CBER CMC BLA Review Memorandum

BLA STN 125742

COVID-19 mRNA Vaccine (nucleoside modified) [COMIRNATY™]

CDR Donald Ertel, Regulatory Officer, OCBQ/DMPQ/MRB1
Laura Fontan, Consumer Safety Officer, OCBQ/DMPQ/MRB1
Alifiya Ghadiali, Consumer Safety Officer, OCBQ/DMPQ/MRBII
Kathleen R. Jones, Biologist, OCBQ/DMPQ/MRB1
Nicole Li, Microbiologist, OCBQ/DMPQ/MRB1
Gregory Price, Biologist, OCBQ/DMPQ/MRB1

CBER CMC BLA Review Memo, STN 125742, COVID-19 mRNA Vaccine (nucleoside modified)

1. **BLA#:** STN 125742

2. **APPPLICANT:** BioNTech Manufacturing GmbH, US License Number 2229

3. **PRODUCT NAME/PRODUCT TYPE**

COVID-19 mRNA Vaccine (nucleoside modified); COVID-19 Vaccine (BNT162, PF-07302048); COMIRNATY

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

   a. **Pharmacological category**
   Vaccine

   b. **Dosage form**
   Liquid

   c. **Strength/Potency**
   30 mcg

   d. **Route of administration**
   Intramuscular

   e. **Indication(s)**
   Active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥16 years of age

5. **MAJOR MILESTONES**

Submitted
Roll 1 Submission: May 6, 2021
Roll 2 Submission (final): May 18, 2021
Received: May 18, 2021
First Committee Meeting: June 3, 2021
Filing Meeting: June 29, 2021
Filing Action: July 16, 2021
PDUFA ADD: January 16, 2022

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
CDR Donald Ertel, Regulatory Officer, OCBQ/DMPQ/MRB1	Drug Product and Diluent (Sections 3.2.P and 3.2.R)
Laura Fontan, CSO, OCBQ/DMPQ/MRBI	Drug Product, Facilities and Equipment (Puurs), and Executed Batch Records (Sections 3.2.P and 3.2.A.1)

Reviewer/Affiliation	Section/Subject Matter
Alifiya Ghadiali, CSO, OCBQ/DMPQ/MRBII	Facilities and Equipment (Chesterfield) (Section 3.2.A.1)
Kathleen R. Jones, Biologist, OCBQ/DMPQ/MRBI	DS and Facilities and Equipment (Chesterfield, ACMF, Andover Suite (b)(4)) (Sections 3.2.S and 3.2.A.1)
Nicole Li, Microbiologist, OCBQ/DMPQ/MRBI	DS and Facilities and Equipment (Chesterfield, ACMF, Andover Suite (b)(4)) (Sections 3.2.S and 3.2.A.1)
Gregory Price, Biologist, OCBQ/DMPQ/MRBI	Drug Product, Facilities and Equipment (Kalamazoo), and Executed Batch Records (Sections 3.2.P and 3.2.A.1)

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
May 6, 2021	STN 125742/0	Original submission (Part 1 of rolling submission)
May 18, 2021	STN 125742/0.1	Part 2 of rolling submission / Reviewed
May 24, 2021	STN 125742/0.4 (response to May 20, 2021 information request (IR))	Manufacturing schedule for Pfizer Andover, Pfizer Puurs, and Pfizer Kalamazoo / Reviewed
July 28, 2021	STN 125742/0.19 (response to July 2, 2021 IR)	(b) (4) / Reviewed

Date Received	Submission	Comments/ Status
July 30, 2021	STN 125742/0.24 (response to July 26, 2021 IR)	(b) (4) [redacted] Pfizer Puurs sterilization/ depyrogenation revalidations and equipment cleaning validation; Pfizer Kalamazoo equipment qualification, information, and cleaning validation; DP sterilizing filter validation and shipping study / Reviewed
August 3, 2021	STN 125742/0.29 (response to July 26, 2021 IR)	DS equipment (due to file size limitation, remaining supporting documentation provided to Question 10, response received July 30, 2021) / Reviewed
August 10, 2021	STN 125742/0.39 (response to August 6, 2021 IR)	Pfizer Puurs (b) (4) [redacted] step / Reviewed

Date Received	Submission	Comments/ Status
August 11, 2021	STN 125742/0.43 (response to August 5, 2021 IR)	Pfizer Chesterfield utilities and equipment information and cleaning validation; Pfizer Andover EM, equipment hold times, manufacturing and equipment information; Pfizer Kalamazoo container closure integrity testing (CCIT) and equipment (b) (4) ; Pfizer Puurs visual inspection and CCIT; Drug product release and stability testing / Reviewed
August 13, 2021	STN 125742/0.47 (response to August 11, 2021 IR)	Diluent supplier manufacturer and shipping procedures / Reviewed
August 17, 2021	STN 125742/0.56 (response to August 16, 2021 IR)	Diluent suppliers / Reviewed
August 17, 2021	STN 125742/0.57 (response to August 13, 2021 IR)	Pfizer Andover computer systems and equipment qualifications; Pfizer Kalamazoo equipment qualifications, utilities information, equipment cleaning validation, and visual inspection; Pfizer Puurs cleaning validation / Reviewed
August 19, 2021	STN 125742/0.62 (response to August 17, 2021 IR)	Drug substance (b) (4) hold time / Reviewed

8. ACRONYM KEY

List of abbreviations and acronyms

Abbreviations/Acronyms	Description
AAVP	active air viable particulates
AC	acceptance criteria
ACMF	Andover Clinical Manufacturing Facility
(b) (4)	
AHU	air handling units
AOAC	Association of Official Analytical Collaboration
AQL	acceptance quality limit
ARD	Analytical Research and Development
ASTM	formerly known as American Society for Testing and Materials
BI	biological indicator
BLA	Biologics License Application
BSC	biosafety cabinet
BSL	biosafety level
CBER	Center for Biologics Evaluation and Research
CCIT	container closure integrity testing
CEA	clean environmental area
CFU	colony forming units
CGMP	current good manufacturing practice
(b) (4)	
(b) (4)	
CHT	clean hold time
CIP	clean-in-place
CMF	Chesterfield Manufacturing Facility
CNC	controlled non-classified
COP	clean-out-of-place
CPF	Chesterfield Pilot Facility
CPP	critical process parameter
DBSQC	Division of Biological Standards and Quality Control
DHT	dirty hold time
DI	data integrity
DMPQ	Division of Manufacturing and Product Quality
DNA	deoxyribonucleic acid
DP	Drug product
DS	Drug substance
DSPC	1,2-distearoyl-*sn*-glycero-3-phosphocholine
(b) (4)	

Abbreviations/Acronyms	Description
(b) (4)	
EIR	establishment inspection report
EM	environmental monitoring
(b) (4)	
ERES	electronic records and electronic signature
EU	endotoxin unit
EUA	Emergency Use Authorization
(b) (4)	
FC	flexible container
(b) (4)	
FDA	Food and Drug Administration
FV	functional verification
(b) (4)	
HEPA	high efficiency particulate air
(b) (4)	
(b) (4)	
HVAC	heating, ventilation, and air conditioning
(b) (4)	
IPT-C	in-process test for control
IPT-M	in-process tests for monitoring
IOQ	installation and operational qualification
IQ	installation qualification
IR	information request
ISO	International Organization for Standardization
(b) (4)	
(b) (4)	
KCl	potassium chloride
KH2PO4	monobasic potassium phosphate
(b) (4)	
(b) (4)	
LNP	lipid nanoparticles
MAL	material air lock
MCB	master cell bank
MCS	manufacturing control system
MOC	material of construction
MVD	maximum valid dilution
MWCO	molecular weight cut-off

Abbreviations/Acronyms	Description
N/A	not applicable
Na2HPO4*2 H2O	dibasic sodium phosphate, dihydrate
NaCl	sodium chloride
NAI	No Action Indicated
NaOH	sodium hydroxide
NMT	no more than
(b) (4)	
OAI	Official Action Indicated
OOS	out-of-specification
OQ	operational qualification
OVRR	Office of Vaccines Research and Review
PAL	personnel air lock
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
PLC	programmable logic controller
PLI	pre-license inspection
PP	polypropylene
PPQ	process performance qualification
PQ	performance qualification
PV	process validation
PW	purified water
q.s	quantum satis (as much as may suffice)
QAT	quality attributes
RAL	residue acceptance limit
RNA	ribonucleic acid
(b) (4)	
(b) (4)	
SCADA	supervisory data and collection
SIP	sterilize-in-place
SOP	standard operating procedure
SS	stainless steel
(b) (4)	
(b) (4)	

Abbreviations/Acronyms	Description
(b) (4)	
TC	thermocouple
TCV	temperature-controlled vehicle
(b) (4)	
(b) (4)	
(b) (4)	
TNTC	too numerous to count
TOC	total organic carbon
TYMC	total yeast microbial count
(b) (4)	
(b) (4)	
(b) (4)	
(b) (4)	
v/v	volume per volume
VAI	Voluntary Action Indicated
(b) (4)	
VNC	validation nonconformances
VRL	visual residue limit
WAL	waste air lock
WCB	working cell bank
WFI	water for injection

9. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Pfizer-BioNTech submitted documentation to Biologics License Application (BLA) 125742/0 to support licensure of COMIRNATY™, a COVID-19 vaccine intended for the prevention of COVID-19 in adults ≥ 16 years of age. DMPQ reviewed and evaluated the (b) (4), DS and DP manufacturing process and facilities proposed for use to manufacture COMIRNATY™. Coverage of information in this review memo includes data to validate and support the consistency of the manufacturing process and product quality; facility information which includes utilities, cross-contamination prevention measures, and maintenance of controlled environments; and equipment for use in manufacturing including qualification, cleaning and sterilization, and types of equipment used (i.e., dedicated or shared, multi-use or single-use). Note, the facilities proposed for use to manufacture COMIRNATY™ under the BLA are facilities that are used to manufacture the Pfizer-BioNTech COVID-19 Vaccine under Emergency Use Authorization (EUA), which was originally issued on December 11, 2020. However, not all facilities used to manufacture the Pfizer-BioNTech COVID-19 Vaccine under EUA are proposed for use under the BLA.

As part of the BLA review, PLIs were performed to ensure the product meets all predetermined specifications, the production process is validated and controlled, and the facility and associated systems and equipment are operated with quality oversight consistent with the CGMP requirements. The PLIs were performed at the DS manufacturing facility at Wyeth BioPharma Division of Wyeth Pharmaceuticals, LLC in Andover, MA (referred to as Pfizer Andover) from July 19 – 23, 2021 and at the DP manufacturing facility at Pfizer Manufacturing Belgium NV in Puurs, Belgium (referred to as Pfizer Puurs) from June 24 – July 2, 2021. Note, Division of Manufacturing and Product Quality (DMPQ's) review and assessment of the Pfizer Andover and Pfizer Puurs facilities are documented in separate establishment inspection reports (EIR). At the conclusion of the Pfizer Andover PLI, a Form FDA 483 was issued on July 23, 2021 with thirteen inspectional observations, which the firm responded to on August 2, 2021. A review of Pfizer Andover's responses with inspectional follow-up recommendations is documented in a separate 483 response memo dated August 21, 2021. All inspectional 483 observations were resolved, and the Pfizer Andover PLI was classified as Voluntary Action Indicated (VAI). No Form FDA 483 was issued at the conclusion of the Pfizer Puurs PLI, and the PLI was classified as No Action Indicated (NAI).

In addition to the PLIs, facility inspections were waived following an evaluation of the inspection compliance histories of the (b) (4) and another DP manufacturer and release testing facilities for Pfizer Inc. in Chesterfield, MO; Pharmacia & Upjohn Company LLC in Kalamazoo, MI; Pfizer Ireland Pharmaceuticals in Dublin, Ireland; (b) (4) , the inspection waivers of the facilities are documented in a separate inspection waiver memo dated August 9, 2021.

The COMIRNATY™ vaccine multi-dose vial requires dilution with 1.8 mL of 0.9% Sodium Chloride Injection, USP prior to administration of the vaccine product. Pfizer-BioNTech will provide the 2 mL or 10 mL vials of 0.9% Sodium Chloride Injection, USP diluent manufactured by Fresenius Kabi USA, LLC (b) (4) or Hospira, Inc. in (b) (4) , respectively. The saline diluent will be supplied separately to healthcare providers shipped in parallel with COMIRNATY™. Both the 2 mL and 10 mL single dose vials of 0.9% Sodium Chloride Injection, USP are packaged in cartons of 25 vials and shipped in a corrugated box with other ancillary supplies (masks, syringes, gloves, etc.). Cartons of the saline diluent will be clearly labeled to indicate that it is for use with COMIRNATY™.

Based on the information submitted to BLA 125742/0 and in conjunction with the PLIs and inspectional compliance history evaluations, the production process, facilities, equipment, and controls appear acceptable for the licensure of COMIRNATY™ and approval is recommended.

B. RECOMMENDATION

I. APPROVAL

Approval is recommended with inspectional follow-up recommendations below.

CBER understands the inspectional recommendations may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

Pfizer Inc. in Chesterfield, MO (known as Pfizer Chesterfield), FEI: 1940118

(b) (5), (b) (7)(E)

Wyeth BioPharma Division of Wyeth Pharmaceuticals, LLC in Andover, MA (known as Pfizer Andover), FEI: 1222181

(b) (5), (b) (7)(E)

Pfizer Manufacturing Belgium NV, Puurs, Belgium (known as Pfizer Puurs), FEI: 1000654629

(b) (5), (b) (7)(E)

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
CDR Donald Ertel, Regulatory Officer, OCBQ/DMPQ/MRB1	Concur	

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Laura Fontan, CSO, OCBQ/DMPQ/MRBI	Concur	
Alifiya Ghadiali, CSO, OCBQ/DMPQ/MRBII	Concur	
Kathleen R. Jones, Biologist, OCBQ/DMPQ/MRBI	Concur	
Nicole Li, Microbiologist, OCBQ/DMPQ/MRBI	Concur	
Gregory Price, Biologist, OCBQ/DMPQ/MRBI	Concur	
Lori Peters, Branch Chief, OCBQ/DMPQ/MRBI	Concur	
John A. Eltermann, Jr., Division Director, OCBQ/DMPQ	Concur	
Mary A. Malarkey, Office Director, OCBQ	Concur	

Module 3

3.2.S DRUG SUBSTANCE

(b) (4)

(b) (4)

(b) (4)

19 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The BNT162b2 DP is supplied as a preservative-free, multi-dose concentrate to be diluted for intramuscular injection, containing six doses. The DP is a sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer. Each vial, containing 0.45 mL of the DP at (b) (4) is designed to contain a total of six doses after dilution by the addition of 1.8 mL of sterile 0.9% sodium chloride solution, with each dose containing 30 µg of RNA in 0.3 mL. There is no manufacturing overage.

The DP is supplied in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap.

The composition of the DP, including amount per vial and function and quality standard applicable to each component, is given in the table below.

Composition of BNT162b2 Drug Product, multi-dose vial (225 µg/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
ALC-0315	In-house specification	Functional lipid	7.17	3.23 mg	0.43 mg
ALC-0159	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	Ph. Eur. and/or USP-NF	Structural lipid	3.1[b]	1.4 mg	0.2 mg
Sucrose	USP-NF and Ph. Eur.	Cryoprotectant	103[b]	46 mg	6 mg
Sodium chloride	USP-NF and Ph. Eur.	Buffer component	6	2.7 mg	0.36 mg[e]
Potassium chloride	USP-NF and/or Ph. Eur.[a]	Buffer component	0.15	0.07 mg	0.01 mg
Dibasic sodium phosphate, dihydrate[c]	USP-NF and Ph. Eur.	Buffer component	1.08	0.49 mg	0.07 mg

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per vial	Amount per dose
Monobasic potassium phosphate[d]	USP-NF and/or Ph. Eur.[a]	Buffer component	0.15	0.07 mg	0.01 mg
Water for Injection	USP-NF and Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.

a. Supplier Certificate of Analysis confirms compliance to both USP-NF and Ph. Eur., however incoming testing may be performed only in accordance with a site's local compendia.
b. Values are rounded to maintain the same level of precision as the label claim, with trailing zeros not shown, where applicable. For example, 46 mg sucrose is rounded from (b) (4) mg (103 mg/mL).
c. Dibasic sodium phosphate, dihydrate (Na2HPO4*2 H2O) is named as (b) (4)
d. Monobasic potassium phosphate (KH2PO4) is named as (b) (4)
e. The diluent (0.9% sodium chloride Injection) contributes an additional 2.16 mg per dose.

