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SUMMARY

(Written by LF)
This FY21 pre-license inspection at the Pfizer Manufacturing Belgium NV site located at Rijksweg 12, 2870 Puurs, Belgium was conducted for BLA STN 125742/0, COMIRNATY™ (COVID-19 Vaccine (BNT162b2, PF-07302048)), indicated for the prevention of COVID-19 in adults 16 years of age and older. Pfizer Manufacturing Belgium NV (also known as Pfizer Puurs) will produce the BNT162b2 drug product, including the steps of Lipid Nanoparticle (LNP) fabrication/formulation bulk drug product, fill/finish, and labelling/packaging.

The inspection was conducted from June 24 through July 2, 2021 and the inspection team included Laura Fontan (CSO/lead inspector) and Zhongren Wu (CSO) both from OCBQ/DMPQ, Anissa Cheung (CSO) from OVRR/DVP, and Susan Jackson (CSO) from ORA/OMPTO/OBPO/BPIS. The scope of the inspection covered the following systems: Quality, Facilities/Equipment, Production, Materials, Packaging/labeling, and

Laboratory Control. The inspection was performed according to eNSpect operation identification number 201736.

The previous Pfizer Puurs inspection was conducted November 9 through 16, 2017. At the end of the previous inspection, no FDA Form 483, Inspectional Observations, was issued.

During the recent inspection, no FDA Form 483, Inspectional Observations, was issued, however there were some discussion items, which are listed at the end of this inspection report.

Documents reviewed included: SOPs, batch records, complaint reviews, deviation investigations, change controls, training records, area cleaning and maintenance, facility layouts, equipment qualifications, cleaning validation, sterilization validation, media fills, environmental monitoring, visual inspection, contamination prevention, and laboratory assays.

No samples were collected, and no refusals were encountered during this inspection.

ADMINISTRATIVE DATA

(Written by LF)

Inspected firm:	Pfizer Manufacturing Belgium NV
Location:	Rijksweg 12 Puurs, Belgium 2870
Phone:	(b) (4)
FAX:	
Mailing address:	Rijksweg 12 Puurs, Belgium 2870
Dates of inspection:	06/24/2021, 06/25/2021, 06/28/2021, 06/29/2021, 06/30/2021, 07/01/2021 and 07/02/2021
Days in the facility:	7
Participants:	Laura Fontan (LF), Consumer Safety Officer Zhongren Wu (ZW), Consumer Safety Officer Anissa Cheung (AC), Consumer Safety Officer Susan Jackson (SJ), Consumer Safety Officer

PERSONS INTERVIEWED
(Written by LF)

During the opening meeting on June 24, 2021, we (LF, ZW, AC and SJ) presented our credentials to Luc Van Steenwinkel, Site Leader, who identified himself as the most responsible official for the site.

On June 30, 2021, Inspector Cheung (AC) discussed her closing remarks with (b) (6), (b) (7)(C) Pieter Verbelen, Launch Excellence Director and (b) (6), (b) (7)(C) At the final close-out meeting on July 2, 2021, we (LF, ZW and SJ) discussed our closing remarks with site leadership which included Luc Van Steenwinkel, Site Leader and (b) (6), (b) (7)(C) (b) (6), (b) (7)(C)
See **Exhibit LF-1a-d** for a list (prepared by the firm) of those present at the opening and closing meetings, as well as participants in the inspection.

Each member of the inspection team contributed to the establishment inspection report (EIR). The sections of the EIR written by each team member are denoted by their initials.

BACKGROUND AND HISTORY
(Written by LF)

- Pfizer Manufacturing Belgium NV, having its corporate address at Rijksweg 12, B-2870 Puurs, Belgium was incorporated under the laws of the Kingdom of Belgium on the 9th day of September 1960.
- Operations started in 1963.
- The current (b) (4) was built in 1980. Commercial manufacturing started in 1982. Since 1982 several extensions and facility modifications have been implemented, which include the (b) (4) (b) (4) in 2011. In 2015, a (b) (4) was implemented.
- In 1998 a (b) (4) was built for the manufacturing and packaging of (b) (4) was used for manufacturing at that time (b) (4)
- In 2013 the (b) (4) was finished (b) (4) (b) (4) was performed in 2014/2015 and (b) (4) started in 2015.
- In 1999 (b) (4) technology was introduced and (b) (4) (b) (4) In this area Xalatan (b) (4) manufactured. Xalatan is a product on the US market.
- In 2004, a (b) (4) was constructed about 1 mile from the manufacturing plant. This building contains (b) (4)

- The (b) (4) the facility where (b) (4) (b) (4) are aseptically filled (b) (4) was built in 1998 (b) (4) (b) (4) In 2012, the facility was finished, (b) (4) (b) (4) was performed in 2013 and (b) (4) started in January 2014.
- In 2013, a (b) (4) was built for the manufacturing of (b) (4) a vaccine against pneumococcal infections. This (b) (4) has been operational since end of 2014.
- From 2017 to 2020, a wide range of projects were started, which included:
  - Construction projects at the Puurs Plant: (b) (4) (b) (4) (b) (4)
  - Expansion and optimization projects, such as the (b) (4) (b) (4) (b) (4)
  - Continuous improvements projects such as: (b) (4) (b) (4) and an Integrated Manufacturing Excellence (IMEx) program
- In 2018, Pfizer Manufacturing Belgium NV started building (b) (4) (b) (4) Construction works continued in June 2020 (b) (4) (b) (4) and in March 2021 with (b) (4)
- In 2020 several expansions were made to provide for the COVID-19 vaccine with the installation and validation of formulation booths (b) (4) For the packaging and cold chain of COVID-19 vaccine, the freezer farm and shipping lines were installed. In 2021, (b) (4) were added to scale up the capacity for the COVID-19 vaccine.

