# BNT162b2 (COMIRNATY)

## BLA STN 125742/0

## Response to 02 August 2021 CBER Information Request Regarding

## Validation Report VR-MVR-10077

**05 August 2021**

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## LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| BLA | Biologics License Application |
| CBER | Center for Biologics Evaluation and Research |
| CI | confidence interval |
| COVID-19 | coronavirus disease 2019 |
| CV | coefficient of variation |
| dLIA | direct-binding Luminex immunoassay |
| EUA | Emergency Use Authorization |
| FDA | United States Food and Drug Administration |
| (b)(4) | (b)(4) |
| IgG | immunoglobulin G |
| IR | Information Request |
| LLOQ | lower limit of quantitation |
| NA | not applicable |
| NIBSC | National Institute of Biological Standards and Control |
| QCS | quality control sample |
| RMSE | root mean square error |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| ULOQ | upper limit of quantitation |
| WHO | World Health Organization |

## 1. INTRODUCTION

Reference is made to BLA STN 125742/0 for the Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥16 years of age.

The purpose of this document is to respond to CBER's Information Request (IR) communicated from Captain Michael Smith, PhD (CBER) to Elisa Harkins Tull (Pfizer Inc.) via email on 02 August 2021, with questions regarding the validation report VR-MVR-10077. CBER has requested a response by 05 August 2021.

CBER's comments/requests in ***bold italics*** are followed by the Sponsor's responses below.

## 2. CBER REQUESTS

***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) ***that was submitted in STN 125742.0.19 on July 28, 2021.***

### 2.1. CBER Request 1

***In your C4591001 clinical protocol amendment 17 (submitted to IND 19736 in amendment 414 on July 20, 2021), you stated that*** (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) ***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.***

**Response**

The S1 IgG dLIA (and not the (b) (4)) was qualified and used for immunogenicity assessments in Phase 1 (C4591001 sentinel cohort) and Phase 2 (C4591001 Phase 2 immunogenicity cohort) studies. Only data from these immunogenicity studies using the qualified S1 IgG dLIA assay have been submitted to the EUA and the BLA. The S1 IgG dLIA was discussed and agreed previously with CBER under BB-IND 19736. Final qualification reports were submitted to the IND as part of the Response to 29 July 2020 Information Request – Clinical Assay Qualification on 25 August 2020 (Serial Number 0068) and are also included in the BLA. The validated (b) (4) will be used for the (b) (4) study and several other studies that, based on agreement with CBER, will not be part of the original BLA filing.

Given that the validation of the (b) (4) is not pertinent to the BLA at this time, Pfizer respectfully requests to provide all information requested for the assay at a later time in a separate submission to BB-IND 19736. Does CBER agree?

**2.2. CBER Request 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.***

**Response**

Cross-reactivity of the (b) (4) was assessed outside of the formal validation and demonstrated excellent specificity to the (b) (4) of SARS-CoV-2. The results of these assessments will be submitted to BB-IND 19736 at a later date.

**2.3. CBER Request 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.***

**Response**

Assay robustness of the (b) (4) was assessed outside of the formal validation. The results of these assessments will be submitted to BB-IND 19736 at a later date.

**2.4. CBER Request 4**

***Please provide information on the source, preparation instructions, and titer assignment for the reference standard and quality control samples that contains (b) (4) (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.***

**Response**

Information on the (b) (4) reference standard and QCS will be submitted to BB-IND 19736 at a later date.

### 2.5. CBER Request 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***

**Response**

The (b) (4) was fully validated using both COVID-19 (b) (4) (b) (4) The sample type is coded as (b) (4) (b) (4) (b) (4) as shown in Table 11.2 for (b) (4) linearity and Table 11.3 for precision in the VR-MVR-10077 validation report.

### 2.6. CBER Request 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.***

**Response**

Unfortunately, Pfizer was not invited to participate in the development of the WHO SARS-CoV-2 International Antibody Standard. We have obtained a limited supply of this reagent and have tested it in the (b) (4). Results of this analysis will be submitted to BB-IND 19736 at a later date.

### 2.7. CBER Request 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.***

**Response**

A further explanation of how the LLOQ was set for the (b) (4) will be submitted to the BB-IND 19736 at a later date.

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

**Response**

We will verify these analyses and an update will be submitted to BB-IND 19736 at a later date.

**2.9. CBER Request 9**

***You stated in Section 5.2.7.2 of the report that the mean, standard deviation, and*** (b) (4) (b) (4) (b) (4) ***However, as shown in Table 8 on Page 21 of the report,*** (b) (4) (b) (4)

**Response**

Further explanation on this statistical analysis will be submitted to BB-IND 19736 at a later date.

**2.10. CBER Request 10**

***Please submit the data sets used for the*** (b) (4) ***linearity and precision analyses in an analyzable format (e.g., spreadsheet).***

**Response**

The validation datasets in spreadsheet format for (b) (4) linearity and precision will be submitted to BB-IND 19736 at a later date.

