

Davidson, Mark

From: Tull, Lori
Sent: Monday, July 24, 2017 5:10 PM
To: Davidson, Mark
Subject: FW: BLA 125643 CMC information request

From: Tull, Lori
Sent: Wednesday, July 19, 2017 9:46 AM
To: 'Rizwana Sproule'
Subject: BLA 125643 CMC information request

Hi Rizwana,

The CMC reviewers have the following request for information. We are requesting a one-week response time.

1. In your responses to the 6/5/17 information request (Amendment 29) you did not adequately respond to FDA Comment #7. Please provide data supporting the accuracy of the cell viability measurement.
2. In your responses to the 6/19/17 information request (Amendment 34) you indicated that (b) (4) was prospectively validated according to QP-1327. Please provide QR-1327 as well as the following additional information:
 - a. Details regarding the types of samples used for each assessment performed as part of the QP-1327 validation.
 - b. Data on the validation of robustness and stability.
3. In your responses to the 6/19/17 information request (Amendment 34) you indicated that method transfer validation of (b) (4) was conducted retrospectively using the data obtained during the original (b) (4) method transfer validation. Please provide data validating the intermediate precision of the (b) (4) during method transfer.
4. Regarding the validation of the (b) (4) vector (b) (4) release assay, we do not agree that this is a limit test as defined in ICH Q2(R1). Please provide an assessment of linearity, accuracy, sensitivity, and specificity with prospectively established acceptance criteria based on manufacturing experience to demonstrate this assay is suitable for its intended use.
5. Regarding the method validation of the (b) (4) of the (b) (4) vector (b) (4) release assay, please provide the following information:
 - a. The number of replicates/lots tested for the assessment of repeatability.
 - b. The number of analysts participating in the assessment of intermediate precision.
 - c. The (b) (4) values and the identity of the different CAR used during the assessment of specificity.

6. Regarding the validation of the (b) (4) vector (b) (4) assay (QR-1174)

- a. You state that (b) (4) is accomplished using a (b) (4); please provide a justification with data supporting the appropriateness of this (b) (4) for this purpose.
- b. We believe that the identification of (b) (4) is critical to this assay, therefore, please provide data to assess the suitability (i.e., linearity, specificity, accuracy, precision (including intermediate precision) and robustness) of the detection of (b) (4) in your (b) (4) assay. Please also include prospective acceptance criteria.
- c. Please indicate whether all (b) (4) analysts conducted their own (b) (4) and acquisition/analysis or if they acquired/analyzed the same samples.
 - i. If the same samples were used by all (b) (4) analysts, please indicate how the (b) (4) were stored over the (b) (4) days this validation was conducted.
- d. Please provide justification and supporting data for the calculated working range of this assay
- e. Please provide data supporting the limit of quantitation (LOQ) using virus diluted to the proposed LOQ.
- f. Please provide justification and supporting data for the robustness of this assay. In particular, please provide data supporting the use of (b) (4) prepared on the day of (b) (4) as well as data supporting the storage of the (b) (4) prior to testing (in case retesting is necessary). Please also indicate if the (b) (4) are (b) (4) (b) (4).
- g. Please provide a justification for the wide acceptance criteria for each assessment conducted as part of this validation.

7. Regarding 3.2.S.4.3 Validation of Analytical Procedures - (b) (4)

Please provide the RCR Test Operator Worksheets (or a detailed description of the test methods) for the following assays:

RCR: (b) (4) ASSAY (VPPO0323.R00)

RCR: (b) (4) ASSAY (VPO0322.R00)

8. Regarding 3.2.S.4.4 Batch Analyses – (b) (4)

Please provide RCR testing raw data for the following (b) (4) Lots;

(b) (4)

9. Regarding Process Performance Qualification (PPQ) (3.2.S.2.5 Process Validation and/or Evaluation): Please specify the (b) (4) unit used for the small scale lots

10. Regarding (b) (4) data for PPQ Lots (3.2.S.2.5 Process Validation and/or Evaluation, Table 16, Impurity Data for PPQ Lots): If (b) (4) is considered a contaminant (as you indicate) then increased (b) (4) purity should be reflected by increases in (b) (4) values. Therefore, a lower limit for (b) (4) should be set rather than an upper limit.
11. Please provide a description (or SOP) for transport of MCB and WCB materials between sites.
12. Please provide updated tables of all equipment and product contact consumables used in the manufacture of axicabtagene ciloleucel and (b) (4) Please indicate the manufacturer and quality of these materials.

Regards,

Lori Tull
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