Further history is detailed in **Exhibit LF-2**. The opening presentation is attached in **Exhibit LF-3**.

Hours of Operation:
Aseptic Manufacturing, Packaging, Warehousing: (b) (4) (b) (4)

(b) (4)

Operations: (b) (4) (b) (4)

Administrative: Week: Monday through Friday - flex time (core time between 9 am to 5 pm)

Employees:
Manufacturing Operations: (b) (4)
Packaging and Warehouse: (b) (4)
Quality Operations: (b) (4)
Support Functions: Engineering, Site Technical Services, Launch Excellence, Supply Chain Management, OPEX, EHS & site services: (b) (4)
Enabling Functions: BT, HR, Finance, Procurement: (b) (4)
Total: (b) (4)

DRUG PRODUCT MANUFACTURING OVERVIEW
(Section written by AC)

The manufacturing process for BNT162b2 drug product includes lipid nanoparticle (LNP) production (b) (4) and bulk drug product formulation (b) (4) followed by fill and finish (**Exhibit AC-1**).

(b) (4)

Sterile filtration of the bulk drug product (b) (4) (b) (4) then filled aseptically into vials (b) (4) (b) (4) A stopper is inserted (b) (4) into each vial immediately after filling, followed by capping of the stoppered vials. After the filling operation, the vials are automatically inspected, labeled, and frozen at -90 to -60˚C.

All manufacturing operations and in-process holds are conducted at (b) (4) unless otherwise specified and the worst-case hold times are challenged during the process validation runs.

WALKTHROUGH
(Written by AC)

On the first day of inspection (June 24), we (AC, LF, ZW and SJ) started the facility walkthrough in the warehouse (b) (4) where all the raw materials are received through the (b) (4) system. Then we moved to the (b) (4) room at (b) (4) to observe the (b) (4) (b) (4) (b) (6), (b) (7)(C) also showed us the (b) (4) room. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) (b) (4), (b) (6), (b) (7)(C) and Thomas Deproost (Sr Manager Aseptic Mfg, accompanied us on the walkthrough of the LNP production (b) (4) (b) (4) We started at the (b) (4) (b) (4) Pfizer personnel stated that all operations are captured under the electronic batch record, and they showed us how (b) (4) data was captured in the electronic batch record.

On June 30, Jan Dams (Sr Project Manager, Aseptic Mfg), Abo Steels (Team Leader Production), and Koen Vastenavondt (Operational director, Aseptic Mfg (b) (4) led a walkthrough of the freezer farm located at (b) (4) Building. (b) (4) ultra-low freezers are placed in this (b) (4) (b) (4) (b) (4) I observed the transfer of pizza boxes (firm's terminology for vaccine storage box) from (b) (4) to the designated (b) (4) pizza boxes (b) (4) (b) (4) pizza boxes/bundle) will be stored in (b) (4)

(b) (4) for the transfer to (b) (4) transport box is filled with dry ice (b) (4) (b) (4) The temperature probe is located (b) (4) to monitor the temperature (b) (4) There are (b) (4) packaging lines located (b) (4) (b) (4) and I observed the operation on Line (b) (4) packing pizza boxes into the shipping box (softbox). (b) (4) pizza boxes are packed (b) (4) softbox and a probe is placed (b) (4) softbox with dry ice (b) (4)

Facility Walkthrough
(Written by SJ)

During the inspection, I participated in a walk-through of the (b) (4) (b) (4) area and observed formulation booths (b) (4) where COVID19 vaccine is (b) (4) I observed the (b) (4) for the lipid component of the vaccine and I observed (b) (4) filling and visual inspection of batch (b) (4) A walk-through of (b) (4) Grade (b) (4) areas and the (b) (4) filling operation including visual inspection for COVID 19 mRNA vaccine batch (b) (4) were observed. In addition to the walk-through of the production areas (b) (4) we went to the incoming goods warehouse, (b) (4) freezer farm where the COVID 19 mRNA vaccine is (b) (4)

Warehouse Walkthrough
(Written by ZW)

On 6/24/2021, Inspectors Fontan, Jackson, Cheung and I conducted the walk-through inspection of the (b) (4) warehouses, located in (b) (4) with assistance from (b) (6), (b) (7)(C) guided us and answered questions. He stated that the warehouse is temperature-controlled, and the temperature is monitored through (b) (4) (b) (4) (b) (6), (b) (7)(C) stated that the inventory is also computer-based and governed by a (b) (4) (b) (4) All incoming materials will be checked per the checklist for any damages. I noticed there are (b) (4) used in the receiving area. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) stated all the (b) (4) are from shippers and they are (b) (4) or will be rejected. I confirmed that the accepted (b) (4) (b) (4) (b) (6), (b) (7)(C) stated that all the external (b) (4) will be (b) (4) acceptance into the warehouse. He stated that there are no physical compartments for quarantine, and release. The regulatory status of the raw material is maintained by the (b) (4) however, for the rejected materials, they are (b) (4) (b) (4) area. I inspected this area and checked the (b) (4) construction and I did not identify any issues.

