From: Patel, Manisha
To: Giordano, Erica
Cc: Riggins, Cindy; Ahmed, Narin; Azevedo Santos, Joana; Wonnacott, Keith
Subject: RE: BL 125646 CMC Information Request
Date: Thursday, May 04, 2017 11:06:15 AM
Attachments: image001.png
Sensitivity: Confidential

Dear Erica,

I confirm receipt of this request.

Kind regards,
Manisha

From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Thursday, May 04, 2017 11:04 AM
To: Patel, Manisha <manisha.patel@novartis.com>
Cc: Riggins, Cindy <cindy.riggins@novartis.com>; Ahmed, Narin <narin.ahmed@novartis.com>
Subject: BL 125646 CMC Information Request
Sensitivity: Confidential

Good afternoon,

Please see the information requests below. Please provide a response directly to this e-mail by the requested response date specified in each information request and follow up by submitting the information as an amendment to the BLA.

1. Regarding the multiplicity of infection (MOI) assay (AM64150A): (Please submit your response by noon on May 12, 2017)

   a. Analysis of the (b) (4) vector DP batches indicates that the MOI (and the related parameter, volume for (b) (4) transduction) is trending upward with time (date of DP batch manufacturing). Other independent parameters that measure the concentration or activity of the vector ((b) (4) qPCR titer, (b) (4) FACS titer, RNA copy number, (b) (4), vp:IU ratio) do not show any apparent time-related trends. Please provide your analysis of trends in the MOI and volume for (b) (4) transduction results. We recommend that you re-analyze retain samples of older lots to help to resolve this issue.

   b. Please comment on how this upward trend in the vector MOI assay relates to the possible time-related upward trend of the %CAR positive T-cells in the CTL019 DP.

   c. Please explain whether these trends in the MOI and volume for (b) (4) transduction results were detected by Novartis, and if not, please explain why not. If trends were detected, please explain what actions were taken.

   d. The MOI assay may include a reference control vector, but it is not clear whether such a control was included routinely, or how any resulting control data were used. Please clarify.

e. Please explain whether this assay has any system suitability criteria. Are there formal criteria to determine whether each assay run is valid?

f. Please explain the banking system for the donor cells that are used in the MOI assay, and explain how you control the potential impact of donor variability on the results of the MOI assay.

2. Regarding the validation of the multiplicity of infection (MOI) assay, VR64150A is inadequate for the following reasons: (Please submit your response by noon on June 7, 2017)

a. Insufficient data was generated at the intended testing site, Novartis Morris Plains.

b. The validation is a retrospective report instead of a prospective study as outlined in the FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics (2015).

c. The data is reflective of the assay at early stages of Novartis' experience with the product and procedures, and it's evaluation of current testing is unclear.

Please submit, by June 7, 2017, a validation report for Determination of MOI of Lentiviral Vectors using Human T-cells (VR64150A) conducted at Novartis Morris Plains in accordance with ICH Q2(R1) guidelines and the FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics (2015).

We recommend that the linearity of the assay should be validated between (b) (4) transduction, the effect of donor variability should be evaluated, and robustness testing should include more replicates to evaluate the effects of the stressed condition.

3. Regarding the CTL019 Phenotyping assay: (Please submit your response by May 12, 2017)

a. As you described in amendment 14 submitted on 4/7/2017, general cellular markers used to identify target cell populations, such as T-cells and CAR+ cells, are maintained between the assays used to characterize cellular populations in the clinical study and proposed commercial process. However, the two assays differ in the master mix composition (e.g. (b) (4) . Therefore, a side-by-side comparison of (b) (4) by these two processes is necessary to assess the impact of assay changes on patient dosing. This comparison should include:

i. A comparison of data generated from the final cell product using the (b) (4) procedure used during the clinical study and the proposed commercial method. Please include a variety of transduction rates.

ii. A table of the composition for each (b) (4) .

iii. Sample scatter plots of tested material for each (b) (4) protocol and

material.

b. Please provide the flow cytometry scatter plots, with gating present, for characterization of the following incoming apheresis or CTL019 DP lots manufactured during clinical study B2202:

   i. Apheresis: (b) (4)

   ii. DP: (b) (4)

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
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