Exhibit A

CMC REVIEW MEMORANDUM

Date: AUGUST 21, 2021

To: The Biologics License Application (BLA) File STN 125742

From: Xiao Wang, OVRR/DVP, CMC Product Reviewer

Through: Anissa Cheung, OVRR/DVP

Keith Peden, Lab Chief, OVRR/DVP

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CC: Ramachandra Naik, Chair, OVRR/DVRPA
Capt. Michael Smith, RPM, OVRR/DVRPA
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Applicant: BioNTech Manufacturing GmbH (in partnership with Pfizer Inc.)

Subject: CMC Review of Original BLA STN 125742.0;

Product: Pfizer-BioNTech COVID-19 Vaccine; Human Coronavirus mRNA Vaccine for the Prevention of Coronavirus Disease 2019 (COVID-19)

The following abbreviations are used throughout the memorandum:

AMTE	Analytical Method Transfer Exercise
ATM	Animal Trial Material
BLA	Biologics License Application
BNT	BioNTech Manufacturing GmbH
(b) (4)	
CMC	Chemistry, Manufacturing, and Control
CoA	Certificate of Analysis
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CTM	Clinical Trial Material
dLIA	(b) (4) Direct Luminex Assay
DS	Drug Substance
DP	Drug Product
EUA	Emergency Use Authorization
(b) (4)	
FC	Final Container
GMP	Good Manufacturing Practice
IM	Intramuscular
IPT-C	In-process Tests for Control
IPT-M	In-process Tests for Monitoring
IR	Information Request
(b) (4)	
(b) (4)	
(b) (4)	
LNP	Lipid Nanoparticle
LPQ	Laboratory Process Qualification
MCB	Master Cell Bank
modRNA	Nucleoside-modified Messenger RNA
NHP	Nonhuman Primate
PAI	Pre-approval Inspection
PPQ	Process Performance Qualification
RBD	Receptor Binding Domain
RH	Relative Humidity
RPH	Relative Process History
(b) (4)	
(b) (4)	
WCB	Working Cell Bank

Table of Contents

1. Product Name/Proprietary Name/Product Type

Product: Pfizer-BioNTech COVID-19 Vaccine

Proprietary name: COMIRNATY

Nonproprietary name: COVID-19 Vaccine, mRNA

Product Type: Human Coronavirus mRNA vaccine expressing SARS-CoV-2 spike glycoprotein (BioNTech code number BNT162b2, Pfizer code number PF-07302048); the mRNA (variant RBP020.2) is formulated with lipids (b) (4), DSPC, and cholesterol to form lipid nanoparticles (LNPs).

2. Submissions reviewed

Date Received	Submission	Contents/Comments
May 6, 2021	STN 125742/0	BLA Roll 1 submission including nonclinical pharmacology and pharmacokinetics studies and clinical assays
May 18, 2021	STN 125742/0.1	BLA Roll 2 submission encompassing all quality-related information in Module 3
July 9, 2021	STN 125742/0.10	Lot-release protocol template for the drug product including the assay performed and acceptance criteria
July 15, 2021	STN 125742/0.11	Request for an exception to the 21 CFR 610.15(a) for the vaccine as a preservative-free presentation
July 23, 2021	STN 125742/0.16	Response to DVP/DBSQC IR regarding the validation of RNA (b) (4) testing by (b) (4)
July 28, 2021	STN 125742/0.19	Response to DVP IR regarding multiple CMC-related issues (DS and DP manufacturing process and testing, and clinical assays) and the categorical exclusion for an environment analysis
August 2, 2021	STN 125742/0.27	CMC-related information described in the draft package insert
August 5, 2021	STN 125742/0.31	Response to DVP/Statistical IR regarding the validation studies for the (b) (4) direct Luminex assay (dLIA) for IgG antibody quantification in human sera
August 6, 2021	STN 125742/0.33	Response to DVP IR regarding manufacturing process validation issues
August 6, 2021	STN 125742/0.34	Response to DVP/Statistical IR regarding the validation report (VAL100147509) for (b) (4) of the vaccine DP by (b) (4)
August 9, 2021	STN 125742/0.35	Response to DBSQC/DVP IR regarding validation of the assay methods and lot release
August 9, 2021	STN 125742/0.36	Response to DMPQ IR regarding the saline diluent
August 10, 2021	STN 125742/0.39	Response to DVP IR regarding a (b) (4) step executed during the (b) (4) process at Pfizer Puurs
August 13, 2021	STN 125742/0.47	Response to DMPQ IR regarding the saline diluent

Date Received	Submission	Contents/Comments
August 17, 2021	STN 125742/0.55	Stability data to support a shelf-life extension of the undiluted DP up to 9 months when stored at the intended long-term storage condition
August 19, 2021	STN 125742/0.61	Response to DVP IR regarding the final commercial shelf life of the BNT162b2 DP and date of manufacture
August 19, 2021	STN 125742/0.62	Response to DVP IR regarding the final (b) (4)

3. Executive Summary and Recommendation

The BNT162b2 COVID-19 vaccine, developed under a collaborative agreement between Pfizer and BioNTech (BNT), is a nucleoside-modified messenger RNA (modRNA)-based vaccine candidate indicated for active immunization for the prevention of coronavirus disease 2019 (COVID-19). The single-stranded mRNA encodes the SARS-CoV-2 full-length spike (S) glycoprotein, which is codon-optimized and modified to express the P2 mutant, a pre-fusion S protein (P2 S; version 9). The modRNA is stabilized by formulation with lipids consisting of DSPC, cholesterol, (b) (4) to generate lipid nanoparticles (LNPs). Other ingredients in the BNT162b2 vaccine include potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

The final vaccine product is a white to off-white, sterile, preservative-free, multi-dose frozen suspension to be diluted with 0.9% sodium chloride injection, USP, for intramuscular (IM) injection. The vaccine is filled in a 2 mL clear glass vial with a rubber stopper (not made of natural rubber latex) as a multi-dose concentrate (after dilution each vial contains 6 doses of 0.3 mL) and is administered as a series of two IM immunizations with each dose containing 30 µg of modRNA. The second dose is administered 21 days after the first dose. The undiluted vaccine vials should be stored frozen between -90°C to -60°C and they may be stored at -25°C to -15°C for up to two weeks. To facilitate storage and administration of the BNT162b2 vaccine at the point of use, the thawed vials can be stored between 2°C to 8°C for up to 1 month (31 days) prior to dilution; the diluted vaccine must be stored between 2°C to 25°C and used within 6 hours from the time of dilution. The vaccine is indicated for use in individuals 16 years of age or older.

The manufacturing process for the BNT162b2 drug substance (DS) consists of two major steps: (b) (4). Two manufacturing facilities (Pfizer ACMF and Pfizer Suite (b) (4)) located in Andover, MA are involved in the commercial production of the BNT162b2 DS. The DS manufacturing process was validated at both facilities by process-performance qualification (PPQ) studies ((b) (4) and (b) (4) PPQ lots manufactured at Pfizer ACMF and at Pfizer Suite (b) (4), respectively). Consistency of the DS manufacturing process was demonstrated by maintaining process parameters within defined ranges and obtaining satisfactory in-process and release testing results. Additionally, data obtained from the analytical comparability assessment for the ACMF

and Suite (b) (4) DS batches further support the DS manufacturing process for the consistent production of the BNT162b2 DS with acceptable quality.

The manufacturing process for the BNT162b2 drug product (DP) involves (b) (4) the modRNA DS with lipid excipients during LNP formulation followed by fill and finish. The two facilities proposed for the manufacture of the BNT162b2 DP are Pfizer Puurs (located in Puurs, Belgium) and Pfizer Kalamazoo (located in Kalamazoo, Michigan, USA), both of which have been authorized for the manufacture of the BNT162b2 DP under the Emergency Use Authorization (EUA 27034). Validation of the DP manufacturing process took place in two Phases. The Phase I network PPQ study, which involved multiple authorized DP manufacturing facilities under the EUA, was executed to demonstrate that the manufacturing process consistently produces DP lots of acceptable quality across multiple supply nodes. The Phase II process validation occurred at the proposed commercial facilities with (b) (4) batches at (b) (4) and (b) (4) batches at (b) (4) batch sizes being manufactured at Pfizer Puurs and (b) (4) batches at (b) (4) and (b) (4) batches at (b) (4) batch sizes being manufactured at Pfizer Kalamazoo. Both Phase I and Phase II process-validation studies were executed successfully according to pre-established protocols, thereby demonstrating that the DP manufacturing process is consistent and well-controlled. Additionally, a (b) (4) batch size for the manufacture of BNT162b2 DP was validated at the Pfizer Puurs site. Analytical comparison of the process-validation batches to clinical and emergency supply lot data further demonstrated comparable product quality from clinical through commercial supply of the BNT162b2 DP. Overall, the process validation data support the capability of the commercial manufacturing process to produce a consistent DP with acceptable quality at the proposed commercial manufacturing facilities.

Stability studies have been generated for both the DS and DP lots to support the licensure of the BNT162b2 vaccine. All available stability data generated to date support the initial commercial shelf life of (b) (4) for the BNT162b2 DS when stored at the intended storage condition of (b) (4) For DP shelf-life determination, up to (b) (4) months of stability data are available for one clinical batch at the intended storage condition of -70 ± 10°C and up to 9 months of stability data are available for (b) (4) emergency supply DP lots when stored at the intended storage condition of -90 to -60°C. As comparable product quality has been demonstrated from clinical through commercial supply of the BNT162b2 DP, the stability data from both the clinical trial materials (CTMs) and the emergency supply lots are considered supportive of the proposed shelf life of 9 months for the commercial BNT162b2 DP. The final commercial shelf life of the BNT162b2 DP is intended to be (b) (4) months when stored at the intended storage condition of -90 to -60°C; stability studies are ongoing. The available stability data from the emergency supply/PPQ DP lots will be submitted post licensure at intervals (9, (b) (4) months) as data become available to support future shelf-life extensions.

The analytical procedures developed and used for the release and stability monitoring of BNT162b2 DS and DP include tests to ensure their identity, purity, quality, and

potency. The assay methods are appropriately established and performed routinely according to the established standard operating procedures (SOPs). Validation of each assay method was performed at all the proposed testing sites (either through validation/co-validation or by analytical method transfer exercise) and the results have demonstrated that the assay methods are accurate, specific, robust, and precise over the specified range, indicating that they are suitable for the intended use.

