

1. Please provide a description of the reagent testing plan you have in place for release for use all incoming critical reagents including media, media components, (b) (4), and excipients used in axicabtagene ciloleucel manufacturing. Your description should list for each component all of the testing performed and the acceptance criteria for each test.
2. You have provided validation reports for the lot release assays, please provide validation protocols for these assays.
3. Regarding your appearance assay:
  - a. You have not provided a validation report for this assay. Please indicate if you are using a compendial method for this assay and what controls/reference standards are being used to ensure it is being performed consistently.
  - b. You have not provided an SOP number for the qualification of the (b) (4) used to assess its output. Please provide this SOP number or indicate how this equipment is qualified for use in this assay.
4. Regarding the (b) (4) assay validation (QR-0778):
  - a. Please indicate the expected concentration of the positive control used during the assessment of assay precision (Section 3.2).
  - b. Please provide a justification for the acceptance criteria used for the assessment of assay accuracy, robustness and reagent stability.
  - c. Please provide a more detailed description of the 'replicate test samples at approximately (b) (4) used for the assessment of assay sensitivity (Table 5A). Please also provide a justification for the (b) (4) %CV observed when using these samples.
  - d. Please indicate the number of sample replicates performed during the assessment of assay robustness (Section 3.6). Please also provide a rationale for the validity of the assessment of reagent/kit robustness when all the concentrations achieved were below the limit of quantitation.
  - e. Please indicate the type of test sample used during the assessment of assay reagent stability (Section 3.7).
5. Regarding the Gentamicin (b) (4) assay validation (QR-0877):
  - a. Please indicate the concentration of the gentamicin spike used during the assessment of assay precision (Section 3.2).
  - b. Please provide a justification for the acceptance criteria used for the assessment of assay accuracy (Section 3.3).

- c. Please provide a more detailed description of the 'replicate test samples at or adjusted to approximately (b) (4) of external gentamicin' used for the assessment of assay sensitivity (Table 5).
  - d. Please indicate the number of sample replicates performed during the assessment of assay reagent robustness (Table 7B).
  - e. Please indicate the number of sample replicates performed during the assessment of assay stability (Section 3.7). Please also clarify whether the samples used to assess freeze-thaw stability (data presented in Table 8B) contained cells.
6. Regarding both the (b) (4) Gentamicin (b) (4) assays:
- a. Please confirm that the test samples used in these assays for lot release of axicabtagene ciloleucel do not contain cells.
  - b. Please confirm that the (b) (4) samples used in the validation of these assays do not contain cells.
  - c. The SOPs provided for these assays (TM-0010-QC3 & TM-0033-QC3) indicate that either the (b) (4) may be used, however, only the (b) (4) was used in the validation of these assays. Please provide a justification for including the (b) (4) in these SOPs when no data has been provided supporting its suitability for these applications.
7. Regarding your cell viability and concentration assay:
- a. SOP (TM-0005-QC3) doesn't provide sufficient detail to conduct this procedure consistently. Please provide the following information and consider updating the SOP to clarify the following points:
    - i. Please indicate the number of replicate samples assessed in order to determine the cell concentration and viability of each lot of axicabtagene ciloleucel for lot release and dose determination.
    - ii. Please indicate whether all samples are run (b) (4) is needed or whether samples are (b) (4) as indicated in Attachments 1-3 prior to running this assay.
    - iii. When (b) (4) samples as indicated in Attachments 1-3, are samples then run across the (b) (4) or are they chosen from (b) (4)? If samples are chosen from (b) (4), how is that (b) (4) chosen?
    - iv. There are multiple ways to obtain invalid results from this assay (b) (4)

(b) (4) Procedures for handling invalid results due to sample concentration were described; however, instructions for handling other types of assay invalidity were not included in the SOP nor was a second SOP referenced that may contain such instructions. Please provide a detailed description of the actions to be taken in response to other types of assay invalidity, particularly if the (b) (4) This description may include actions taken with the sample as well as the product lot from which sample originated. Please include a reference to these instructions in SOP TM-0005-QC3.

- b. Regarding the assay validation (QR-0435):
  - i. The assay validation submitted is insufficient, please evaluate the following aspects of this assay or provide data indicating the following aspects of this assay if it is available.
  - ii. Accuracy of the assay with regard to cell count or viability determination.
  - iii. Precision, sensitivity and robustness of the assay with regard to viability determination.
- c. Regarding transfer for the assay from (b) (4) (QR-0653):
  - i. Please provide justification for only evaluating assay precision (repeatability, intermediate precision, reproducibility).
  - ii. Please provide justification for not assessing the precision of this assay with regard to viability determination.
  - iii. Please provide a rationale for only using (b) (4) to determine assay repeatability and intermediate precision.
  - iv. Please indicate the number of sample replicates performed during the assessment of assay intermediate precision.
- 8. Please provide a copy of the reference ((b) (4) 2012) from which the (b) (4) (b) (4) formula in Section 3.2.A.2.3.1 is taken. In addition, please explain why the (b) (4) of (b) (4) used to calculate the (b) (4) was set at (b) (4) rather than (b) (4)
- 9. Please describe the calculations for maximum allowable concentration (MAC) of the organic extractables from the (b) (4) bags in section 3.2.S.2.6 (acicabtagene ciloleucel). Specifically, how were MACs of (b) (4) obtained?
- 10. To facilitate the timely review and reduce the chance of miscalculations due to transcriptional error, please provide the data in section 3.2.R.1 Acicabtagene Ciloleucel Clinical Lot Data in an electronic format (e.g. excel, csv). Additionally, for each product

batch please include the following clinical data: highest AE score, duration of persistence, best response, and duration of response.