Abbreviations:
ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine
q.s. = quantum satis (as much as may suffice)
(b) (4)

3.2.P.2 Pharmaceutical Development
3.2.P.2.1 Components of the Drug Product
3.2.P.2.1.1 DS
The RNA component of the DS is the only active ingredient in the BNT162b2 DP. The DS is a single-stranded, 5'-capped mRNA produced by in (b) (4) and provided for DP manufacture as a (b) (4) aqueous solution (b) (4) in (b) (4)

3.2.P.2.4 Container Closure System
The container closure system for the commercial BNT162b2 DP is a 2 mL Type I borosilicate glass vial and a 13 mm bromobutyl stopper. Multiple vendors of the glass vial are utilized on a global basis.

The glass vial meets (b) (4) requirements for chemical testing for Type I glass containers. The elastomeric stoppers meet (b) (4) chemical testing requirements for elastomeric closures.

Reference Section 3.2.P.7 Container Closure System for description of container closure and stopper functional testing; reference Section 3.2.P.5.3 for CCIT evaluation.

> ***Reviewer's comment****: The evaluation of suitability, chemical compatibility & resistance, extractables/leachables, safety of the materials of construction, biological activity, and photostability is deferred to the OVRR reviewer.*

3.2.P.2.5 Microbiological Attributes

The manufacturing process utilizes pre-sterilized raw materials and supplies, HEPA-filtered, classified production areas, and personnel gowning controls. During manufacturing, the formulated bulk DP is (b) (4) sterile filtered prior to being aseptically filled into vials. The sterilizing filter is integrity tested.

The final product storage conditions do not support microbial growth, as the product is stored frozen at -90°C to -60°C. The container closure system and its components were selected based on their ability to protect the quality of the product over its shelf life and have been qualified for use.

The BNT162b2 container closure system has been tested by both (b) (4) CCIT methods. Both studies have produced acceptable data and verify that the stopper/vial/cap combination maintains integrity when challenged with a (b) (4). Container closure integrity testing is covered in Section 3.2.P.5.3.

3.2.P.2.6 Compatibility

The initial in-use period for the thawed, undiluted vial is room temperature for not more than 2 hours. Pfizer initiated formal thermal cycling stability studies on both emergency use lots and PPQ lots in order to further support the in-use period.

(b) (4)

***Reviewer's comment**: The in-use period of 6 hours is supported by the results of the microbial in-use study, which demonstrates safe use of the multi-dose vials over 6 hours at ambient temperatures.*

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Table P.3.1-2 in the submission (recreated with additional information below) lists the manufacturing and testing facilities for BNT162b2 DP manufacturing and release testing.

Site	FEI/DUNS Number	Responsibility
Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs, 2870 Belgium	FEI: 1000654629 DUNS: 370156507	LNP production and bulk DP formulation Fill and finish Primary packaging Secondary packaging Release and stability testing: Sterility (including (b) (4) sterility), Endotoxin, Appearance, Appearance (Visible Particulates), (b) (4), Container Content, LNP (b) (4), LNP (b) (4), RNA (b) (4), RNA Content, ALC- 0315 Content, ALC-0159 Content, DSPC Content, Cholesterol Content, Lipid Identities, RNA (b) (4)
Pharmacia & Upjohn Company LLC[c] 7000 Portage Road Kalamazoo, MI 49001 United States	FEI: 1810189 DUNS: 618054084	LNP production and bulk DP formulation Fill and finish Primary packaging Secondary packaging Release and stability testing: Sterility (including (b) (4) sterility), Endotoxin, Appearance, Appearance (Visible Particulates), (b) (4), Subvisible Particles, Container Content, LNP (b) (4), LNP (b) (4), RNA Content, RNA (b) (4), ALC-0315 Content, ALC-0159 Content, DSPC Content, Cholesterol Content, Lipid Identities, RNA (b) (4), Container Closure Integrity
Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC[a] 1 Burtt Road Andover, MA 01810 United States	FEI: 1222181 DUNS: 174350868	Release and stability testing: Identity of encoded RNA sequence, (b) (4)

Site	FEI/DUNS Number	Responsibility
(Analytical Research & Development) Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC a 1 Burtt Road Andover, MA 01810 United States	FEI: 1222181 DUNS: 174350868	Drug Product release and stability testing: Appearance, Appearance (Visible Particulates), (b) (4), Container Content, LNP (b) (4), LNP (b) (4), RNA (b) (4), RNA Content, ALC-0315 Content, ALC-0159 Content, DSPC Content, Cholesterol Content, Lipid Identities, Identity of encoded RNA sequence, (b) (4), RNA (b) (4), Container Closure Integrity In-process testing
Pfizer Inc. 875 Chesterfield Parkway West Chesterfield, MO 63017 United States	FEI: 1940118 DUNS: 004954111	Release and stability testing: Appearance, Appearance (Visible Particulates), (b) (4), Container Content, LNP (b) (4), LNP (b) (4), RNA (b) (4), RNA Content, ALC-0315 Content, ALC-0159 Content, DSPC Content, Cholesterol Content, Lipid Identities, Identity of encoded RNA sequence, (b) (4), RNA (b) (4), Container Closure Integrity
Pfizer Ireland Pharmaceutical Grange Castle Grange Castle Business Park Clondalkin, Dublin 22 Ireland	FEI: 3004145594 DUNS: 985586408	Release and stability testing: (b) (4), Identity of Encoded RNA Sequence, (b) (4)
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Release testing: Sterility
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Release testing: Sterility
Fresenius Kabi USA, LLC (b) (4)	FEI: (b) (4) DUNS: (b) (4)	Diluent Manufacturer

Site	FEI/DUNS Number	Responsibility
Hospira, Inc. (b) (4)	FEI: (b) (4) DUNS: (b) (4)	Diluent Manufacturer

[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 part of Pfizer´s GMP system.
[b] (b) (4) is a wholly owned subsidiary of Pfizer Inc.
[c] Pharmacia & Upjohn Company LLC is a wholly owned subsidiary of Pfizer Inc.

3.2.P.3.3 Description of Manufacturing Process

The following paragraphs describe the DP manufacturing process, which occurs at both the Pfizer Kalamazoo and Pfizer Puurs locations:

The manufacturing process for BNT162b2 DP includes LNP production and bulk DP formulation followed by fill and finish activities.

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

Fill/Finish Operations

Two locations, Pfizer Kalamazoo and Pfizer Puurs, each with multiple filling lines, are used for fill and finish manufacturing operations. Process controls are the same for both sites unless otherwise described. Please refer to 3.2.A.1 for a description of the facilities and equipment.

Sterile Filtration

(b) (4)

The process parameters for sterile filtration are summarized in Table P.3.3-1 and IPT-C tests are summarized in Table P.3.3-2. Tests for monitoring (IPT-M) are summarized in Table P.3.3-3. The tables are reproduced below.

(b) (4)

The following two tables describe the in-process acceptance criteria for sterile filtration.

(b) (4)

Preparation of Vials and Stoppers

The vials are processed through the vial washer, where they are rinsed with (b) (4). After washing, the vials are depyrogenated by means of (b) (4) application.

Bulk stoppers are washed and depyrogenated with (b) (4).

Aseptic Filling

The (b) (4)
DP is aseptically filled into vials. Prior to filling, (b) (4)

All non-conforming vials are rejected.

The process parameters for aseptic filling are summarized in Table P.3.3-4 and IPT-C tests are summarized in Table P.3.3-5, both reproduced below.

Process Parameters for Aseptic Filling

(b) (4)

(b) (4)

Stoppering and Capping

At the end of aseptic filling, a stopper is (b) (4) seated onto each filled vial. Vials are subsequently transferred to the capping station. The stoppered vials are transferred to the capper. A 100% check on the presence and position of the stopper is performed. The capper automatically rejects vials unless the stopper is (b) (4) seated. The stoppered vials are capped with aluminum overseals under (b) (4) airflow and crimped onto each vial.

(b) (4)

Visual Inspection

Vials are 100% inspected for defects either through automated visual inspection or manual visual inspection.

During the 100% automated inspection process the vials are fed to the inspection machine. The vials undergo a check for product (b) (4) defects. The rejected vials are segregated in prelabeled reject trays. The acceptable vials are transferred to trays.

For automated inspection, prior to each batch, (b) (4)

If required, vials may undergo 100% manual visual inspection. Vials are manually inspected for product (b) (4) defects. The stoppers and caps are inspected for (b) (4). All rejected vials are segregated into prelabeled reject trays. The remaining acceptable vials are placed into trays.

Vials passing automated or manual inspection are statistically sampled to meet Acceptance Quality Limit (AQL). Throughout the inspection process, samples are taken

for AQL testing. Defects are classified as Critical, Major or Minor and are addressed according to site procedures.

Labeling, Packaging, and Freezing

The labeling and packaging of the BNT162b2 vaccine vials for commercial distribution is performed on a fully automated or semi-automated packaging line. Inspected vials are individually labeled with a vial label. A printer on the vial labeler is used to print batch-specific information on the vial labels. The labeler has (b) (4)

After labeling, the vials are placed into trayboxes using an automated trayer or a manual traying process. After filling of the boxes, vial quantities are verified, an insert may be added, and the boxes are manually closed and labeled.

A sample for identity testing is taken after labeling operations are completed.

Packaged BNT162b2 vials are frozen and stored in a freezer at -90°C to -60°C pending shipment for commercial distribution.

Storage, Packaging and Shipment of BNT162b2 Drug Product

Drug product (DP) vials are stored according to conditions supported by Section 3.2.P.8.1 Stability Summary and Conclusions (modRNA).

DP is shipped under qualified conditions as supported by Section 3.2.P.3.5 Shipping Validation, validating shipping conditions of -90°C to -15°C including a maximum cumulative time of (b) (4) at (b) (4) . The final packaged products are transported by established transportation routes to point of use.

When DP is shipped at -90°C to -60°C, the trayboxes containing the vials are moved from the freezer and placed into validated shippers that use dry ice for temperature control. Temperature monitoring devices are inserted and activated for all shipping containers. Temperatures during shipment are verified to ensure that the product maintains -90°C to -60°C. The product can be warmed up to a maximum of (b) (4) to perform transfers and redistribution during shipping with multiple transfers allowed within that timeframe. The product temperature in the shipper can be maintained by adding additional dry ice. Alternative qualified insulated thermal conveyances may be used following appropriate qualification.

When DP is shipped at -20±5°C, the trayboxes containing the vials are moved from the freezer and may be shipped using a temperature-controlled vehicle (TCV). All TCV shipments are monitored for temperature during shipment to ensure that the temperature within the TCV remains within -20±5°C, and temperatures during transport are verified. Upon arrival at a qualified distribution center or logistics service provider,

the trayboxes containing the vials are transferred to a freezer for storage at -90°C to -60°C.

The DP shipment may also be shipped directly at -20±5°C in thermal conveyances that use (b) (4) material for temperature control or following deconsolidation at a qualified distribution center or logistics service provider into smaller bundles or quantities. Temperature monitoring devices are inserted and activated for all shipping containers. Temperatures during shipment are verified to ensure that the product is maintained at -90°C to -15°C. Alternative qualified insulated thermal conveyances may be used following appropriate qualification.

A maximum cumulative time of (b) (4) is allowed at (b) (4) during shipping and deconsolidation of the DP until arrival at point of use. Process parameters for storage and shipping are summarized in Table 3.2.P.3.3-8, reproduced below.

(b) (4)

Reviewer's comment: *The description of the manufacturing process is complete and sufficiently detailed. Please refer to 3.2.P.3.5 for review of the validation studies supporting these processes.*

Hold Times

The hold times of the DP in-process materials during (b) (4) are provided in Table 3.2.P.3.3-9 of the submission and are reproduced below. All hold times following (b) (4) are in alignment with the validated media fill times, ensuring acceptable microbial control during the DP manufacturing process. The (b) (4) processing steps are performed within the maximum times determined by the (b) (4) validation.

Material or In-Process Hold Description	Process Steps	Target Hold Time
(b) (4)		

(b) (4)

(b) (4)

3.2.P Diluent

The COMIRNATY™ vaccine requires dilution with 0.9% Sodium Chloride Injection, USP diluent prior to administration of the vaccine product. Pfizer did not include information in the BLA, Module 3, regarding the suppliers for this diluent. The original labeling proposal (in Module 1) provides a description of the plan as follows:

For the licensed commercial vaccine, a similar approach will be used as was done under EUA. Pfizer-BioNTech will provide the same 0.9% Sodium Chloride Injection, USP diluent manufactured by Fresenius Kabi LLC or the Hospira, Inc. saline diluent (if needed). The saline diluent will be supplied separately to healthcare providers (shipped in parallel with shipments of the COMIRNATY™, with arrivals synchronized so that diluent is delivered before the vaccine is delivered). Cartons of the saline diluent will be clearly labeled to indicate that it is for use with COMIRNATY™, specifically: cartons of the 0.9% Sodium Chloride Injection, USP diluent supplied by Fresenius Kabi LLC will be ink print stamped on the side of the carton opposite the Fresenius Kabi diluent label with the following text: “For Use with COMIRNATY™ [COVID-19 mRNA Vaccine (nucleoside modified)]”. The information is printed from a (b) (4) printer in dot matrix font in a default font size of 7 in black ink. No physical label can be applied, as the packaging line is fully automated and does not have this capability. Cartons of the 0.9% Sodium

Chloride Injection, USP diluent supplied by Hospira, Inc., will be labeled, same text as mentioned, on the side of the carton opposite the Hospira diluent label.

Images of the cartons and relevant stamps were supplied as attachments.

> ***Reviewer's Comment****: Per amendment 125742/0.47, the manufacturers table and FDA Form 356h have been updated with the diluent manufacturers. Pfizer provided a description of the diluent shipping and controls in Module 3. Pfizer identified three manufacturers of diluents. It was found that one of the three manufacturers,* (b) (4) *. (FEI#* (b) (4) *), currently has a pending Warning Letter (reference WL* (b) (4) *issued* (b) (4) *) and Official Action Indicated status. An IR was issued and, per amendment 125742/0.56, Pfizer has removed all references to this supplier from the BLA, including in the recently added Diluent Manufacturers table. All diluents have been verified as approved under ANDA / NDA as follows:*

Proprietary Name	NDC Package Code	Appl. #.	Labeler Name	Product NDC	Package Description
Sodium Chloride	63323-186-02	ANDA 088912	Fresenius Kabi USA, LLC (b) (4) FEI: (b) (4)	63323-186	25 VIAL, SINGLE-DOSE in 1 TRAY (63323-186-02) > 2 mL in 1 VIAL, SINGLE-DOSE (63323-186-04)
Sodium Chloride	0409-4888-10	NDA 018803	Hospira, Inc. (b) (4) FEI: (b) (4)	0409-4888	25 VIAL, SINGLE-DOSE in 1 TRAY (0409-4888-10) > 10 mL in 1 VIAL, SINGLE-DOSE (0409-4888-02)

> *The information provided appears acceptable.*

3.2.P.3.4 Controls of Critical Steps and Intermediates (Pfizer Puurs and Pfizer Kalamazoo)

In-Process Monitoring and Control of Fill and Finish

Sterile filtration process controls and target range/acceptance criteria, and microbial process controls and acceptance criteria are provided in Table 3.2.P.3.4.1 and Table 3.2.P.3.4.2 in the submission and are reproduced below.

One page has been determined to be not releasabe: (b)(4)

(b) (4)

Aseptic Filling

During production, an in-process fill (b) (4) test is performed at (b) (4) The filling process controls and target ranges/acceptance criteria are provided in Table 3.2.P.3.4-5 in the submission, and are reproduced below.

(b) (4)

Capping

Capping process controls and acceptable ranges are provided in Table 3.2.P.3.4-6 and are reproduced below.

(b) (4)

Process Step Hold Times – (b) (4)

The table below provides the hold times of the DP in-process materials during (b) (4) . All hold times following (b) (4) were verified and are consistent with the validated media fill times, ensuring acceptable microbial control during the DP manufacturing process. The (b) (4) processing steps are within the maximum times determined by the (b) (4) validation which is reviewed below in Section 3.2.P.3.5.

(b) (4)

Freezing process controls and acceptable ranges are provided in Table 3.2.P.3.4-7. The acceptable range for freezing is -90°C to -60°C and is defined as a critical process parameter (CPP).

Reviewer's comment: *In process monitoring and controls were defined for the BNT162b2 manufacturing fill finish steps. The parameters defined are supported by the process validation provided and appear acceptable. The controls defined for sterile filtration agree with the parameters established from the* (b) (4) *studies discussed in the* (b) (4) *validation for* (b) (4) *(3.2.P.3.5). The integrity test parameters and wetting agents defined also agree with the integrity test limits defined in 3.2.P.3.5. The* (b) (4) *filters from* (b) (4) *will be used for the sterile filtration of the DP bulk in the commercial operations. The information appears acceptable.*

The time limit defined for aseptic processing agrees with the parameters established during the media fills for each line (3.2.P.3.5). The media fills on the (b) (4) *filling line support up to* (b) (4) *filling time; however, the production limit has been set at* (b) (4) *. The media fills on the* (b) (4) *filling line support up to* (b) (4) *filling time; however, a production limit has been set at* (b) (4) *.*

The process controls set for capping on filling lines (b) (4) *are within the validation parameters defined in the capping process validation provided in 3.2.P.3.5. In process monitoring and controls appear acceptable.*

3.2.P.3.4.2 Time Out of Freezing

The BNT162b2 DP has an allowable time out of freezing during movement from freezers to packaging and into shippers of (b) (4) each for transfer and limited to (b) (4) total transfers. (b) (4) is used to ensure the product temperature in the secondary packaging material does not exceed (b) (4).

