From: Riggins, Cindy
To: Giordano, Erica; Patel, Manisha
Cc: Ahmed, Narin
Subject: RE: BL 125646 CMC Information Request
Date: Friday, June 16, 2017 3:40:11 PM
Attachments: image001.png
Sensitivity: Confidential

Thank you Erica. I confirm receipt of this request.
Cindy

From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Friday, June 16, 2017 3:37 PM
To: Patel, Manisha
Cc: Riggins, Cindy; Ahmed, Narin
Subject: BL 125646 CMC Information Request
Sensitivity: Confidential

Good afternoon,

Please see the information requests below and provide a response by the response dates specified in each item. As usual please respond directly to this e-mail and follow up by submitting the information as an official amendment to the BLA.

Please respond to comment 1 by Monday June 19th, 2017 at 9 am:

1. Please provide an excel table of the lot release and characterization data for all lots used in the process validation study submitted on June 16, 2017. Additionally, each lot should be identified as clinical or healthy donor lots.

Please respond to comments 2-4 by Wednesday June 21, 2017 at 9 am:

2. MOI assay

    a. Regarding the design of your MOI assay (AM64150) and your "CMC-response-FDA-16" document (SN 29, submitted 5/30/17), we have the following requests:
        i. You stated that you would implement a reference vector control after completion of the validation study. Now that the validation study has been completed, please confirm that you have implemented a reference vector control, and describe how this control will be used to evaluate system suitability and data trending.
        ii. When a new healthy donor cell bank is required, you will conduct a cross-over study to qualify a new cell bank. You further state that a conversion factor may be necessary.
        iii. Please describe your approach to selecting and qualifying a new donor cell bank.
        iv. Please describe how you will perform the cross-over study.
        v. Please describe under what circumstances a conversion factor will be necessary, how this conversion factor will be calculated, and whether revalidation of the assay for accuracy will be necessary under these circumstances.

b. In the validation report for your MOI assay (VR64150B), you reference the LOQ for flow cytometry with the anti-CAR stain for non-transduced cells to be (b) (4) (page 4 of 16). However, in the validation of flow cytometry assay (VR64008B), the LOQ for anti-CAR staining is (b) (4) (page 38 of 54).
    i. Please clarify how these LOQs were determined and how they relate to each other.
    ii. Please confirm the LOQ for detection of transduced and non-transduced cells with the anti-CAR stain.

Flow cytometry (FMO) control

3. Regarding detection of CAR-positive cells by flow cytometry, please incorporate a fluorescence minus one (FMO) control into your protocol to accurately set gates for release of each CAR T cell lot. The FMO control is necessary for control of flow cytometry assays detecting low frequency (b) (4) cell populations.

Please respond by June 21, 2017:

4. Assay acceptance criteria for the vector DS and DP:

    a. The proposed acceptance criterion for (b) (4). Based on the data distribution in (b) (4) batches, the proposed limit of (b) (4) is too high. For the purpose of manufacturing a consistently pure product, please reduce this criterion to (b) (4).
    b. The proposed acceptance criterion for DP endotoxin is (b) (4). Based on the data distribution in (b) (4) DP batches, the proposed limit of (b) (4) is too high. Please reduce this criterion to (b) (4).
    c. The proposed acceptance criterion for DP (b) (4) is (b) (4) l. Based on the data distribution in (b) (4) DP batches, the proposed limit of (b) (4) is too high. For the purpose of manufacturing a consistently pure product, please reduce this criterion to (b) (4).
    d. The proposed acceptance criterion for DP (b) (4). Based on the data distribution in ' ' DP batches, the proposed limit of (b) (4) is too high. For the purpose of manufacturing a product with consistent activity and purity, please reduce this limit to (b) (4)

Please confirm receipt of this request.

Thank you,

Erica Giordano
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