



DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125690

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Anil Choudhary	Lead Reviewer	12/04/2019		Dr. Muhammad Shahabuddin	
Simleen Kaur	Reviewer	8/29/2019		Dr. James L. Kenney	
Ritu Agarwal	Reviewer	12/2/2019		Francis Kori	

Through: Maryna Eichelberger PhD., Division Director, DBSQC

Applicant: Merck

Trade Name: ERVEBO

Subject: Review of CMC Analytical Methods used for Lot Release of Ebola Zaire Vaccine, Live, (b) (4) Drug Product

Recommendation: Approval.

Summary:

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

1. Sterility (Simleen Kaur)
2. Endotoxin (Simleen Kaur)
3. (b) (4) (Simleen Kaur)
4. Identity (Anil Choudhary)
5. Potency (Anil Choudhary)
6. Opalescence (Ritu Agarwal)
7. (b) (4) (Ritu Agarwal)
8. (b) (4) (Ritu Agarwal)
9. Total protein (Ritu Agarwal)

Conclusion: The analytical methods and their validations and/or qualifications reviewed for the ERVEBO (b) (4) drug product were found to be adequate for their intended use.

Documents Reviewed

1. Section 3.3.R Assay Method: SOP-1-P-QM-WI-9034077: Client Specific: V920 (b) (4) assay.
2. Section 3.3.R Assay Method: SOP#QOV-PM-171 (ver.-001) Determination of the virus concentration of recombinant VSV in the (b) (4) test.
3. Section 3.3.R Validation Report for (b) (4) method for Ebola vaccine rVSV-ZEBOV-GP based on SOP QOV-PM-171 (-) Document#Q-VB-01837.00.
4. Section 3.2.S.4.3.12 and 3.3.R Validation Report#15-006531-47965.03 for detection and quantitation of V920- (b) (4) assay at (b) (4), WP75A, October-2016 (SOP-1-P-QM-WI-9034077)- Document#56085-2016-TC-0078.
5. Technical report for V920 (b) (4) potency assay robustness study in GVBC, WP75, October 2017- Document# 56085-2017-TR-0001, Provided in email communication on August 22, 2019.
6. Section 3.3.R Assay Method: SOP# 1-P-QM-WI-9044684: Confirmation of V920 Identity by (b) (4), Merck & Co. Inc.
7. Section 3.3.R Assay Method: SOP# QOV-PM-187: Detection by means of (b) (4) of the expression of ZEBOVGP by a recombinant VSV vaccine.
8. Section 3.2.S.4.3.11 and 3.3.R. and Amendment# 0007, February 22, 2019 Method Validation Report, Final Report for Validation of the Method for Confirmation of V920 Identity by (b) (4), under sample NG- 1793668.
9. Section 3.2.S.4.3 Validation of Analytical Procedures- (b) (4) Test
10. Sections 3.2.S.4.3 and 3.2.P.5.3 Validation of Analytical Procedures- Sterility Test
11. Section 3.2.P.5.3 Validation of Analytical Procedures- Endotoxin Test
12. Section 3.2.S.4.2 Test Procedure for Opalescence and Test Procedure for (b) (4)
13. Section 3.2.P.5.2 Analytical Procedures Test Procedure for (b) (4), Test Procedure for (b) (4), Test Procedure for Total Protein.
14. Section 3.2.P.5.3 Validation of Analytical Procedures: Validation of the Test method for (b) (4), Validation of the Test method for Total Protein
15. STN125690/0.16 — 1.11.1 Quality Information Amendment; Response to IR dated 10 April 2019; Received 01 May 2019.

Background:

Merck & Co., Inc submitted BLA STN 125690 for ERVEBO, an Ebola Zaire Vaccine (r-VSVΔG-ZEBOV-GP, Live) also known as V920, on October 31, 2018. The Drug Substance (DS) and Drug Product (DP) will be manufactured at Merck (b) (4)

(b) (4) facility. The release testing for DP will be performed by (b) (4)

(b) (4) This product is proposed for active immunization of at-risk individuals 18 years of age and older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus.

1. Sterility [Simleen Kaur]

Sterility Test for (b) (4) DP

The (b) (4) sterility test used for (b) (4) products is performed in accordance with (b) (4). The sample is (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Qualification of Sterility Test Method for DP

The Ebola Zaire DP was qualified using the (b) (4) method by performing B&F qualification studies to demonstrate the matrix is suitable for the intended test method by the subcontractor as for (b) (4). The test was performed using (b) (4) indicator microorganisms (i.e., (b) (4)

(b) (4) on (b) (4) lots (i.e., (b) (4)) of Ebola Zaire

DP. The test for each microorganism was performed using (b) (4) vials of DP following the same procedure as for (b) (4) qualification study (mentioned above).

