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Sent: Monday, August 2, 2021 4:40 PM

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Cc: Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>; Gottschalk, Laura <Laura.Gottschalk@fda.hhs.gov>

Subject: STN 125742.0: Questions regarding the Validation Report VR-MVR-10077

Elisa,

The review team has the below set of questions for Pfizer regarding the Validation Report (VR-MVR-10077) entitled "Validation Report for a (b) (4)

(b) (4) " that was submitted in STN 125742.0.19 on July 28, 2021.

1. In your C4591001 clinical protocol amendment 17 (submitted to IND 19736 in amendment 414 on July 20, 2021), you stated that (b) (4) (b) (4) assay or S1-binding IgG assay will be used for the exploratory immunogenicity endpoint. Please clarify which immunoassay has been used for the assessment of binding antibodies for your Phase 2 and 3 studies. If both assays are used, please provide the validation study report for the S1 IgG dLIA assay. In addition, please provide the SOP of the (b) (4) (b) (4) assay (VR-TM-10309), including a description of critical materials (e.g., reference standard, quality control sample (QCS), (b) (4) antigen, (b) (4), etc.), assay validity criteria, sample validity criteria, and interpretation of results. Please also provide the test method VR-TM-10309, and the validation protocol VR-MVP-10077.
2. We note that assay cross-reactivity was not assessed in your validation studies. Please provide data for specificity analysis, including inhibition experiments comparing the effects of heterologous antigens (e.g., (b) (4) antigen from other coronaviruses) and homologous antigens (e.g., antigens at different concentrations) when spiked into the panel of samples. Alternatively, you can evaluate the assay cross-reactivity using a set of antibodies or serum samples with known reactivity to distinct strains of human seasonal coronaviruses.
3. We note that assay robustness was not assessed in your validation studies. Please consider evaluating the assay robustness for any variables that may

potentially affect assay results, for example, stability of the antigen-coated beads, assay incubation time and temperature, etc.

4. Please provide information on the source, preparation instructions, and titer assignment for the reference standard and quality control samples that contains (b) (4) in the validation study. A negative QCS below or at the lower limit of quantitation (LLOQ) level should be included in routine testing for the (b) (4) assay. Please explain how you determine the cut-off values for specific (b) (4) levels in the seronegative samples.
5. Please note that your assay needs to be validated using incurred samples from the vaccine trials for precision and accuracy via (b) (4) linearity including verification of the LLOQ, ULOQ, and the assay range. The assay should be fully validated prior to testing the Phase 3 clinical samples.
6. Performance of your assay would be strengthened by inclusion of the WHO SARS-CoV-2 International Antibody Standard. You might inquire from the National Institute of Biological Standards and Control (NIBSC) about the availability of this reagent. We recommend assessing the performance of your assay using the International Antibody Standard and convert your results to International Units.
7. You set the LLOQ to be (b) (4), which was obtained by (b) (4)
(b) (4)
(b) (4)
Such LLOQ could serve as a theoretical LLOQ, but data are needed to support adequate assay performance at such LLOQ. We note that the precision near the lower assay limit on well concentration level was evaluated mostly with data at the (b) (4)
(b) (4) (green stars and light green diamonds in Figure 2 on Page 17 of the report). We also note that the lowest incurred sample included in the precision evaluation has concentration of (b) (4) (Table 12 on Pages 36-37 of the report), which is far above the theoretical LLOQ (i.e., (b) (4)). Please explain how the current data support adequate precision at the proposed LLOQ of (b) (4) or provide additional data.
8. We note that, in Table 10 on Page 34 of the report, the (b) (4)
(b) (4) do not include the (b) (4) for some samples. Taking Sample (b) (4) as an example, the (b) (4)

(b) (4) (b) (4) which does not include the (b) (4)
(b) (4) Please verify the numbers in this table and make corrections, if needed.

9. You stated in Section 5.2.7.2 of the report that the mean, standard deviation, and (b) (4)
(b) (4) However, as shown in Table 8 on Page 21 of the report, (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
10. Please submit the data sets used for the (b) (4) linearity and precision analyses in an analyzable format (e.g., spreadsheet).
11. The x-axis in Figure 4 on page 35 of the report is blurry. Please resubmit the figure in higher quality so that it is readable.

Regards,

Mike

- Please confirm receipt of this e-mail and let us know if you have any questions.

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