Per (b) (6), (b) (7)(C) the concept using the (b) (4) is important in his (b) (4) warehouses, because (b) (4) (b) (4) The vaccine manufacturing-related raw materials such as (b) (4) and glass vials used in the filling line, are stored in the (b) (4) warehouses.

On the (b) (4) are the (b) (4) (b) (6), (b) (7)(C) explained that the warehouse personnel are responsible for (b) (4) (b) (4) (b) (4)

I conducted a (b) (4) inspection of the (b) (4) freezer. The (b) (4) freezer has a size of (b) (4) It is in the (b) (4) There is a (b) (4) and the (b) (4) (b) (4) to keep the temperature balanced. The (b) (4) door is locked, and open only to authorized personnel (b) (4) according to (b) (6), (b) (7)(C) With his permission, I tried (b) (4) and was rejected to enter the (b) (4) The door (b) (4) closes automatically (b) (4)

This freezer (b) (4) in 2015 and requalified in (b) (4) Currently, the (b) (4) (b) (4) are stored here. While (b) (4) the freezer (b) (4) I inspected the labels and packaging integrity of (b) (4) (b) (4) and verified the lot numbers without concerns.

The (b) (4) room is (b) (4) We interviewed (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) stated that the (b) (4) can be conducted at (b) (4) or in a (b) (4) (b) (4) (b) (4) We observed a few (b) (4) (b) (4) section of the room designated as the (b) (4) area (b) (4) We also observed the (b) (4) which has the capacity of (b) (4) According to (b) (6), (b) (7)(C) when (b) (4) (b) (4) the (b) (4) is set at (b) (4) We also observed the (b) (4) which is under qualification. Currently, the (b) (4) (b) (4) is more commonly used, according to (b) (6), (b) (7)(C)

At the (b) (4) room, I requested to review the batch record. (b) (6), (b) (7)(C) stated that (b) (4) batch records are digital. He demonstrated that the batch record for the (b) (4) process is filled out on the (b) (4) I had no issues with the (b) (4) process.

Walkthrough of (b) (4)
(Written by LF)

On June 28, 2021, SJ and I went to the (b) (4) Room (b) (4) to witness filling of BNT162b2 batch (b) (4) We were accompanied by (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) (b) (4), (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) The 2 mL vials enter (b) (4) (b) (4) (b) (4) The vials are (b) (4) (b) (4) (b) (4) The (b) (4) was operating (b) (4) (b) (4) the vials (b) (4) I was told that the (b) (4) was (b) (4) There is also an SOP for (b) (4) after such an event. The direct product contact equipment used in the filling (b) (4) (b) (4) The direct product contact equipment and miscellaneous parts needed for filling are (b) (4) (b) (4) The filler has (b) (4) (b) (4) stoppers also enter (b) (4) I was told that each batch uses (b) (4) (b) (4) of stoppers. The (b) (4) typically (b) (4) batches at a time, (b) (4) however, the direct product contact filling parts are (b) (4) per batch in a (b) (4) At the (b) (4) line is a (b) (4) capper (b) (4) Grade (b) (4) The capper (b) (4) rejects (b) (4) (b) (4) These rejects were (b) (4) entered into the batch record. The capper was operating at a speed of (b) (4) The validated maximum speed for the 2ml vial is (b) (4) is performed every (b) (4) and documented on a (b) (4) record that is reviewed as part of the batch record. The capped vials are then inspected using the (b) (4) automated visual inspection machine. No concerns were noted.

On July 1, 2021, I went into (b) (4) accompanied by (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) (b) (4), (b) (6), (b) (7)(C) Pieter Verbelen, Launch Excellence Director and (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) (b) (4), (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) to witness BNT162b2 sterile filtration operations in (b) (4) The BNT162b2 bulk in (b) (4) was lot (b) (4) is (b) (4) in (b) (4) room (b) (4) The sterile filtration (b) (4) in the (b) (4) room (b) (4) and then (b) (4) When I was in Room (b) (4) operations personnel were (b) (4) (b) (4) in preparation for sterile filtration. (b) (4) is (b) (4) to (b) (4) bulk drug product (b) (4) samples are taken from (b) (4) filtration. See **Exhibit LF-4** (b) (4)

(b) (4) Sample port (b) (4) No concerns were noted.

On July 2, 2021, I inspected the freezer farm located at (b) (4) Building with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) Abo Steels, Team Leader Production, and Koen Vastenavondt, Operational director, Aseptic Mfg (b) (4) BNT162b2 filled vials fits inside each (b) (4) freezer. I watched the (b) (4) product being (b) (4) (b) (4) with the product (b) (4) pizza boxes each containing 195 vials. (b) (4) fit inside each freezer (b) (4) (b) (4)

A (b) (4) is used to transport the frozen vial bundles to be packaged for shipping. The (b) (4) is kept cold using (b) (4) at the (b) (4) I watched two operators load bundles into the (b) (4) (b) (4) while checking/scanning batch numbers on each bundle during transfer. I also watched the loading of (b) (4) pizza boxes (b) (4) into one softbox with dry ice. The shipping logger is installed (b) (4) the shipping box has an expiration of (b) (4) and provides live monitoring of temperature in the box and GPS tracking. See **Exhibit LF-5.**

QUALITY SYSTEMS

Quality System
(Written by SJ)

All SOPs requested in the FDA Pre-Request List were translated from Dutch to English for the inspection.