The tests were performed and compliant with (b) (4). The test results indicate there is no product inhibition on microorganism growth; thus, indicating the Ebola Zaire DP matrix is suitable for testing via (b) (4) sterility test method.

The test did not include (b) (4) known environmental strains (i.e., (b) (4)) from MSD site- (b) (4) facility. However, Merck has agreed to perform post-licensure supplemental sterility qualification study using the (b) (4) environmental isolates and submit the results as a Product Correspondence (amendment BLA 125690/0.19 received 21 June, 2019).

Conclusion:

The Sterility test is adequately described and qualified for determining sterility of (b) (4) DP.

2. Endotoxin [Simleen Kaur]

The amount of endotoxin in DP is measured by (b) (4) Bacterial Endotoxin Test (b) (4) BET). Endotoxin (b) (4) method measures (b) (4) that is directly related to the endotoxin concentration in a sample. The test sample is (b) (4)

Qualification of (b) (4) Bacterial Endotoxin Test (b) (4) -BET for DP

A contracting laboratory, (b) (4), qualified their (b) (4) BET method for Ebola Zaire DP matrix to verify the product matrix is suitable for the intended test method in accordance with (b) (4). The (b) (4) was calculated to be (b) (4) by (b) (4)

A suitable testing dilution and inhibition/enhancement tests were performed at the same time on (b) (4) lots (i.e., (b) (4)) where the samples were tested (b) (4). The results showed acceptable positive product control spike ((b) (4)) recoveries with inhibition/enhancement at (b) (4), respectively and enhancement at (b) (4) for (b) (4). Based on the results, (b) (4) dilution was selected as the sample testing dilution. The test was performed and compliant with (b) (4); thus, indicating Ebola Zaire DP matrix is suitable for testing via their (b) (4) BET method.

Conclusion:

The (b) (4) BET is adequately described and qualified for determining endotoxin content of DP.

4. Potency [Anil Choudhary]

Introduction

The sponsor provided multiple documents for validation and qualification of identity and potency assays used for release of (b) (4) DP. These methods were originally performed at (b) (4), but are currently performed at (b) (4) for lot release testing. Only recently validated, currently used potency and identity assays and the validations performed at (b) (4), were reviewed in detail.

Potency Test for (b) (4) DP

SOP QM-WI-9034077 is the Potency assay for determining the amount of infectious virus particles present in a sample by (b) (4) assay. This method was validated to test V920 Drug Product, (b) (4) at (b) (4). (b) (4)

(b) (4) VSV is genetically engineered to express the Ebola glycoprotein (GP) by substitution of its native envelope G (rVSVΔG-ZEBOV-GP, live attenuated). Serial dilutions of (b) (4) DP and positive control are (b) (4)

The test design is usually as follows:

The test is performed by (b) (4)

In order for an assay to be valid, negative controls must remain negative for the test (no (b) (4)); and positive controls must have potency results from the test within acceptable range, as qualified by the sponsor.

Validation of Potency Test

Validation of the ZEBOV potency assay for SOP# QOV-PM-171 performed at (b) (4)

The SOP# QOV-PM-171 was validated at (b) (4) and the results were reported in validation report# Q-VB-01837 version 001 (July, 2016). The (b) (4)

(b) (4) was used to design the validation studies for V920 (b) (4) assay. In validating the test method at (b) (4) lots of V920 were used: (b) (4) Lot# (b) (4) final drug product (FDP) and lot# (b) (4) (FDP). The positive control used in the study was lot# (b) (4) with range of (b) (4). The validation assessment of (b) (4) potency assay at (b) (4) using SOP# QOV-PM-171 are briefly reviewed as follows:

For assessment of linearity, results for % bias per (b) (4)-fold dilution were between (b) (4), and met acceptance criteria of (b) (4). The %RSD of replicate measurements at each dilution used to determine linearity, were (b) (4), and were within the acceptance criteria of %RSD (b) (4). For Intermediate Precision and Repeatability, the acceptance criteria of overall relative standard deviations (RSD) across all the tests and within a day were set to be (b) (4), respectively. The repeatability results of (b) (4) RSD met the acceptance criteria. The results for intermediate precision when calculated according to the validation plan using (b) (4), were (b) (4) RSD, thereby

failing the preestablished acceptance criteria of RSD (b) (4). But, when the reportable results were calculated as applied to routine release testing using (b) (4) operators across (b) (4), were found to be between (b) (4) RSD, meeting the acceptance criteria. The range and accuracy of the test method was inferred from precision and linearity. The range takes into account the sample dilutions and was reported to be from (b) (4). Only those (b) (4) where the number of (b) (4) ranged from (b) (4) were read.