Two notable issues were identified during the previous EUA 27034 review and were resolved. The first issue involves the occurrence of (b) (4) in DP lots produced for emergency use, and the second issue involves the occasional observation of visible intrinsic particles detected during visual inspection of filled DP vials. Investigation of the (b) (4) identified that the (b) (4) are only associated with the (b) (4) batches that were manufactured with a (b) (4) operation at (b) (4) (a supplier of the (b) (4)). Since the implementation of a (b) (4) process at (b) (4), the resulting DP lots have been consistently demonstrating (b) (4) . Regarding the intrinsic particles, the frequency of occurrence is low and DP vials containing intrinsic particles can be detected and discarded through 100% automated/manual visual inspection. The intrinsic particles consist of (b) (4) components used for (b) (4) (b) (4) (i.e., they are not foreign particles) and the available data suggest that they have minimal potential to impact product safety and quality.

Two clinical diagnostic assays (Cepheid Xpert Xpress RT-PCR assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA. Validation of both assays has been performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY), and the results support the suitability of both assays for their intended use in clinical studies.

Final Recommendation:

I recommend approval of this BLA.

4. BNT162b2 Drug Substance

4.1 General Description

The BNT162b2 drug substance (DS) is a single-stranded, 5'-capped mRNA encoding the full-length SARS-CoV-2 spike glycoprotein (S1S2 protein) derived from the Wuhan-Hu-1 isolate (GenBank MN908947.3 and GenBank QHD43416.1). The antigen-coding RNA sequence is codon-optimized and contains two proline mutations ((b) (4)), which ensure expression of an antigenically optimal trimerized pre-fusion confirmation (P2 S). The RNA also contains common structural elements, including 5'-cap, 5'-UTR, 3'-UTR, and poly(A) tail, all of which are designed for mediating high RNA stability and translation efficiency. (b) (4) is replaced with the (b) (4) during the RNA transcription. This nucleoside substitution has been demonstrated to enhance translation of *in vitro* transcribed mRNA while reducing its reactogenicity.

The final BNT162b2 DS is a clear to (b) (4) and is formulated at a target concentration of (b) (4) in DS (b) (4) .

4.2 Manufacturers

Facilities and manufacturing sites involved in the commercial DS manufacturing and testing are presented in Table 1.

Table 1. Sites and Responsibilities for Manufacture and Testing of BNT162b2 DS

Site	FEI/DUNS Numbers	Responsibility
(Pfizer, Andover, ACMF) (Pfizer, Andover Building (b) (4) and Building (b) (4)) Wyeth BioPharma Division of Wyeth Pharmaceuticals, LLC[a] 1 Burtt Road Andover, MA 01810 United States	FEI: 1222181 DUNS: 174350868	ACMF/Suite (b) (4): Manufacture of drug substance Bldg. (b) (4): Release and Stability Testing
Pfizer Inc 875 Chesterfield Parkway West Chesterfield, MO 63017 United States	FEI: 1940118 DUNS: 004954111	Release and Stability Testing

a. The legal entity name was changed at the acquisition by Pfizer in 2009; since then, the Wyeth Pharmaceuticals manufacturing site in Andover, Massachusetts belongs to Pfizer's production sites and is embedded in Pfizer´s GMP system.

Reviewer's Comments:

Two manufacturing nodes were employed for DS manufacture under the initial EUA 27034 request: (1) Pfizer, Andover, ACMF and (2) BioNTech, Mainz, and (b) (4) Germany. Pfizer, Andover, Suite (b) (4) was introduced as an additional DS manufacturing site under the EUA 27034. Both Andover ACMF and Suite (b) (4) manufacturing facilities are included in the BLA submission. The

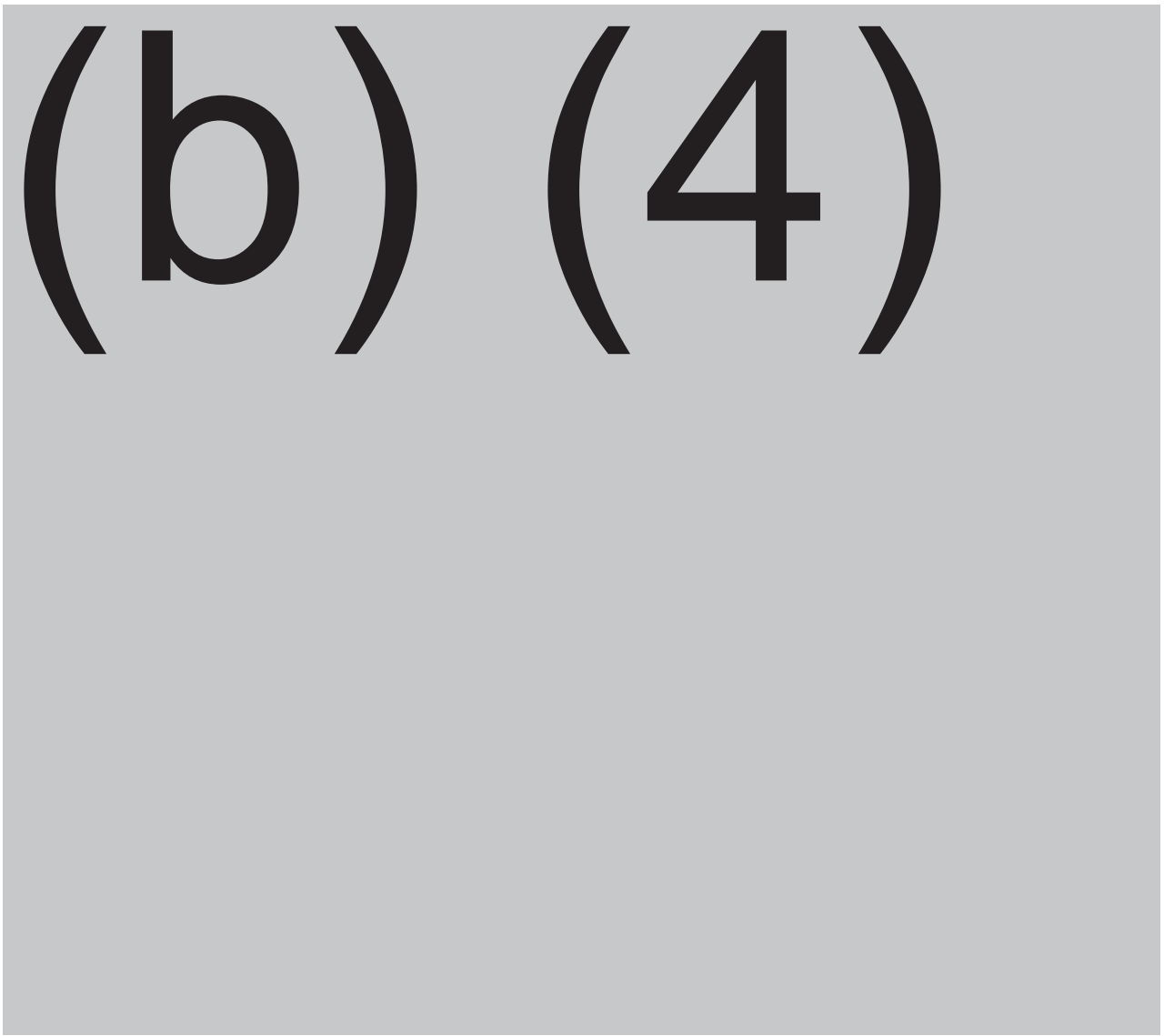
BNT/(b) (4) manufacturing node is not intended for the manufacture of commercial DS.

4.3 Control of Materials

Control of Non-Compendial Starting Materials and Raw Materials

Raw materials used in the DS manufacturing process are purchased from approved suppliers and are tested and released upon receipt in accordance with the applicant's internal quality control program.

The current acceptance criteria for non-compendial starting materials and raw materials used during the manufacture of the BNT162b2 DS are presented in Table 2 below. Note that starting materials are defined as a reagent or material used during the manufacture of the BNT162b2 vaccine product that is intended to be part of the final product, such as (b) (4) .



4.8 Adventitious Agents Safety Evaluation

The adventitious agent control program includes the engineering systems of the facility and vessels, the control of raw materials, various filtration steps to control microbial burden in buffers and the process stream, and in-process and environmental testing to monitor the level of adventitious agents in and around the process stream.

All raw materials used in the production of DS are evaluated as part of a comprehensive program to identify and manage transmissible spongiform encephalopathy (TSE) / bovine spongiform encephalopathy (BSE) risks. The only raw material of direct animal origin was identified to be (b) (4) Based on the comprehensive adventitious-agent control program, all raw materials were found to be compliant with the EMA Note for Guidance (EMA/410/01 rev.3) and associated with minimal risk for TSE/BSE.

Other materials of animal origin may be used in the production of polymer for filters, manifolds, containers, and/or filter components. These equipment components may contain traces of animal tallow derivatives. The tallow is processed under rigorous conditions and is considered compliant with the TSE note for guidance (EMA/410/01).

4.9 Characterization Studies on Drug Substance

(b) (4)

(b) (4)

5. BNT162b2 Drug Product

5.1 General Description and Composition

The BNT162b2 DP is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous (b) (4) buffer. It is filled into multi-dose vials containing 0.45 mL of the DP at (b) (4). After dilution with 1.8 mL of sterile 0.9% sodium chloride solution, each vial contains a total of six 0.3 mL doses, with each dose containing 30 µg of RNA. The composition of DP, including the BNT162b2 DS, lipid excipients, buffer, and (b) (4), are listed in Table 22 below. The concentration and amount of each component per DP container, and the corresponding amount per dose are also listed.

Table 22. Composition of BNT162b2 Drug Product, Multi-dose Vial

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per vial	Amount per dose
BNT162b2 DS	In-house specification	Active ingredient	0.5	225 µg	30 µg
(b) (4)	In-house specification	Functional lipid	7.17	3.23 mg	0.43 mg
(b) (4)	In-house specification	Functional lipid	0.89	0.4 mg	0.05 mg
DSPC	In-house specification	Structural lipid	1.56	0.7 mg	0.09 mg
Cholesterol	(b) (4)	Structural lipid	3.1	1.4 mg	0.2 mg
Sucrose	(b) (4)	(b) (4)	103	46 mg	6 mg
Sodium chloride	(b) (4)	Buffer component	6	2.7 mg	0.36 mg[c]
Potassium chloride	(b) (4) [a]	Buffer component	0.15	0.07 mg	0.01 mg
Dibasic sodium phosphate, dihydrate	(b) (4)	Buffer component	1.08	0.49 mg	0.07 mg
Monobasic potassium phosphate	(b) (4) [a]	Buffer component	0.15	0.07 mg	0.01 mg
(b) (4)	(b) (4)	Solvent/vehicle	q.s.[b]	q.s.[b]	q.s.[b]

a. Supplier Certificate of Analysis confirms compliance to both (b) (4).; however, incoming testing may be performed only in accordance with a site's local compendia.
b. q.s. = quantum satis (as much as may suffice)
c. The diluent (0.9% sodium chloride Injection) contributes an additional 2.16 mg per dose

The four lipids used to encase the modRNA include:

- (b) (4): ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
- (b) (4): 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
- DSPC: 1,2-distearoyl-sn-glycero-3-phosphocholine
- Cholesterol

Diluent vials of sterile 0.9% Sodium Chloride Injection, USP are provided but shipped separately by the applicant. The provided diluent is supplied as either a 10 mL or a 2 mL single-use vial. Alternate brand of sterile 0.9% sodium Chloride Injection, USP may be used as the diluent and also for single use. The diluent vials should be discarded after 1.8 mL is withdrawn.