Coverage of the Quality System included the review of the following written procedures:

Quality Manual
SOP (b) (4) version (b) (4) *Quality Manual* effective 10-June 2021 describes the Quality Management System at the Pfizer Manufacturing Belgium NV (Pfizer Global Supply (PGS) Puurs facility). The Quality Manual addresses the Quality Management System (QMS) requirements for design, development, manufacturing, packaging, testing, disposition, storage, distribution and post market surveillance of all drug products, medicinal products, biological products, (b) (4)
The Quality Manual describes the senior management responsibilities to include the development and maintenance of the Quality Policy ensuring a suitable and effective QMS is in place. Senior management is also responsible for adequate resources and that roles, responsibilities and authorities are defined, communicated, implemented throughout the organization.

The Quality Manual describes the QMS documentation process and contains (b) (4)

(b) (4) Quality Manual and Organization
Master Standard Operating Procedures (Master SOP)
Standard Operating Procedures SOP and /or Work Instructions
Forms
Records

SOP (b) (4) version (b) (4) *Organization* effective May 27, 2021 details the key roles and responsibilities of management. The SOP gives the site management organizational chart, quality management organizational chart and key roles and responsibilities of the senior management such as the Site Leader, Site Quality Operation Lead, Site Data Integrity Lead and the Release Operation Manager and Manager of COVID Project. The SOP also gives additional roles and responsibilities of the Site Quality Review Team (SQRT).

Management Review
(Written by SJ)

SOP (b) (4) version (b) (4) *Management Review Process* effective 18 May 2020, describes the process used to review the quality management system at documented, planned intervals by top management at the site to ensure continuing suitability, adequacy, and effectiveness. The Site Quality Review Team (S-QRT) meets on a (b) (4) frequency and the scope of their review is site quality and compliance metrics (QMS processes). Actions from the management review are (b) (4) and incorporated into the CAPA system.

Internal Audit
(Written by SJ)

SOP (b) (4) version (b) (4) *Internal Audits Quality* effective 05 March 2021, this procedure manages the periodic site self-audit. Internal audits are a system-based audit which are conducted at a frequency such that each system is audited (b) (4) and the associated sub systems are audited (b) (4) Examples of systems include but are not limited to quality, production, facilities and equipment, laboratory control materials, and validation. Example of a subsystem includes but is not limited to the following: change control, production areas, supplier qualification, utilities, complaint management etc.

I reviewed the internal audit plan for the 2021 which included the system and subsystem for (b) (4) The internal audit plan documents that an audit of (b) (4) is scheduled in (b) (4) and an audit of (b) (4) (b) (4) is scheduled for (b) (4) 2021. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) explained the internal audit process and provided evidence of the

executed internal audits for (b) (4) for 2021. Additionally, I requested to verify that during the internal audits electronic data is retrieved and reviewed as part of the audit. (b) (6), (b) (7)(C) presented executed internal audit agenda/scope and audit conclusions that stated that all elements of the audit were executed including the review of electronic records and data.

Change Management
(Written by SJ)

SOP (b) (4) *Change Management, effective 09 December 2020,* details the introduction of a new change, change or decommissioning of an existing product, validation process, direct impact system and quality management system. Every change is identified in one of four groups consisting of: product, process, systems and QMS. All changes are categorized as either a permanent change, emergency change, procedural change and planned change and they are managed by the site change management procedures in SOP (b) (4) The SOP describes and defines the primary action within a permanent change as change description, impact assessment (IA)/action plan, pre-approval, implementation, and closure. Other changes such as procedural change, planned temporary change and emergency change are also described. QA is required to approve changes (b) (4) (b) (4) All changes are managed in (b) (4)

Deviation
(Written by SJ)

SOP-(b) (4) version (b) (4) *Deviation Reporting* effective 19 May 2021, manages reporting and documenting unplanned incidents for drug products activities, including but is not limited to production, testing, distribution in support of Pfizer Products at Pfizer Puurs. All unplanned incidents are documented in (b) (4) To document an incident in (b) (4) an area specific SOP is followed based on the incident type. The following are the area-specific SOPs:

- SOP-(b) (4) Manufacturing Investigation
- SOP- Manufacturing Investigation for Utility Issues
- SOP- Manufacturing Investigation from Environmental Monitoring Issues

The SOPs appeared acceptable.

