**From:** Wonnacott, Keith
**To:** Giordano, Erica
**Cc:** Riggins, Cindy
**Subject:** RE: BL 125646 OTAT CMC Information Request
**Date:** Wednesday, March 29, 2017 11:24:21 AM
**Attachments:** 7008911_ANSW_MC_840_8.pdf
**Sensitivity:** Confidential

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Erica,
Please find enclosed our answers to the questions you sent to us on Thursday, March 23, 2017. This answer document does *not* have any accompanying attachments. If you have any questions, please feel free to contact us. We will follow up with a BLA submission through the gateway of this document.

Keith Wonnacott, PhD
Director, Regulatory Affairs
Novartis

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**From:** Giordano, Erica [mailto:Erica.Giordano@fda.hhs.gov]
**Sent:** Thursday, March 23, 2017 9:06 AM
**To:** Patel, Manisha
**Cc:** Riggins, Cindy; Ahmed, Narin
**Subject:** BL 125646 OTAT CMC Information Request
**Sensitivity:** Confidential

Good morning,

Please see the information request below and provide a response by March 28, 2017 by COB.

In Section 2 of 3.2.P.5.2 Analytical Procedures, you detail changes during development in analytical methods for cell counting and viability, mycoplasma, and cell phenotyping. We note that no CTL019 batches have been analyzed using the proposed (b) (4) and flow cytometry procedures and 2 batches from the pivotal study B2022 have been analyzed using the (b) (4)

Is each of these methods being used currently for manufacture of CTL019?

Please provide the prospective comparability protocol and analysis for each assay or indicate where it can be found in the BLA. The comparability protocol should reflect ICH guidelines, include clinical batches in the analysis, and provide a description of the predetermined limits for acceptable variance and discussion of the statistical analysis.

For the flow cytometry-based assays, which are used for dose determination and as a safety measure, please provide the following additional information:

i. A table comparing the flow cytometry staining cocktails (including antibody-fluorochrome combinations and dilutions) used in each panel for the released B2202 batches and the proposed panel for the licensed product

ii. Comparison of (b) (4) strategy, including a table indicating (b) (4) hierarchy for each

cell type and representative (b) (4) plots of control and patient samples

iii. Data, graph or table, assessing the effect of the staining panel on cellular population designation. Please include an assessment of the dose determination in patient samples between the two methods.

In SOP AM6008A, but not in the Analytical Procedures, cellular staining may be accomplished by the incubation in manually prepared staining cocktail or by use of a custom (b) (4) . However, a comparison of cell phenotyping by these two methods was not included in the assay validation report. Additionally, no information on the stains included in the (b) (4) was provided (b) (4) , test and control wells, etc). Please comment.

On page 9 of 3.2.P.5.2 analytical procedures, "the analysts (b) (4) using locked protocols as specified in Table 1-5." However, in SOP AM6008A the (b) (4) strategy is according to locked protocols with the analyst instructed "to adjust (b) (4) accordingly." Please clarify. Does the (b) (4) strategy correspond to the order of (b) (4) Does it place (b) (4) for each cell type? Under what circumstances does an analyst adjust the (b) (4) How are the adjusted (b) (4) recorded? Are the adjusted (b) (4) based on controls and applied to all samples in a run or set on an individual sample basis? Are the adjusted (b) (4) subject to supervisory review prior to lot release? Have these adjustments been associated with a CTL019 lot meeting lot release criteria that did not originally?

In Table 1-5 the of 3.2.P.5.2 analytical procedures, you detail the (b) (4) strategy for each sample.
Are the (b) (4) hierarchies switched for the (b) (4) controls?

We note that the viability (b) (4) is absent in the (b) (4) control. Please comment.

We note that the (b) (4) hierarchy for the sample differs from that for the positive control. Please comment on how this affects placement of (b) (4) in relation to controls.

Please submit data confirming that the compensation setting used in your (b) (4) panel will not affect the percent positive cells obtained from both CAR +and CD19 + channels. As your specification for %CAR+ and CD19+ cells requires detection below 10%, we recommend inclusion of a FMO (fluorescence minus one) control for these two markers to confirm compensation setting and population gating of each sample. Please comment.

Please confirm receipt.

*Thank you,*

**Erica Giordano**
*Regulatory Project Manager*

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**Office of Tissues and Advanced Therapies**
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