5.2 Manufacturers

Facilities and manufacturing sites involved in the commercial BNT162b2 DP manufacturing and testing are presented in Table 23 below.

Table 23. Sites and Responsibilities for BNT162b2 Drug Product Manufacture

Site	FEI/DUNS Numbers	Responsibility
Pharmacia & Upjohn Company LLC[c] 7000 Portage Road Kalamazoo, MI 49001 United States	FEI: 1810189 DUNS: 618054084	LNP production/bulk DP formulation Fill and finish Primary packaging Secondary packaging Release and stability testing
Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs, 2870 Belgium	FEI: 1000654629 DUNS: 370156507	LNP production/bulk DP formulation Fill and finish Primary packaging Secondary packaging Release and stability testing
Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC[a] 1 Burtt road Andover, MA 01810 United States	FEI: 1222181 DUNS: 17430868	Release and stability testing
Pfizer Inc. 875 Chesterfield Parkway West Chesterfield, MO 63017 United States	FEI: 1940118 DUNS: 004954111	Release and stability testing
Pfizer Ireland Pharmaceuticals Grange Castle Grange Castle Business Park Clondalkin, Dublin 22 Ireland	FEI: 3004145594 DUNS: 985586408	Release and stability testing
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Release testing (Sterility)
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Release testing (Sterility)

a. The legal entity name change from Wyeth BioPharma Division of Wyeth Pharmaceuticals was changed at the acquisition by Pfizer in 2009, since then the Wyeth Pharmaceuticals manufacturing site in Andover, Massachusetts belongs to Pfizer's production sites and is embedded in Pfizer's GMP system. Pfizer will be utilized throughout the CTD
b. (b) (4) is a wholly owned subsidiary of Pfizer Inc.
c. Pharmacia & Upjohn Company LLC is a wholly owned subsidiary of Pfizer Inc.

Reviewer's Comments:

Four manufacturing nodes were employed for BNT162b2 DP manufacture at the time of the initial EUA request: (1) Pfizer Puurs, (2) Pfizer Kalamazoo, (3) (b) (4) *for LNP formation/bulk DP formulation followed by fill and finish at Pfizer Puurs, and (4)* (b) (4) *for LNP formation/bulk DP formulation followed by fill and finish*

at Pfizer Puurs. Additional DP manufacturing sites were introduced for emergency supply production under EUA 27034, including Pfizer (b) (4) for DP fill and finish and (b) (4) for LNP formation and bulk DP formulation.

For commercial BNT162b2 DP production, the Pfizer Puurs and Pfizer Kalamazoo manufacturing facilities are included in the BLA submission. The Pfizer (b) (4) site for the fill and finish will be added as a supplement after BLA approval.

Facilities and manufacturing sites for the production and testing/release of 0.9% sodium chloride, USP diluent and their specified functions are listed in Table 24 below.

Table 24. Sites and Responsibilities for 0.9% Sodium Chloride, USP Manufacture

Site	FEI/DUNS Numbers	Responsibility
Fresenius-Kabi USA, LLC (b) (4)	FEI# (b) (4) DUNS# (b) (4)	Manufacture, testing and release (of 2 mL size diluent vials)
Hospira, Inc (b) (4)	FEI# (b) (4) DUNS# (b) (4)	Manufacture, testing and release (of 10 mL size diluent vials)

Hospira is a wholly owned subsidiary of Pfizer Inc.

Reviewer's Comments:

The saline diluent will be supplied as either a 10 mL single-use vial manufactured by Hospira, Inc. (NDC 0409488810) or a 2 mL single-use vial manufactured by Fresenium Kabi USA, LLC (NDC 6332318602). In amendment 47 submission (submitted on August 13, 2021), the applicant listed an additional manufacturing facility, Pfizer (b) (4), for the production of the saline diluent. However, due to the Warning Letter (reference WL (b) (4) issued on (b) (4)) and Official Action Indicated status, the agency will not approve the facility as the saline diluent supplier as part of this BLA. The applicant acknowledged the request and removed Pfizer (b) (4). from the Diluent Manufacturers table in a follow-up submission (amendment 56 submitted on August 17, 2021).

5.3 Control of Excipients

The (b) (4) excipients used in the manufacture of BNT162b2 DP and their quality standards are provided in Table 25 below.

Table 25. Specifications for (b) (4) Excipients

Excipient	Reference to Standard
Cholesterol	(b) (4)
Sucrose	
Sodium chloride	
Potassium chloride	
Dibasic sodium phosphate, dihydrate	

Excipient	Reference to Standard
Monobasic potassium phosphate	(b) (4)
(b) (4)	

a. Specification also includes test for microbial contamination per (b) (4)

Among the four lipid components used in the BNT162b2 LNP production, cholesterol is a (b) (4) excipient, and the other three lipids, (b) (4), and DSPC, are (b) (4) excipients. The supplier's release specifications for all four lipids include testing for (b) (4) To ensure the quality of the lipids and the resulting BNT162b2 DP, in-house control tests are performed for all four lipid excipients including (b) (4), prior to release of the LNP DP. For cholesterol, an additional in-house test for (b) (4) is also performed.

Table 26 below summarizes the source of the lipid excipients used for clinical study, emergency supply, and commercial BNT162b2 DP.

Table 26. List of Lipid Manufacturers with Phase of Use

Lipid	Clinical Trial Material	Emergency Supply	Commercial Supply
(b) (4)	(b) (4)		
(b) (4)			
DSPC			
Cholesterol			

Manufacturers' full names: (b) (4)

(b) (4)

5.4 Description of Drug Product Manufacturing Process and Process Controls

Flow diagrams for the DP manufacturing process and process controls are illustrated in Appendices C and D for LNP production/bulk DP formulation and fill/finish operations, respectively. For emergency supply/commercial DP manufacture, a scale-out approach was used to increase capacity of the LNP-(b) (4) process with up to (b) (4) used (b) (4) . The process scale approximates (b) (4) RNA per (b) (4), such that (b) (4) can be used to process as much as (b) (4) RNA corresponding to a bulk DP batch (b) (4) of approximately (b) (4). The current batch size ranges at the two commercial DP manufacturing sites are set to be (b) (4) at Pfizer Kalamazoo and (b) (4) at Pfizer Puurs.

The manufacturing process for the BNT162b2 DP includes the following major steps:

(b) (4)

Steps (b) (4) *– Fill and Finish*

For DP filling, (b) (4) sterile bulk DP is aseptically filled into glass vials. At the end of filling, each vial is stoppered, capped, and crimped. During filling, an in-process (b) (4) is performed at routine intervals for (b) (4). All non-conforming vials are rejected.

Filled vials are 100% inspected for defects either through automated visual inspection or manual visual inspection. Vials passing inspection are statistically sampled for meeting Acceptance Quality Limit (AQL) testing.

The labeling and packaging of the vaccine vials for commercial distribution is performed on a fully automated or semi-automated packaging line. After labeling, the vials are placed into trayboxes, and the boxes are manually closed and labeled.

Packaged BNT162b2 vials are frozen and stored in a freezer at -90°C to -60°C.

Critical-Process Parameters and In-Process Controls

To ensure DP manufacturing process consistency and the quality of the BNT162b2 DP, relevant process parameters and IPT-Cs with acceptable ranges/acceptance criteria have been established (Table 31). The critical process parameters (CPPs) were conservatively identified using Cause and Effect (C&E) Risk Assessment based on product and process understanding, scientific rationale, and manufacturing experience and available data. IPT-Cs are used during the manufacturing process to control a quality attribute/critical quality attribute within a specified range. In addition, IPT-Ms are

implemented throughout the process to ensure a continuous state of control and to enable forward processing.

Table 31. Process Controls for the Manufacture of BNT162b2 DP

Unit Operation	Process Control/parameter	Acceptance Range/ Acceptance Criteria		Category
		Kalamazoo	Puurs	
(b) (4)				

Reviewer's Comment:

Following further review of the (b) (4) *parameters evaluated during process validation at Pfizer Puurs, the following two process parameters were tightened as submitted in BLA125742/0 amendment 19 on July 28, 2021:*