Review of Deviations/OOSs Investigation
(Written by AC)

I reviewed more than 50 product or process-related deviations. The majority of these were recurrent. One deviation involved multiple final DP batches that demonstrated lower than expected (b) (4)

Deviation (b) (4) was created due to the (b) (4) (b) (4) Three (b) (4) DP batches (b) (4) (b) (4) were rejected. This issue was communicated to the agency late last year, and during this inspection the firm provided additional data to further support that the (b) (4) (b) (4) was the root cause. Pfizer (b) (4) (b) (4) identified that the impurities present in (b) (4) caused the (b) (4) Currently, as a corrective action, (b) (4) is implemented (b) (4) (b) (4) The firm provided (b) (4) DP manufactured with (b) (4) (b) (4) produced with the process (b) (4) and all release test results are within specifications with no significant detection of (b) (4)

Five deviations were reviewed that were related to the (b) (4) assay (b) (4) The root cause of these deviations was either due to the operator error or issues with the (b) (4) I checked the training records of all the operators that are qualified for performing this test and the records indicated that they finished the training and are fully qualified to perform the assay. In response to these deviations and further improving the robustness of this assay, the firm has a plan in place to implement a revised (b) (4) assay (b) (4) (b) (4) (b) (4) A change control request (b) (4) was created in May 2021 (b) (4) (b) (4) The revision of (b) (4) assay appears acceptable.

(Written by LF)

Process Record PR (b) (4) was discovered on December 3, 2020 and reported on December 4, 2020. In-process bioburden samples were taken (b) (4) on November 17, 2020. The (b) (4) sample was taken (b) (4) (b) (4) The results from the (b) (4) were (b) (4) exceeding the limit of (b) (4)

The corrective action taken after the event was to perform a (b) (4) cleaning and disinfection of the (b) (4) (December 21, 2020). A detailed cause and effect analysis was performed including machine, method, human, materials, measurement system, and environmental factors. The detailed root cause analysis for the incident included:

- Reviewing the (b) (4) process and all bioburden and endotoxin results from Batch (b) (4) All other results met the expected limits.
- Review of sample flow and testing analysis

- Description of process and incident step by step including sampling and transportation, bioburden analysis, disinfection of (b) (4) preparation of materials, environmental control (b) (4) execution of bioburden analysis and reading of bioburden results
- Frequency of the issue, including historical bioburden and endotoxin data in the (b) (4) of (b) (4) reoccurrence of identified microorganism (*Stenotrophomonas maltophilia)*, raw materials used during the batch, and witnessing of the set-up of (b) (4) and (b) (4)

Many of the potential root causes came from witnessing the set-up of (b) (4) (b) (4) (b) (4) was removed and a (b) (4) was connected. The main root cause was identified as (b) (4) Operators that cleaned up a (b) (4) spill on the floor, attached the (b) (4) without disinfecting their gloves.

Contributing factors were:

- Possibility of contamination from the environment
- Part of product path is (b) (4)
- (b) (4) are not able to withstand the (b) (4) generated by the system

Four corrective actions were listed and were completed. All other bioburden and endotoxin results, (b) (4) tests, (b) (4) EM data (b) (4) and release results for the batch were within the expected limits, so it was concluded that there was no quality impact to this lot. The investigation appeared thorough. Subsequent lots produced through (b) (4) did not have bioburden or endotoxin results that exceeded limits. The information appears acceptable.

PR ID (b) (4) was created May 21,2021, occurred May 20, 2021
Short description: Non-inspected COVID vials were labelled and packaged (batch (b) (4) This issue was discovered during (b) (4)
Corrective actions were identified and implemented. An effectiveness check was required. The investigation was approved for extension (b) (4)
No concerns noted.

CAPA
(Written by SJ)

Corrective and preventive action role, responsibility and process are described in SOP (b) (4) version (b) (4) The procedure applies to all actions (b) (4) A correction is defined as (b) (4) The CAPA system manages correction from systems such as deviations, complaints, APR, and internal

and external audits. The CAPA flow for corrective action and preventive action requires a root cause analysis and then the implementation of the defined corrective action and preventive action. When a defined effectiveness check has been identified for a corrective action, a successful effectiveness check is required before the CAPA can be closed.

Biological Product Deviation Reporting (BPDR)
(Written by SJ)

SOP (b) (4) version (b) (4) *Biological Product Deviation Report (BPDR)* describes the requirement, responsibilities and the workflow for potential incidents that require a BPDR. In the event of an incident impacting a product (b) (4) (b) (4) the Release Site Quality Operations Leader (SQOL) is responsible for preparing the draft BPDR with input from the (b) (4) Additionally, (b) (4) must be identified in the BPDR. SOP (b) (4) describes the timeframe for reporting BPDR to CBER as no later than 45 days from the date of discovery.

Document Management
(Written by SJ)

The written procedure SOP- (b) (4) version (b) (4) *Document Management* manages GMP related documents within the Pfizer Puurs facility. GMP related documents can be managed (b) (4) or they can be managed (b) (4) for storage and management of the electronic versions of documents. SOP- (b) (4) details a high-level workflow for the creation of a new document. Periodic review of GMP documents is set at a minimum of (b) (4) however the review of the Quality Manual and the Organization SOP requires a review frequency of (b) (4) All documents identified as pertaining to GMP are required to have three approvals by three different persons. One of these approvals must be from the Quality Unit.

(b) (4) is used when making GMP related fill-in documents. (b) (4) ensures a unique sequential number is shown on documents and the document has a limited shelf life of (b) (4) after printing.

