



DEPARTMENT OF HEALTH & HUMAN SERVICES

**Public Health Service
Food and Drug Administration**

Memorandum

Date: December 15, 2019

From: Arifa S. Khan, Ph.D., LR/DVP/OVRR

Subject: Review of (b) (4) for Adventitious Virus
Detection

Established Name: Ebola Zaire Vaccine, Live

Proprietary Name: ERVEBO

Sponsor Name: Merck (Merck Sharp & Dohme Corp / Merck & Co. Inc)

To: FILE BLA STN 125690/0

Through: Robin Levis, Ph.D., Deputy Director, DVP

Cc: Hana Golding, Ph.D. Chief, LR, DVP

Jerry Weir, Ph.D. Director, DVP

Stephanie Polo, BLA Committee Chair, DVRPA

REVIEWER’S RECOMMENDATION:

Sponsor-initiated (b) (4) for adventitious virus detection was performed as a characterization test on selected test materials. These included:

(b) (4)

Since (b) (4) policy has not yet been established in OVRR, the results submitted were deemed to be acceptable as an investigational assay to complement the results of the conventional virus detection assays demonstrating absence of adventitious virus detection and support approval of this BLA.

FULL REVIEW: ERVEBO

Ebola Zaire Vaccine, Live

I have reviewed the (b) (4) information for adventitious virus detection submitted to the BLA in amendments 1 and 27 (dated Dec 13, 2018 and Aug 27, 2019, respectively), appendix 3.2.A.2 Adventitious Agents, and responses to CBER’s questions in the Information Request (IR) letter dated November 25, 2019, submitted to the BLA in amendment 51 (dated Dec 2, 2019).

- The sponsor has included results of the (b) (4) analysis in the BLA amendment 1; however, detailed information on the development and execution of the (b) (4) testing and (b) (4) analyses were provided in IND 16131 and not reiterated in the BLA. It is noted that in the IND, ERVEBO was referred to as rVSVΔG-ZEBOV-GP or V920. This memo includes summary review and critical comments related to IND amendments as indicated below. (b) (4) was used as an investigational assay to complement adventitious virus testing. The results demonstrated absence of adventitious viruses based on performing (b) (4) on the following test samples: (b) (4)

(b) (4)

- It is noted that the only change in the information submitted in BLA amendment 27 was correction of (b) (4) with “(b) (4)” on page 3 (summary paragraph 3 in Section 1).
- The sponsor provided responses to Questions 1 – 3 in the IR dated November 25, 2019 (BLA, amendment 51) regarding plans for using (b) (4) post-licensure. In this regard, CBER sent a request to the sponsor on December 17, 2019 indicating early discussions with the CBER and to submit all of the relevant information and results to the BLA as they become available.

Details of (b) (4) were submitted in the IND 16131. I have reviewed the information on (b) (4) for adventitious virus detection submitted in response to IR letters in the following amendments to the Original IND 16131 [Ebola Virus Recombinant Vesicular Stomatitis Virus-Vectored (expressing Zaire strain envelope glycoprotein; Vero cells; rVSVΔG-ZEBOV-GP) Vaccine, Live / Merck].

- Amendment 116 (Oct 28, 2016) contains sponsor’s responses to questions following the Type C meeting with CBER on September 15, 2016 on data submitted in Amendment 105 (details are provided in the review memo by Dmitriy Volokhov for Amendment 105 and the FDA/sponsor final summary of the Type C meeting). At the Type C meeting, CBER requested an overview of the adventitious agents control strategy planned by Merck for the manufacture of V920. The plan included the proposal to remove (b) (4) specific for potential contaminating viruses from the current release test plan.

