From:	Azevedo Santos, Joana
To:	Giordano, Erica
Cc:	Ahmed, Narin; Patel, Manisha; Riggins, Cindy; Wonnacott, Keith
Subject:	RE: BL 125646 CMC Information Request
Date:	Friday, April 28, 2017 8:58:59 AM
Attachments:	image001.png 7008911_ANSW_MC_840_14.pdf 7008911_P43_MC_840_2.pdf
Sensitivity:	Confidential

Dear Erica,

Attached is the response document to the CMC information request received on April 24, 2017 (7008911_ANSW_MC_840_14). Along with the response document there is an updated section of the BLA, P43 – Validation of Analytical Procedures (Excipients), so you will receive a total of 2 documents. We will follow up with a BLA amendment through the gateway of these documents.

Kind regards,
Joana

From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Monday, April 24, 2017 11:04 AM
To: Ahmed, Narin <narin.ahmed@novartis.com>; Patel, Manisha <manisha.patel@novartis.com>
Subject: RE: BL 125646 CMC Information Request
Sensitivity: Confidential

Hi Narin,

The CMC team has agreed to an extension to Friday April 28th by 9 am.

I hope this will be helpful.

Thanks
Erica

From: Ahmed, Narin [mailto:narin.ahmed@novartis.com]
Sent: Monday, April 24, 2017 9:43 AM
To: Giordano, Erica; Patel, Manisha
Subject: RE: BL 125646 CMC Information Request
Sensitivity: Confidential

Dear Erica,

Would it be possible to grant an extension for this response to Friday, April 28th to allow sufficient time for us to coordinate with our lentiviral vector partner, (b) (4), who are not local to the Novartis team?

Thank you.

Best regards,
Narin

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From: Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
Sent: Monday, April 24, 2017 7:18 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 morning,

Please see the attached information request and provide a response by 4 pm on Wednesday on April 26, 2017. Please provide a response directly to this e-mail and follow-up by submitting this information as an amendment directly to the BLA.

1. In relation to Determination of MOI of Lentiviral Vectors using Human T-cells: analytical method AM64150 and SOP-464 and validation report VR64150A
    a. The validation is performed a (b) (4) and MP, however it appears that the test is only performed at MP. Please clarify if this assay was performed at (b) (4) during the clinical trials supporting the BLA and when this assay is used at either location for the proposed commercial testing.

    b. (b) (4) SOP-464 is not provided in the BLA. Please provide this SOP with a summary of how it differs from AM64150 if this testing will be performed at (b) (4) SOP-470 "Determination of CART19 Expression by Flow Cytometry" was provided, but it is our understanding that this is a different assay.

    c. VR64150A Table 2-1 has acceptance criteria for Linearity, Precision and Robustness marked as "to be established in validation report" and no pre-set acceptance criteria are defined as described in ICH Q2(R1). Please comment.

2. In validation report VR64070A: Functional test of expressed transgene by lentiviral vector transduction, you explain that the acceptance criteria was incorrectly set due to the complexity of the assay. Please clarify the following:

    a. What constitutes each replicate? Specifically are the (b) (4) replicates derived from (b) (4) different transductions or (b) (aliquots of supernatant that were collected from the same culture?

    b. For both measures of precision, repeatability and intermediate precision,

the MOI tested was (b) (4) based on the MOI determination assay. This MOI has the highest level of variance in the MOI validation assay. When using a higher MOI, is a similar level of variability observed in the functional assay?

2. Please describe the shipping conditions for vector test samples, for example to (b) (4) for adventitious agent testing, and how the integrity of the test article is maintained during shipping.

3. In reference to eCTD section 3.2.P.4.2 and 3.2.P.4.3 for qualification of Cryoserv:

    a. To better understand the Cryoserv qualification process, please clarify the amount tested. How many vials are subjected to chemical analysis? Are all vials of a lot tested by visual inspection?

    b. You indicate that the compendial methods were verified; however there is no verification report. Please update the section to include a summary of the verification reports for particulate matter, sterility, and endotoxin testing procedures.

    c. The validation of the analytical procedures does not include a description of the validation protocol for all assays (e.g., Table 1-1 does not provide the number of replicates assessed in the validation of repeatability of the titration assay). Please update all sections to include an adequate summary of the validation protocol for review. Additionally, there is no validation table for Identity testing by IR. Please provide a summary table of this report.

    d. The legend for Figure 1-1 is illegible. Please clarify the description for each sample on the chromatograph overlay; is the blue line an acetone blank?

Please confirm receipt of this request.

Thank you,

Erica Giordano
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