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**Sent:** Friday, July 02, 2021 6:34 PM  
**To:** 'Harkins Tull, Elisa' <Elisa.HarkinsTull@pfizer.com>  
**Cc:** Gottschalk, Laura <Laura.Gottschalk@fda.hhs.gov>; Smith, Michael (CBER) <Michael.Smith2@fda.hhs.gov>; Aghajani Memar, Neda <Neda.AghajaniMemar@pfizer.com>; Devlin, Carmel M <Carmel.Devlin@pfizer.com>  
**Subject:** STN 125742/0 – COMIRNATY – CBER comments regarding CMC information and categorical exclusion for an environment analysis

Dear Ms. Harkins,

Our review of the information provided in your BLA STN 125742 for COMIRNATY (COVID-19 mRNA Vaccine), for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older, is ongoing. We have the following comments and requests for additional information.

**Regarding the manufacture of drug substance (DS):**

1. The (b) (4) was listed as one of the process parameters under IND/EUA. In your BLA 125742 submission, this process parameter was removed as shown in Table 3.2.S.2.2-3 (b) (4) Parameters. Please specify the acceptable (b) (4) range of the (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)
2. In Section 3.2.S.2.5, you stated that the (b) (4) for UDFD (b) (4) at commercial scale is (b) (4). Please provide the performance test results for the commercial-scale (b) (4), including the (b) (4) (b) (4) data and evaluation of the (b) (4) performance during (b) (4) (b) (4)
3. In Figure 3.2.S.2.2-1 RNA Manufacturing Process, step yield is designated as a process performance attribute throughout the manufacturing process. Please specify the acceptable range/control limit at each manufacturing step (i.e., (b) (4) ) to ensure appropriate monitoring and controls during the manufacture of DS.
4. Regarding the action limits for bioburden and endotoxin testing listed in document 3.2.S.2.2 Manufacturing Process Andover, it appears that there are multiple typographical errors (“≤” instead of “>”) in Table 3.2.S.2.2-4 In-Process Tests (Monitoring) for (b) (4) Control and in Table 3.2.S.2.2-7 In-Process Tests (Monitoring) for (b) (4) Control. Please confirm and correct the errors.

**Regarding the LNP production and bulk drug product (DP) formulation:**

5. Please update the documents 3.2.P.3.3 Description of Manufacturing Process and Process Controls – LNP Production and Bulk Drug Product Formulation [Puurs] to include a brief description for the primary areas and equipment involved in BNT162b2 LNP production and bulk DP formulation.
6. You stated that (b) (4) (b) (4) ". Please provide relevant supportive data (e.g., stability of the (b) (4)) to demonstrate that this (b) (4) step has no significant impact on the quality of the (b) (4) (b) (4)
7. You stated that (b) (4) (b) (4) between lots. (b) (4) (b) (4)
8. Please clarify whether the (b) (4) (b) (4) (b) (4) steps) at Pfizer Kalamazoo submitted to IND/EUA will also be implemented under the BLA. Please update the relevant documents if you intend to include (b) (4) for the manufacture of the DP at Pfizer Kalamazoo.
9. Regarding the process control/parameters, please address the following at each manufacturing site (Puurs and Kalamazoo):
  - a. Please specify the (b) (4) for DS (b) (4)
  - b. Please specify the (b) (4) (b) (4)

**Regarding the fill and finish manufacturing process:**

10. Please update the documents 3.2.P.3.3 Description of Manufacturing Process and Process Controls – Fill and Finish [Puurs] to include a brief description for the primary areas and equipment involved in BNT162b2 DP fill and finish operations.
11. Please update the Table 3.2.P.3.3-8 Process Parameters for Storage Shipping to define the maximum allowable numbers of (b) (4) (b) (4) EUA 27034 in amendment 176 on May 17, 2021.

**Regarding the analytical procedures:**

12. Please identify all the test sites that will be used for the release and stability testing of the BNT162b2 DS and DP under the BLA submission and include listings for analytical procedures performed at each site. Please note that site-specific

validation studies for analytical procedures or the demonstration of comparable assay performance of the receiving site to the transfer site that completed the validation are required for BLA submission.

13. We acknowledge that qualifications of the analytical assays were originally conducted to support vaccine distribution under the EUA. However, validation of the analytical release assays for DS and DP is required for the BLA submission and pre-established acceptance criteria should be based on your previous qualification studies. Please provide the full validation reports for the following analytical procedures:
  - a. Quantification of Poly(A) tail in BNT162b2 DS by ddPCR
  - b. Quantification of residual DNA template content in BNT162b2 DS by qPCR
  - c. Quantification of total RNA concentration and the relative percentage of encapsulated RNA in BNT162b2 DP by (b) (4) fluorescence assay
  - d. Determination of the in-vitro expression of the BNT162b2 DP by cell-based flow cytometry

**Regarding the reference standards used in the analytical assays:**

14. Please confirm that the BNT162b2 DS assay control used in multiple DS analytical procedures (i.e., CGE for RNA integrity, RP-HPLC for 5'-cap, ddPCR for poly(A) tail, and immunoblot for dsRNA) is the same one ((b) (4) ) as described in Section 3.2.S.5 Reference Standards or Materials.
15. Please update the document 3.2.P.6 Reference Standards and Materials to describe the BNT162b2 DP assay control(s) used in multiple DP analytical procedures (e.g., CGE for RNA integrity, in vitro expression potency assay, fluorescence assay for RNA content and RNA encapsulation, and DLS for LNP size and polydispersity), including the DP lot number, the lot-release testing results, the qualification data to support its intended use as a reference standard, and any available stability data.

**Regarding the clinical assays:**

16. Please submit the SOP VR-TM-10295 for the Cepheid Xpert Xpress SARS-CoV-2 RT-PCR assay.
17. Please provide the method validation report(s) for the Single-plex Direct Luminex assay (dLIA) for quantification of IgG antibodies to SARS-CoV-2 S1 and RBD proteins in human serum.

**Regarding the categorical exclusion for an environment analysis:**

18. Please provide background information for the lipids in the LNP to support the claim that each of the lipids is naturally occurring and does not alter significantly

the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

Please provide your response in an Amendment to STN 125742/0, as soon as possible. If you have any questions about this communication, please feel free to contact me.

Best regards,  
Ram

**Ramachandra S. Naik, Ph.D.**

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