The sponsor provided a brief and general outline of the (b) (4) strategy in Amendment 116. I was assigned (b) (4) review starting from this amendment and was not involved in earlier review and discussions for the IND. I have reviewed the sponsor’s plans for (b) (4) analysis for adventitious viral agents regarding the (b) (4)

The sponsor included this additional characterization testing strategy since the vaccine live virus is capable of (b) (4)

. Thus, vaccine virus interference precluded execution of the (b) (4) method for (b) (4) testing as well as adventitious agent testing *in vitro* of (b) (4). While the (b) (4) method for (b) (4) testing can be substituted with a (b) (4) method, a multifaceted strategy was adopted to ensure freedom of the vaccine from adventitious

agents and overcome the inability to perform the *in vitro* adventitious agents test.

I provided my (b) (4) comments regarding the samples selected for evaluation, sample preparation and spike recovery studies as well as regarding the (b) (4) analysis in my memo dated Dec 26, 2016 (updated Dec 31, 2016). Also, CBER recognized that (b) (4) is a new and evolving technology and encourages dialogue for its application for adventitious agent detection. My comments were combined with comments from Dmitriy Volokhov and emailed to the sponsor by Stephanie Polo on Dec 29, 2016. This was deposited in the EDR in the CBER TCON record dated Dec 29, 2016.

It should be noted that (b) (4) files, (b) (4) files, and quality data files were not requested from the sponsor, since further internal DVP/OVRR discussions were needed regarding data submission.

- Amendment 129 (Feb 1, 2017) contains responses to FDA's IR of December 29, 2016, to provide additional information on viral (b) (4) analysis. The responses provided in this submission included an initial (b) (4) analysis, which evaluated spike recovery in some samples using a preliminary (b) (4) , as well as slides from a recent public presentation. It was noted to the sponsor that since the technology and (b) (4) are evolving, we agree it would be beneficial for Merck to submit key elements of the new analyses for our review as they are generated and have ongoing discussions on the technical and (b) (4) aspects of the (b) (4) analysis, including, for instance, (b) (4) . Merck committed to (b) (4) analysis using the recently released (b) (4) . Given the scale of the analyses, and time and resource commitment necessary, Merck does not currently plan to further pursue the initial analysis based on the (b) (4) generated by (b) (4) and (b) (4) . My review and further comments to some of the sponsor's responses are provided in my memo dated April 13, 2017. It was noted there was no *in vitro* adventitious agent testing of the (b) (4) itself, but extensive testing including (b) (4) was done for the (b) (4) . CBER further indicated to continue efforts to improve the sensitivity of virus detection using (b) (4), if there were future plans to replace the (b) (4) assays for adventitious virus testing of the (b) (4) .

- Amendment 146 (May 25, 2017) contains responses to CBER's comments regarding review of Amendment 129. The responses were acceptable. Furthermore, the sponsor submitted the key elements of the new analysis, including but not limited to, (b) (4) [redacted] in Attachment 1 of Amendment 146. There were no further comments.
- Amendment 153 (Sept 20, 2017) contains responses to IR letter April 25, 2017 based on review of Amendment 129, where CBER requested additional information pertaining to viral (b) (4) [redacted] analysis. The sponsor submitted the Viral (b) (4) [redacted] Analysis of V920 (b) (4) [redacted] and Controls in Amendment 153. The (b) (4) [redacted]

The sponsor's responses, along with several supporting attachments, reside in Module 1.11.1. The response is included in a Technical Report dated Sept. 8, 2017 (*date corrected to 2017*) with details of the data, and the attachments include: Reference 1, the Technical Report of the preliminary analysis of the V920 (b) (4) [redacted] that was previously submitted in amendment 146; and Reference 2 and 3, the currently submitted results provided in excel files (in addition to discussions in the Technical Report). The present report uses the same analysis pipelines and approaches as previously reported (Amendment 146), and describes any details not presented previously. CBER comments submitted in the Information Request were adequately addressed with information provided in the current Amendment 153 and previously in Amendment 146.

The sponsor performed extensive (b) (4) [redacted] of the samples and provided in-depth review and follow-up of the results with interpretation and their current thinking to support their conclusions. They have noted issues and how they were addressed or provided their thinking on the topic. Furthermore, they provided excel sheets for additional in-house review of the results. Additionally, representative (b) (4) [redacted] are submitted in Appendix 1 for the (b) (4) [redacted]

(b) (4) pipelines used in the V920 (b) (4) studies.