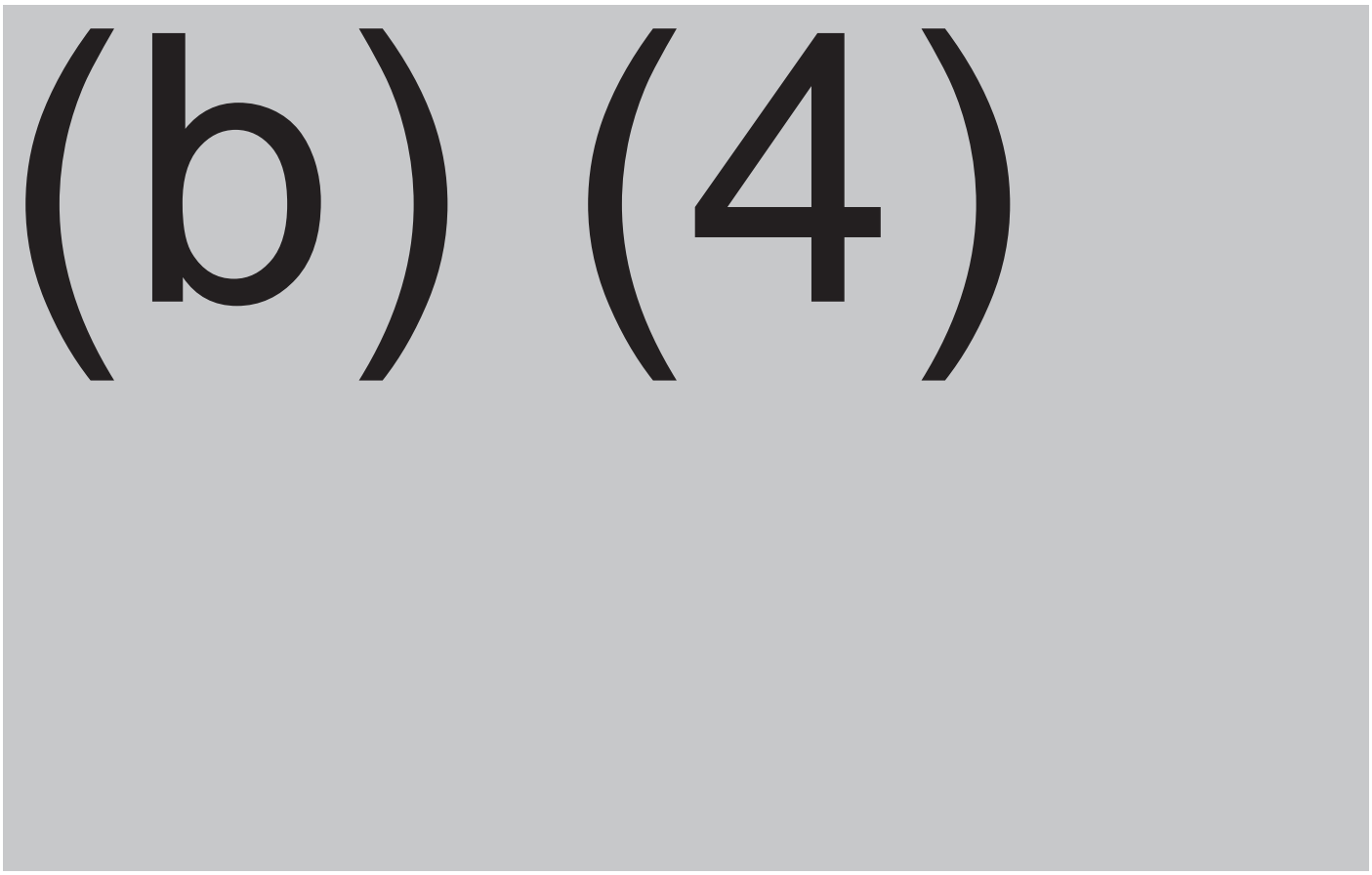
(b) (4)

The control limits applied for (b) (4) *testing and the process controls for capping were reviewed by the facility reviewer.*

Hold Times During DP Manufacturing Process

The hold times of the DP in-process materials during (b) (4) are provided in Tables 32 and 33, respectively.

(b) (4)



Reviewer's Comment:

Hold time for (b) (4) *step was tightened from* (b) (4) *with up to* (b) (4) *of this time allowed at up to* (b) (4) *with up to* (b) (4) *of this time allowed up to* (b) (4)*. This change was made to ensure that the revised* (b) (4) *-acceptance criterion for DP can be met. The process hold time change has been validated via cumulative hold-time PPQ execution.*

Hold Time Out of Freezing for the BNT162b2 DP

The Table 34 below summarizes the allowable times out of intended storage condition of -90 to -60°C during manufacture, packaging and transport.

Table 34. Time Out of Storage Condition for BNT162b2 Drug Product

(b) (4)

Hold Time for the Diluted BNT162b2 Vaccine Prior to Administration

The BNT162b2 final vaccine product is a concentrated suspension prepared in a multidose vial free of preservatives. Following dilution with saline, the in-use hold period and storage condition for the vaccine product is set to be up to 6 hours at 2°C to 25°C. To support this hold condition, an in-vial dilution hold-time study was conducted in which the physicochemical stability of the BNT162b2 DP, held in glass vials and diluted with saline as intended, was evaluated at 2-8°C, 25°C, and (b) (4) C. The results indicate that the diluted vaccine can be stored at ambient temperature (25°C) for (b) (4) hours and can be exposed to elevated ambient temperature ((b) (4)) for (b) (4) hours with no impact on product quality. In addition, a microbial challenge with selected model diluents and surrogate DP solutions as well as a BNT162b2-specific microbial challenge were conducted to evaluate the potential for microbial growth in a matrix representative of saline-diluted vaccine. In both studies, (b) (4) microorganisms listed in (b) (4) and growth of the microorganisms was monitored. The results demonstrate that at (b) (4), which is (b) (4) the proposed in-use time, no increase in growth was observed for any of the organisms with the spiked test samples stored at 20-25°C.

Reviewer's Comments:

The result was close to the acceptance criterion of (b) (4) *increase from T_0 for* (b) (4) *at the* (b) (4)*-hour time point (*(b) (4)*). Overall, the results support the proposed in-use period of 6 hours at ambient temperature after dilution with saline.*

5.5 Process Validation

A global approach to development has been undertaken across multiple manufacturing facilities in order to maximize BNT162b2 vaccine production and availability. The process-validation approach for all DP supply nodes included within the emergency/commercial supply network is composed of two phases. The Phase I validation covers the overall DP manufacturing network by performing minimally one (1) process validation (PV) run of each manufacturing supply node. The Phase II validation covers the full validation of each of the supply nodes with separate protocols at each site. Note that for the BLA submission, only Pfizer Puurs and Pfizer Kalamazoo are the proposed DP manufacturing sites for licensure.

Phase I Network PPQ Validation

Hold Time for Packing, Shipping and Point of Use

(b) (4)

DP Shipping Conditions of -90 to -15°C with an Allowance for a Maximum Cumulative Time of (b) (4) at (b) (4)

The shipping condition of -90 to -15°C with an allowance for a maximum cumulative time of (b) (4) at (b) (4) is supported by the following:

(b) (4)

5.6 DP Manufacturing Process Development

Introduction of a Scaled-up Process for the Production of LNPs

(b) (4)

(b) (4)

5.7 Impurity Profile of the Drug Product

Possible process-related impurities include (b) (4), introduced from the DP manufacturing process, and (b) (4), which are part of the (b) (4), may be present in the final vaccine container. All these impurities are present in low amounts and are further reduced during the DP manufacturing process by (b) (4).

Part of the process validation included evaluation of consistent removal of process-related impurities throughout the manufacturing process. Results from the BNT162b2 DP process validation lots have demonstrated robust and consistent removal of (b) (4) for all PPQ lots made at Pfizer Puurs and Pfizer Kalamazoo, which is well below the safety concern limit of (b) (4). For (b) (4), a comprehensive safety risk assessment has been performed to compare the theoretical worst-case concentration of impurities that could be introduced into the final DP assuming no impurity clearance during the manufacturing process. The evaluation results as shown in Table 42 below demonstrate that none of the impurities pose a safety concern. Additionally, removal of (b) (4) was further demonstrated during process validation (quantification limit of (b) (4) in all PPQ BNT162b2 DP lots, which is equivalent to (b) (4)).

(b) (4)

Overall, based on the demonstration of consistent removal and the safety-based risk assessment, all the process-related impurities from the DP manufacturing process do not necessitate testing as part of BNT162b2 DP release.

5.8 Characterization Studies on Drug Product

The DP characterization assays were developed to further describe and demonstrate the structure and physicochemical properties of the DP. The enhanced analytical characterization assays employed for the BNT162b2 DP and the testing results are briefly described as follows:

(b) (4)

5.9 Control of Drug Product

Specifications

The specifications for BNT162b2 DP at release and throughput shelf life are shown in Table 43 below.

Table 43. BNT162b2 Drug Product Specifications

Quality Attribute	Analytical Procedure[a]	Acceptance Criteria
Appearance	Appearance (Visual)	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles) (b) (4)	May contain white to off-white opaque, amorphous particles
(b) (4)	(b) (4)	
(b) (4)		
(b) (4)		
LNP (b) (4)		
LNP (b) (4)		
RNA (b) (4)		
RNA Content		
(b) (4) Content		
(b) (4) Content		
DSPC Content		
Cholesterol Content		
Vial Content (Volume)		
Lipid Identities		
Identity of Encoded RNA Sequence		
(b) (4)		
RNA (b) (4)		
Bacterial Endotoxin	Endotoxin (b) (4) (b) (4)	(b) (4)
Sterility	Sterility[e] (b) (4)	No growth detected
Container-Closure Integrity	(b) (4)	Pass

a. All assays performed on stability unless otherwise noted
b. In accordance with (b) (4), with minor difference in instrument calibration
c. Assay not performed on stability
d. Acceptance criteria values reflect (b) (4) correction
e. (b) (4) sterility test, which is performed in accordance with the (b) (4) with the exception of (b) (4) method, may also be used
f. Tested at release and on stability for stability batches only

The acceptance criteria used for stability during shelf life will be predominantly the same as the acceptance criteria used for lot release, with the exception of the LNP (b) (4) and RNA (b) (4) attributes, for both of which a separate stability acceptance criterion has been established to enable alternative storage at -20°C and 2-8°C at the point of administration.

Reviewer's Comment:

- *The proposed commercial acceptance criteria for the following attributes at release and during stability have been tightened for the commercial BNT162b2 DP compared with the DP product under the EUA. The changes were made based on the capability of the manufacturing process, historical release data for the emergency supply/commercial lots, as well as considerations of the assay variability.*

