



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: December 19, 2019

From: Dmitriy V. Volokhov, D.V.M., Ph.D., OVRP/DVP/LMD

STN: BLA 125690-60

Product: ERVEBO [Ebola Zaire Vaccine, Live]

Sponsors: Merck

Subject: Response to Request for Information

To: Stephanie Polo, DVRPA RPM

Through: Robin Levis, Ph.D., OVRP/DVP

Cc: Sara Gagneten, Ph.D., OVRP/DVP
Ritu Agarwal, Ph.D., OCBQ/DBSQ
Maryna Eichelberger, Ph.D., OCBQ/DBSQ

OVERVIEW:

In amendment 60 Merck submitted responses to a December 16, 2019 CBER information request regarding an agreement on the post-licensure submission of outstanding CMC information to BLA 125690. Below please see the CBER comments to the sponsor and the sponsor's responses.

CBER Question #1:

To ensure process consistency, as part of your future continued process verification, please assess and, where appropriate, adjust process operating ranges. These ranges should reflect the actual manufacturing process. In addition, please address all discrepancies between target and operating ranges described in the manufacturing sections of the BLA and the blank batch records for the Drug Substance submitted to the BLA. Please submit the updated operating targets and ranges in the manufacturing sections of the BLA and the blank batch records covering all Drug Substance and Drug Product unit operations as a Prior Approval Supplement (PAS).

Merck's Response #1:

Merck commits to assess and adjust process operating ranges as appropriate as part of our continued process verification (CPV). Any updated operating targets and ranges will be submitted in the manufacturing sections of the BLA in a Prior Approval Supplement (PAS). Subsequently, the blank batch records covering all Drug Substance and Drug Product unit operations will be updated and submitted after the changes are approved.

Reviewer's Note: *the sponsor's response is acceptable.*

CBER Question #2:

Provide data to support the requested total processing time of (b) (4) for the final Drug Product process, including the determination for a cumulative time out of refrigeration of up to (b) (4). Submit the data as a Product Correspondence – Final Study Report.

Merck's Response #2:

The data to support the requested total processing time of (b) (4) for the final Drug Product process, including the determination for a cumulative time out of refrigeration of up to (b) (4), will be submitted as part of the Final Drug Product PPQ Report by May 29, 2020.

Reviewer's Note: *the sponsor's response is acceptable.*

CBER Question #3:

Provide the final stability results for the ongoing studies of the (b) (4) Drug Product PPQ lots when the stability studies are completed. Submit your final report as a Product Correspondence – Final Study Report.

Merck's Response #3:

The final stability results for the ongoing studies of the (b) (4) Drug Product PPQ lots will be added to Modules 3.2.S.7.3.3 and 3.2.P.8.3.3 when the stability studies are completed and submitted in a Product Correspondence.

Reviewer's Note: *the sponsor's response is acceptable.*

CBER Question #4:

Provide the final validation report for the Total Protein Test performed on the (b) (4) Drug Product to support the intended use of the assay and, specifically, to show that the assay results are not affected by the (b) (4) Drug Product matrix by assessing the spike recovery of the standard (b) (4) over the assay range and (b) (4) between the standard (b) (4) and the product over the assay range. Submit your final report as a Product Correspondence – Final Study Report.

Merck's Response #4:

(b) (4)

Drug Product (DP)

As noted in section 3.2.P.5.6, the Total Protein test is used to verify that the correct rHSA buffer (2.5 mg/mL used in DP vs. (b) (4) used in (b) (4)) was (b) (4) to dilute the BDS into (b) (4) during the drug product manufacturing process. The acceptance range is (b) (4). The drug product matrix is deemed qualified in the assay as it is equivalent to (b) (4) in this test (as described in 3.2.P.5.3.9). The matrix qualification performed demonstrates that the test is capable of distinguishing between the (b) (4) solutions and supports the intended use of the assay.

