From: Riggins, Cindy
To: Giordano, Erica; Patel, Manisha
Cc: Ahmed, Narin
Subject: RE: BL 125646 CMC Information Request
Date: Tuesday, June 27, 2017 9:28:47 AM
Attachments: image001.png
Sensitivity: Confidential

Hi Erica, we confirm receipt.

Cindy

From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Monday, June 26, 2017 7:48 PM
To: Patel, Manisha
Cc: Riggins, Cindy; Ahmed, Narin
Subject: BL 125646 CMC Information Request
Sensitivity: Confidential

Please see the information request below and provide a response by noon on June 30, 2017. As usual please submit a response directly to this e-mail and follow up by submitting the information as a formal amendment to the BLA.

1. The proposed tisagenlecleucel specifications (3.2.P.5.6) were set based on data from batches that were produced prior to use of the validated manufacturing process with CPPs, and before uniform use of the (b) (4) pathway. Thus, the proposed specifications may not be fully representative of lots produced using the commercial manufacturing process. Please recalculate the proposed tisagenlecleucel lot release specifications based on batches produced using the current manufacturing process and controls. Please include a description and list of the batches used in the new analysis. We recommend that you include batches for the treatment of pediatric ALL and DLBCL produced after implementation of CPPs. Please ensure that proposed lot release specifications include both an upper and lower limit.

2. Additionally, your lot release assay for vector copy number (VCN) should divide the VCN by the number of transduced cells, not by the total number of cells. This measurement of VCN per transduced cell will likely be more indicative of the safety risks associated with high levels of transduction. Please recalculate the VCN data accordingly, and propose appropriate lower and upper limits as acceptance criteria.

3. The proposed appearance test for commercial lot release consists of only visual inspection of color, with the acceptance criterion of colorless to slight yellow. During the early clinical development stages the appearance test also included visual inspection of opacity and cell clumps. You have deemed that the opacity test is unnecessary, because the appearance assessment for opacity does not measure a quality attribute that is not already captured by other release assays. While the opacity test may be redundant, we recommend that visual inspection for cell clumps and other particles or aggregates in the final cell product should be a part of the appearance test. We note that you have optional manufacturing steps to remove cell clumps before transduction steps. However, cell clumps may be formed again after transduction steps and may be present in the final product. Due to potential adverse effects of cell clumps, cell suspension with visible cell clumps or other aggregates should be rejected.

Please confirm receipt of this request.

Thank you,

Erica Giordano
Regulatory Project Manager
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
U.S. Food and Drug Administration
Tel: 240-402-8298
Erica.Giordano@fda.hhs.gov