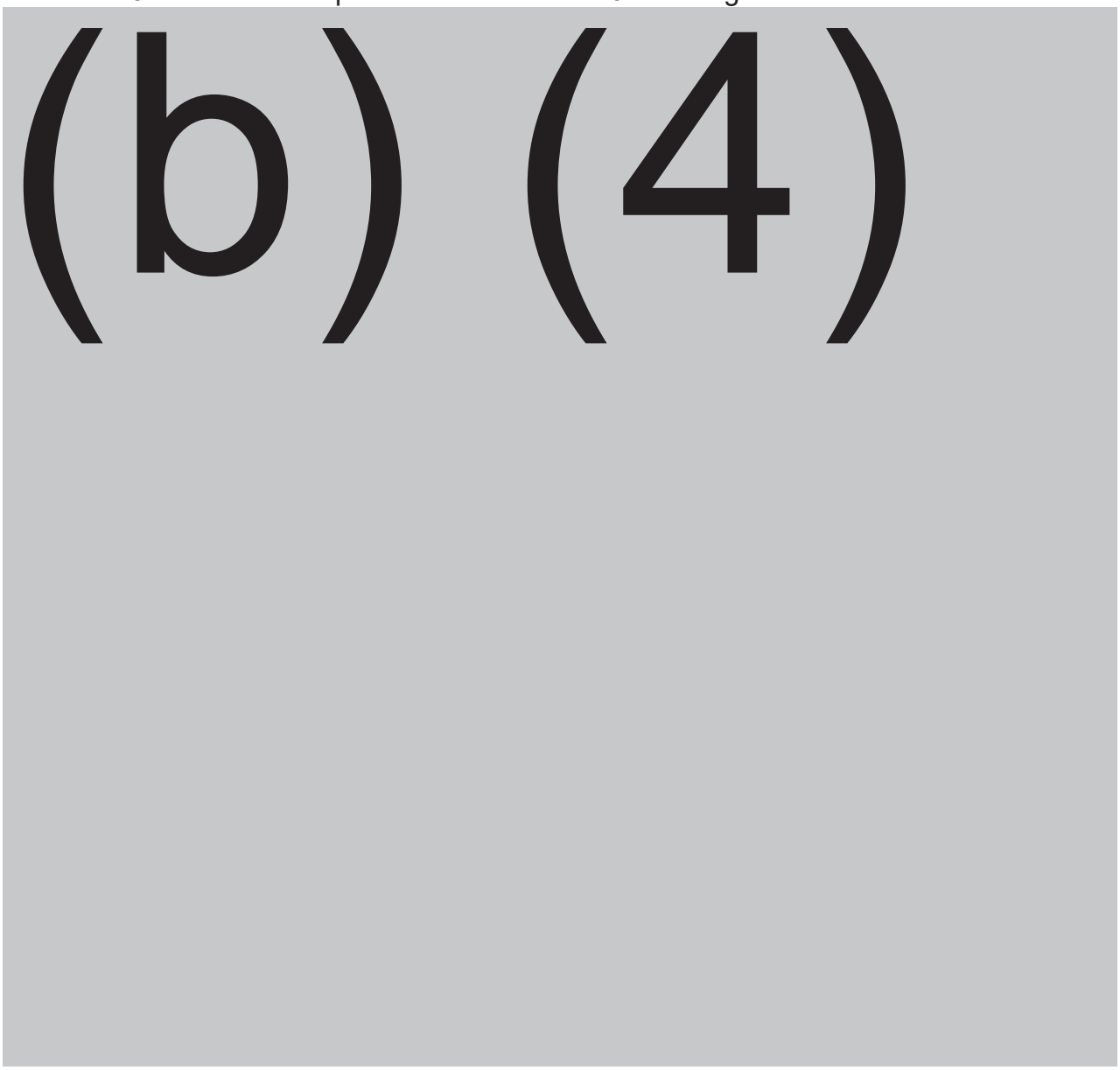
(b) (4)

Justification of Specifications

The acceptance criteria in the DP specification reflect the current understanding of criticality of quality attributes, their impact on product performance, and the quality of the product used in clinical trials to ensure consistent manufacture of DP. The lots used in the establishment of the commercial specification include nonclinical toxicology lot ((b) (4)), clinical lots manufactured from process 1 DS ((b) (4)), and commercial-scale emergency supply DP lots manufactured from process 2 DS ((b) (4) lots manufactured between August 2020 and January 2021, including (b) (4) PPQ lots with (b) (4) manufactured at the Pfizer, Kalamazoo facility and (b) (4) manufactured at the Pfizer, Puurs site). Statistical analysis was applied to the release data for the (b) (4) commercial-scale DP lots. The

mean, standard deviation and mean ± k*SD (k is the factor) for the release data set were calculated for each quality attribute, if applicable. Based on the statistical analysis results, the acceptance criteria were further adjusted and justified. For those attributes not subjected to statistical analysis, acceptance criteria were determined based on understanding of formulation robustness, compendial requirements, clinical experience and/or literature references.

Table 44. Justification of Specifications for BNT162b2 Drug Product



(b) (4)

(b) (4)

(b) (4)

5.10 Analytical Procedures for Drug Product

The testing sites that are involved in assay performance and validation activities are listed in Table 46 below.

Table 46. BNT162b2 Commercial DP Testing Sites

Analytical Procedure	Testing Site	Release, Stability
Appearance (Visual) Appearance (Particles)	ARD, PGS-Puurs, PGS-KZO	Release, Stability
(b) (4)	ARD, PGS-GC, PGS-KZO	Release, Stability
(b) (4)	ARD, PGS-Puurs, PGS-KZO	Release, Stability
(b) (4)	ARD, PGS-Puurs, PGS-KZO	Release
(b) (4)	ARD, PGS-Puurs, PGS-KZO	Release, Stability
(b) (4)	ARD, PGS-Puurs, PGS-KZO	Release, Stability
(b) (4)	ARD, PGS-Puurs, PGS-KZO	Release, Stability
Container Content	ARD, PGS-Puurs, PGS-KZO	Release
(b) (4)	ARD, PGS-AND, PGS-GC	Release
(b) (4)	ARD, PGS-AND, PGS-GC	Release, Stability
(b) (4)	ARD, PGS-Puurs, PGS-KZO	Release, Stability
Endotoxin (b) (4)	PGS-Puurs, PGS-KZO	Release, Stability
Sterility	PGS-Puurs, PGS-KZO	Release, Stability
(b) (4) Sterility	PGS-Puurs, PGS-KZO	Release, Stability

- Pfizer Analytical Research and Development (ARD) Laboratories at Chesterfield, MO (ARD-STL) and at Andover, MA (ARD-AND)
- Pfizer Global Supply, Andover, MA (PGS-AND)
- Pfizer Global Supply, Grange Castle, Ireland (PGS-GC)
- Pfizer Global Supply, Kalamazoo, MI (PGS-KZO)
- Pfizer Global Supply, Puurs, Belgium (PGS-Puurs)

Appropriate analytical procedures were established to monitor and assess the BNT162b2 DP as detailed below.

(b) (4)

(b) (4)

5.11 Validation of Analytical Procedures

Compendial procedures were qualified for use in accordance with the applicable pharmacopeias, excluding endotoxin and sterility. Endotoxin, in alignment with (b) (4), and sterility in alignment with (b) (4), were validated in the course of release testing of the (b) (4) CTM batches. The validation of bacterial endotoxins and sterility tests are reviewed by DBSQC reviewers.

All the analytical procedures used for the BNT162b2 DP have been validated. The assay may be originally validated or co-validated in selected testing sites. Upon transfer to additional testing location, reproducibility is evaluated in the validation or transfer.

A summary of the parameters evaluated for each analytical assay, the acceptance criteria and the results are described in the following tables.

(b) (4)

(b) (4)

5.13 Summary of Batch Analysis

The BNT162b2 DP lots included in the section were used for nonclinical toxicology, clinical trials, process performance qualification (PPQ), emergency supply, and stability. The batch analysis data are presented for the DP lots manufactured across multiple manufacturing sites, including from sites that are not being licensed under the BLA submission . All batches met the specification at the time of release. Overall, the results demonstrate the capabilities of the manufacturing process for consistent production of quality DP.

The PPQ batch range data at Pfizer Puurs and at Pfizer Kalamazoo are shown in the Table 38.

5.14 Container-Closure System of the Final Container

The primary container-closure system for the BNT162b2 vaccine consists of the vial components listed in Table 47.

Table 47. List of Components in Container Closure System

Component	Description
Vial	2 mL Type (b)(4) borosilicate glass vial, 13 mm finish
Vial Stopper	13 mm vial stopper composed of gray (b) (4) elastomer (bromobutyl rubber) coated with (b) (4) [a]
Vial Seal	13 mm aluminum vial seal with tamper-evident polypropylene flip off cap

a. (b) (4) lubricant complies with (b) (4) requirements for (b) (4) requirements for (b) (4) . requirements for (b) (4) Used as a Lubricant, (b) (4)

Extractables for the DP Container-Closure System

Controlled extraction studies were performed on the product contact bromobutyl rubber stopper material ((b) (4)) using model solvents, including (b) (4) . In one extraction study, stoppers were extracted (b) (4) . In a second extraction study, stoppers were (b) (4) . For both extraction studies, volatile, semi-volatile, non-volatile and elemental extractables were analyzed.

A Safety-Concern Threshold (SCT) was initially defined as (b) (4) total daily intake (TDI) for each compound, a level at which unidentified or identified leachable compound presents negligible safety concern to patients. The putative hazard of each potential leachable compound was further assessed and the SCT adjusted accordingly based on the presence or absence of a mutagenic concern. Potential leachable compounds without a mutagenic concern are assigned a SCT of (b) (4) TDI. Based on the results from the extraction studies, the following compounds and elements were selected and monitored as potential leachables: (b) (4) .

Leachables for the DP Container-Closure System

Leachable studies are in progress to support the BNT162b2 commercial container closure system with representative DP lots (b) (4) . Vials stored at -90°C to -60°C are being tested using methods validated for the potential leachables (identified in the extractables studies as well as unexpected compounds) at the initial timepoint, 6 months, (b) (4) . Currently available leachables information, including detection limits for validated methods and initial time point results from (b) (4) DP lots, demonstrated that all leachable compounds are below the SCT of (b) (4) TDI. Among the tested potential leachables, only (b) (4) were detected at (b) (4) , respectively. In addition, no unidentified leachable compounds have been detected. Based on a comprehensive review of available safety data, the presence of elements at or below the method quantitation limits in BNT162b2 DP pose negligible risk to patients. The rest of the leachable data will be reviewed in the next GMP inspection.

5.15 Stability of Drug Product

At Pfizer Kalamazoo, the date of manufacture for the final drug product is defined as the date of the final sterile filtration operation. At Pfizer Puurs, however, the date of manufacture is defined as the date of (b) (4) . In either case, the date of manufacture is no later than the date of final sterile filtration.

The proposed initial commercial shelf life of the BNT162b2 DP is 9 months when stored at the intended storage condition of -90°C to -60°C. The initial shelf life is determined based on up to 9 months of currently available stability data on (b) (4) emergency supply lots, and up to (b) (4) months of stability data on clinical and non-clinical lots. The stability data generated to date on the emergency supply and PPQ lots also support an additional storage condition at -20 ± 5°C for up to 2 weeks, as well as short-term storage at 5 ± 3°C for up to one month (within the (b) (4) month shelf life).

The final commercial shelf life of the BNT162b2 DP is intended to be (b) (4) months when stored at the intended storage condition of -90°C to -60°C. The applicant commits to submitting stability data to support extension of the DP shelf life beyond the 9-month period at intervals ((b) (4) months) when supporting data are available.

Materials used for the DP stability studies include emergency supply and PPQ lots manufactured by Pfizer Puurs ((b) (4)), Pfizer Kalamazoo ((b) (4)), (b) (4) (with fill/finish at Pfizer Puurs, (b) (4)), and (b) (4) (with fill/finish at Pfizer Puurs, (b) (4)), and (b) (4) clinical and (b) (4) non-clinical DP manufactured by (b) (4) .

The stability protocols for emergency supply/PPQ lots are described in Table 48 for the long-term -90°C to -60°C and the accelerated -20 ± 5°C and 5 ± 3°C conditions.