Validation of the ZEBOV potency assay for SOP QM-WI-9034077 currently performed at (b) (4)

The potency assay for drug product V920 (SOP#1-P-QMWI-9034077) was validated at (b) (4). The (b) (4)

(b) (4) was used to design the validation studies for V920 (b) (4) assay. The validation characteristics were evaluated and reported in validation report #15- 006531-32638 version 01, November, 2015 and validation report #15- 006531-47965, Version 03, October, 2016. The parameters evaluated were Accuracy, Repeatability, Intermediate Precision, Linearity, and Range as described in Technical Communication for the Validation of V920 (b) (4) Assay at (b) (4) (56085-2016-TC- 0078). The validation of Robustness was performed in a separate study and reported in document: Technical report for V920 (b) (4) potency assay robustness study in Merck Global Vaccines and Biologics Commercialization GVBC, WP75, - Document# 56085-2017-TR-0001.

In validation report #15- 006531-47965, (b) (4) lots of V920, Lot#(b) (4) and positive control Lot# (b) (4) were used to perform the studies. Initial potency specifications in the (b) (4) (potency) assay (SOP 1-P-QMWI-9034077) were set using results obtained from testing in the (b) (4) assay (SOP# QOV-PM-171).

(b) (4) analysts performed tests across (b) (4). (b) (4) by each analyst to ensure the assay run met the system suitability criteria. Each test included (b) (4) batches, with (b) (4) replicates per batch to determine Repeatability ((b) (4) variability). Below is a review of the validation parameters evaluated by the sponsor:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Summary:

The potency assay performed at (b) (4) (SOP# QOV-PM-171) was described in sufficient detail and met the predefined validation acceptance criteria. This SOP is not currently used for testing potency of current commercial lots. The basic format of (b) (4) potency assay was the same as being currently performed by (b) (4) (SOP#I1-P-QM-WI-9034077). The major difference in the two assays is that in the (b) (4) assay, (b) (4) and in the assay performed at (b) (4). The (b) (4) Assay performed at (b) (4) met predefined validation criteria for Accuracy, Repeatability, Intermediate Precision, Linearity, Range and Robustness.

Conclusion:

The current potency assay (SOP#I1-P-QM-WI-9034077) is adequately described and validated for testing (b) (4) DP at (b) (4). The test method serves the intended purpose of measuring the amount of infectious virus in Ebola vaccine lots.

5. Identity **[Anil Choudhary]**

Identity Test for (b) (4) DP

The identity method used for lot release is performed at (b) (4), following SOP #1-P-QM-WI-9044684, "Confirmation of V920 Identity by (b) (4), Merck & Co. Inc." The initial steps are the same as performed for the potency assay procedure which is performed (b) (4) to the (b) (4) procedure. (b) (4) is performed by (b) (4)

(b) (4)

(b) (4)

Validation of Identity Test

Initially, the Identity assay SOP# QOV-PM-187, was validated at (b) (4). The validation documents supporting the assay were submitted to BLA: Document# Q-TP-00676.00 (ver. 001) and Q-TB-00676.00 (ver. 001, February, 2012). This assay was based on (b) (4)

. These documents demonstrate that the assay was sufficiently validated to confirm the identity of the PPQ (b) (4) DP lots manufactured at (b) (4) facility, during Phase 1 to 3 clinical trials. However, this (b) (4) based assay is not currently being used by the sponsor to release any commercial lots and has been replaced by Test Method: SOP# 1-P-QM-WI-9044684: Confirmation of V920 Identity by (b) (4), Merck & Co. Inc. The test is performed at (b) (4) and is described in Section 3.2.S.4.3 and 3.3.R. of the submission. The current method is an (b) (4) method as described above in section 3.2.3 of this document. Therefore, validation of only the current Identity assay was reviewed.

