



DEPARTMENT OF HEALTH & HUMAN SERVICES

**Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality**

To: Administrative File BLA STN 125690/0

From: Anthony Lorenzo, Lead CSO, CBER/OCBQ/DMPQ/MRB2

Through: CDR Qiao Bobo, Branch Chief, CBER/OCBQ/DMPQ/MRB2
John Eltermann, Division Director, CBER/OCBQ/DMPQ

Cc: Randa Melhem, Consult, CBER/OCBQ/DMPQ/MRB2
Stephanie Polo, Chair, CBER/OVRR/DVRPA
Iryna Zubkova, RPM, CBER/OCBQ/DMPQ/ARB

Subject: Addendum Review Memo: Ebola Zaire Vaccine, Live

Action Due Date: December 13, 2019

RECOMMENDATION

Approval with the following Postmarketing Commitment:

“To provide the Final Drug Product process performance qualification final validation report as a “Postmarketing Commitment – Final Study Report”

SUMMARY

Based on the decisions from the Pre-License Inspection (PLI), the review of the Applicant's Form 483 response (dated December 6, 2019), and the Applicant's agreement to the Postmarketing Commitment, approval of this BLA is recommended.

Additionally, the reviewer and inspection team have the following recommendations during the next follow up inspection of (b) (4) facility (FEI# (b) (4)):

1. (b) (5), (b) (7)(E) Deficiencies were noted with the thoroughness of investigations (e.g.,

initial assessments), lack of justification for extension requests, and failure to implement associated CAPAs.

2. (b) (5), (b) (7)(E) [REDACTED]
3. The following equipment's qualification reports were not available during PLI. Please verify their adequacy.
(b) (4), (b) (5), (b) (7)(E) [REDACTED]
4. (b) (4), (b) (5), (b) (7)(E) [REDACTED]
Please review the justification for such a [REDACTED] (b) (4), (b) (5), (b) (7)(E)
to provide contamination control.
5. (b) (4), (b) (5), (b) (7)(E) [REDACTED]

CBER understands that the recommendation may or may not be taken by the ORA investigators (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion."

REVIEW NARRATIVE

This rolling BLA submission was the result of an agreement between the FDA and the Applicant prior to the submission of the first module. The rationale for this agreement is the urgent need for a US licensed Ebola Vaccine to combat the current outbreak on the African Continent. It was agreed that (b) (4) successful lots of Drug Substance and (b) (4) successful lot of Drug Product (DP) would be submitted to support licensure (IND 16131.191 CRMTS #11436, meeting minutes for Thursday, October 11, 2018 meeting with Merck).

At the completion of the primary review memo by DMPQ's CSO Richard Lewis (dated November 22, 2019), he concluded that a recommendation could not be provided. This was based on the Applicant's insufficient information to support the claim that they could execute their manufacturing process without critical process deviations that could call into question the potential safety and/or efficacy of the units distributed. This determination was reached based on a combination of inspectional findings, Aseptic Process Simulation Results, and Drug Product PPQ (b) (4) results. As CSO Lewis was leaving the agency, he deferred the final decision to management to complete the assessment of the Applicant's submission. The following were his lists of concerns from the Primary Review Memo:

Section 3.2.S.2.5 Process Validation and/or Evaluation:

Drug Substance (DS) Product Performance Qualification (b) (4) (PPQ (b) (4)) and PPQ (b) (4) were verified during the inspection and issues discovered were addressed in the EIR. PPQ (b) (4) was disqualified as it failed potency. As a result, DS PPQ (b) (4) was requested and submitted

after the PLI which was reviewed and documented in CSO Lewis's Primary Review Memo.

CSO Lewis concluded that the information provided by the Applicant for PPQ (b) (4) appears to indicate that the staff can consistently manufacture Bulk Drug Substance according to their established specifications. However, the Quality System's maturity was not substantiated and poses risks to product quality issues as recurring problems raised during the PLI are repeated in PPQ (b) (4). Examples are as follows:

1. Deviation DV0014538 merged several deviations together. However, the primary issue was the recording of expiration dates for raw materials cannot be performed contemporaneously with the charging of materials. This was due to the lack of expiration dates on labels which must be verified separately at a different time on an enterprise computer system.
2. Deviation DV0012846 reported that a discarded (b) (4) used in the manufacture of batch (b) (4) was not recorded due to human error. This had no product impact but reinforces consistent documentation errors.
3. Deviation DV0012827 reported a (b) (4) due to a (b) (4) to the tubing in the (b) (4). No CAPA was reported.
4. The firm's responses in amendment 125690/0.24 regarding the compressor leak in a walk in cold room freezer used for (b) (4) storage did not provide a deviation investigation nor a product impact assessment. This demonstrated the quality system continued failure to fully document deviations and incidents. Only a completed work order was submitted to follow up IR's and no deviation investigation was generated with no justification provided.

Reviewer comment: Based on these recurring Quality System issues, the nature of these deviations being minor, and due to time constraints, which prevented review resolution, I recommend that these issues be followed up on the next inspection.

Section 3.2.P.3.3 Description of Manufacturing Process

CSO Lewis recommended an IR be sent to the firm once time out of cold was established for the (b) (4) filled drug product. However this information would not be available until the Final Drug Product PPQ report is completed.

Reviewer Comment: I recommend the (b) (4) to be verified during the next follow up inspection to ensure the values have been established and implemented

Section 3.2.P.3.5 Process Validation and/or Evaluation

The FDA inspection team was present for the filling of DP PPQ (b) (4). Under more typical circumstances for BLA reviews the inspection team would have been able to review completed DP batch records for PPQ runs at this time and any inconsistencies or deficiencies would have been addressed.

CSO Lewis assessment of the filled drug product reconciliation issue observed during the PLI required extensive changes (Re-Training, Label Confirmation, Locked Carts, New Worksheets, Color-coded Caps) that is being proposed by the applicant. The results of these extensive Correction Actions and Preventive Actions (CAPAs) will not be made available during the current review timeframe.

CSO Lewis reviewed the interim Drug Product PPQ validation report and concluded that all process deviations were investigated and the impact to product was assessed. However, the actions the applicant has taken in response to the observed deviations as corrective and preventative actions were not provided for review. Given the status of the manufacturing site's Quality System observed during the PLI and in conjunction with the information that has been provided in the interim report, he could not make a determination regarding the applicant's ability to manufacture a consistent drug product to their specifications, adequately identify issues that may impact product quality, or appropriately address issues in real-time.

Reviewer Comment: Based on the interim report a PMC is recommended for the completed Drug Product PPQ report in order to evaluate the effectiveness of the Quality System to address the observed deviations. Additionally, a recommendation that the CAPAs implemented to improve the reconciliation of filled vials be (b) (5), (b) (7)(E) .

Conclusion:

Deficiencies were found in the review of the submission and during the PLI of the (b) (4) manufacturing facility. The main review issue found involved the submission of the final DP PPQ report. The interim report reviewed was sufficient to assure the successful demonstration of the manufacturing facility's capability to manufacture product to required specifications. However, the quality system of the manufacturing facility cannot be fully evaluated until all deviations and investigations are closed and justified. Review of this determination is addressed by the PMC.

Additional issues raised regarding the maturity of the quality system and the complete review of equipment qualification are (b) (5), (b) (7)(E) .

Responses to the questions regarding how the quality system addresses the deviations appear to address the issues but the success of these CAPAs to address repeating issues requires additional follow up. Equipment summary reports appear to indicate the firm has completed the qualification after the PLI but verification of the full validation reports could not be completed. (b) (5), (b) (7)(E)