaceuticals Incorporated

Subject: Analytical Methods for the Lot Release of critical gene editing reagents and drug product (DP) of Exagamglogene autotemcel (exa-cel)

Recommendation: Approval

Summary:

The following analytical methods used for lot release of critical gene editing reagents and drug product (DP) of Exagamglogene autotemcel (exa-cel) from Vertex, and the associated validations and qualifications, were reviewed:

1. (b) (4) (Tao Pan),
2. (b) (4) (Tao Pan),
3. (b) (4) (Tao Pan),
4. (b) (4) (Tao Pan),
5. (b) (4) (Tao Pan),
6. (b) (4) (Tao Pan),
7. (b) (4) (Tao Pan),
8. (b) (4) (Tao Pan),
9. (b) (4) (Tao Pan),
10. (b) (4) (Tao Pan),
11. (b) (4) (Tao Pan),
12. Appearance of Exa-cel DP (Tao Pan),
13. (b) (4) (Hyesuk Kong),
14. Sterility of (b) (4) DP (Hyesuk Kong),

15. Endotoxin of (b) (4) DP (Hyesuk Kong),
16. Mycoplasma of DP (Hyesuk Kong),
17. (b) (4) (M. Nahid Parvin),
18. (b) (4) (M. Nahid Parvin),
19. (b) (4) (M. Nahid Parvin),
20. (b) (4) (M. Nahid Parvin).

Conclusion: The analytical methods and their validations/qualifications reviewed for Exagamglogene autotemcel (exa-cel) from Vertex, were found to be adequate for their intended uses.

Documents Reviewed

Information in sections of the original submission that describe control of DP (3.2.P.5) and DS (3.2.S.4), including descriptions of the specifications, analytical procedures of and validation of these analytical procedures was reviewed. Additional information in amendments #125787/0.17, #125787/0.29, #125787/0.31, #125787/0.49 and #125787/0.74 received on May 18, June 01, June 23, August 30, and October 30, 2023, was also reviewed.

Background:

Exagamglogene autotemcel (exa-cel) is intended for the treatment of sickle cell disease; the DP is a single dose of at least 3 million autologous CD34+ human Hematopoietic Stem and Progenitor cells (hHSPCs) per kg of patient weight, modified by CRISPR-Cas9-mediated gene editing and suspended in cryopreservation medium. The gene editing disrupts a binding site of the transcription factor GATA1 of the erythroid lineage-specific enhancer region of the BCL11A transcription factor, leading to the decrease of BCL11A and in turn an increase of fetal hemoglobin (HbF).

The manufacturing of the exa-cel DP involves the electroporation of autologous CD34+ cells with Ribonucleoprotein (RNP) complex. The RNP complex consists of two components, Cas9 and SPY101 single guide RNA (sgRNA): Cas9 is manufactured as a (b) (4) SPY101 sgRNA is a 100-mer synthetic oligonucleotide manufactured as a (b) (4)

(b) (4) both are shipped for exa-cel DP manufacturing at (b) (4)

Review Narrative:

1. (b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

12. Appearance of Exa-cel (DP)

The appearance of Exa-cel DP is determined by visual inspection, and its specification for both release and stability is “Translucent cell suspension, practically free of visible foreign particles”; the lot release test is performed and verified at (b) (4)

(b) (4)

Method:

The appearance method for Exa-cel DP is to make visual assessment on translucency and presence or absence of visible foreign particles of (b) (4) DP

(b) (4) SOP-0043: Visual Inspection, Appearance and Particulate Testing of a Reagent or Product). In brief, a final container of (b) (4) DP is visually inspected for the translucency of its cell suspension and presence or absence of visible foreign particles in the cell suspension at (b) (4)

The description of the method is acceptable with sufficient details.

Method Verification:

The appearance of Exa-cel DP method was verified at (b) (4) (b) (4) Qualification/Validation Summary Report Appearance Operator Training Enhancement) and (b) (4) Appearance Precision Assessment Report for Exa-cel DP Release and Stability Testing at (b) (4)

For the verification, in (b) (4) (b) (4) different analysts inspected (b) (4) lots of DP, (b) (4) vials each, on different days for their appearance, and all the inspected vials, (b) (4) in total, met the release specification; in (b) (4) (b) (4) analysts inspected total (b) (4) lots of DP, and all met the release specification. The precision of the method was demonstrated, and the method was verified at both sites.

Conclusion:

Based on information provided, the appearance method has been verified for its intended use of release testing of Exa-cel DP.