Table 48. Stability Protocol for BNT162b2 Drug Product

Analytical Procedure	Test Intervals		
	-90 to -60°C (long-term)[a]	-20 ± 5°C (Accelerated)[e]	5 ± 3°C (Accelerated)[g]
Appearance (Visible)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
Appearance (Visible Particulates)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4) (DSPC Content)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4) (Cholesterol Content)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4)	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4) (RNA (b) (4))	0, 1W[d], 2W, 1M, 2M, 3M, 6M, 9M, (b) (4)	0, 1W, 2W, (b) (4)	0, 1W, 2W, 1M, (b) (4)
(b) (4)	0, 3M[c], 6M, (b) (4)	0, (b) (4)	0, (b) (4)
Container Closure Integrity Test	0, (b) (4)	Not Tested	Not Tested
Endotoxin	0, (b) (4)	Not Tested	Not Tested
Sterility	0, (b) (4)	Not Tested	Not Tested

a. Testing not performed at the 1W, 2W, or 2M time point for lots (b) (4) ; Testing not performed at the 2M point for lots (b) (4) ; Testing not performed at the 1W or 2W time point for lot (b) (4)
b. Being performed at 3M and 6M time points for lots (b) (4)
c. Being performed at 3M time point for lots (b) (4)
d. 1W testing performed on lots (b) (4)
e. 1W testing performed on lot (b) (4) only; Testing not performed at the 1W, 2W, or (b) (4) time point for lots (b) (4) ; Testing not performed at the 1W or 2W time point for lots (b) (4)
f. Testing not performed on lots (b) (4)
g. 1W testing performed on lots (b) (4) ; 1M, (b) (4) testing performed on lots (b) (4) ; (b) (4) testing not performed on lots (b) (4) ; 1M and (b) (4) testing performed on lots (b) (4) ends at (b) (4) time point
h. Testing not performed on lots (b) (4)

W = Week, M = Month

For emergency supply/PPQ lots, the updated stability results include the following:

- Lots (b) (4) : up to 9 months of stability data at the intended storage condition of -60 to -90°C, up to (b) (4) of data at the accelerated condition of -20 ± 5°C, and up to (b) (4) months of data at the accelerated condition of 5 ± 3°C. For Lot (b) (4), up to (b) (4) of data are available at the stress conditions of (b) (4) and (b) (4)
- Lots (b) (4) : up to (b) (4) of stability data at the intended storage condition and the accelerated conditions of -20 ± 5°C, up to (b) (4) of data at the accelerated condition of 5 ± 3°C, as well as up to (b) (4) of data at the stress condition (b) (4)
- Lots (b) (4) : up to (b) (4) of stability data at all three tested storage conditions (-60 to -90°C, -20 ± 5°C and 5 ± 3°C)
- Lots (b) (4) : up to (b) (4) of stability data at all three tested storage conditions (-60 to -90°C, -20 ± 5°C and 5 ± 3°C), For lots (b) (4), up to (b) (4) of stability data are available at the stress conditions of (b) (4)
- Lots (b) (4) : up to (b) (4) of stability data at all three tested storage conditions (-60 to -90°C, -20 ± 5°C and 5 ± 3°C).

For clinical and non-clinical DP lots, the updated stability results include the following:

- Lots EE3818, ED3938, BCV40720-C, BCV40720-A, BCV40620-E, and BCV40620-A: up to 6 months of stability data at -70 ± 10°C and up to (b) (4) of stability data at 5 ± 3°C
- Lot BCV40420-A: up to (b) (4) months of stability data at -70 ± 10°C and up to (b) (4) of stability data at 5 ± 3°C
- Non-clinical lot (b) (4) : up to (b) (4) of stability data at -70 ± 10°C and 5 ± 3°C.

Summary of Stability Data

Long-term storage stability

For emergency supply and PPQ lots stored at -90°C to -60°C and for clinical and non-clinical lots stored at -70 ± 10°C, all results, generated to date, met the acceptance criteria at the time of testing. Stability data from (b) (4) up to (b) (4) months of data available) and (b) (4) emergency lots ((b) (4), up to 9 months of data available) support the proposed shelf-life of 9 months at the intended storage conditions of -90°C to -60°C. Additionally, trending on critical stability-indicating quality attributes (LNP (b) (4), LNP (b) (4), RNA content, RNA (b) (4), lipid content, RNA (b) (4)) has been analyzed for stability lots and the data show that there are no significant trends that would impact the shelf life of the DP through the 9-month time point when stored at the long-term condition of -90°C to -60°C.

Accelerated (b) (4) ***stability***

(b) (4)

Accelerated (b) (4) ***stability***

(b) (4)

Accelerated -20 ± 5°C stability

All (b) (4) PPQ and eight emergency supply lots have been placed on formal stability at the accelerated -20 ± 5°C storage condition. All data generated to date were within the stated specifications through at least the (b) (4) time point. Out of the specification results were were observed for LNP (b) (4) from multiple PPQ/emergency supply lots beginning from the (b) (4) time point.

Reviewer's Comments:

Even though all stability data generated through the (b) (4) time point for DP lots stored at -20 ± 5°C are within the specifications, trending for LNP (b) (4) is observed. The available (b) (4) stability data showed that, except for (b) (4), all other lots (n = (b) (4)) demonstrated an (b) (4) in LNP (b) (4) by (b) (4). At the (b) (4) time points, the trending is more evident, with the LNP (b) (4) ranging from (b) (4), which represents an average (b) (4) when compared with the LNP (b) (4) at release that ranges from (b) (4).

Accelerated 5 ± 3°C stability

For emergency supply and PPQ lots, all data generated to date are within the specifications through at least the 1-month time point, with the exception of (b) (4), both of which did not meet the specification of RNA (b) (4) (2-week time point for (b) (4) and 1-month time point for (b) (4)). Both lots (b) (4) were manufactured using a (b) (4) lot of (b) (4) made from the original lipid manufacturing process. The (b) (4) process was later updated by (b) (4), and since the change, the resulting BNT162b2 DP all met the specification of RNA (b) (4) when stored at 5 ± 3°C at all timepoints tested to date, which are 1 month for some lots and (b) (4) months for other lots.

For clinical DP lots, out-of-specification results were observed for RNA (b) (4) beginning from the (b) (4)-month time point, and for LNP (b) (4) and LNP (b) (4) beginning from the (b) (4)-month time point. It is not unexpected to see trends under the accelerated storage condition and the results have no impact to the overall stability study.

Thermal Stress (b) (4) ***stability***

(b) (4)

Reviewer's Comments:

As all the emergency supply BNT162b2 DP lots included in the stability protocol were made using the commercial process, their stability data are being used to support the commercial use DP expiry of 9 months when stored at the intended storage condition of -90 to -60°C. Additionally, the stability data generated to date support the DP shelf life of up to two weeks at -20 ± 5°C and up to 1 month (31 days) at 5 ± 3°C.

Additional Stability Studies for the BNT162b2 DP

(b) (4) ***stability***

(b) (4) studies have been initiated for the emergency supply and PPQ lots to provide support to the in-use period for the DP. The design of the thermal cycling studies includes the following:

(b) (4)

(b) (4)

Photostability

(b) (4) was subjected to the (b) (4) photostability condition ((b) (4)). DP vials were exposed to a light source providing an overall illumination of not less than (b) (4)

Post Approval Stability Protocol and Commitment

Upon completion of the stability protocol, post-approval, a minimum of (b) (4) of BNT162b2 DP manufactured will be enrolled in the commercial stability program at the long-term storage condition of -90°C to -60°C each year. The post-approval commercial stability protocol for the BNT162b2 DP is described below in Table 49.

Table 49. Post-Approval Commercial Stability Protocol for DP Stored at -90 to -60°C

Analytical Procedure/Quality Attribute		Test Intervals (Months)[a]
Appearance (Visible)		1, 6, (b) (4)
Appearance (Visible Particulates)		1, 6, (b) (4)
(b) (4)		1, 6, (b) (4)

Analytical Procedure/Quality Attribute		Test Intervals (Months)[a]
(b) (4)		1, 6, (b) (4)
	LNP (b) (4)	1, 6,
	LNP (b) (4)	1, 6,
	RNA (b) (4)	1, 6,
	RNA Content	1, 6,
	(b) (4) Content	1, 6,
	(b) (4) Content	1, 6,
	DSPC Content	1, 6,
	Cholesterol Content	1, 6,
	(b) (4)	1, 6,
	RNA (b) (4)	1, 6,
Container Closure Integrity Test		Annually through end of shelf life
Sterility		0, End of shelf life
Endotoxin		0, End of shelf life

a. Additional test intervals may be included for the purpose of extending expiry.

6. Other CMC-related Information Not Covered in Module 3

Environmental Assessment or Claim of Categorical Exclusion

The applicant states that the pharmacologically active moiety or DS in COMIRNATY is messenger RNA (mRNA), which is recognized as naturally occurring. Therapeutic use of the vaccine product will not significantly alter the concentration or distribution of mRNA, its metabolites, or degradation products in the environment.

The vaccine contains four pharmacologically inactive lipid excipients. The phospholipid (DSPC) and the sterol lipid (cholesterol) are both recognized as naturally occurring membrane lipids, therefore, the use of the vaccine product will not alter significantly the concentration or distribution of these lipids, their metabolites, or degradation products in the environment. The other two novel lipids (b) (4) are not recognized as naturally occurring. However, the presence of both (b) (4) lipids is not expected to have an impact on the environment based on the conservatively estimated concentrations of each lipid at the point of entry into the aquatic environment (expected introduction concentration of (b) (4)).

Exception to the 21 CFR 610.15(a) Requirement for a Preservative

Under 21 CFR 610.15(a), a vaccine product in multiple-dose containers should contain a preservative. On July 15, 2021, the applicant submitted to STN 125742/0 in amendment 11, a request for exception to the 21 CFR 610.15(a) requirement. The justification for the unpreserved multi-dose presentation of the BNT162b2 vaccine product includes the following:

- (b) (4) , the multi-dose preservative-free vial presentation remain an important tool to enable sufficient global supply to deal with the COVID-19 emergency.

- The BNT162b2 vaccine product is frozen at -90 to -60°C for storage and distribution with provisions for short-term storage for up to two weeks at -20 ± 5°C and up to 1 month at 2 - 8°C until administration. On the day of administration, sterile saline diluent is added into the thawed vial to provide 6 doses of the vaccine. Any unused vaccine must be discarded 6 hours after dilution.
- The risks of this multi-dose preservative-free approach have been assessed by taking into consideration of formulation factors, including (b) (4) , DP storage temperature, and solution properties, which may impact the ability of the finished DP to support or inhibit microbial growth. Dilution and administration risks have also been evaluated from prior extensive experience with other products and data from platform formulations and commonly used (b) (4) studies. The microbial challenge assessment using the panel of microbes described in (b) (4) support the in-use period of 6 hours to ensure adequate time to prepare and administer 6 doses of the vaccine.
- Successful distribution of more than (b) (4) doses of vaccine in this multi-dose, non-preserved presentation under the US EUA 27034 and other global authorizations.