The BNT162b2 DP has allowable out of condition post freezing at -90°C to -60°C during manufacture, packaging and transport of up to (b) (4) cycles reaching a maximum of (b) (4) Table 3.2.P.3.4-2, reproduced below, shows the time allowed out of freezing for the BNT162b2 DP.

Note: The same acceptable ranges are listed in the manufacturing process description in Table 3.3-8 Process Parameters for Storage and Shipping.

(b) (4)

(b) (4)

***Reviewer's comment**: The allowable times out of freezing are supported by stability data for DP. Container closure integrity testing was performed on samples that were exposed to worst case shipping hazards. All lots tested were integral.*

In addition, transfers of DP to freezers, into (b) (4) *, and into shipping containers were observed during the recent inspection from June 24 to July 2, 2021. Each of these transfers was timed and was far less than* (b) (4) *. The information provided appears acceptable.*

3.2.P.3.5 Process Validation and Evaluation
MANUFACTURING PROCESS

3.2.P.3.5 Process Performance Qualification (PPQ) Data

The PPQ data from the LNP production and bulk DP formulation and fill/finish locations (Pfizer Puurs, Pfizer Kalamazoo) were provided. An overview of the process validation phases is described below.

(b) (4)

7 pages have been determined to be not releasable: (b)(4)

(b) (4)

Visual Inspection

During inspection of the BNT162b2 filled vials, 100% automated or manual inspection of the validation batches was performed, followed by Acceptable Quality Level (AQL) sampling of the inspected vials. The requirement for the inspection process is that the vials for AQL inspection must not exceed the acceptance criteria for critical ((b) (4)), major ((b) (4)) and minor defects ((b) (4)). For each process validation lot,

the number of filled vials that were inspected along with the total rejection percentages are presented in the table below.

Drug Product Lot	Number of Vials Inspected	Number of Vials Accepted	Number of Vials Rejected	Vials Rejected (%)
(b) (4)				

An IR was submitted for clarification on the visual inspection process and a response was received under STN 125742/0.57. According to Pfizer all PV lots above were inspected via automated visual inspection. The allowable alert limit of rejects for visual inspection is (b) (4) (critical), (b) (4) (major), and (b) (4) (minor). All PV lots passed this acceptance criteria.

All validation lots were AQL sampled following inspection ((b) (4)) and met the AQL acceptance criteria for critical ((b) (4)), major ((b) (4)) and minor ((b) (4)) defects.

> ***Reviewer's comment:*** *Pfizer did not provide adequate information regarding the visual inspection validation including which lots were inspected by automated methods and which were inspected visually as well as the acceptance criteria for the allowable limit of rejects. The information provided appears acceptable.*

Labeling and Packaging

The validation of integrated labeling and secondary packaging operations for commercial distribution involved running (b) (4) of product-filled vials through the automated labeling and packaging equipment. This validation run included (b) (4) testing.

The process validation run included enhanced inspection to established Acceptable Quality Level (AQL) limits for critical, major, and minor defects. The results complied with the acceptance criteria which demonstrates suitable validation of the labeling and packaging operations.

> ***Reviewer's comment****: Labeling and packaging of the BNT162b2 DP were reviewed during the recent surveillance inspection conducted by OBPO in May 2021. No major issues were identified. Labeling and packaging appear acceptable.*

Freezing

After the labeling and secondary packaging process, the packaged DP was frozen for storage and distribution. The freezing of the product was monitored to ensure that the

process performs within the established limits. The process parameter for freezing of the BNT162b2 DP is a freezing temperature of -90 to -60°C. All (b) (4) PV lots passed this acceptance criteria.

> ***Reviewer's comment****: Freezing operations of the BNT162b2 DP were reviewed during the recent surveillance inspection conducted by OBPO in May of 2021. No issues were identified regarding this operation. The information appears acceptable.*

Hold Times Pfizer Kalamazoo

The routine in-process hold times for the BNT162b2 DP manufacturing process were confirmed during the manufacture of the process validation lots. Process validation lots (b) (4) were subjected to a cumulative hold time study. The study evaluated the cumulative effect of the maximum process hold times for each process step, from (b) (4), on the microbiological and physicochemical quality of the DP. The maximum hold times are established based on the hold times of the cumulative hold process validation lot. Microbial testing was performed for (b) (4) held (b) (4), or as otherwise deemed appropriate. Hold time relevant to (b) (4) operations ((b) (4)) are within those qualified by media fill which will be presented in its own section below. The (b) (4) processing steps are within the maximum (b) (4) time determined by (b) (4) validation. Additional information is presented below.

The in-process hold times for each step in the manufacturing train were provided for each PV lot, and will be deferred to OVRR for review.

(b) (4)

One page has been determined to be not releasable: (b)(4)

Hold Times Pfizer Puurs

The routine in-process hold times for the BNT162b2 DP manufacturing process were confirmed during process validation lot manufacture.

Process validation lots (b) (4) were subjected to cumulative hold times to evaluate the maximum process hold times for each process step, from (b) (4) , on the microbiological and physicochemical quality of the DP. The maximum hold times are established based on the hold times of the cumulative hold process validation lot.

In addition, microbial testing was performed for (b) (4) held (b) (4) or as otherwise deemed appropriate.

The evaluated in-process hold times for the process validation lots are listed in Table 3.2.P.3.5-1, which includes hold time data from DP lots (b) (4) . The following table incorporates the hold time data from Table 3.2.P.3.5-1 and process hold times defined in Table 3.2.P.3.4-1 for (b) (4) manufacturing activities.

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

Validation of (b) (4) **at Kalamazoo**

(b) (4)

8 pages have been determined to be not releasable: (b)(4)

(b) (4)

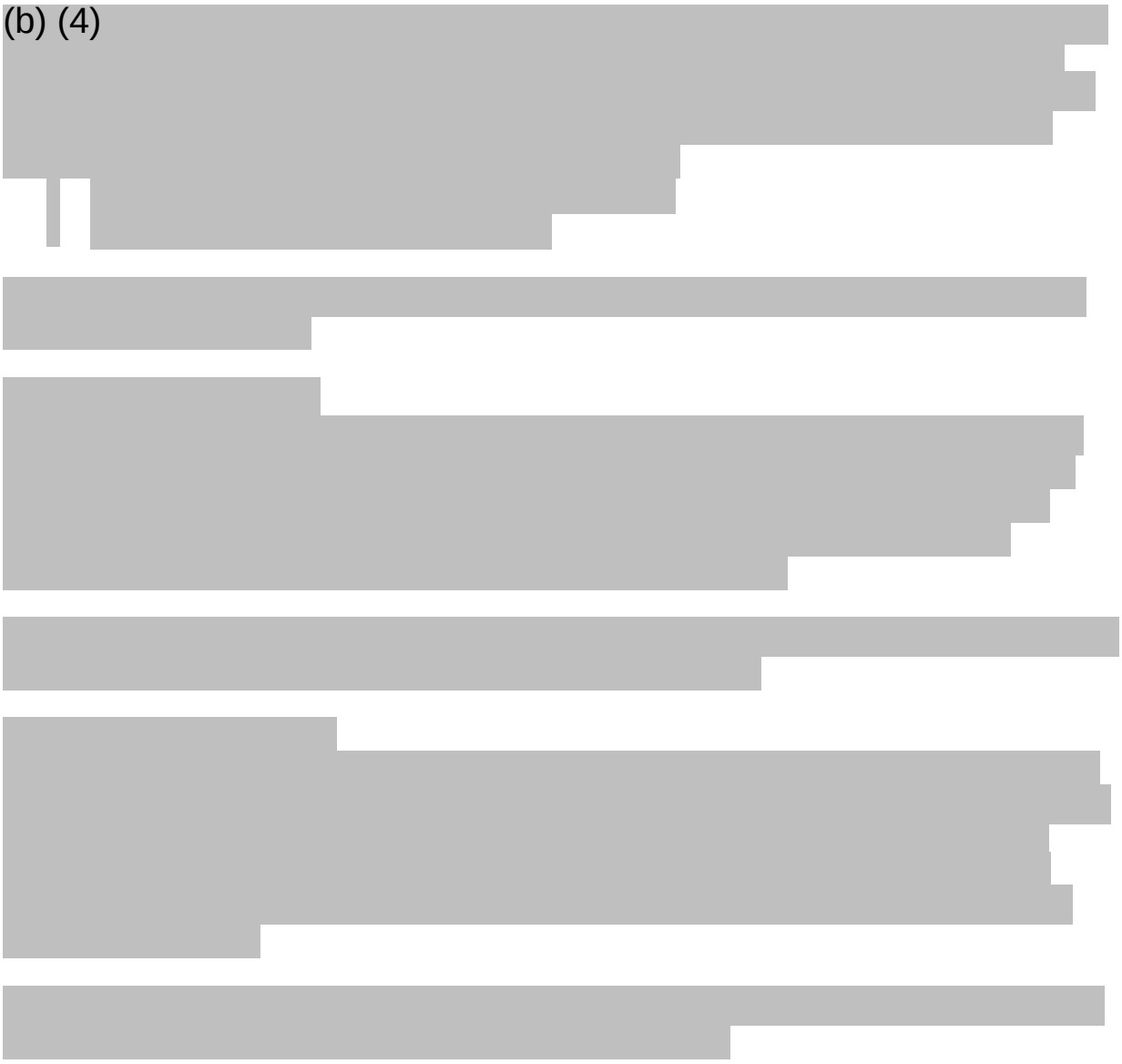
Validation of Aseptic Filling Process by Media Fills (Pfizer Kalamazoo)

Media fills were conducted for (b) (4) Lines (b) (4) to validate of the aseptic processing steps for consistent manufacture of sterile products. Media fills are conducted (b) (4) with all shifts included in the routine media fill schedule. Environmental and personnel monitoring are also performed for each media fill.

(b) (4)

- Acceptance criterion (b) (4) .

(b) (4)



Reviewer's comment: (b) (4) *Lines* (b) (4) *are existing fill lines used to fill FDA approved products and have been validated for filling other products. The media fill studies included in this application appear acceptable with no issues identified and the filling line and environment appear to be in a state of control.*

Validation of Aseptic Filling Process by Media Fills (Pfizer Puurs)

Media fills were performed to validate the aseptic process at Puurs for 2mL components on the (b) (4) filling line and (b) (4) vial line. Media fill re-qualification is required (b) (4) for each filling line. All personnel that enter the filling area including process control technicians, maintenance personnel, and quality assurance must take part in at least (b) (4) .

6 pages have been determined to be not releasable: (b)(4)

(b) (4)

Sterilization Processes for Product-Contact Equipment and Components (Pfizer Kalamazoo)

(b) (4)

11 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Shipping Validation
Pfizer's facilities in Kalamazoo, MI and Puurs, Belgium perform DP manufacturing, primary packaging, labeling, and secondary packaging operations for BNT162b2 DP. Following these activities, BNT162b2 DP is shipped in its final packaging to US receiving agencies and dosing sites directly or via the Pfizer US logistics center in Pleasant Prairie, WI (PPLC).

The following shipping methods are used (or planned):

- Transport to Logistics Centers and distribution sites occur at shipping conditions of -90 to -60°C via passive thermal conveyance or at shipping conditions of -20±5°C via active or passive shipping conveyances. Shipments at -90 to -60°C occur within thermal shipping conveyances that passively maintain temperature conditions of -90 to -60°C using dry ice.

- Shipments at -20±5°C may occur under active control via temperature-controlled vehicle (TCV). All TCV shipments are monitored for temperature during shipment to ensure that the temperature within the TCV remains within -20±5°C, and temperatures during transport are verified.

- (b) (4) Planned for future implementation (estimated November 2021).

All shipments of BNT162b2 DP are continuously temperature monitored to confirm that the appropriate temperatures are maintained. The worst-case location identified during the OQ of the thermal shipper, i.e., (b) (4), is identified for placing temperature monitor during routine shipments.

Shipment Methods

Method	Temperature requirements	Qualification status	Controls used/ comments
Softbox	-90°C to -60°C using dry ice.	OQ completed: -Minimum and maximum chamber studies (worst case temperature conditions for (b) (4)) PQ completed: -(b) (4) shipments using representative (b) (4) (average transit time of (b) (4)) from Puurs, Belgium, to Kalamazoo, Michigan, US -Simulated transportation hazards such as (b) (4)	Continuously temperature monitored in worst case location with GPS
Temperature Controlled Vehicle	-20°C ±5°C	OQ completed PQ ongoing	Continuously temperature monitored and active control in Vehicle
(b) (4)	(b) (4)	OQ ongoing PQ ongoing	Currently not in use

Qualification of Passive Thermal Conveyance with Dry Ice

The results from the three OQ tests for the (b) (4) temperature conditions are presented in Table 3.2.P.3.5-1 (Maximum temperature recorded was (b) (4) for a (b) (4) duration).

Summary results from the performance qualification are shown in Table 3.2.P.3.5-2. The monitor data demonstrated that the shippers performed within the -90°C to -60°C temperature range. The lowest recorded temperature between the three shipments was (b) (4) and the highest was (b) (4).

OQ of the Passive Thermal Conveyance with Phase Change Material (b) (4)
A chamber test performed with a minimum load and maximum volume strategy simulating worst-case temperature conditions and shipping durations demonstrated the thermal conveyance is capable of maintaining (b) (4) . Results for the (b) (4) temperature conditions are presented in Table 3.2.P.3.5-3. Additional OQ studies and PQ studies are planned.

Qualification of the Frozen Temperature Controlled Vehicle (TCV)
DP manufacturing facilities may ship BNT162b2 DP in its final packaging to Logistics Centers and distribution sites for temporary storage and deconsolidation via -20°C ±5°C TCV).

OQ testing was performed (b) (4)

Qualification of TCVs for transport from manufacturing sites in the US to Logistics Centers and distribution sites in the US and for transport from manufacturing sites in the EU to Logistics Centers and distribution sites in the EU are ongoing.

> **Reviewer's comment:** *In BLA 125742/0.24 Pfizer stated that all shipments of BNT162b2 DP will be continuously temperature monitored to confirm that the appropriate temperatures are maintained via passive thermal conveyance in the TCV.*
>
> *In addition, Pfizer clarified that they have not yet started shipping using the* (b) (4) *controlled shipping method from either Pfizer Puurs or Pfizer Kalamazoo and qualification studies are expected to be completed by November 2021. Pfizer also stated they will provide results of these studies prior to implementation.* (b) (5), (b) (7)(E) *The studies supporting the shipping method and transport were on-going at the time of BLA approval.*
>
> *The shipping information appears acceptable.*

Simulated Shipping Study (exposure to (b) (4))
A simulated shipping study was performed to simulate realistic shipping conditions that expose representative product to concurrent shipping hazards based on (b) (4)

(b) (4) standards. After exposure to simulated distribution hazard conditions, samples were evaluated for CCI and DP quality to determine the physical and chemical stability of the product in its primary container.

The simulation included (b) (4) Results are shown in Table 3.2.P.3.5-11 in the BLA. and indicate that container closure integrity was maintained during shipping simulations.

> ***Reviewer's comment:*** *Container closure integrity testing is performed on samples that were exposed to worst case shipping hazards. All samples tested were integral. Therefore, the hazards of routine shipping do not appear to impact the integrity of the container closure system. The shipping hazards were performed to mimic the global supply chain shipping logistics as a worst-case scenario. The information appears acceptable.*

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Pfizer lists (b) (4) quality attributes (QATs) as specifications for BNT162b2 DP (tested at release and throughout shelf life). DMPQ performs primary review of CCIT. The analytical methods used by Pfizer are (b) (4) analysis. Refer to 3.2.P.5.3 for more information.

3.2.P.5.3 Validation of Analytical Procedures (Container Closure Integrity Testing)

(b) (4) is Pfizer's standard CCIT method for routine testing (at T_0, (b) (4) months) on stability lots. Separate 3.2.P.2 Microbiological Attributes documents were provided for both the Puurs and Kalamazoo sites.

