

1. Please provide stability test method descriptions and validation reports for the (b) (4) retroviral vector, (b) (4), and final product.
2. Please provide a copy of SOP-0408-QC3 and full testing results for cryobag vendor qualification referred to in section 3.2.P.7 Table 2.
3. Please provide the following information concerning the vapor phase liquid nitrogen shippers:
  - a. A description of how these vessels are charged with liquid nitrogen (including details of volume of liquid N2 per shipper)
  - b. A description of how product will be packed into the dewar, including information on any packing material used to prevent damage to the product/aluminum cassette
  - c. A description of the temperature monitoring devices included in each shipment
4. Please provide standard deviations for the average flow rates listed in Table 2 ((b) (4) test qualification results) and Table 3 (Phase II CCI test results) in section 3.2.P.2.5.
5. Please provide a description of the (b) (4) container ((b) (4)) used for shipping apheresis bags.
6. (b) (4) is identified as a critical step in the axicabtagene ciloleucel manufacturing process that is required for (b) (4). In this aspect, (b) (4) may be considered a critical manufacturing reagent. With respect to information provided in your BLA submission (STN 125643) pertaining to the (b) (4) reagent, we request that you give consideration to the following, providing additional information where feasible:
  - a. In Section 1.4: References, you provide a letter of cross-reference authorization from (b) (4) dated 20March2017 granting FDA permission to review information contained in the Type II Master File BB-MF (b) (4) pertaining to the (b) (4) in support of your biologic license application (BLA-STN 125643). Taking into account possible risk posed to your BLA and subsequent license due to ongoing regulatory activity involving the status of the Master File held by (b) (4) that describes manufacture of the critical (b) (4) reagent we prefer sufficient information be included in your BLA submission pertaining to this critical reagent to allow for the BLA to serve as a stand-alone source document of key information to the extent this is possible. Accordingly, we recommend you request (b) (4) supply you with the following for incorporation into the BLA:
    - i. A non-proprietary description of the manufacturing process used for production of (b) (4) that provides a summary of information pertaining to materials used in the manufacturing process and the procedures followed.

- ii. Given the (b) (4) reagent, please request (b) (4) identify the steps in the manufacturing process that provide for viral clearance and/or inactivation and indicate the sum total of log<sub>10</sub> viral reduction that is achieved.
  - iii. (b) (4) performs more extensive release testing of the (b) (4) that comprises the (b) (4) reagent than is summarized in the example Certificate of Analysis for this reagent supplied in Section 3.2.S.2.3: Control of Materials of your BLA submission. We request you ask (b) (4) to supply you with a copy of the more detailed summary of release testing performed for the (b) (4) reagent in addition to the Certificate of Analysis documentation you currently receive with the (b) (4) reagent.
- b. It is unclear from information provided in Section 3.2.S.2.3: Control of Materials, whether determining suitability of the critical (b) (4) reagent for use in the manufacture of axicabtagene ciloleucel is based solely on inspection upon receipt of the Certificate of Analysis provided by the supplier or if additional in-house testing, such as an assay for (b) (4) as referenced in QR-0795: Process Performance Qualification Report for Axicabtagene Ciloleucel, 6.4: (b) (4) (3.2.S.2.6: Manufacturing Process Development) is performed to verify the activity of each lot of the critical (b) (4) reagent. Please clarify whether any in-house testing is performed in addition to inspection of the Certificate of Analysis for qualification of the (b) (4) reagent.