My memo dated Dec 23, 2017 (revised Dec 27, 2017) contains detailed review of the (b) (4) data. There were no further comments regarding the (b) (4) analysis.

- Amendment 191 (Sept 10, 2018) includes adventitious agents testing information in the submission for the (b) (4). I reviewed this information and provided comments that were included in an IR letter sent from the Review Team to the sponsor on Oct. 26, 2018 (by Stephanie Polo). It was indicated that while the proposed adventitious agent testing is acceptable, in an effort to reduce the use of animals in product testing, we encourage sponsors to consider adoption of alternative methods. Furthermore, we noted that since (b) (4) was used for adventitious viral agent testing to characterize the (b) (4), the sponsor may consider the use of this method for routine testing of (b) (4). The assessment can be limited to specific viral agents of concern, such as those previously proposed for (b) (4) testing (see Table 40 on page 106 of the meeting background materials submitted in Amendment 105). If (b) (4) are tested by (b) (4) for specific viruses of concern, the sponsor can discontinue all in vivo testing listed in Table 1 (including for (b) (4)). However, due to the potential for (b) (4) than *in vitro* testing for adventitious agents because of differences in the volume of material tested by each method, *in vitro* testing of (b) (4) for adventitious agents should be maintained.
- Amendment 194 (Oct 11, 2018) includes sponsor's responses to the Information Request received from CBER on April 25, 2017, after review of IND 16131 Amendment 129, where CBER requested additional information pertaining to (b) (4) analysis. CBER comments submitted in the Information Request have been adequately addressed with information provided in amendments 146 and 153. The summary and detailed review of the previously submitted (b) (4) analysis was provided in my memo for amendment 153, which included preliminary analysis reports for the (b) (4), and also included the preliminary analysis report of the V920 (b) (4), which was previously submitted in amendment 146.

In this amendment, the sponsor submitted the complete and final report for (b) (4) Analysis of V920 (b) (4) and V920 (b) (4). The technical reports reside in Module 1.11.1. The most significant of correction compared with the preliminary

reports was in the (b) (4) report Table 4: Recovery of (b) (4) spikes in the absence or presence of (b) (4); the recovery of low spikes in presence of (b) (4) was corrected (values were out of order in the preliminary report). The final report includes an analysis of (b) (4)

. Additionally, in Appendix 1 of the latter report, representative (b) (4) are included for the (b) (4) pipelines used in the V920 (b) (4) studies. (This was also submitted in the preliminary report in Amendment 153).

Two analyses were extended in the final reports, compared with the preliminary reports. 1) (b) (4) were further evaluated based on additional data, and a summary was added as a new table, *Table 2b: Summary of spike virus stock titers*; in the (b) (4) report. 2) Additional specificity review was summarized for (b) (4) *Table 7: Profile of (b) (4) across unspiked samples based on (b) (4)*; and (b) (4) report *Table 6a: Comparison of profile of hits across unspiked samples based on (b) (4)*.

The results indicated absence of specific hits to adventitious viruses. There were no comments regarding the information provided in Amendment 194.

- Amendment 197 (Oct 30, 2018). On Oct. 19, 2018, CBER sent an IR letter to the sponsor asking to indicate the differences in the results in the final analysis reports compared to the results submitted previously in the preliminary reports (provided on Sept 20, 2017, amendment 153) The sponsor provided this information in amendment 197 (submission dated Oct. 30, 2018). There were no further comments.
- Amendment 200 (Nov 19, 2019) contains responses to CBER's comments dated Oct. 26, 2018 regarding amendment 191. The sponsor indicated in amendment 200 they will not be able to pursue (b) (4) as an alternative to *in vivo* testing (b) (4). Furthermore, upon identification of a testing strategy and computational analysis strategy that they consider appropriate, the sponsor would appreciate the opportunity to continue to receive feedback from CBER on their proposal, (b) (4).