According to Pfizer, the original validation of the (b) (4) test method verified (b) (4)

At Kalamazoo, Pfizer performs the (b) (4)

At Puurs, Pfizer performs the (b) (4)

Acceptance criteria for the (b) (4) test method consist of the following:

(b) (4)

For the (b) (4) test method, the challenge consisted of (b) (4)

***Reviewer's comment**: CCIT validation incorporated worst-case capping and shipping conditions. The CCIT method at Pfizer Kalamazoo appears consistent with standard industry methods. Pfizer reports that the CCIT method at Pfizer Puurs is validated, but the method appears less than optimal with the* (b) (4) *positive control and* (b) (4) *analysis. An IR was sent for further evaluation of the* (b) (4) *method validation protocol, summary*

report and assay performance procedure that is followed at Pfizer Puurs and Pfizer Kalamazoo. In amendment 125742/0.43, Pfizer states that Pfizer Puurs is not currently registered as a site for CCIT for DP stability. Protocol #CCT-052421-R0-JJB provides documented evidence of the transfer of the CCIT (b) (4) Test (Test Method TM100010635) from the Pfizer Andover, MA site to the Pfizer Kalamazoo, MI site. The test method at the Pfizer Kalamazoo, MI site is now identified as TM-01-9305A / MCD-086951. TM100010635 was evaluated, see section 3.2.R. The information appears acceptable.

3.2.P.5.4 Batch Analyses

The Batch Analysis section reflects the global development effort and the DP lots included are not limited to those produced in market-specific registered manufacturing facilities. In the submission, in Table 3.2.P.5.4-1, Pfizer listed (b) (4) batches that were identified as non-clinical (the first batch produced in March 2020), clinical or emergency supply. Of those (b) (4) batches, (b) (4) batches support either stability, PPQ, or both. From that list, Pfizer identified the following batches (total of (b) (4) at the respective DP facilities) that support PPQ (or process validation) and/or stability, as indicated, for the BLA:

DP Lot #	Manufacture Date	LNP Site	DP Fill / Finish Site	# Vials	On Stability (yes/no)
(b) (4)		Puurs	Puurs	(b) (4)	Yes
		Puurs	Puurs		Yes
		Kalamazoo	Kalamazoo		Yes
		Puurs	Puurs		Yes
		Puurs	Puurs		No
		Puurs	Puurs		Yes
		Kalamazoo	Kalamazoo		Yes
		Puurs	Puurs		No
		Kalamazoo	Kalamazoo		No
		Kalamazoo	Kalamazoo		No
		Kalamazoo	Kalamazoo		Yes
		Puurs	Puurs		No

The analytical testing strategy applied to BNT162b2 DP has evolved throughout the development history. Pfizer reports that all of the PPQ batches were tested against (b) (4) quality attributes, including, those tests under DMPQ purview with acceptance criteria defined the same as in 3.2.P.5.1 Specifications, appearance, appearance (visible particulates), (b) (4), vial content (volume), bacterial endotoxin, and sterility.

Pfizer provided summaries of the results in tables in the submission for all prementioned batches. Pfizer reports that all results met the acceptance criteria (AC) at the time of release.

***Reviewer's comment**: Pfizer reports no out-of-specification (OOS) results for appearance, appearance (visible particulates), (b) (4), vial content (volume), bacterial endotoxin, or sterility at release for any of the PV or additional PPQ batches. All the PV batches ((b) (4) for Kalamazoo and (b) (4) for Puurs) are accounted for in the batch analysis. The AC for the quality attributes, under DMPQ purview, did not change from the reported commercial AC (specification). Evaluation of the results and AC, including analytical method evolution, for the other (b) (4) quality attributes is deferred to the OVRR reviewer. Pfizer did not include CCIT results in the batch analysis; however, Pfizer reports that CCIT is tested at release and stability at (b) (4) months. No CCIT failures were reported. The information provided appears acceptable.*

3.2.P.7 Container Closure System

Pfizer provided separate 3.2.P.7. Container Closure System documents for the Puurs and Kalamazoo facilities, respectively.

The primary container closure system for the BNT162b2 vaccine consists of the following components:

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

Vial (Product Container)

The vial consists of a clear and colorless Type I borosilicate glass vial with a 2 mL nominal fill volume and 13 mm finish (lip/flange) diameter. Pfizer reports the following vial manufacturers (suppliers):

Vial Manufacturer	Vial used at Pfizer site:
(b) (4)	Puurs
	Puurs
	Puurs
	Puurs
	Puurs
	Kalamazoo
	Kalamazoo
	Kalamazoo
	Kalamazoo
	Kalamazoo

Pfizer reports that the vials from all the manufacturers have the same materials of construction and critical dimensions, and the vials from each supplier are considered equivalent in terms of processability, container closure integrity and DP interaction. The

vial meets (b) (4) requirements for Type I glass containers. The vials are sterilized by (b) (4) by Pfizer at each DP facility.

Pfizer reports the same dimensions for vials from all suppliers as follows:

Measurements	Limits
Finish Outside Diameter	(b) (4)
Finish Inside Diameter	
Finish Lip Height	
Body Outside Diameter	
Overall Height	

The testing performed on the vials at the DP manufacturing sites is as follows:

Test	Requirements
Visual Inspection	Performed per (b) (4)
Physical Inspection	Performed per (b) (4)
(b) (4) Type I Glass tests	Manufacturer's certification per (b) (4)

Vial Stopper

The elastomeric closure is a vial stopper composed of (b) (4) gray bromobutyl rubber that is not manufactured from dry natural rubber (latex). The vial stopper meets the requirements of (b) (4) requirements for functional tests of (b) (4). Vial stoppers are sterilized by (b) (4) depyrogenated by Pfizer at each DP facility. Both facilities, Puurs and Kalamazoo, use the same stopper suppliers, (b) (4) .

The dimensions of the vial stoppers:

Measurements	Limits
Height	(b) (4)
Plug Outside Diameter	
Flange Thickness	

Stopper Functional Properties:

For functional properties, Pfizer performed testing as follows:

(b) (4)

(b) (4)

The testing performed per (b) (4) on the vial stoppers is:

- Visual Inspection
- Dimensional testing
- Identification of (b) (4)

Vial Seal (Cap)

The vial seal is a 13 mm flip-off design constructed of aluminum with a PP tamper-evident flip-off vial seal that has no embossing. For both facilities, Pfizer Puurs and Pfizer Kalamazoo, the cap is supplied by (b) (4) and, for Kalamazoo only, (b) (4) is included as an additional supplier.

Pfizer reports the dimensions for seals as follows:

Description	Limits
Flip-Off Cap Diameter	(b) (4)
Seal Inner Diameter	
Overall Height	

The testing performed per (b) (4) on the vial seal is visual and physical inspection.

Secondary Packaging Components
DP vials are placed into corrugated boxes with lids.

3.2.A APPENDICES
3.2.A.1 Facilities and Equipment

PFIZER, INC., CHESTERFIELD, MO (USA): (b) (4)
MANUFACTURING AND DS/DP RELEASE AND STABILITY TESTING

(b) (4)

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

Utilities Pfizer Chesterfield

Critical utilities include purified water (PW), clean steam, compressed air, (b) (4) . The water system has been qualified to meet (b) (4) requirements; furthermore, the (b) (4) PW is routinely sampled and tested to meet chemistry and microbial limits of (b) (4) .

***Reviewer's comment**: Pfizer Chesterfield PW is routinely sampled and tested to meet* (b) (4) *standards.* (b) (4) *The information appears acceptable.*

Heating, Ventilation, and Air Conditioning Pfizer Chesterfield

There are (b) (4) air handling units that supply conditioned air to the BNT162b2 (b) (4) production areas. Air handling units (AHU) (b) (4) provide 100% filtered outside air with (b) (4) to (b) (4) (ISO-(b) (4)), where the (b) (4) were manufactured and the (b) (4) is performed. (b) (4) provides 100% filtered outside air with (b) (4) and clean preparation areas (non-classified). (b) (4) provides 100% filtered outside air with (b) (4) manufacturing suite for BNT162b2. While the manufacturing area is classified as (b) (4), the supply air is high efficiency particulate air (HEPA) filtered to minimize the introduction of environmental contaminants. Qualified (b) (4) provide additional environmental control.

***Reviewer's comment:** Pfizer provided the AHUs that service all BNT162b2 manufacturing areas, and there is* (b) (4) *within these rooms. Pfizer Chesterfield has updated the level of control by* (b) (4) *of supply air to the manufacturing areas. The* (b) (4) *step is the beginning of the BNT162b2 manufacturing process with* (b) (4) *steps in the subsequent DS and DP manufacturing operations. This information appears acceptable.*

Environmental Monitoring Pfizer Chesterfield

The (b) (4) Suite (b) (4) environmental monitoring (EM) qualification served as justification for the routine EM program, EM frequencies, acceptance criteria (alert and action levels), and facility environmental control procedures. EM parameters were conducted both at rest and in operations.

Controlled, classified areas ((b) (4), ISO (b) (4), and ISO (b) (4)) are monitored for (b) (4). Applicable standard operating procedures (SOPs) contain summaries of the EM tests performed,

frequencies, and alert/action levels. EM trend reports are generated on a (b) (4) basis to evaluate adequacy of environmental controls and quality levels.

(b) (4) action levels are provided in Table 3.2.A.1-2 in the submission, and (b) (4) action levels are provided in Table 3.2.A.1-3 in the submission (combined below).

(b) (4)

(b) (4) monitoring action levels are provided in Table 3.2.A.1-4 in the submission (duplicated below).

ISO Class	Action Level
(b) (4)	

(b) (4) air and personnel monitoring action levels are provided in Table 3.2.A.1-5 in the submission (duplicated below).

Sample Type	Action Level
(b) (4)	

Reviewer's Comment: *EM is performed routinely. The* (b) (4) *acceptance criteria appear appropriate for upstream production. The information appears acceptable.*

Contamination and Cross Contamination Controls Pfizer Chesterfield

General contamination controls include: (b) (4)

Additional microbial controls include: (b) (4)

(b) (4)

Reviewer's comment: *Cross-contamination and microbial controls designed to minimize contamination from multiple sources including people, product, equipment, waste, and environment appear acceptable.*

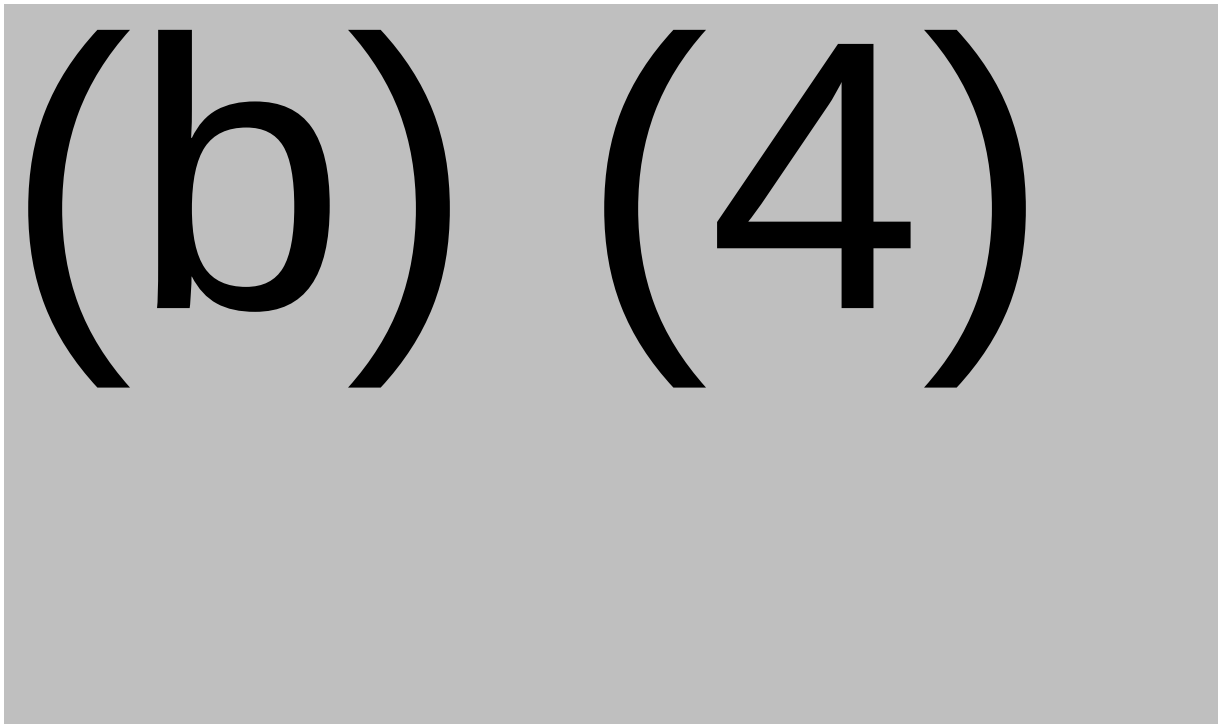
Equipment Summary Pfizer Chesterfield

This section contains an overview of the process equipment, equipment qualifications, and the equipment cleaning and sanitization (if applicable) for the equipment used to manufacture the (b) (4) at Pfizer Chesterfield. Prior to use for BNT162b2 (b) (4) manufacturing, all critical equipment underwent an equipment verification process to verify that equipment is properly calibrated, maintained, and deemed fit for use in manufacturing.

(b) (4)

(b) (4)

One page has been determined to be not releasable: (b)(4)



The information appears acceptable.

Equipment Cleaning Validation Pfizer Chesterfield

All equipment utilized in the CMF for (b) (4) manufacturing is either single-use or dedicated. All dedicated equipment undergoes a complete (b) (4) to use, is thoroughly cleaned and sampled to ensure no product carryover prior to use. Components on each piece of equipment that control parameters that could potentially impact product quality are calibrated prior to use and maintained on a calibration schedule.

The production equipment is regularly cleaned per site procedures. Fixed equipment is cleaned using the (b) (4) or per the appropriate SOP ((b) (4)). Portable equipment, such as (b) (4) in a parts or glass washer. In general, (b) (4) procedures consist of (b) (4) are used as cleaning agents. All final rinse steps utilize (b) (4) .

Equipment cleaning validation was performed during routine processing. Samples were collected in accordance with approved site procedures. The results of the cleaning validation (Table 3.2.A.1-3 through Table 3.2.A.1-12) were provided in the submission (summarized below).

One page has been determined to be not releasable: (b)(4)

Reviewer's comment: *Acceptance criteria were met for all equipment for which cleaning validation results were provided.* (b) (4)

[redacted]

The information provided appears acceptable. However, during the execution of the cleaning validation, fifteen deviations were encountered, (b) (5), (b) (7)(E)

[redacted]

Disinfectant Effectiveness Pfizer Chesterfield

The effectiveness of the various disinfectant agents used against microbial isolates recovered from the manufacturing areas, as well as (b) (4) test organisms have been evaluated following (b) (4) guidance. The effectiveness of general and sporicidal disinfectants was determined using a minimum (b) (4) reduction for vegetative bacteria and yeast and effectiveness of sporicidal disinfectants was determined using a minimum (b) (4) reduction for spore-forming bacteria and mold.

Reviewer's Comment: *The sponsor stated that the disinfectant efficacy study was performed using* (b) (4) *methodology and with* (b) (4) *microorganisms. The study was not provided as part of the BLA. The study INX100155064, a general summary report of disinfectant efficacy study performed at other FDA approved/licensed buildings was reviewed as part of the EUA and found acceptable. Additionally, facility cleaning SOP-MG-05206 was reviewed as part of the EUA and found acceptable. The qualification of the cleaning efficacy study for CPF appears to be low risk given the operations performed and the compliance history of the site. The information provided appears acceptable.*

WYETH PHARMACEUTICALS LLC, ANDOVER, MA (USA): DRUG SUBSTANCE MANUFACTURING AND DS/DP RELEASE AND STABILITY TESTING

<u>Pfizer Andover Clinical Manufacturing Facility (ACMF)</u>

ACMF, located in Building (b) (4) is a new multi-product building that commenced manufacturing operations in March 2019 and is intended to manufacture DSs for

various clinical products. Building (b) (4) is part of the Pfizer Andover campus that includes other production facilities and laboratories that have been inspected numerous times by the FDA. ACMF is managed by Pfizer Biotherapeutics Pharmaceutical Sciences and is operated under Pfizer Global Quality Standards and Pharmaceutical Sciences Quality procedures. ACMF has experience with similar routine manufacturing operations (including (b) (4)) for other biological products.

ACMF has (b) (4) separate cleanroom production suites. Production suites consists of (b) (4) suites ((b) (4)) and (b) (4) suites ((b) (4)). Suite (b) (4) is dedicated for the manufacturing of BNT162b2. Suite (b) (4) is located on the (b) (4) floor and solutions preparation and support are also located on the (b) (4) floor.

The facility layouts for the (b) (4) floor were provided in Section 3.2.A.1: Andover ACMF General Facility Layout Building (b) (4). Both Suites (b) (4) are equipped with personnel air locks (PAL), material air locks (MAL), and waste air locks (WAL). Suite (b) (4) includes an (b) (4) Suite (b) (4) contains a (b) (4) . Between the suites is a (b) (4) suites contain (b) (4) (ISO-(4)). Solution preparation is performed on the (b) (4) floor (ISO-(b) (4)) and weighing and dispensing (ISO-(b) (4)) is on the (b) (4) floor.