GMP documents that are managed in (b) (4) applications are as follows: Master Batch Record managed within the (b) (4) Lot Plans managed in (b) (4) and Maintenance Records managed within (b) (4)

Document control
(Written by ZW)

The firm handles the document control per SOP- (b) (4) "Document and record management", effective date 9/28/2020. (b) (6), (b) (7)(C)

(b) (6), (b) (7)(C) showed me the flow chart indicating how the document or record is determined to be GMP related and the sub-SOP to be followed. Currently, most of the documents, such as (b) (4) are (b) (4) For the (b) (4) (b) (4) documents, such as (b) (4) they are issued by the QA unit and will be reconciliated.

Electronic Batch Record (EBR) system
(Written by LF)

The COVID-19 vaccine manufacturing process is conducted using a (b) (4) (b) (4) batch records. The end goal is to have a (b) (4) batch record, however, currently (b) (4) manufacturing steps are initiated in (b) (4) (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) (b) (4), (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) presented an overview of the EBR system.

The current processes in (b) (4) include:
(b) (4)

Master Batch records (MBR) are maintained under change control and (b) (4) currently approved master record exists for each product at a specific time. In order to change an EBR the initiator must request a change and qualified authors (Site Technical Services) design/configure, test and prepare the MBR updates. Any changes are verified by a qualified secondary author, the production authority and the quality authority. These steps are described in Work Instruction SOP- (b) (4)

The EBRs do not allow any blanks, and steps cannot be skipped. The limits are (b) (4) checked based on configured values, such as (b) (4) (b) (4) can also be set for requirements before use such as preparation required (b) (4) and expiry times. The electronic signatures are configured based on the role.

During batch record execution, measured (b) (4) values are inputted by (b) (4) The limits for the (b) (4) values are part of the batch record and if (b) (4) an exception is triggered. Exceptions are also triggered by (b) (4)

(b) (4) Deviations can be initiated by production and are added to exceptions. The exceptions are reviewed according to SOP-(b) (4) Evaluation of batch records of product produced in Puurs, Ver. (b) (4) All exceptions are reviewed by production and quality. Automatically generated alarms are also reviewed by quality.

Unauthorized persons cannot access the application. In addition, (b) (4) (b) (4) in (b) (4) which is linked to (b) (4) The (b) (4) shows (b) (4) (b) (4) The (b) (4) data is reviewed during the batch record review. (b) (4) (b) (4) The (b) (4) discussed in procedure (b) (4) (b) (4) Policy is validated. (b) (4) has specific roles defined for access to the different (b) (4) based on an employee's function and training. No concerns were identified.

Quality Agreements
(Written by SJ)

During the inspection, I reviewed the Quality & Technical Agreement (b) (4) (b) (4) for contract manufacturing between Pharmacia & Upjohn Company LLC, Pfizer Manufacturing Belgium NV, Biotherapeutics Pharmaceutical Sciences (ARD & ACMF aka Wyeth Pharmaceutical), Pfizer Biotherapeutics Pharmaceutical Science (ARD Chesterfield) and BioNTech Manufacturing GmBH. The agreement was signed by all the manufacturing sites and BioNTech. The agreement delineates responsibilities between Pfizer and BioNTech. The specific responsibilities for each manufacturing site identified in the agreement was however not delineated. Quality agreements were discussed with (b) (6), (b) (7)(C) who also presented the overview of Quality Agreements.

I requested to review the quality agreement between the Pfizer Manufacturing Puurs and Pfizer Andover Clinical Manufacturing (ACMF) the supplier of the drug substance for the US market. (b) (6), (b) (7)(C) explained that there is (b) (4) (b) (4) as it relates to the COVID 19 mRNA drug substance.

The quality agreement between the Pfizer Manufacturing Belgium and Pfizer Ireland Pharmaceutical Grange Castle dated 03 September 2020 was reviewed during the inspection. Pfizer Pharmaceutical Grange Castle is a contract testing site for the COVID 19 vaccine (b) (4) and drug product testing. This quality agreement delineates the responsibilities of the Pfizer Puurs and Pfizer Grange Castle. No objections were noted.

Before the closeout of the inspection, (b) (6), (b) (7)(C) addressed the issue of reporting responsibilities to the US FDA. (b) (6), (b) (7)(C) presented an amended quality agreement between the Pfizer manufacturing sites and BioNTech

signed 29 June 2021. The quality agreement was updated to clarify the relationship for COVID 19 vaccine (b) (4) (b) (6), (b) (7)(C) also explained that in the Pfizer Purrs site written procedure SOP (b) (4) version (b) (4) *Biological Product Deviation Report* (BPDR) (b) (4) states that if there is an incident impacting a product (b) (4) it is the responsibility of the release site Quality Operations Leader to prepare the draft BPDR with input from (b) (4) No objection was noted.

Pest Control
(Written by SJ)

SOP (b) (4) version (b) (4) *Pest Control* effective June 29, 2020, describes the procedures for implementing and maintaining a site pest control program. The site pest control coordinator is responsible for ensuring that an adequate pest control program is established, implemented, and maintained for each building in Pfizer Puurs. An external global contractor is responsible for managing and implementing the pest control program. The list of authorized biocides used the external contractor is documented in SOP (b) (4) Form (b) (4) There are three types of pest control treatments performed by the external contractor: emergency, follow-up, and routine treatment. The routine treatment is performed (b) (4) times per year. (b) (6), (b) (7)(C) presented the schematic of pest control traps locations, detector types and executed routine treatment proof of service. During the inspection, I walked through the warehouse, controlled areas, classified areas and the (b) (4) facility and no objectionable conditions were noted as it relates to pest control.