Reviewer's Comments:

The request for an exception to the 21 CFR 610.15(a) for the BNT162b2 vaccine as a multi-dose preservative-free presentation is considered acceptable.

UNII code designations

The UNII code designations were reviewed and they appear to be acceptable.

7. Follow-up on Ongoing Issues Identified at the Time of EUA Request

RNA (b) (4) of BNT162b2 Drug Product – (b) (4)

(b) (4)

(b) (4)

Intrinsic Particles During Visual Inspection

At the time of the EUA request, the sponsor reported that during the visual inspection step of the DP manufacturing process, white-colored particles have been observed to a varying degree across many lots spanning multiple manufacturing sites, including (b) (4) and two fill/finish sites and across different (b) (4) sources (vendors and batches). Upon investigation by (b) (4), the visible particles were identified to be composed of (b) (4), and thus intrinsic to the product. Based on these observations, the specification for appearance (visible particulates) was updated from “essentially free from visible particulates” for clinical lots to “may contain white to off-white opaque, amorphous particles” for emergency supply/commercial lots.

Vials containing particles will be rejected and discarded during the 100% automated or manual inspection and Acceptable Quality Limit (AQL) sampling procedure for the inspected vials are further conducted to assess the robustness of the inspection method. The percentage of vials rejected due to particles during visual inspection has been low, ranging from (b) (4). Additionally, visible particles are rarely observed in vials during routine release or stability testing, indicating a low propensity for particle formation post-inspection. Further evaluation of samples from DP lot (b) (4) with and without visible particles demonstrated that product quality (RNA content and (b) (4)) was not impacted by the presence of visible particles.

Although visible particles may occasionally be observed in undiluted vials, following dilution with sterile 0.9% sodium chloride and mixing, the dosing solutions are expected to be free from visible particles. Any vials with visible particles observed after dilution should not be administered and should be discarded.

Reviewer’s Comments:

The impact of visible intrinsic particles appears to be minimal due to the following reasons: (1) the particles are intrinsic to the product (i.e., they are not foreign particles); (2) the frequency of occurrence is low; (3) the rare vials with intrinsic

particles can be identified during 100% visual inspection and discarded; (4) the vials with intrinsic particles are not associated with changes in RNA content or (b) (4) *; (5) the intrinsic particles are dispersible upon dilution with saline; and (6) given that the particulates are composed of the* (b) (4)*, the toxicity of which has been characterized in non-clinical repeat-dose toxicity studies, and their presence as visible particulates would not be associated with any unique chemical toxicological concern. In addition, as a precautionary measure, the instruction for the preparation of vaccine directs the healthcare provider to withhold administration if visible particles are observed after dilution with saline.*

8. Pre-Approval Inspection

The pre-approval inspection (PAI) for the Pfizer Puurs facility was conducted from June 24, 2021 through July 2, 2021. No 483 items were issued. The facility is considered capable of consistently manufacturing the BNT162b2 DP with acceptable quality.

The PAI for the Pfizer Kalamazoo facility was waived. In May 2021, ORA/OBPO performed a Level I surveillance inspection with focus on the production of the BNT162b2 DP. A form 483 was issued; the observations were deemed Voluntary Action Indicated (VAI) based on the adequacy of the firm's responses.

The PAI for the Pfizer Andover site was performed from July 19, 2021 through July 23, 2021. A form 483 with thirteen (13) observations was issued. On August 2, 2021, the applicant submitted the response to STN 126742/0.25 to address all the 483 issues identified during the Pfizer Andover PAI. The inspection was classified as VAI based on the adequacy of the firm's response to the Form 483.

During the PAI at Pfizer Andover, a recurring issue of (b) (4) out-of-specification (OOS) in DS batches was noticed. An expedited investigation effort was made by the firm focusing on evaluating raw materials, operation parameters, and stability data. The investigation was still ongoing and no definite root cause was yet identified during the inspection. (b) (5), (b) (7)(E)

9. Nonclinical Studies

This review focuses on selected studies relevant to nonclinical pharmacology and pharmacokinetics. Nonclinical toxicity studies and results were reviewed by the toxicology reviewer.

9.1 Nonclinical Pharmacology Studies

Two variants of BNT162b2, "variant 8" and "variant 9" (V8 and V9, respectively) were tested in nonclinical studies. The V8 and V9 variants differ only in their codon optimization sequences but have the same amino acid sequence. Immunogenicity of BNT162b2 (V9) was evaluated in mice, rats, and nonhuman primates. Immunogenicity

of BNT162b2 (V8) was evaluated in rats. However, only BNT162b2 (V9) has been evaluated in the clinic and therefore is the subject of this marketing application.

Immunological assays used in nonclinical pharmacology studies include the following:

- S1 and receptor-binding domain(RBD)-binding IgG ELISA in mouse and rat studies
- SARS-CoV-2 pseudovirus-based neutralization assay (pVNT) in mouse and rat studies
- Direct Luminex-based immunoassay (dLIA) for S1-binding IgG in nonhuman primate (NHP) studies
- Authentic SARS-CoV-2 neutralization assay in NHP studies
- Interferon γ (IFNγ)-specific ELISpot in mouse and NHP studies
- Intracellular cytokine staining flow cytometry in mouse and NHP studies

Immunogenicity in Mice (Study Report: R-20-0085)

Four groups of eight female BALB/c mice (at least 6 weeks of age) were immunized once on day 0 with 0.2, 1, and 5 µg of BNT162b2 or with buffer (control group), by IM injection. Blood was collected on days 7, 14, 21, and 28 after immunization, and antibody immune responses were analyzed by ELISA and pVNT. On day 28, spleens were collected for splenocyte isolation and analysis of T-cell responses using IFNγ ELISpot assays. In addition, Luminex assays and intracellular cytokine staining (ICS) were performed to assess cytokine responses.

The results demonstrated that BNT162b2 was highly immunogenic in mice with strong antigen-binding IgG and high-titer neutralizing antibody responses together with a Th1-phenotype CD4+ response as well as an IFNγ+, IL-2+, CD8+ T-cell response after a single immunization. Total IgG ELISA showed that the vaccine induced a strong, dose-dependent IgG response that recognizes both S1 and RBD. First detection of IgG antibodies was possible 7 days after immunization for all animals throughout the groups with an increase of total antibody amount until day 28. All mice developed functional neutralizing antibodies starting at 14 days after immunization, and the titer increased until the final study day. In addition, by profiling the IgG subtypes, a balanced IgG2a/IgG1 response was detected for the two higher doses (1 and 5 µg), while the low dose induced a response with higher IgG1 than IgG2 levels (0.2 µg). Stimulation of fresh splenocytes with an S protein-specific overlapping peptide pool demonstrated robust CD4+ and CD8+ T-cell IFNγ responses, and a Th1-dominant profile was demonstrated in quantification of cytokines (IL-2 and IFNγ) in the corresponding culture supernatants.

Immunogenicity in Rats (Study Reports: 38166 and 20GR142)

Male and female Wistar Han rats received three weekly IM doses of 100 µg of BNT162b2 (V8) in study 38166 or 30 µg of BNT162b2 (V9) in study 20GR142. For both studies, serum samples were collected on day 17, two days after the 3rd administration, and on day 38, the end of the study. For study 38166, the sera were analyzed by ELISA for IgG that bound S1 and RBD as well as for SARS-CoV-2-S pseudovirus neutralizing

antibodies. For study 20G142, sera were only analyzed for SARS-CoV-2 neutralization activities. After immunization with BNT162b2 (V8), animals developed high titers of antigen-specific antibodies as well as neutralization titers. BNT162b2 (V9) also elicited SARS-CoV-2 neutralizing antibody responses in both male and female rats at the end of the dosing and recovery phases of the study. SARS-CoV-2 neutralizing-antibody responses were not observed in animals prior to vaccine administration or in saline-administered control animals.

Immunogenicity and SARS-CoV-2 Challenge in Nonhuman Primates (Study Report: VR-VTR-10671)

BNT162b2 was assessed for immunogenicity and for protection against an infectious SARS-CoV-2 challenge in rhesus macaques. Groups of 2-4-year-old male rhesus macaques were immunized IM with 30 or 100 µg of BNT162b2 or saline control on days 0 and 21. In the study, a panel of 38 SARS-CoV-2 human convalescent sera (HCS) was included as a currently assessable benchmark to evaluate the quality of the humoral immune response to the vaccine. S1-binding IgG and SARS-CoV-2 neutralizing antibodies (determined by NT50 titers) were readily detectable as early as 14 days after a single immunization, and levels substantially increased further following the second immunization. On day 28, seven days after dose 2, at the 30-µg dose level, the neutralizing geometric mean titer (GMT) reached 8-fold the GMT of the 38 member panel of HCS; at the 100 µg dose level, the neutralizing GMT was 18-fold the HCS GMT. The HCS were drawn from SARS-CoV-2 infected individuals 18 to 83 years of age, at least 14 days after PCR-confirmed diagnosis and at a time when individuals were asymptomatic. A decline of both S1-binding IgG levels and neutralizing titers was observed at the latest measured time point (day 56) but remained above the neutralizing GMT and the S1-binding geometric mean concentration (GMC) of the HCS. As seen following mouse immunization, strong S-specific Th1-dominant INFγ$^+$ but minimal IL-4 T-cell responses were detected in all immunized rhesus macaques after the the second 30 or 100 µg dose of the BNT162b2. By intracellular cytokine staining analysis, there was a dose-dependent increase in S-specific CD4$^+$ T-cell response with a strong Th1-bias evidenced by a high frequency of INFγ$^+$, IL-2$^+$, or TNF-α$^+$ cells. Notably, CD8$^+$ T-cell responses were also detectable in BNT-162b2-immunized animals.