The production suites are supported by process operations support, validated utilities, controlled warehousing for receiving and storage of raw materials and supplies, and shipping of materials. Critical utilities (compressed air, clean steam, and PW) are generated in Building (b) (4). However, (b) (4) are supplied from bulk (b) (4).

The ACMF facility, equipment, and utility systems are supported by preventive maintenance and calibration programs. It is also designed for segregation and unidirectional flow of personnel, equipment, materials, samples, product, and waste.

Heating, ventilation, and air conditioning (HVAC) air filtration and pressurization create different zones (classification), and the EM system ensures that the appropriate cleanliness and segregation is maintained for manufacturing. Temperature is set at (b) (4) for manufacturing areas and is monitored and alarmed. (b) (4) is monitored in the manufacturing areas. To mitigate cross-contamination risks, all open processes are performed in (b) (4), and most operations are performed using (b) (4) systems.

Additionally, ACMF associated Analytical Research and Development (ARD) labs will be used for DS and DP release and stability testing. The ARD laboratories located in Building (b) (4) consists of newly designated BNT162b2 mRNA vaccine laboratory spaces, located within and alongside the pre-existing ARD laboratory areas and systems. Pfizer ARD laboratories in Andover and Chesterfield operate as one organization under one

set of procedures, documentation systems and following the same Pfizer Quality standards.

Facility Flows
Procedures ensure appropriate flows, personnel gowning, and sanitization of the facility and equipment. Flows within the facility are described below.

Access Control and Personnel Flow: All facilities are access-controlled and gowning procedures are supported by defined hygienic measures and guidelines. Increased gowning is required based on operations performed in the manufacturing areas. To reduce the risk of product contamination and provide personnel protection, personnel and material entry into separate manufacturing areas are segregated.

Product Flow: All raw materials are released by the Quality group and are weighed and dispensed into closed, labeled containers. Solution preparation occurs in classified processing areas where solutions are batched and packaged according to master records. Prepared solutions are transported to Suite (b) (4) .

Material and Equipment Flow: Fixed, stainless steel (SS) equipment is (b) (4) per validated automation control and approved instructions. Clean and soiled mobile equipment is staged in separate designated areas within ACMF. Mobile equipment is transferred to and from the production suites and support areas via Controlled Not-Classified corridors and elevator, and non-classified service corridors per approved instruction. Separate paths exist for the flow of clean and soiled equipment.

All process equipment utilized in the BNT162b2 DS process is (b) (4) and introduced into Suites (b) (4) via the MALs. Once in the suite, the equipment is prepared for processing through final cleaning and set up with disposable components. After manufacturing is complete, the single use equipment is disconnected and discarded as waste. Any non-disposable product contact equipment is (b) (4).

Waste Flow: Waste is placed into closed containers prior to transfer. Hazardous waste is appropriately labeled and transferred through the area's waste airlocks.

> ***Reviewer's comment:*** *A general overview of BNT162b2 DS manufacturing areas was provided. The facility appears suitable sized and adequately designed to manufacture BNT162b2 DS. All manufacturing areas are access controlled, and diagrams for personnel, samples, product and product intermediate, consumable materials, equipment, and waste flows were provided. Flow patterns do not appear to present unnecessary challenges that could potentially introduce contaminants during manufacturing.*

Media and Buffer Preparation Area:

(b) (4)

Reviewer's Comment: *From the descriptions provided, the buffer and equipment preparation areas appear acceptable.*

Utilities ACMF

Critical utilities include WFI, clean steam, and compressed air. The WFI storage (b) (4)

Clean steam is generated via (b) (4)

Compressed air is generated by (b) (4)

(b) (4)

Reviewer's comment: *The critical utilities of WFI, clean steam, and compressed air were described in general terms. The qualification of the utilities for ACMF appear acceptable.*

Heating, Ventilation, and Air Conditioning ACMF

Building (b) (4) HVAC systems are designed to provide air volume, air flow, HEPA filtered air, and room pressurization. The supply air processed by the HVAC units is delivered through HEPA filtration. The manufacturing areas were designed to minimize the possibility of product contamination by using separate air handling units, pressure differential zones, air locks, gowning rooms, and defined flows for personnel, equipment, materials, and waste.

Temperature is set at (b) (4) for manufacturing areas and is monitored and alarmed. (b) (4) is monitored in the manufacturing areas. To mitigate cross-contamination risks, all open processes are performed in (b) (4) , and most operations are performed using (b) (4) systems.

The air handling units supporting BNT162b2 DS manufacture are listed in Table 3.2.A.1-2 in the submission (duplicated below).

(b) (4)

The HVAC system has been qualified, demonstrating that the system operates to design specifications and maintains the facility within design parameters. Qualification tests the system's ability to provide required air changes, pressurization, temperature, and relative humidity in the production areas. Rooms were monitored for (b) (4) . The integrity of the HEPA /(b) (4) filters were verified and certified.

Differential pressures are maintained and monitored between adjacent spaces, and (b) (4) . Additionally, temperature is

monitored and alarmed throughout the facilities and relative humidity is monitored within the ISO Class (b) (4) manufacturing areas.

> ***Reviewer's comment:*** *The HVAC system has been qualified and maintains ISO-(b)(4) and ISO-(b)(4) manufacturing areas. Pfizer clarified that each manufacturing suite and buffer preparation area has a dedicated air handling unit to mitigate any risk of cross contamination, and provided the diagrams showing the different air handling units for Level (b)(4) and Level (b)(4). The room classifications, temperature, relative humidity, and gowning are appropriate for the operations performed in each area. While the qualification of the HVAC system in Building (b)(4) was not provided in the BLA, qualification of the HVAC system in approved/licensed buildings at the Andover site have been observed/assessed during previous FDA inspections. The HVAC systems appear acceptable.*

Environmental Monitoring ACMF

ACMF EM qualification of classified areas served as justification for the routine EM program, EM frequencies, acceptance criteria (alert and action quality levels), media types, incubation, maximum personnel room capacity and facility environmental control procedures. EM was conducted both at rest and in operation, and included (b) (4) . At rest is defined as the status of the facility with all services functioning, standard processing equipment installed, and with no personnel or manufacturing activities being performed other than EM. Unlike at rest, the definition of in operation includes routine personnel and production-related activities being performed or simulated. A facility is in operation status from the time of the (b) (4) .

Controlled, classified (ISO-(b)(4), ISO-(b)(4), and ISO-(b)(4)) areas are monitored for (b) (4) . Summaries of the EM tests performed, frequencies, and alert/action levels are found in the applicable SOPs. Trending of EM is generated (b) (4) to evaluate adequacy of environmental controls and quality levels.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comment: *EM is performed routinely. In Amendment 125742/0.43, Pfizer clarified the definition of at rest and in operation, which have been incorporated into the EM narrative above, and that the* (b) (4) *limits are applicable for both at rest and in operation monitoring. The EM program appears acceptable.*

Contamination and Cross-Contamination Controls ACMF

Suites (b) (4) are campaign dedicated to manufacture BNT162b2. Cross contamination controls include use of (b) (4) . All equipment are cleaned, and nondedicated product contact equipment are changed over

between uses for different products. In campaign dedicated areas, a clearance of product, components, documentation, and equipment must be performed with an area inspection at the end of the campaign. Surfaces and equipment exteriors are cleaned according to approved procedures, and procedures are in place for special sanitization activities in response to EM excursions or breaches in normal environmental controls. Routine EM is performed to ensure that room classifications are maintained.

Environmental controls are maintained via HVAC design and control, procedural controls for gowning and flow, and facility and equipment surface sanitization. (b) (4) are used for non-critical operations (sample aliquoting) and critical operations, such as making (b) (4) .

Procedures for labeling, flow, storage, and use of materials and equipment are established to avoid potential mix-ups or cross-contamination in manufacturing areas. Product processing takes place in areas that are product dedicated on a campaign basis. In campaign dedicated areas, a clearance of product, components, documentation, and equipment together with an area inspection at the end of the campaign provides assurance that no batch specific materials or documents remain, and that the area may be used for the manufacture of a different product.

Control and Cross-Contamination Controls are summarized below.
Contamination from other products: Operations take place in areas that are dedicated for use with a single product on a campaign basis, with a documented changeover cleaning verification and clearance between uses for different products. All solutions and materials required for operations are specified in approved procedures and production records. Product and non-product solutions are transferred in portable bioprocess containers. All product and non-product solution containers are identified according to description, batch number, and storage conditions.

Contamination from equipment: Status of fixed equipment is indicated and tracked by validated automation control, and the status of non-fixed equipment is indicated in accordance with approved labeling procedures. Clean and soiled equipment are stored closed, in separate designated areas within the manufacturing suites, and have separate flow paths. Procedural and validated automation controls exist to ensure that equipment is only used with its designated product. In addition, single use technology is utilized within the facility for many product processing operations.

Contamination from people: Gowning procedures are designed to minimize contamination and cross-contamination. Gowning is appropriate for the operations. Gowns are changed when damaged or soiled, and discarded upon exiting each production area. Gloves are changed between working with different products within the facility. Fresh, pre-sterile, single use gowning is required prior to performing open operations in the bulk fill room. Personnel monitoring is conducted per site procedures.

Contamination from system failures: Environmental controls for parameters such as differential pressure, temperature, and relative humidity controls are continuously

monitored and alarmed. Critical equipment and systems are powered by emergency back-up power systems. Critical control systems are on uninterrupted power supply to allow continuous operation during power outages. Site procedures exist for disaster recovery and response to unplanned system failures of monitoring systems and environmental control systems.

Contamination from Waste: Liquid process waste is disposed through the facility waste system, which is equipped with (b) (4) . Liquid waste is treated and discharged in accordance with local and state regulations. All solid waste is removed from the facility on a routine basis. Procedures exist for handling and disposal of biohazardous waste in dedicated, single-use containers. Hazardous chemical waste is removed from the manufacturing areas on a regular basis in accordance with approved procedures. Procedures exist for routine facility cleaning, sanitization, and spill response for containment and remediation of process spills.

The product changeover program is a procedural approach for providing assurance that potential cross-product contamination from one manufacturing process to the next does not occur. The Quality group reviews and approves the changeover documentation.

All product processing areas or systems undergo a product clearance after completion of a product campaign. These area product clearances are performed and documented by trained personnel in accordance with approved procedures and physical inspection of the area. Execution of product clearance is documented in cGMP records, which are reviewed and approved by manufacturing and quality as part of the changeover approval process.

> ***Reviewer's comment:*** *Cross-contamination controls are designed to minimize contamination from multiple sources including people, product, equipment, waste, and environment and appear acceptable. EM is performed in all classified areas, and action and alert limits appear acceptable.*
>
> *In Amendment 125742/0.43, Pfizer clarified the ACMF suites ((b) (4)) are segregated manufacturing suites that were not used for any product prior to BNT162b2 DS manufacturing. The suites and product contact equipment used for BNT162b2 are dedicated to the production of BNT162b2. No other product is manufactured in the ACMF suites or used with the dedicated equipment, and production of BNT162b2 in ACMF is ongoing with no plans to change-over to another product.*

Equipment Summary ACMF

This section contains an overview of the process equipment, equipment qualifications, and the equipment cleaning and sanitization (if applicable) for the equipment used to manufacture the DS at Pfizer Andover.

Critical Process Equipment:

One page has been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Equipment Qualification ACMF

All equipment used in the manufacturing process and equipment preparation meet specific requirements and are qualified for their intended use. Equipment qualification is performed for new equipment or changes to existing equipment. Installation qualification (IQ) and OQ provide evidence that the equipment/systems are installed and consistently operate in accordance with design and pre-defined acceptance requirements. The routine calibration frequency is defined in the qualification report. The PQ demonstrates that equipment or systems will consistently perform per pre-determined acceptance criteria.

(b) (4)

(b) (4)

Equipment Cleaning Overview ACMF
The product contact equipment and parts used for BNT162b2 are single use or campaign dedicated and cleaned using validated procedures.

Cleaning Procedures:
The production equipment is regularly cleaned by (b) (4) (fixed equipment) or (b) (4) (portable equipment, hoses, etc.). Both (b) (4) consist of (b) (4) Monitoring of the cleaning processes during routine production is performed via testing for (b) (4)

Cleaning Validation Overview:
Cleaning validation is performed to demonstrate that the intended cleaning procedure is efficient and can consistently remove residual product, (b) (4) . (b) (4) of equipment and (b) (4) is applied during

cleaning validation, where appropriate. Sample plan and locations (based on most difficult to clean and representative locations) are defined in the cleaning validation protocol and procedures and specific to equipment being cleaned. Cleaning verification is performed when cleaning validation is in process or is not in place. Cleaning verification sampling will be performed on any batches not being sampled for cleaning validation.

Cleaning validation will be performed for the (b) (4) . No product contact parts are washed in the parts washer. Product contact small parts ((b) (4)) are cleaned via (b) (4) cleaning procedure in suite. The procedure includes a (b) (4) .

Cleaning validation consists of the following:

(b) (4)

Post cleaning validation, periodic cleaning verification (based on risk approach) is performed to provide ongoing assurance regarding the state of control of validated cleaning procedures.

> ***Reviewer's comment:*** *A description of the BNT162b2 manufacturing equipment was provided. Cleaning verification is performed if cleaning validation is not performed, as in the case of small product contact items and hoses cleaned manually via* (b) (4) *. The cleaning validation plan appears acceptable.*

Cleaning Validation information
Cleaning validation was performed on only the (b) (4) is product dedicated, and the (b) (4) The acceptance criteria are found in the table below

(b) (4)

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Disinfectant Effectiveness ACMF

The effectiveness of the various disinfectant agents used against microbial isolates recovered from the manufacturing areas, as well as (b) (4) test organisms have been evaluated following (b) (4) information chapter. The effectiveness of general and sporicidal disinfectants was determined using a minimum (b) (4) reduction for vegetative bacteria and yeast and effectiveness of sporicidal disinfectants was determined using a minimum (b) (4) reduction for spore-forming bacteria and mold.

Reviewer's Comment: *The sponsor stated that the disinfectant efficacy study was performed using* (b) (4) *methodology and with* (b) (4) *microorganisms. The disinfectant efficacy study appears acceptable.*

Computer Systems ACMF

The critical steps in BNT162b2 drug manufacturing include (b) (4), which use equipment with automated control by computer systems that are identified in the table below.

(b) (4)

The systems have local control using programmable logic controllers (PLCs) that are part of the overall automation strategy. The Supervisory Data and Collection (SCADA) component of the automation provides an operator interface and a means to collect and archive data in the (b) (4).

ACMF uses (b) (4) to control and monitor equipment. The validation activities of (b) (4) and associated PLCs included installation/operational qualification (IOQ), which were completed and approved by quality assurance and summarized in (b) (4) Qualification Report. An electronic records and electronic signature (ERES) and Data Integrity (DI) assessment of the computerized system was carried out in accordance with Pfizer's DI and Data Lifecycle Controls policy associated with data and operations. (b) (4) recipes for (b) (4) specific to BNT162b2 were approved and implemented in accordance with the change management procedure to create and modify (b) (4) recipes in ACMF. A summary of the critical steps controlled by the computer systems are described below.

(b) (4)

(b) (4)

The parameters controlled and/or monitored by the automated control systems in BNT162b manufacturing process include:

(b) (4)

Reviewer's Comment: *In Amendment 125742/0.57, Pfizer provided a list of the critical BNT162b2 DS manufacturing steps that are computer-controlled with a brief description of the validation process and parameters monitored, which have been incorporated into the narrative above. IOQ was performed according to site procedures and documented, which appears acceptable.*

Pfizer Andover Suite (b) (4)

Pfizer Andover is currently licensed for manufacturing recombinant DNA derived protein DS intermediates and DSs using (b) (4). There is no manufacturing of products containing penicillin, cephalosporins, live viruses, spore-forming organisms, or cytotoxic drugs. The categories of DS are found in Table 3.2.A.1-1 in the submission (duplicated below).

(b) (4)

Facility Overview
Building (b) (4) is a (b) (4)-story building containing manufacturing suites (b) (4), and now Suite (b) (4). Suites (b) (4) are multiproduct suites, and Building (b) (4) allows for concurrent multiproduct manufacturing, with programs and operating procedures for gowning and segregation/directional control of flows of personnel, equipment, tools, instruments, materials, samples, and waste to mitigate contamination/cross contamination. BNT162b2 DS manufacturing operations occur within Suite (b) (4).