(b) (4)

Reviewer's Note: *The (b) (4) matrix qualification results using the validated Total Protein assay are provided in Module 1.11.1. The applicant assessed the effects of the Ebola vaccine product matrix as follows: (i) for the protein content test (b) (4) assay) the applicant assessed Linearity, Precision, and Intermediate Precision using (b) (4) V920 (b) (4) lots; (ii) because the matrix of the (b) (4) V920 DP are similar (both contain the same stabilizer solution consisting of 10 mM Tris, 2.5 mg/mL rice-derived recombinant human serum albumin (rd-rHSA)), DVP concludes that use of these (b) (4) samples to assess matrix effects on the protein content test is acceptable and results of this qualification study can be extended to the DP; (iii) since the quantity of protein in the DP is directly dependent on the quantity of protein in the (b) (4) (based on (b) (4)), there is no significant reason for concern that DP protein will fall outside of the limits (the DP release specification of (b) (4)), and this provides additional reason to conclude that consideration of matrix effects on the (b) (4) is sufficient to address any concerns for the DP and that the overall protein testing scheme is suitable to assure product quality. Based on the data submitted, DVP concludes that this assay is qualified for its intended use and has met the requirements to verify the suitability of testing methods under actual conditions of use as specified under 21 CFR 211.194(a) (2). The qualification study results for the Total Protein assay using the (b) (4) matrix will be provided post licensure. Overall, the sponsor's response is acceptable.*

CBER Question #5:

Execute a one-time supplemental verification for the (b) (4) test, using a (b) (4) to confirm that the combination of medium used in the method and V920 matrix is (b) (4). Submit your final report as a Product Correspondence – Final Study Report.

Merck's Response #5:

A one-time supplemental verification for the (b) (4) test will be executed, using a (b) (4) to confirm that the combination of medium used in the method and V920 matrix is (b) (4). Also, as requested in the 10Apr2019 information request, a one-time supplemental study spiking the (b) (4) in the V920 sterility method will be executed. These will be submitted as Product Correspondences – Final Study Reports.

Reviewer's Note: *the sponsor's response is acceptable.*

CBER Question #6:

Perform (b) (4) testing on future (b) (4) lots with a validated assay to characterize the level of residual (b) (4). Submit your final report and request to remove testing of these residuals as a Prior Approval Supplement (PAS) – Final Study Report.

Merck's Response #6:

A test will be implemented in the (b) (4) process to measure (b) (4). Merck plans to implement the same Total Protein (b) (4) test which is currently used for Drug Product release testing. Since the (b) (4) matrix has a (b) (4). As an alternative, we plan to utilize the (b) (4) matrix to measure (b) (4). The V920 (b) (4) matrix is currently being qualified in the (b) (4) method which was previously validated by (b) (4) and our sample matrix was qualified in the validated assay for the Drug Product release test. The (b) (4) matrix qualification report including the spike recovery study will be submitted in a Product Correspondence. If sufficient data from the (b) (4) matrix supports removal of Total Protein testing, a request to remove testing of these residuals will be submitted as a Prior Approval Supplement.

Reviewer's Note: *the sponsor's response is acceptable.*

CBER Question #7:

A substantial portion of the CMC information that was submitted to the BLA in response to information requests in Module 1 was not included in the CMC sections in Module 3. Therefore, please include all updated CMC information such as description of in-process controls, test methods, validation reports, certificates of analysis, storage conditions, description of manufacturing steps, impurities, and deviation reports in the appropriate sections of Module 3. In Module 1 of your submission, please include a Table listing the CTD location of each update and a brief description of the revision. In addition, please identify and describe any specific information which is not identical to the information provided in the BLA prior to its approval. Submit the Module 3 updates as a Product Correspondence – Module 3 Final CMC Information Updates

Merck's Response #7:

The CMC information that was submitted to the BLA in response to information requests in Module 1 was intentionally not included in the Module 3 sections because we believe the information does not meet the recommendations for content in Module 3 as prescribed in ICH M4Q. We will perform an assessment of all of the responses to questions that were submitted to the BLA and any applicable CMC information will be added to the appropriate sections of Module 3 as prescribed in ICH M4Q. In Module 1, we will include our assessment of the responses and a Table listing the CTD location of each update and a brief description of the revision. In addition, we will also identify and describe any specific information which is not identical to the information provided in the BLA prior to its approval. This will be submitted as a Product Correspondence – Module 3 Final CMC Information Updates.

Reviewer's Note: *the sponsor's response is acceptable.*

Reviewer's Final Conclusion:

All submitted information was reviewed and found to be adequately addressed by the sponsor.
No additional action is needed.