Groups of 2-4 year old male rhesus macaques that had received two IM immunizations with 100 µg BNT162b2 V9 (n=6) or saline (Control; n=3) 21 days apart were challenged 55 days after the second immunization with 1.05×10^6 plaque-forming units of SARS-CoV-2 (strain USA-WA1/2020), which were split equally between the intranasal (IN) and intratracheal (IT) routes. The presence of SARS-CoV-2 RNA was then measured by RT-qPCR in bronchoalveolar lavage fluid, nasal swabs, and oropharyngeal (OP) swabs. Viral RNA was detected in BAL fluid in all three control-immunized animals (2 on Day 3 and 1 on Day 6); however, no viral RNA was detected in BNT162b2-immunized and SARS-CoV-2-challenged animals. For nasal and OP swabs, viral RNA can be detected in most of the control-immunized animals at all tested time points (Days 1, 3, and 6),

whereas it was only detected in BNT162b2-immunized macaques on Day 1 after challenge and became undetected on Day 3 and onward. None of the challenged animals showed clinical signs of significant illness, indicating that the 2-4-year-old male rhesus challenge model is primarily an infection model for SARS-CoV-2 and not a COVID-19 disease model. No radiographic evidence of vaccine-elicited enhanced disease was observed.

9.2 Nonclinical Pharmacokinetics (PK) Evaluation

Assessment included evaluating the PK and metabolism of two novel lipid excipients ((b) (4)) in the LNP and potential biodistribution of BNT162b2.

The biodistribution of BNT162b2 was evaluated using (b) (4) expression as a surrogate reporter in (b) (4) mice. (b) (4) expressing modRNA was formulated like BNT162b2 with the identical lipid composition to generate LNPs. Mice were injected intramuscularly with a total dose of 2 µg/animal of LNP, and (b) (4) expression was measured *in vivo* following (b) (4) application at 6 h, 24 h, 48 h, 72 h, 6 d, and 9 d after injection. (b) (4) expression was identified at the injection site at 6 hours after injection and was not detected after 9 days. Expression in the liver was also present to a lesser extent at 6 hours after injection and was not detected by 48 hours after injection. A tissue distribution study was also performed in (b) (4) Rats using (b) (4) LNPs, which similarly comprised of a proprietary mixture of BNT162b2 lipid components and (b) (4) -encoding mRNA. The test item also contains trace amounts of radiolabeled (b) (4) , a non-exchangeable, non-metabolizable lipid marker in order to monitor the disposition of the LNP. The tested animals (21 male and 21 female) each received a single intramuscular dose of (b) (4) at a target mRNA total dose of 50 µg/animal. Whole blood and tissue samples were collected at 0.25, 1, 2, 4, 8, 24 and 48 hours post-dose (three animals/sex/timepoint). The study results showed that following intramuscular injection, the concentration of (b) (4) was greatest in the injection site at all time points. Outside the injection site, levels of radioactivity peaked in the plasma by 1-4 hours post-dose and distributed mainly into liver, adrenal glands, spleen and ovaries over 48 hours. Total recovery of radioactivity outside of the injection site was greatest in the liver, with much lower total recovery in spleen and very little recovery in adrenals glands and ovaries. The mean concentrations and tissue distribution pattern were broadly similar between the sexes.

An (b) (4) rat PK study, using the (b) (4) -encoding modRNA formulated in an identical lipid composition as BNT162b2, was performed to evaluate pharmacokinetics of both (b) (4) lipids. In this study, plasma samples were collected up to 336 hours following a single (b) (4) administration to male (b) (4) Rats at a dose of 1 mg/kg. The results demonstrated that (b) (4) distribute from the plasma to the liver. Plasma concentrations of (b) (4) decreased rapidly, with initial $t_{1/2}$ of 1.62 and 1.72 h, respectively. (b) (4) were then cleared from plasma, resulting in terminal elimination $t_{1/2}$ of 139 and 72.7 h, respectively. The estimated percent of dose distributed to the liver was ~ 60% for (b) (4) and ~20% for (b) (4) . While there was no detectable excretion of

either lipid in the urine, the percent of lipids excreted unchanged in feces was ~1% for (b) (4) and ~50% for (b) (4).

The *in vitro* metabolism of (b) (4) was evaluated in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans. The *in vivo* metabolism was examined in rat plasma, urine, feces, and liver samples from the PK study. Metabolism of (b) (4) appears to occur slowly *in vitro* and *in vivo*. (b) (4) are metabolized by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

Reviewer's Comments

Based on current hypotheses regarding the etiology of vaccine-associated enhanced disease, the provided data are reassuring due to: (1) the robust induction of functional (i.e., neutralizing) antibodies in mice, rats and rhesus macaques; (2) the Th1-bias in T-cell responses; and (3) the lack of disease in vaccinated rhesus macaques challenged with SARS-CoV-2. The nonclinical ADME studies indicate that the LNP mainly localizes to the site of injection and, to a lesser extent, distributes to the liver. Approximately 50% of (b) (4) *is excreted unchanged in feces, while metabolism appears to play a role in the elimination of* (b) (4).

10. Clinical Assays

10.1 Diagnostic Assays Used to Support Clinical Efficacy Endpoints

Two diagnostic assays (Cepheid Xpert Xpress RT-PCR assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) are described below.

Cepheid Xpert Xpress RT-PCR Assay

The Cepheid Xpert Xpress SARS-CoV-2 assay, which has received FDA authorization under an EUA, is a rapid, automated *in vitro* diagnostic test for the qualitative detection of the nucleocapsid (N) and envelope (E) gene sequences from nasopharyngeal, nasal, or mid-turbinate swab and/or nasal wash/ aspirate specimens collected from patients suspected of having COVID-19 disease. The Cepheid Xpert assay was used to assess viral infection before vaccination and to confirm COVID-19 disease cases during study follow-up. Detection of RNA sequences for the N and E genes are carried out by real-time (b) (4) RT-PCR following a single-step sample processing protocol.

Report VR-MVR-10080 describes the method validation for the Cepheid Xpert Xpress PCR Assay conducted at Pfizer Pearl River. The validation results are summarized below:

Detection limits: Based on simulated samples (generated by spiking with the commercially available AccuPlex SARS-CoV-2 reference material or a live SARS-CoV-2 reporter virus), the detection limits was established to be (b) (4) and (b) (4).

Accuracy: The assay's clinical accuracy was evaluated using simulated samples, patient samples as well as pre-COVID-19 samples.

(b) (4)

Taken together, the validation results for the Cepheid Xpert Xpress SARS-CoV-2 assay support its intended use to test samples from Pfizer's clinical efficacy trial of the SARS-CoV-2 vaccine candidate and other epidemiological studies.

Roche Elecsys Anti-SARS-CoV-2 Assay

The Roche Elecsys Anti-SARS-CoV-2 assay, which has received FDA authorization under an EUA, is a rapid, automated *in vitro* diagnostic test for detecting the presence of antibodies to nucleocapsid (N) protein of SARS-CoV-2 (antigen not present in the BNT162b2 vaccine candidate) in serum or plasma samples. This is a qualitative assay marketed as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, which would indicate a recent or prior infection. The Elecsys Anti-SARS-CoV-2 assay will be used to assess serostatus before vaccination. Detection of N protein antibodies to SARS-CoV-2 is carried out by a two-step immunoassay method in which biotin- and ruthenium-conjugates of N protein are incubated with human serum or plasma. Streptavidin-coated paramagnetic beads are then added to isolate N protein/antibody complexes and chemiluminescent emissions are measured by a photomultiplier. Results are presented in qualitative "Positive" or "Negative" based on N-specific antibody levels above or below a predetermined cutoff index (COI) value.

The specificity of the assay was evaluated using (b) (4)

(b) (4)

The sensitivity of the Elecsys Anti-SARS-CoV-2 assay was evaluated (b) (4)

Reviewer's Comments:

The submitted data are supportive of both the Cepheid Xpert Xpress assay and the Roche Elecsys Anti-SARS-CoV-2 assay being suitable for their intended use in Phase 2/3 clinical studies to evaluate the efficacy of the BNT162b2 vaccine performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY). It is important to note that the validation studies relied on available information generated by the assay kit manufacturers (Cepheid and Roche) in support of assay EUA as well as academic studies assessing assay performance published in peer-reviewed publications; the validation results generated by the applicant were in general agreement with information from these external sources.

10.2 Immunogenicity Assays Used for Exploratory Immunogenicity Endpoints

Two immunogenicity assays, SARS-CoV-2 mNeonGreen virus microneutralization assay and (b) (4) direct Luminex assay (dLIA) for IgG quantification, are used for evaluating the immune responses from clinical trial samples.

SARS-CoV-2 mNeonGreen Virus Microneutralization Assay (SARS-CoV-2 mNG NT)

The SARS-CoV-2 mNG NT is a biofunctional assay that measures neutralizing antibodies against SARS-CoV-2. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been engineered to contain an mNeonGreen (mNG) reporter gene in open reading frame 7 of the viral genome. The recombinant virus is rescued by reverse genetics and upon productive infection of cells, green fluorescence is produced. This reporter virus generates similar plaque morphologies and indistinguishable growth curves from wild-type virus.

(b) (4)

(b) (4)

Report VR-MVR-10083 describes the method validation for the SARS-CoV-2 mNG NT assay conducted at Pfizer Hackensack. The validation results are summarized below:

(b) (4)

Reviewer's Comments

Assay specificity was assessed in the evaluation of the limit of detection. This validation study at Pfizer Hackensack involved assessing (b) (4)

(b) (4) Direct Luminex Assay (dLIA)

The (b) (4) S1 IgG dLIA measures IgG antibody levels to the subunit 1 (S1) of the SARS-CoV-2 spike protein in human serum samples. (b) (4)

Report VR-MQR-10211 summarizes qualification results for the (b) (4) S1 IgG dLIA. The qualification results are also summarized below:

(b) (4)

(b) (4)

Reviewer's Comments

The qualification study reports for the S1 IgG dLIA and RBD IgG dLIA were submitted to the original BLA. Upon request for the validation reports for both assays, the applicant submitted to STN125742/0 amendment 19, the dLIA validation report (VR-MVR-10077) for quantification of IgG antibodies to SARS-CoV-2 full-length S protein. Additional IR was issued on August 2, 2021 to obtain clarification on which immunogenicity assay was used in the clinical studies. The applicant provided the response to amendment 31 on August 5, 2021, stating that the S1 IgG dLIA was used for immunogenicity assessments in Phase I (C4591001 sentinel cohort) and Phase 2 (C4591001 Phase 2 immunogenicity cohort) studies. The validated full-length S-binding IgG dLIA will be used for the lot consistency study and is not part of the original BLA filing.

The qualification study report for the S1 IgG dLIA assay is considered acceptable for this BLA submission with the reasons as follows: 1) the vaccine efficacy is determined by the clinical endpoints and the dLIA assay was used for the exploratory immunogenicity endpoint; and 2) appropriate assay parameters were evaluated during the qualification study, including precision, (b) (4) *linearity, lower limit of detection/quantification, range, reference standard bias, and assay run performance.*

The qualification results for the S1 IgG dLIA assay support its intended use for the quantification of anti-S1 IgG antibodies in human sera.