- Suite (b) (4) is a new segregated manufacturing suite dedicated to the production of BNT162b2 created from existing Suite (b) (4). Suite (b) (4) of Building (b) (4) has been inspected by the FDA (January 2019; Voluntary Action Indicated (VAI)) and is used to manufacture other FDA approved products (b) (4)).
- Suite (b) (4) has dedicated personnel, equipment and material entrances and exits, serviced by a dedicated HVAC system.
- Suite (b) (4) design, construction, and materials of construction details are consistent with existing suites.
- All support services and utilities utilized in Suite (b) (4) are utilized by existing suites.
- All raw materials, supplies, and shipping of materials utilize the same controlled warehousing, receiving and storage as other suites.
- All facilities, process equipment, and utility systems are supported by procedure-based preventive maintenance and calibration programs utilized by the existing suites.
- All current operations in Suite (b) (4) will be consistent with the general operational and quality policies and procedures as the existing suites.

Quality Control laboratories associated with COVID-19 are located in Building (b) (4) and Building (b) (4).

The process flow diagram indicates that any open operations, consisting of aseptic connections, are performed in the (b) (4) and no open operations occur outside of the (b) (4). All components in the (b) (4), and final filtration and dispensing are (b) (4). The equipment used in the (b) (4) are dedicated and (b) (4).

Area Classifications

Areas in Suite (b) (4) used for the manufacturing of BNT162b2 are classified based on the manufacturing operations occurring in those areas. Area classifications are found in Table 3 in the submission (duplicated below).

Area Classification and Biosafety Level (BSL) for the COVID-19 Vaccine Drug Substance Manufacturing Facility

(b) (4)

Temperature and Relative Humidity

Temperature is monitored and alarmed in the raw material and solution storage areas, and manufacturing suites. The processing areas, Suite (b) (4), and solution preparation area are set to (b) (4) and monitored and alarmed at (b) (4). The raw materials warehouse is monitored and alarmed at (b) (4). All ISO-(b) (4) and ISO-(b) (4) manufacturing areas are operated and monitored within a relative humidity range of (b) (4).

Flows

Personnel Flow: Personnel flow is controlled through restricted access and signage. Personnel may not move between these areas freely but must de-gown and exit one area and enter another through the designated gowning rooms.

Product, Material, and Waste Flow: All raw materials used in Suite (b) (4) are released by the Quality group. The exterior surfaces of instruments and supplies are (b) (4) Suite (b) (4). The exterior surfaces of material containers are (b) (4) into the controlled areas of Suite (b) (4) through designated equipment and MALs. There are no transfers of process intermediates from Suite (b) (4), and in-process samples are transported in (b) (4). Drug substance is dispensed into (b) (4) within the designated areas of Suite (b) (4). (b) (4) BNT162b2 DS exits Suite (b) (4) for (b) (4) via the MALs and (b) (4) corridor. Waste is placed into closed containers prior to transfer. Hazardous waste is appropriately labeled and transferred to the suite out-lock. Waste is transferred through the area's equipment and material in/out-lock.

Equipment Flow: Process equipment is labeled with status. Fixed equipment is (b) (4). Clean and soiled, product contact mobile equipment and parts are staged in a contained fashion in separately designated areas within Suite (b) (4) and are cleaned within the suite. Non-product contact mobile equipment and small parts may be transferred to and from the Product Services Equipment Processing areas. Separate paths exist for the flow of clean and soiled equipment. All process equipment utilized in the BNT162b2 DS process are (b) (4). The equipment are introduced into Suite (b) (4) via the materials airlocks associated with each suite where the equipment are (b) (4). Once in the suite the equipment are prepared for processing through final

cleaning and set up with disposable components. After manufacturing is complete the single use equipment are disconnected and discarded as waste.

> ***Reviewer's Comment:*** *A general overview of BNT162b2 DS manufacturing areas in Suite (b)(4) is provided. All manufacturing areas are access controlled, and gowning is progressive. Diagrams for personnel, product, consumable materials, equipment, and waste flows were provided. There are different flows for clean and soiled equipment. Flow patterns do not appear to present unnecessary challenges that could potentially introduce contaminants during manufacturing. The information appears acceptable.*
>
> *Drug substance is manufactured in ISO-(b)(4) areas with DS (b)(4) in a (b)(4). The area classification appears acceptable, as the majority of the process is closed and performed in (b)(4) systems. Additionally, all open manipulations occur in the (b)(4).*

Description of Buffer Preparation Area

Buffer preparation for BNT162b2 is performed within a dedicated suite. The suite consists of (b)(4) preparation rooms ((b)(4)) that are separated by airlocks. Solutions are formulated in (b)(4)

> ***Reviewer's Comment:*** *From the descriptions provided, the buffer and equipment preparation areas appear acceptable.*

Utilities Suite (b)(4)

Critical utilities such as WFI, clean steam, and compressed air are existing utility systems in Building (b)(4). The utilities for Building (b)(4), including Suite (b)(4), have been evaluated during multiple past FDA inspections. Suite (b)(4) was made from space in Suite (b)(4) and the utilities for Suite (b)(4) were reviewed during the recent PLI of Pfizer Andover.

There were no changes to the WFI, including no additional WFI drops, or clean steam points of use due to the addition of Suite (b)(4). The WFI system has been installed, validated, and is operational for use in manufacturing commercial products in Building (b)(4). Routine sampling is performed to verify bioburden (action limit: (b)(4)) and endotoxin (action limit: (b)(4)). The system is monitored, alarmed, and trended for (b)(4) to verify the system is in a state of chemical control.

The clean steam system has been installed, validated, and is operational for use in manufacturing commercial products in Building (b)(4). Routine sampling is performed to verify that the system is in a state of control for chemical ((b)(4))

and (b) (4) and (b) (4) . Steam quality testing for the clean steam distribution system is performed for (b) (4)

> ***Reviewer's Comment:*** *The critical utilities of WFI and clean steam were described in general terms and appear acceptable.*

Compressed Air System

The compressed air system provides compressed air to various process and instrument use points in Building (b) (4) . Compressed air is produced by (b) (4) Points-of-use are equipped with a (b) (4) in product contact applications including, but not limited to, (b) (4) The compressed air distribution piping was modified to add (b) (4) additional points of use within Suite (b) (4) . The new compressed air distribution points of use were validated for (b) (4)

Compressed air is sampled from representative points and routinely tested for the (b) (4) are continuously monitored and alarmed at the compressed air sources.

> ***Reviewer's Comment:*** *Compressed air was described in general terms. Validation data were not provided for the compressed air but monitoring data from July to December 2020 were provided in the EUA (27034.76).* (b) (4) *new points of use were added to the compressed air in Suite* (b) (4) *. All samples met acceptance criteria. The information provided appears acceptable.*

Heating, Ventilation and Air Conditioning Suite (b) (4)

The HVAC systems supplying the air to the manufacturing areas in Building (b) (4) are designed to provide air volumes, air flows, HEPA filtered air, and room pressurization appropriate for the required environmental classification.

Suite (b) (4) has its own dedicated HVAC unit (HVAC (b) (4) ; Drawing A-8034902 in section 3.2.A.1). Construction of Suite (b) (4) involved (b) (4) All the make-up air consists of air drawn from outside and conditioned resulting in (b) (4) . The supply air is delivered to manufacturing areas through HEPA filters. A gowning room or air lock is located between all corridors of lower and higher classification.

The HVAC systems were designed and qualified to maintain pressure-controlled environments that are based on manufacturing operations performed in that area that

are monitored between adjacent spaces. Temperature is monitored and alarmed in the raw material and solution storage areas as well as throughout the manufacturing suites. Additionally, relative humidity in classified manufacturing areas is monitored.

HVAC Validation

The HVAC system for Building (b) (4) production areas has been validated. As part of the performance validation, all classified production areas are tested under (b) (4) conditions. Rooms were monitored for (b) (4) . The integrity of the HEPA/(b) (4) filters was verified and certified.

> ***Reviewer's Comment:*** *The HVAC system has been validated and maintains ISO (b) (4) manufacturing areas. The HVAC system for Suite (b) (4) was reviewed as part of the January 2019 FDA inspection. Manufacturing suites, Suites (b) (4), each have dedicated air handling units. The HVAC controls and segregation for each suite appears acceptable.*

Environmental Monitoring Suite (b) (4)

The existing EM program used in the classified areas within Building (b) (4) was applied to include Suite (b) (4).

EM Qualification

Area classification served as justification for routine EM program, EM frequencies, acceptance criteria (alert and action limits), media types, incubation, and facility environment control procedures. EM testing was conducted at (b) (4)

Routine EM

Suite (b) (4) has been assigned an environmental classification of ISO-(b) (4) with (b) (4) (ISO-(b) (4) air supply). (b) (4) are used for non-critical operations ((b) (4)) and critical operations ((b) (4)). Buffer preparation and autoclaving used for BNT162b2 manufacturing is performed in product service areas of Suite (b) (4) and Suite (b) (4). These areas are controlled classified manufacturing spaces with established routine EM programs. Additionally, periodic monitoring for mold and fungi is conducted with specialized media and incubation conditions for areas. The routine EM tests and action limits are found in the Table 3.2.A.1-4 in the submission (duplicated below):

(b) (4)

(b) (4)

Reviewer's Comment: *All alert and action limits appear acceptable. Action limits are appropriate for the operations performed in the* (b) (4)*.*

In Amendment 125742/0.43, Pfizer clarified the definition of at rest and in operation, which have been incorporated into the ACMF EM narrative above and apply to Suite (b) (4)*, and that the* (b) (4) *limits are applicable for* (b) (4) *monitoring. The EM information appears acceptable.*

Contamination and Cross-Contamination Controls Suite (b) (4)

Suite (b) (4) is dedicated to manufacturing of BNT162b2 and has dedicated personnel. Product contact equipment are either single use (i.e., disposable) or multi-use (i.e., reusable stainless-steel equipment) but dedicated to BNT162b2. Cross contamination controls include (b) (4) Procedures for labeling, flow, storage, and use of materials and equipment are established to avoid mix-ups and cross contamination. Batch records include a specific product code designation.

Contamination and cross-contamination controls are summarized below:

Contamination from equipment: Status of fixed equipment is indicated and tracked by validated automation control, and the status of non-fixed equipment is indicated in accordance with approved labeling procedures. Clean and soiled equipment is stored closed, in separate designated areas within the manufacturing suites, and have separate flow paths. Procedural and validated automation controls exist to ensure that equipment is only used with its designated product. In addition, single use technology is utilized within the facility for many product processing operations.

Contamination from people: Gowning procedures are designed to minimize contamination and cross-contamination. Gowning is appropriate for the operations. Gowns are changed when damaged or soiled, and discarded upon exiting each production area. Gloves are changed between working with different products within the facility.

Contamination from system failures: Environmental controls for parameters such as differential pressure, temperature, and relative humidity controls are continuously monitored and alarmed. Critical equipment and systems are powered by emergency back-up power systems. Critical control systems are on uninterrupted power supply to allow continuous operation during power outages. Site procedures exist for disaster recovery and response to unplanned system failures of monitoring systems and environmental control systems.

Contamination from waste: Liquid process waste is disposed through the facility waste system, which is equipped with (b) (4). Liquid waste is treated and discharged in accordance with local and state regulations. All solid waste is removed from the facility on a routine basis. Procedures exist for handling and disposal of biohazardous waste in dedicated, single-use containers. Hazardous chemical waste is removed from the manufacturing areas on a regular basis in accordance with approved procedures. Procedures exist for routine facility cleaning, sanitization, and spill response for containment and remediation of process spills.

> ***Reviewer's comment:*** *Cross-contamination controls are designed to minimize contamination from multiple sources including people, product, equipment, waste, and environment. EM is performed in all classified areas, and action and alert limits appear acceptable (see EM section). The information provided appears acceptable.*
>
> *In Amendment 125742/0.74, Pfizer clarified Suite (b)(4) is a segregated manufacturing suite that was not used for any product prior to BNT162b2 DS manufacturing. The suite and product contact equipment used for BNT162b2 are dedication to the production of BNT162b2. No other product is manufactured in Suite (b)(4) or used with the dedicated equipment, and production of BNT162b2 in Suite (b)(4) is ongoing with no plans to change-over to another product.*

Equipment Summary Suite (b)(4)

This section contains an overview of the process equipment, equipment qualification, and the equipment cleaning and sanitization (if applicable) for the equipment used to manufacture the DS at Pfizer Andover Suite (b)(4).

Critical Process Equipment:

(b) (4)

7 pages have been determined to be not releasable: (b)(4)

(b) (4)

The parameters controlled and/or monitored by the automated control systems in BNT162b manufacturing process in Suite (b) (4) are the same parameters in ACMF. For additional details about the controlled and monitored parameters, refer above to the ACMF Computer Systems section.

> ***Reviewer's Comment:*** *In Amendment 125742/0.57, Pfizer provided a list of the critical BNT162b2 DS manufacturing steps that are computer-controlled with a brief description of the validation process and parameters monitored, which have been incorporated into the narrative above. IOQ was performed according to site procedures and documented in reports. The information appears acceptable.*

DRUG PRODUCT MANUFACTURING FACILITY, PFIZER, KALAMAZOO, MICHIGAN

The Pharmacia & Upjohn Company LLC site located at 7000 Portage Road, Kalamazoo, MI 49001-1099, (referred to as Pfizer Kalamazoo) is a DP manufacturing site for sterile injectable products, including biological medicinal products such as human vaccines. This site has an acceptable compliance history with the FDA and recently underwent a Level 1 surveillance inspection in May 2021 which included Building (b) (4) which houses the BNT162b2 manufacturing areas. Within Building (b) (4), the (b) (4) areas are used for LNP formulation and filling of the BNT162b2 DP, respectively. The May 2021 surveillance inspection covered the licensed biological products manufactured at the site and also included the observation of the BNT162b2 DP manufacturing operations

and review of associated quality documentation. The inspection did not identify significant deficiencies and was classified as Voluntary Action Indicated (VAI).

Heating, Ventilation, and Air Conditioning Pfizer Kalamazoo

The HVAC systems are designed to provide properly filtered air with volumes, air velocities and room pressurization schemes commensurate with the required room classifications for each respective area. The manufacturing rooms with their respective grades are listed below.

Differential pressure is maintained and monitored between adjacent rooms. Room pressures are set up in (b) (4)

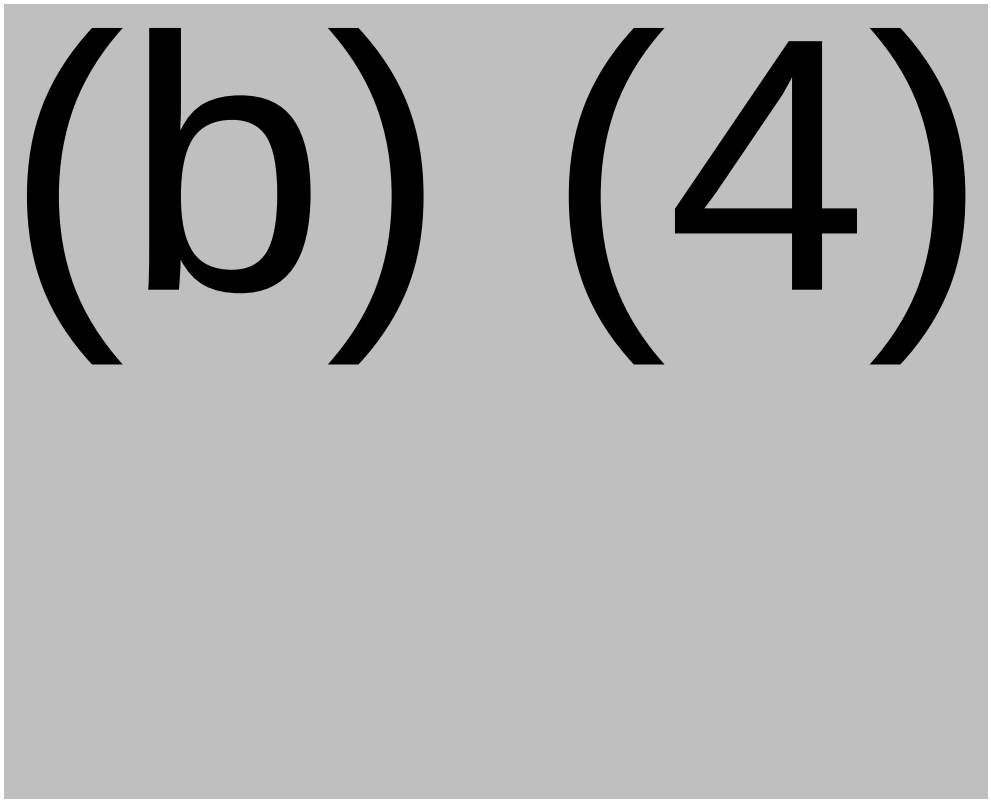
All fresh air is taken from outside, (b) (4)
AHUs that supply the cleanrooms.

HVAC systems have been qualified, demonstrating adherence to the parameters required for each respective area classification designation. Monitoring is performed for pressures, temperature, and humidity as appropriate.