(b) (4)

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(b) (4)

14. Sterility (b) (4) DP)

Introduction

Sterility testing is performed on (b) (4)

(b) (4)

exa-cel DP testing

is performed at (b) (4) (b) (4)

Acceptance

criteria of 'No Growth' must be met for the lot release of (b) (4) exa-cel DP.

Method

The membrane filtration sterility test is used in accordance with (b) (4) Test samples are (b) (4)

The method is described in more detail below together with the tests that were performed to determine suitability of the test method.

The (b) (4) sterility test is used for various liquids, solids, and device in accordance with (b) (4) Test samples are (b) (4)

The original qualification reports for sterility lacked sufficient information to complete the review: 1) sterility testing of DP was performed using (b) (4) at (b) (4) 2) a small sample volume i.e., (b) (4) mL in (b) (4) mL of media was used at the (b) (4) site, and 3) the qualification studies performed at (b) (4) (b) (4) did not include evaluation of environmental isolate; therefore, IRs were sent requesting: 1) a qualification study be performed with at least (b) (4) lots, 2) a reduced media volume in order to have an appropriate sample to media ratio to increase the sensitivity of the method or to perform an additional sterility test using (b) (4) mL of (b) (4) removed prior to DP formulation to provide assurance for the use of their small sample volume. Responses were received on June 1, 2023 (Amendment 29), June 23, 2023 (Amendment 31) and August 30, 2023 (Amendment 49) which were found acceptable and reviewed as part of the DP sterility testing below.

In addition, Vertex initially contracted their sterility test for exa-cel DP out to (b) (4) and their sterility qualification was also found incomplete since it was performed using (b) (4) An IR was sent out on May 18, 2023, requested missing information described above with an additional sterility supplemental qualification. In an amendment 49 received on August 30, 2023, Vertex withdrew the

(b) (4) [REDACTED] sterility testing site, as they were unable to initiate the study in time due to equipment issues.

(b) (4)

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Conclusion

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

15. Endotoxin (b) (4) DP)Introduction

Endotoxin testing for (b) (4) is performed at (b) (4) (b) (4) respectively, while exa-cel DP testing is performed at (b) (4)

Acceptance criteria of: (b) (4) for (b) (4) (b) (4) and (b) (4) must be met for release of exa-cel DP.

Method

(b) (4)

The original qualification report for the endotoxin study did not include information required for completion of the review; therefore, an IR was sent requesting missing information and responses were received on June 1, 2023 (Amendment 29), June 23, 2023 (Amendment 31), and August 30, 2023 (Amendment 49), which were found acceptable and explained below.

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(b) (4)

Conclusion

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

16. Mycoplasma (DP)

Introduction

Mycoplasma testing is performed using (b) (4) (b) (4) method in exa-cel final harvest cell suspension, which was initially validated at (b) (4) and later transferred to (b) (4) (b) (4) Acceptance criteria of 'Negative' must be met for the release of the exa-cel final harvest cell suspension.

Method

(b) (4)

(b) (4)

The validation reports for mycoplasma test submitted in the original submission lacked sufficient information to complete the review; therefore, an IR was sent requesting data and clarification to fulfill these deficiencies. A response was received on June 1, 2023 (Amendment 29), which was found acceptable and explained below.

(b) (4) Mycoplasma Test Validation for DP

(b) (4) performed detailed validation studies using their (b) (4) mycoplasma test for exa-cel DP that covered specificity, limit of detection (LOD), and robustness as well as a comparability study with (b) (4) mycoplasma method to determine if the (b) (4) method provides assurance equal to or greater than the (b) (4) method in accordance with (b) (4). In addition, (b) (4) performed an additional product-specific qualification (PSQ) and a product-specific bridging study of (b) (4) method vs. (b) (4) method on exa-cel patient and HD cells to demonstrate the comparability between the two methods for exa-cel DP as reported in validation report # AVR-57579 (Amendment 29).

Specificity is the ability of the method to (b) (4)

(b) (4)


Limit of Detection is the (b) (4)

(b) (4)

Robustness is the ability of a test method to (b) (4)



Comparability of (b) (4) to (b) (4) (b) (4) Method
(b) (4)



(b) (4)

(b) (4)

Conclusion

The method validation tests for the DP were performed and compliant with (b) (4) (b) (4) and the test results indicate there is no product interference from the test sample. The test was shown to provide assurance equal to or greater than the (b) (4) method. Therefore, the mycoplasma test method is appropriate under the actual conditions of use at (b) (4) (b) (4) facility for exa-cel DP.

(b) (4)

(b) (4)

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