Training
(Written by SJ)

SOP (b) (4) version (b) (4) *GMP Training* describes the GMP training program for Pfizer employees, contingent workers, third party resources and contractors with direct or indirect impact on the quality of product. SOP (b) (4) details the scope, roles, and responsibilities. This GMP training SOP details the training for new hires (on boarding phase), development phase for current co-workers (developing phase) and the maintenance of a general awareness with current co-workers (ongoing phase).

GMP orientation for new hires is an introduction to GMP concepts via (b) (4) followed by (b) (4) (b) (4) The developing phase consists of (b) (4) (b) (4) The ongoing phase involves (b) (4) (b) (4)

During the inspection, the training records for a select number of employees in the COVID 19 vaccine formulation area, vaccine filling, visual inspection (AQL) and QC

laboratory were reviewed for specific position-related training and (b) (4) GMP refresher training. No deficiencies were noted during the review of these training records.

Annual Product Review
(Written by AC)

No Annual Product Review is written for BNT162b2 DP; however, (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) explained that a continued process verification (CPV) program for BNT162b2 DP is established. It consists of (b) (4) The objective of (b) (4) is to continue monitoring the (b) (4) after process validation. (b) (4) sampling (b) (4) after process validation is considered. During (b) (4) CPV reports are written on a regular basis. (b) (4) (b) (4) The purpose of (b) (4) CPV is to gather (b) (4) product data from (b) (4) to assess whether the process remains in a controlled state and to give the opportunity to act proactively in case the process shows a trend to go out of control.

(b) (4)

(b) (4) CPV has no endpoint and continues for the whole life cycle of BNT162b2 DP. A (b) (4) is used to (b) (4) for the obtained data and control limits are set based on the (b) (4) Any out-of-control data from (b) (4) will initiate (b) (4) Product SME will review (b) (4) and the SME is responsible to review (b) (4) and put comments to explain why (b) (4) (b) (4) (b) (4) test results will be recorded and documented in the future Annual Product Review.

In addition, (b) (6), (b) (7)(C) described the Quality Performance Report (QPR) that the QA performs (b) (4) The recent one was performed between (b) (4) 2021. No outstanding finding was observed in this report. The report includes information to monitor the following items:

(b) (4)

Consumer Complaints
(Written by ZW)

(b) (6), (b) (7)(C) explained to me the procedures for handling complaints. She stated that the firm uses a triage system to categorize the nature of each complaint. The following are a few representative examples of the categories:
(b) (4)

I reviewed the SOP (b) (4) "Complaint handling", version (b) (4) effective date. (b) (6), (b) (7)(C) walked me through the process flow chart. According to this SOP, once a complaint is received, the firm will determine the investigation priority depending on the nature of the complaint, with three levels of urgency such as "Expedited", "High" and "Normal". The time frame is set for (b) (4) calendar days for Expedited and High, and (b) (4) calendar days for Normal. The investigation procedures consist of (b) (4)
(b) (4)
(b) (4)

I requested to review the most recent trending analysis data. (b) (6), (b) (7)(C) showed me the analysis between December 2020 and May 2021. She stated that the complaints (b) (4) (b) (4) is used in the trending analysis, and as more vaccine is manufactured, (b) (4) is decreasing, as shown in the container category, from approximately (b) (4)

The firm provided the complaint list prior to the inspection, in the pre-request package. I noted that since December 2020, there are approximately 11,000 complaints filed. As of May 2021, the firm has manufactured approximately (b) (4) doses. I randomly selected the following consumer complaints to evaluate how the firm conducted the complaint investigation (**Table ZW-8**):

ZW Table 8. Complaint investigations

Doc ID	Date received	Date closed	Category	Batch #	Summary
(b) (4)	5/10/2021	6/25/2021	Container	EW4811	A customer complained of container leakage during the reconstitution and the samples were returned for evaluation. The firm started the investigations including but not limited to trending analysis, batch

Doc ID	Date received	Date closed	Category	Batch #	Summary
					record review, deviation investigation review, and retained sample inspection without issues. No root cause was found. And no CAPA is taken.
(b) (4)	6/16/2021	Open		(b) (4)	(b) (4)
(b) (4)	12/18/2020	12/19/2020	Foreign objects	Not available	A customer was asking for the process to report a product with particles in it. When the firm called the customer, there was no answer.
(b) (4)	1/6/2021	2/17/2021		EJ0724	Small black particles were found after dilution. The customer was not able to return the sample. The firm performed the internal investigation including but not limited to review of batch record, deviation investigation and retained samples. No root cause was found and no CAPA was taken.
(b) (4)	12/17/2020	1/29/2021		EK4175	After the reconstitution*, the customer found a film/sediment on the outside of the vial and the contents did not contain enough to draw up even one dose. The performed the investigation and no root cause can be identified.
(b) (4)	1/7/2021	2/19/2021	External cause investigation	EL1484	The effectiveness of the vaccine was questioned. Four clinicians received the first dose and then tested COVID-positive. The expiry of the vaccine is April 2021. The complaint sample was not returned. The firm's internal investigation found no quality issues. After the inspection, I was able to review this complaint in more depth and noted (b) (6), (b) (7)(C) related to the batch EL1484. (b) (4), (b) (6), (b) (7)(C) (b) (4), (b) (6), (b) (7)(C)

Doc ID	Date received	Date closed	Category	Batch #	Summary
					(b) (4), (b) (6), (b) (7)(C)
(b) (4)	4/15/2021	5/28/2021	Product appearance	EW2246	After reconstitution, the customer found discoloration upon visual inspection, with whitish dispersion. The firm performed the internal investigation including but not limited to review of batch record, deviation investigation and retained samples. No root cause was found and no CAPA was taken.