- The operating temperature specification is (b) (4) in all Grade (b) (4) areas.
- Relative humidity measurements are continuously monitored in critical rooms if required ((b) (4)).
- Supply HEPA filters installation measurements show no leakage of (b) (4) of the measured upstream concentration.
- (b) (4) testing ((b) (4) testing) for Grade (b) (4) processing areas are performed.
- (b) (4) / Area Classifications were executed to monitor and evaluate the (b) (4) under (b) (4)' and (b) (4)' conditions in classified areas.
- Environmental Qualifications were also performed. As part of the qualification, all classified production areas were tested under (b) (4) conditions. Rooms were monitored for (b) (4) .

Environmental Monitoring Pfizer Kalamazoo

A facility EM program is in place to sample air, surfaces, and equipment for the presence of microorganisms. The cleaning and sanitization program is evaluated by performing microbiological surveys and reviewing and trending data to ensure the program is effective. The routine EM program is in place to detect an adverse change in microbiological conditions. Specifications for each room grade are defined as follows:



One page has been determined to be not releasable: (b)(4)

(b) (4)

All personnel entering the cleanrooms are trained and certified for the work required. The personnel monitoring program is to provide information on the type and possible sources of microorganisms that are isolated from and potentially transmitted by cleanroom personnel. Personnel aseptic technique and behavior as well as the adequacy of gowning procedures are monitored using this approach. A total of (b) (4) sites per operator are monitored including (b) (4) the sites were chosen because (b) (4) Routine personnel monitoring is conducted for all personnel who have entered the aseptic area under operational conditions at least (b) (4) per shift.

> ***Reviewer's comment:*** *The HVAC system was qualified, and EM is in place for* (b) (4) *. The recent surveillance inspection conducted by ORA/OBPO in May 2021 covered the HVAC and EM trends in Building* (b) (4) *from May 1, 2019 to May 11, 2021 and no trends were noted. The information provided in the BLA appears acceptable.*

Purified Water and Water for injection Pfizer Kalamazoo

Purified water is generated from (b) (4)

Microbial control is achieved by (b) (4)

through looped distribution piping at a rate that ensures turbulent flow and positive distribution loop return pressure during normal operating conditions. Hoses used to dispense PW and WFI are drained after use. WFI and PW are stored and distributed at (b) (4) temperatures. WFI system temperature is (b) (4) and PW system is (b) (4). The water is delivered at the use points based on user-defined temperatures.

WFI and PW water quality criteria are provided below:

WFI

(b) (4)

PW

(b) (4)

For microbial control the systems are routinely tested for (b) (4). Testing is conducted to ensure the water quality meets current (b) (4) requirements. (b) (4)

(b) (4)

Clean Steam Pfizer Kalamazoo

(b) (4) grade clean/ pure steam is prepared from (b) (4)

The clean steam (b) (4) are continuously monitored in-line. Clean steam is tested at representative test stations tested at least (b) (4) . Clean steam meets the minimum quality (b) (4) requirements for (b) (4). Additionally, the following thermodynamic properties of clean steam are tested at least (b) (4) at representative use points:

(b) (4)

Water (b) (4) are continuously monitored in-line. Water quality is also monitored by physical, chemical, and microbiological tests in conformance with applicable compendial requirements.

> ***Reviewer's comment:*** *The water systems and clean steam systems were reviewed during the recent surveillance inspection conducted by ORA/OBPO in May 2021 and no trends were noted.*
>
> *An information request was sent to Pfizer to request more information about the water quality criteria for WFI and PW as well as the water monitoring programs at Kalamazoo (STN 125742/0.57 The information is presented in the water systems sections above. The information provided appears acceptable.*

Compressed Air Pfizer Kalamazoo

(b) (4) grade compressed air is prepared from (b) (4)

Compressed air for BNT162b2 manufacture at Kalamazoo is used during the (b) (4) . The compressed air alert limit is (b) (4) . An action level is reached following an investigation of an alert limit where follow-up testing also meets or exceeds alert limits. All organisms are identified following positive tests and an action level is also reached if there is a trend identified (i.e., the organism has been identified at that sample location in the last (b) (4)). The compressed air is (b) (4) at the POU.

> ***Reviewer's comment:*** *The compressed air is a qualified utility and undergoes routine sampling. An information request was sent to Pfizer to obtain more information regarding air and* (b) (4) *usage in BNT162b2 manufacture as well as the monitoring limits which were also not provided in the original submission (STN 125742/0.57). Pfizer confirmed* (b) (4) *is not used in the manufacture of BNT162b2. The information for the compressed air appears acceptable.*

Equipment Summary Pfizer Kalamazoo

New equipment for manufacturing BNT162b2 (i.e., (b) (4)), (b) (4) freezers and ultra-low temperature storage freezers, etc.) were installed within the existing footprint of the main DP production building (Building (b) (4)). The critical equipment used in the manufacture of BNT162b2 along with the description of product contact status is presented in the table below.

Critical Equipment Used in Manufacturing of BNT162b2 at Pfizer-Kalamazoo

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

All equipment was qualified prior to use according to Pfizer. It should be noted that all product-contact equipment is either BNT162b2 dedicated or single-use.

An IR was submitted to Pfizer regarding any new product contact equipment that may have been added to BNT162b2 manufacture that was not included in the original EUA 27034 submission and to confirm all equipment is BNT162b2-dedicated (STN 125742/0.24. Pfizer provided a list of equipment and the qualification status. All equipment has been qualified and is dedicated to BNT162b2 manufacture.

An additional IR was sent to Pfizer to obtain the qualification summary documents for the operational and performance qualification (OQ/PQ) of the new equipment at Pfizer Kalamazoo (STN 125742/0.57).

Pfizer provided the release report (b) (4) *COVID Vaccine* (b) (4) *Summary System Acceptance* which was provided to confirm that verification testing was conducted on all equipment and equipment software/hardware utilized for BNT162b2 manufacture.

Pfizer stated all verification documentation was reviewed by the qualified subject matter experts and any non-conformances during qualification were addressed and resolved. All testing for each piece of equipment was provided along with whether the testing passed acceptance criteria, or a non-conformance occurred. Pfizer provided an explanation of all non-conformances and these were reviewed. Following an investigation all non-conformances were resolved.

In addition, Pfizer provided the *Release Report* and the (b) (4) *COVID Vaccine Formulation* (b) (4) *System Acceptance and Release Report* which they state is representative of all groupings of (b) (4) in terms of testing. This testing included installation and functional verification (FV). For this report (b) (4) was provided. All non-conformances were investigated and resolved.

> ***Reviewer's comment (Equipment Qualifications):*** *From the data provided, it appears all new pieces of equipment have been qualified for their intended use*

which included installation, software/hardware, and FV. Pfizer listed all non-conformances during the various qualifications and according to Pfizer all were resolved. The information provided appears acceptable.

Equipment Cleaning Validation Pfizer Kalamazoo

All product contact equipment is (b) (4) , with an automated system that uses cleaning recipes or is manually cleaned with appropriate cleaning agents. The DP stoppering parts and tank change parts are disassembled and (b) (4) in a qualified (b) (4) washer.

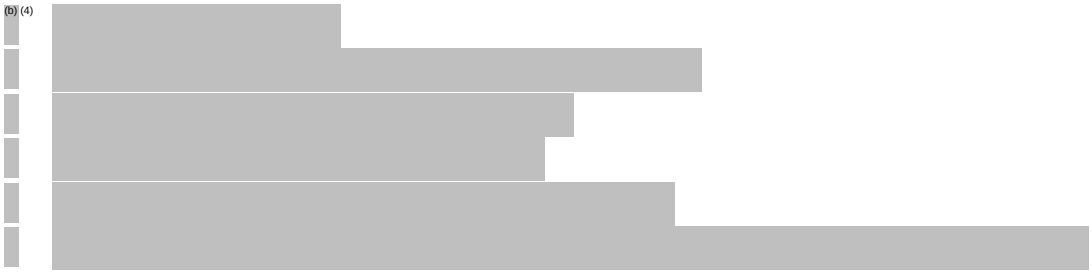
The cleaning procedure consists of the following steps:

The final rinse steps use (b) (4) and the wash steps in some cases employ the use of cleaning additives.

Cleaning validations (CV) were performed on all BNT162b2 product contact equipment. Each CV consisted of 3 consecutive successful runs using a representative or challenge material held for a defined extended DHT. Sample locations were defined as the most difficult to clean and representative of product contact locations.

Pfizer Kalamazoo provided the cleaning validation sample requirements for the various pieces of equipment used in the manufacture of BNT162b2. All equipment has a validated soiled hold time of (b) (4) except for the (b) (4) which have a soiled hold time of (b) (4) . The following bullets summarize the cleaning validation for the major manufacturing equipment:

The maximum validated CHTs for each piece of equipment are as follows:



BNT162b2(b) (4) CV Results

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

Contamination and Cross-Contamination Controls Pfizer Kalamazoo

The Building (b) (4) facility is designed as a multi-product facility and is used in the manufacture of aseptically processed DPs. All new products are evaluated for potential impact to existing products prior to introduction into the area. There is no manufacture of products containing penicillin, cephalosporin, live viruses, spore forming organisms or cytotoxic drugs. The Pfizer Kalamazoo Building (b) (4) facility is licensed as a multi-product facility.

Contamination Controls Pfizer Kalamazoo

The Building (b) (4) facility has been designed to minimize the potential of product contamination and personnel exposure using a combination of controls including pressure differential zones, airlocks, gowning rooms and defined pathways for the flow of personnel, equipment, materials and waste. Manufacturing areas are classified as Grade (b) (4) and Grade (b) (4) controlled environments and are appropriate to the operations that take place within each area. Air pressure cascades are maintained from areas of (b) (4) . A gowning room or airlock is located between all areas of lower and higher classification. A Grade (b) (4) environment is used in the aseptic filling area. Room finishes are durable, smooth and cleanable.

Site standard operating procedures (SOPs) describe the flow of materials, equipment and personnel through the facility to prevent contamination and mix-up. Procedures also ensure that appropriate storage conditions are met throughout the manufacturing process. Routine EM is performed in the aseptic area to ensure that microbial and particulate levels remain in control.

Cross-contamination Controls Pfizer Kalamazoo

Introductions of new product families, updates to manufacturing processes, and changes to the facility design or equipment are assessed via the site change management process.

The general principles to prevent cross-contamination within the Aseptic Manufacturing facility include:

- A controlled utilities system
- Validated cleaning and sanitization procedures for equipment
- Material, personnel, and waste flow controls through air locks with access controls
- Different pressure zones
- Gowning requirements
- A documented EM program for classified rooms

Contamination from other products Pfizer Kalamazoo

The following are the strategies applied to mitigate cross-contamination from other products:

- Only one lot of product is filled at a time.
- The (b) (4) facility is fully dedicated to formulation of the BNT162b2 DP.
- Production and formulation areas are regularly cleaned and sanitized as per site procedures.
- Clean and clearance procedures are in place for formulation and filling lines according to site procedures.

Contamination from Equipment Pfizer Kalamazoo

The following are the strategies applied to mitigate cross-contamination from equipment:

- Equipment is cleaned per site procedures. Cleaned and soiled equipment are identified and segregated.
- Product contact equipment and components are cleaned and either depyrogenated or sterilized via validated processes prior to use for each batch.
- Product contact tubing and hoses are either one time use and discarded after each process order or prepared for re-use using site procedures.
- Equipment is properly maintained through a preventive maintenance program.

Contamination from People Pfizer Kalamazoo

The following are the mitigation strategies:

- Personnel entering production areas require gowning training or a trained escort per site procedures.
- Site procedures adhere with CGMPs and are used for production activities.
- Personnel monitoring is conducted per site procedures.

Contamination from System Failures Pfizer Kalamazoo

The following are the mitigation strategies:

- Classified production areas and cold rooms are monitored for temperature through automated control systems, with appropriate warnings and alarms, and are maintained as per site procedures.

- Differential pressure between rooms of the same and different classifications are monitored and maintained as per site procedures.
- Recovery from a disruption to a controlled area is performed as per site procedures.

Contamination from Waste Pfizer Kalamazoo

- Production waste is disposed according to site procedures.
- Production waste receptacles are emptied and sanitized as applicable per site procedures.

Product Changeover Operations Pfizer Kalamazoo

Product changeover procedures provide a high level of assurance that potential cross-product contamination from one manufacturing process to the next does not occur. The product changeover process is executed and documented according to approved procedures that are designed to ensure that cross-product contamination risks are minimized.

Product Clearance Pfizer Kalamazoo

Product processing areas undergo a clearance process after completion of a product lot. These product clearances are performed and documented by trained personnel in accordance with approved site procedures. Successful completion of these activities provides documented evidence of control over product, product specific components, product specific documentation, and equipment between uses for processing of different products.

Disinfectant Effectiveness Pfizer Kalamazoo

The effectiveness of the various disinfectant agents used against microbial isolates recovered from the manufacturing areas, as well as (b) (4) test organisms, have been evaluated following (b) (4) guidance and (b) (4) methodology and their effectiveness of disinfection has been demonstrated on representative surfaces in the facility. The effectiveness of general and sporicidal disinfectants was determined using a minimum (b) (4) reduction for vegetative bacteria and yeast and effectiveness of sporicidal disinfectants was determined using a minimum (b) (4) reduction for spore-forming bacteria and mold.

> ***Reviewer's comment:*** *Pfizer provided flow and air classification diagrams which appear acceptable. An EM system is in place and was reviewed above. The Building (b) (4) contamination controls, cleaning and disinfectant efficacy studies were reviewed during the recent surveillance inspection conducted by ORA/OBPO in May 2021 and no issues were noted. The information provided appears acceptable to support the cross-contamination measures.*

DRUG PRODUCT MANUFACTURING FACILITY, PFIZER, PUURS, BELGIUM

The Pfizer Manufacturing Belgium NV site, located at Rijksweg 12, 2870 Puurs, Belgium (also known as Pfizer Puurs), will produce BNT162b2 Drug Product (DP), including the steps of LNP formation/Formulation Bulk DP, Fill/Finish, and Labeling and Packaging. Manufacturing areas for the commercial supply at Pfizer Puurs are located in several buildings across the campus, including:

- (b) (4) Building (which includes the (b) (4) and (b) (4), stopper processors and the (b) (4) area used for BNT162b2 production) is an existing building. The building is approved as multiproduct. (b) (4) is an existing suite that is used to formulate multiple products; however, these products are not approved in the US. (b) (4) and the (b) (4) area are existing suites that are respectively used to formulate and (b) (4) multiple US licensed products.

- (b) (4) Building consisting of (b) (4) areas, which includes the (b) (4) Vial Filling Line used for filling BNT162b2 DP. (b) (4) Vial Filling Line is an existing suite that is used to fill multiple products; however, these products are not approved in the US.

- (b) (4) Building consisting of (b) (4) and (b) (4) includes the (b) (4) and the (b) (4) filling line. (b) (4) are new suites inside the licensed facility. The vaccine building has been inspected by FDA and other regulatory agencies. The building is licensed/approved as multiproduct. (b) (4) and the (b) (4) Filling Line have been recently inspected by FDA. (b) (4) are used for LNP (b) (4) and sterile filtration of the BNT162b2 product. (b) (4) vial filling line is used for filling BNT162b2 DP.

The Pfizer Puurs facility, equipment, and utility systems are supported by preventive maintenance and calibration programs. Procedures ensure appropriate flows, personnel gowning, and sanitization of the facility and equipment. The Heating, Ventilation, and Air Conditioning (HVAC) system air filtration and pressurization create different classification zones coupled with EM to ensure appropriate cleanliness and segregation are maintained for manufacturing. To additionally mitigate cross-contamination risks, (b) (4) process steps are performed under (b) (4) in a Grade (b) (4) environment, in either a (b) (4).

Facility Description Pfizer Puurs

The DS is (b) (4) in the (b) (4) Building in Room (b) (4) which is (b) (4). LNP/Formulation activities of BNT162b2 are conducted in the (b) (4) Facility. The (b) (4) Facility is a (b) (4)-story structure, divided into a manufacturing area on the (b) (4) floor with a technical area (i.e., area used for (b) (4), etc.) and offices on the (b) (4) floor. On the (b) (4) floor, (b) (4), (Room (b) (4)), (b) (4) (Room (b) (4)) and (b) (4) (Rooms (b) (4)) are used for LNP (b) (4) /Formulation Bulk DP and

filtration of BNT162b2 (b) (4) DP. (b) (4) are in Grade (b) (4) classified areas.

The BNT162b2 DP filling takes place in a Grade (b) (4) filling line (b) (4) (Room (b) (4)), surrounded by Grade (b) (4) environment. Visual inspection of the filled product is also conducted on the (b) (4) floor in Room (b) (4) (Grade (b) (4) environment).