The identity test used for lot release, Test Method: SOP# 1-P-QM-WI-9044684, was validated in accordance with (b) (4)

wherein specificity (the ability to assess unequivocally the analyte in the presence of components which may be expected to be present) was evaluated. The assay validation criterion for specificity was that 100% of the (b) (4) identified by (b) (4) must also be positive by (b) (4). All non-Ebola Zaire wells must be negative for (b) (4).

The material used in the validation as the Positive Control (PC) was (b) (4) tested at (b) (4) different dilutions, (b) (4) per dilution. The (b) (4) Drug Product matrices contain the same biological and chemical components and only differ in (b) (4) therefore both matrices are considered qualified in the Identity method through validation of the method using the (b) (4) sample matrix.

(b) (4) operators performed the validation; each operator performed (b) (4) assay runs. The total number of assay runs tested was (b) (4). To demonstrate that positive (b) (4) is Ebola Zaire- specific and not caused by (b) (4) negative controls were evaluated during validation: (b) (4)

Conclusion:

All assays met the acceptance criterion, with 100% of the Ebola Zaire (b) (4) identified by (b) (4) and all non-Ebola Zaire (b) (4) were negative for (b) (4). The Identity test performed at (b) (4) is adequately described and validated for testing (b) (4) DP. The test method serves the intended purpose of evaluating the Identity of Ebola lots.

6. Opalescence [Ritu Agarwal]

(i) Opalescence for (b) (4)

The method of physical assessment by opalescence is qualitative, and the specification for Ebola vaccine (b) (4) is that the opalescence of the sample should be greater than or equal to (b) (4). The test is performed at (b) (4)

(b) (4)

Method

This assay is based on the assessment of degree of opalescence of the test sample by visual examination against reference solutions. The method is compliant to the (b) (4) test method.

(b) (4) opalescence reference suspensions are prepared, and tested as per the (b) (4). The test sample and reference suspensions are transferred to vials, and the solutions are compared in (b) (4). A test sample is considered clear if it is the same as water or less opalescent than that of (b) (4). A test sample is considered to meet specification if the opalescence is greater than or equal to (b) (4).

Review of Method Verification

The verification was performed by analyzing (b) (4) sample each from (b) (4) of (b) (4) lots of drug product in an intermediate precision study. The (b) (4) drug product are formulated in (b) (4) buffer (containing Tris and rHSA), and differ only in the (b) (4). Thus, the verification using drug product is applicable to (b) (4) samples. The results for intermediate precision using the drug product were acceptable, and complied with the opalescence specification for the drug product. Additionally, the batch data of (b) (4) and (b) (4) PPQ (b) (4) lots, were within the specified limits.

Conclusion:

This is a well-established qualitative method. Further information is not required. The assay is suitable as a release test for Ebola vaccine (b) (4).

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

9. Total Protein [Ritu Agarwal]

Total protein concentration of DP is measured using the (b) (4) Method. The (b) (4) test is performed at (b) (4). The proposed specification for Total Protein in Ebola vaccine drug product is from (b) (4).

Method

The concentration of protein in Ebola vaccine product is determined by (b) (4) method as described in SOP OPBT2148. This method is based on (b) (4)

The concentration of protein in sample is measured from the linear regression curve prepared using (b) (4) in the range of (b) (4). The assay is considered valid if the correlation coefficient of the standard curve is (b) (4). The assay procedure did not incorporate the use of a positive control.

Review of Validation

The method is used as a quantitative assay for total protein content in the Ebola vaccine drug product. While the method is widely used, it is necessary for the firm to demonstrate the suitability for its intended use, i.e., for measuring the protein concentration of the drug product. This is achieved by demonstrating that the assay accuracy, linearity and precision are not impacted by the drug product or its matrix.

The following validation characteristics were evaluated for the standard: linearity, accuracy, repeatability, intermediate precision and robustness. For verification of assay performance

using the (b) (4) matrix, only precision was evaluated using (b) (4) lots. The (b) (4) drug product have (b) (4), but are formulated in the same buffer. As per the sponsor, the (b) (4) has negligible impact on the protein content and the majority of protein content is due to the rHSA that is present in the formulation buffer, and thus the (b) (4) drug product matrix can be considered as equivalent.

Linearity

(b) (4)

[Redacted text block]

Conclusion:

The (b) (4) method is clearly described in the SOP. The firm has demonstrated acceptable precision of the assay performed with Ebola vaccine (b) (4), and since the drug product has (b) (4) matrix, the data infers acceptable precision of the assay when measuring the drug product protein content. The method is qualified for its intended purpose of verifying addition of the correct rHSA buffer.