## 2.11. CBER Request 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.***

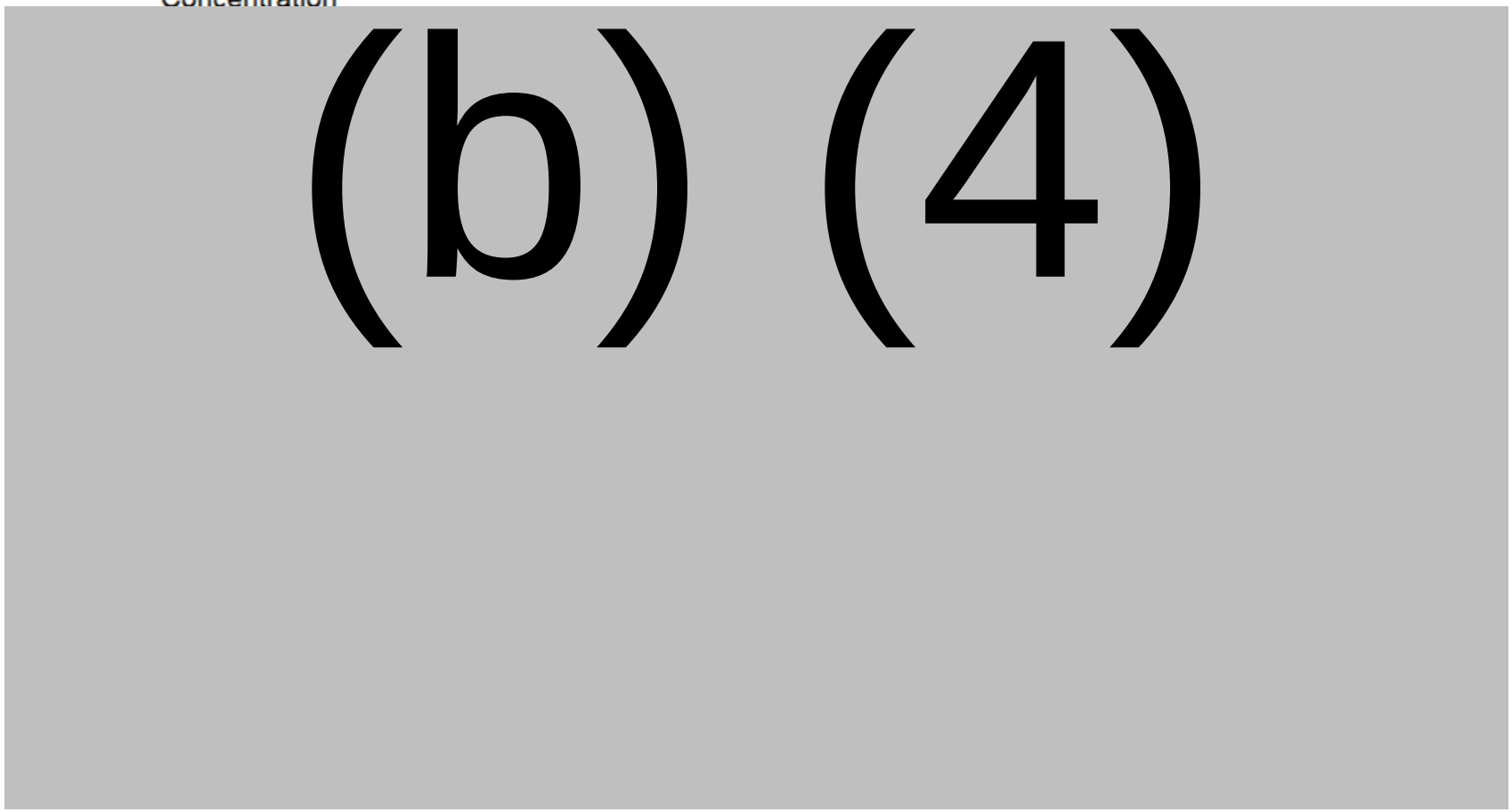
**Response**

A higher resolution version of Figure 4 will be replaced in the validation report, submitted to BB-IND 19736 at a later date, and is also included in Appendix 1 below.

## 3. APPENDICES

**Appendix 1.**
**Figure 4. (b) (4) Linearity for SARS-Cov-2 (b) (4) - Reportable Sample Concentration**

Figure4. (b) (4) Linearity for SARS-CoV-2 (b) (4)- Reportable Sample Concentration



# Document Approval Record

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|---|---|
| **Document Name:** | Aug 2021 Response to 02Aug2021 CBER Request- COVID-19 Vaccine Validation Report VR-MVR-10077 |
| **Document Title:** | Aug 2021 Response to 02Aug2021 CBER Request- COVID-19 Vaccine Validation Report VR-MVR-10077 |

| Signed By: | Date(GMT) | Signing Capacity |
|---|---|---|
| Cooper, David | 05-Aug-2021 14:15:16 | Final Approval |