Buffer formulation activities and DS (b) (4) are conducted in the (b) (4) Building. The (b) (4) Building is a (b) (4)-story structure, divided into a manufacturing area on the (b) (4) floor and a technical area on the (b) (4) floor. On the (b) (4) floor, (b) (4) are used for buffer formulation. Also, BNT162b2 DS is (b) (4) area on the (b) (4) floor.

Filling and inspection are also conducted in the (b) (4) Building (Filling Line (b) (4)). The (b) (4) Building is a (b) (4)-story structure, divided into a packaging area on the (b) (4) floor, a filling and preparation area on the (b) (4) floor and a formulation and preparation area on the (b) (4) floor. The BNT162b2 DP filling takes place in a Grade (b) (4) filling line (b) (4) (Room (b) (4)), surrounded by a Grade (b) (4) environment. Inspection of the filled product is also conducted on the (b) (4) floor in Room (b) (4) (Grade (b) (4)).

Area classification drawings and flows were provided in Section 3.2.A.1 for the (b) (4) Building, (b) (4) Building and the (b) (4) Building. The production suites are supported by technical support, validated utilities, controlled warehousing for receiving and storage of raw materials and supplies, and shipping of materials. Critical utilities (clean steam, WFI, and purified water) are generated in mechanical areas and supplied to the (b) (4) Building, (b) (4) Building and the (b) (4) Building. Compressed air and (b) (4) systems are installed in the (b) (4) Building, (b) (4) Building and in the (b) (4) Building. The (b) (4) and (b) (4) are also located in the mechanical areas.

The Pfizer Puurs facility, equipment, and utility systems are supported by preventive maintenance and calibration programs. It is also designed for segregation and directional flow of personnel, equipment, materials, samples, product, and waste. Procedures ensure appropriate flows, personnel gowning, and sanitization of the facility and equipment. HVAC air filtration and pressurization create different zones (classification), and the EM system ensure that the appropriate cleanliness and segregation are maintained for manufacturing.

> ***Reviewer's comment:*** *A general overview of BNT162b2 DP manufacturing areas was provided. The room classifications appear appropriate for the operations performed in each area. All diagrams for personnel, product, consumable materials, and waste flows were provided. The flow patterns appear acceptable.*

Formulation, filtration, filling and capping Pfizer Puurs

The BNT162b2 DP solution is manufactured in (b) (4). Manufacturing (b) (4) are disassembled and cleaned using manual and/or (b) (4) procedures. The manual method is considered a back-up method to the (b) (4).

(b) (4)

Product is dispensed into containers by volume and periodically checked for fill (b) (4).

Aseptic processing is conducted using (b) (4) technology. The main function of the (b) (4) is the protection of the aseptic filling process against (b) (4) contamination by creating a Grade (b) (4) environment. This is achieved by (b) (4)

Prior to capping, (b) (4) stopper detection systems are set-up and verified to ensure rejection of improperly seated stoppers. The capping station is set-up with parameters specific to the BNT162b2 DP stopper used for the 2 mL presentation.

> ***Reviewer's comment:*** *The overview of the formulation, filtration, filling, and capping appears acceptable. See Section 3.2.P.3.5 for evaluation of individual sterilization validations.*

Utilities Pfizer Puurs

Clean Steam System

The clean steam system serving the (b) (4) Building, (b) (4) Building as well as the (b) (4) Building consists of several Clean Steam Generators (CSG). The CSG process feed water ((b) (4)) to produce clean steam. The clean steam is delivered to (b) (4) clean steam headers and distributed to the points of

use located in the clean rooms and technical areas. The CSG uses (b) (4) to prevent cross contamination from the industrial steam.

(b) (4)

The clean steam systems serving the (b) (4) Building, (b) (4) and the (b) (4) Building have been validated. The validation demonstrated that the system operates according to design specifications and maintains the system within the design parameters.

The clean steam system for the commercial manufacturing areas was designed and qualified to meet the criteria for the following attributes as specified in (b) (4) (as appropriate):

(b) (4)

The clean steam quality is monitored by routine (b) (4) sampling of the clean steam (b) (4) at least (b) (4) . Representative user points are tested on a (b) (4) basis for (b) (4) .

Water for injection System

A WFI system is installed in the (b) (4) Building, (b) (4) Building and (b) (4) Building. The water system serving the (b) (4) Building, (b) (4) Building and (b) (4) Building consists of a (b) (4)

(b) (4)

(b) (4)

The following test functions have been met for the WFI system:

- All critical controls, alarms, and indicators operate according to design specification.

(b) (4)

The WFI distribution system is sampled and tested (b) (4) for (b) (4) analysis and every (b) (4) for (b) (4) analysis. Each WFI system has inline measurements for (b) (4). All WFI points of use are routinely sampled and tested at least every (b) (4) for (b) (4) analysis. The testing is performed to current (b) (4) WFI requirements for (b) (4) analysis.

(b) (4) Compressed Air

A (b) (4) compressed air system is installed in the (b) (4) Building, (b) (4) Building as well as in the (b) (4) Building. The systems comply with the description and requirements described hereafter.

The compressed air system consists of (b) (4)

The validation demonstrated that the system operates according to design specifications.

The following test functions have been met during validation of the compressed air system:

- All of the critical controls, alarms and indicators operate per design specifications.
- System critical points of use meet the following acceptance criteria:

(b) (4)

Routine sampling is performed for (b) (4) are monitored continuously at the (b) (4) .

(b) (4)

Reviewer's comment: *Descriptions and the respective qualification/validation overviews were provided for Clean Steam, WFI, PW, compressed air, and* (b) (4) *. The descriptions provided were applicable to the* (b) (4) *Building,* (b) (4) *Building and the* (b) (4) *Building and supplied adequate detail. The acceptance criteria provided for the systems appear acceptable.*

Heating, Ventilation, and Air Conditioning Pfizer Puurs

Several HVAC systems serve the (b) (4) Building, (b) (4) Building and (b) (4) Building. Each clean room has its own recirculation unit.

The HVAC Systems serving the (b) (4) building, (b) (4) Building and (b) (4) Building consist of an arrangement of (b) (4) AHUs and a number of recirculation AHUs. The Qualified Building Information System monitors temperature, RH, and pressurization of each clean room.

All fresh air is taken from outside (b) (4) air is supplied either directly to the cleanroom or indirectly via the recirculation AHUs.

The supply air is delivered to the manufacturing areas through HEPA filters for the (b) (4) Building, (b) (4) Building and (b) (4) Building. All HEPA filters are included in an existing routine program for performance testing. The return air from the rooms is removed through return air grids. The installation is equipped with necessary airflow measuring stations; (b) (4) sensors. All classified areas are equipped with terminal HEPA filters.

The HVAC systems were designed and qualified to meet criteria that include the following:

(b) (4)

As part of the qualification, all classified production areas were tested under (b) (4) conditions. Rooms were monitored for (b) (4) .

In addition, the room pressure, temperature, and RH are continuously monitored, with control elements in the HVAC system modulated to maintain the desired parameters.

Reviewer's comment: *The HVAC systems serving the* (b) (4) *buildings used for BNT162b2 manufacturing have been qualified and maintain Grade* (b) (4) *manufacturing areas. The utilities appear acceptable. Also refer to the EM (EM) review below.*

Manufacturing Rooms Used for BNT162b2 Manufacturing Pfizer Puurs

Tables 3.2.A.1-1 through 3 summarize room locations and classification for the formulation area, buffer preparation area and support areas for equipment such as parts washers, autoclaves and stopper processors, filling lines and inspection areas used for the manufacture of BNT162b2 DP. The tables are reproduced below.

(b) (4)

(b) (4)

Equipment Summary Pfizer Puurs

This section contains an overview of the process equipment, equipment qualifications, and the equipment cleaning and sanitization (if applicable) for the equipment used to manufacture the BNT162b2 DP at Pfizer Puurs.

Qualified equipment is cleaned and dried prior to use and sterilized or sanitized when necessary. The equipment detailed in Table 3.2.A.1-4 and Table 3.2.A.1-5 (reproduced below) supports the BNT162b2 manufacturing process. The BNT162b2 manufacturing process equipment is qualified for use through installation, operational, and performance qualification (IQ, OQ, PQ) activities to demonstrate that the equipment operates according to design specifications and is maintained within its design parameters.

Product Contact Equipment/Materials Pfizer Puurs

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

Reviewer's comment: *The building locations of the major equipment to be used in manufacturing were provided for reference. The BNT162b2 manufacturing process equipment has been qualified and performance qualifications performed. The product contact equipment/materials were also provided, including the materials of construction, cleaning and sterilization/sanitization method. Most of the direct product contact equipment is dedicated or single use.*

Sterilization/depyrogenation performance qualification summaries for the product contact equipment were submitted under 3.2.P.3.5 and appear acceptable. In addition, the capper qualification summary was submitted in 3.2.P.3.5 and appears acceptable. A cleaning validation summary was submitted in 3.2.A.1 and is discussed in the cleaning validation section.

The equipment qualification and cleaning/sterilization validation studies were reviewed and appear acceptable. Further details regarding the equipment cleaning can be referenced in the cleaning validation section of this review memo.

Preparation of Equipment and Components Pfizer Puurs

Equipment is cleaned and dried prior to use and sterilized or sanitized when necessary. Cleaned and/or sterilized equipment is stored in order to prevent contamination before use.

All equipment and primary packaging components (i.e., vials and stoppers) used in the production of parenteral products, such as BNT162b2, are sterilized/ depyrogenated according to approved, validated cycles. Equipment that cannot be sterilized by these two methods is (b) (4) and enter through dedicated airlocks.

Vials

Vials are processed through (b) (4)

(b) (4)

Stoppers

The preparation of sterile stoppers is performed in the preparation areas of the (b) (4) Building or the (b) (4) Building. (b) (4)

Stopper validation (b) (4)

Product contact equipment Pfizer Puurs

Product contact line equipment parts are assembled from (b) (4) . Accessories, such as filters, etc., are assembled and (b) (4) .

Validation of (b) (4)

(b) (4)

Reviewer's comment: *The overview of the equipment preparation, cleaning, sterilization and depyrogenation provided, appears acceptable. Reference memo Section 3.2.P.3.5 for evaluation of individual sterilization validations.*

Visual Inspection Pfizer Puurs

The BNT162b2 DP vials are one hundred percent inspected for cosmetic, particulate, and other product defects using manual inspection techniques in the inspection department, an in-line automated visual inspection machine, or an off-line automated inspection line.

The automated inspection (b) (4) vial lines are qualified to inspect BNT162b2 DP vials for cosmetic, fill level and particulate defects.

(b) (4)

The automated visual inspection lines are fully automated systems that inspect filled vials for cosmetic, fill level and particulate defects. Equipment verification and performance qualification were performed to qualify the system for inspection of BNT162b2 vials.

The Installation Verification verified that the Automated Inspection Lines were installed in accordance with specifications and the intended use of the system.

The Operational Verification verified that the Automated Inspection Lines operate as defined and that the system is fit for its intended use.

The Performance Qualification (PQ) verified that the Automated Inspection Lines perform in accordance with expected quality attributes when inspecting BNT162b2 vials. The PQ consisted of the following parts:

(b) (4)

A verification run is performed at the (b) (4) in routine production (mode) to verify that the system, the set-up and the BNT162b2 Inspection Program is

capable of rejecting defective samples at 100% on the right camera. It also checks the functioning of the reject system. The purpose of this test was to verify that all samples of the verification set were rejected correctly.

PQs verified that the automated visual inspection systems could detect the following:

(b) (4)

(b) (4)

The results are summarized in Table 3.2.A.1-6, Table 3.2.A.1-7 and Table 3.2.A.1-8 of the submission.

> ***Reviewer's comment:*** *The overview of the automated visual inspection system qualification appears acceptable. The goal of the phase 1 testing was to identify* (b) (4) *. Phase 2 PQ testing focuses on batch quality control by increased AQL testing* (b) (4) *and defect trending to assess process variability at batch scale. The qualification documents reviewed appear acceptable. No concerns were noted.*

Contamination and Cross-Contamination Controls Pfizer Puurs

The (b) (4) Building is a multi-product facility dedicated for vaccine manufacturing. Formulation and filling of BNT162b2 DP is performed in the (b) (4) Building.

The (b) (4) Building and (b) (4) Building are multi-product facilities and are used in the manufacture of aseptically processed DPs. Filling of BNT162b2 is performed in the (b) (4) Building.

The introduction of new product families, updates to manufacturing processes, and changes to the facility design or equipment are assessed via the site change

management process. Site Standard Operating Procedures describe the flow of materials, equipment and personnel through the facility to prevent contamination and mix-up. Procedures also ensure that appropriate storage conditions are met throughout the manufacturing process.

Cross contamination controls include use of (b) (4)

Reviewer's comment: *Cross-contamination controls are designed to minimize contamination from multiple sources including people, product, equipment, waste, and environment. EM is performed in all classified areas, and action and alert limits appear acceptable. Performing the aseptic filling of BNT162b2* (b) (4) *Grade* (b) (4) *greatly mitigates potential microbiological contamination.*

Product contact (mRNA and LNP) BTN162b2 formulation and filling equipment is not shared with other products and is currently dedicated. The (b) (4) *filling line is used for BNT162b2 DP filling activities only.*

Environmental Monitoring Pfizer Puurs

Classified areas in the manufacturing buildings are routinely monitored for (b) (4) . Summaries of the action levels for Grade (b) (4), Grade (b) (4) and Grade (b) (4) areas are detailed in Table 3.2.A.1-8.

(b) (4) levels on (b) (4) in the (b) (4) are monitored according to site procedures. During operation, (b) (4) are monitored at the completion of the batch or campaign (if applicable) prior to (b) (4) .

Reviewer's comment: *EM is performed in all classified areas, and action and alert limits appear acceptable per review of the information in the BLA.*

The procedures describe the types of EM, sampling locations, frequency and the alert and action limits for the classified rooms. The firm performs (b) (4) *. The Grade* (b) (4) *monitoring includes* (b) (4)

(b) (4) *monitoring which is managed under an SOP.* (b) (4) *is also described per SOP. Both filling lines* (b) (4) *are equipped with a* (b) (4) *consisting of* (b) (4) *that are controlled per line by a* (b) (4) *.*

Equipment Cleaning Overview Pfizer Puurs
All the equipment and parts used in the manufacture of BNT162b2 will be cleaned using validated processes before use. Large equipment, such as tanks, are cleaned by (b) (4) methods. Small, removable, easy to disassemble equipment, may alternatively be cleaned by (b) (4) method.

The (b) (4) cleaning process generally consists of (b) (4)

Routine monitoring of the cleaning process is performed by (b) (4)
The results are held to the same requirements as those established during the cleaning validation for each applicable cleaning process and any excursions over action limits would be investigated.

Equipment Cleaning Validation Pfizer Puurs
There are two approaches taken for cleaning: 1) cleaning validation and 2) cleaning verification. A cleaning validation approach is currently being implemented for the BNT162b2 DP manufacturing process.

The equipment used for BNT162b2 is cleaned manually or automatically by trained operators. Dirty and cleaned equipment are stored in separate clean rooms to prevent cross contamination.

Prior to cleaning validation, commissioning, qualification and cleanability/development studies are performed to demonstrate, through testing, that the equipment/systems perform as designed and are able to reduce challenge material to within the predefined acceptance criteria. Cleaning validation studies consist of three consecutive, successful cleaning validation runs using a representative or challenge material.

Sample plans and sample locations are clearly defined in the cleaning validation protocols and are dependent on the equipment being cleaned. Sample locations are selected based on the most difficult to clean and representative product-contact locations. Sampling and testing are performed to demonstrate that the intended cleaning is effective, robust and consistently meets the cleaning validation requirements.

The cleaning validation execution includes the following evaluations:

(b) (4)

4 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (5), (b) (7)(E)

Facility Cleaning Overview Pfizer Puurs
Cleaning and sanitization of the facilities are performed on a regular and routine basis according to established procedures. Maximum time intervals for cleaning are established for production lines. Additionally, complete sanitizations are performed at regularly scheduled intervals. During these sanitizations, all ceilings, walls, cabinets, tabletops, partitions, etc., are cleaned and sanitized. Floors are also cleaned and sanitized. Monitoring is performed to verify the efficacy of the sanitization.

> ***Reviewer's comment:*** *An overview of the facility cleaning was provided, however, the validation demonstrating the efficacy of the cleaning agents was not provided in the BLA.*

3.2.R Regional Information (USA)

Executed Batch Records
Executed batch records were provided with this submission for filling and inspection of Lot (b) (4), LNP formulation for Lot (b) (4), and Packaging for Lot (b) (4). This information appears acceptable.

Method Validation Package
Pfizer provided Test Method TM100010635, (b) (4) Test for Container Closure Integrity Testing of Stoppered, Capped and Crimped Vials for PF-07302048 COVID-19 Drug Product.

> ***Reviewer's comment:*** *This method was reviewed. The method appears to be consistent with the summary provided in section 3.2.P.2 Microbiological Attributes and appears acceptable.*