*Note: "Reconstitution" is the term used in the Pfizer complaint documents. I interpret this as the dilution of the drug product vial.

I have no concerns with my review of the consumer complaints.

FACILITIES AND EQUIPMENT SYSTEMS

Facility Changes
(Written by ZW)

Since the last FDA inspection in 2017, particularly since the start of the COVID-19 pandemic, the firm has added more people and multiple facilities and equipment. There are currently approximately (b) (4) employees and that number was approximately (b) (4) in 2017. The following table shows the major changes related to the current application and because of the time constraint, I focused my review and evaluation on the major changes, specifically (b) (4) (Table ZW1).

Table ZW1. Major changes

Category	Facilities or Equipment	Location
(b) (4)		

Category	Facilities or Equipment	Location
(b) (4)		

Per Pieter Verbellen, Director Launch Excellence, the firm currently uses (b) (4) for preparation/formulation of the bulk liquid. The filling process and vial inspection are performed at (b) (4)

No concerns were identified regarding changes to the facilities and equipment.

Preventive Maintenance of HEPA Filters
(Written by SJ)

SOP (b) (4) Version (b) (4) *Filter* (Qualified) effective January 7, 2021 describes the preventive maintenance (PM) program on HEPA filters. It should be noted that the filling operation is (b) (4) (Grade (b) (4) /ISO (b) (4) and the (b) (4) is a Grade (b) (4) /ISO (b) (4) The PM program is managed by the (b) (4) (b) (4) The frequency for PM on the ISO (b) (4) HEPA filters is every (b) (4) PM is performed in house and the parameters used during the HEPA filter PM are as follows: (b) (4)

The PM program for HEPA filters was discussed with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) The review of PM includes the work order for the ISO (b) (4) HEPA filter in (b) (4) along with the traceability of the in-house equipment used to measure the key parameters of the HEPA filters. All equipment used in the HEPA filter PM was traceable back to a standard and within calibration at time of use. During the initial IQ/OQ/PQ of (b) (4) in May 2020, (b) (4) filters were replaced as it failed (b) (4) new filters were installed and retested as part of the initial IQ/OQ/PQ; the HEPA filter retest results met all specifications. No objectionable conditions were noted for the ISO (b) (4) HEPA filter PM records reviewed.

Validation
(Written by LF)

SOP-(b) (4) *Systems Validation* ver.(b) (4) effective May 28, 2021, describes the general approach for the validation of systems. The procedure pertains to direct impact systems that support the manufacturing, storage and distribution that include facilities, utilities, equipment and related automation. Lab equipment and computer systems were not within the scope of this procedure. Lab equipment validation is covered under SOP-(b) (4) *Laboratory Equipment Qualification* and Computer systems are covered under SOP-(b) (4) *Computer Systems Validation*. System validation includes verification (IQ and OQ) and Performance Qualification (PQ) of a system.

The general approach for sterilization validation is discussed in SOP-(b) (4) *Sterilization Validation* ver. (b) (4) effective March 14, 2019. This procedure includes sterilization of (b) (4) (b) (4) Periodic requalification of these processes is required (b) (4) No concerns noted.

EQUIPMENT QUALIFICATION

Qualification of the (b) (4) *warehouses and computer security*
(Written by ZW)

The (b) (4) warehouse is also called (b) (4) (b) (4) From a (b) (4) door, which is (b) (4) we observed a (b) (4) retrieve or place (b) (4) on (b) (4) From the ground to the ceiling, there are (b) (4) (b) (4) The (b) (4) on the (b) (4) (b) (4) for locations and materials.

On 6/25/2021, I reviewed the qualification of the (b) (4) system for the warehouse, with (b) (6), (b) (7)(C) She stated that the (b) (4) (b) (4) was implemented in 2014. Since then, more improvements have been made and the qualification of the (b) (4) was conducted and approved in March 2018. She showed me the qualification report. I reviewed the report of (b) (4) (b) (4) and it appears all the acceptance criteria were met. I asked about the security measures in (b) (4)(b) (6), (b) (7)(C) stated that only authorized personnel have access to the (b) (4) and the computer security is governed by the (b) (4) (b) (4) I further requested and reviewed the policy for computer security. This document describes the computer configuration, policies for account lockout, audit and network security. For example, the password must have (b) (4)

(b) (4) The account will be locked out after (b) (4) I have no issues with the computer security measures.

Temperature mapping of the (b) (4) *warehouse*
(Written by ZW)

The (b) (4) warehouse has (b) (4) storage (b) (4) The capacity is (b) (4) Because of limited time, I focused my review on the qualification of the (b) (4) warehouse.

(b) (6), (b) (7)(C) walked me through the temperature mapping process. She stated that the (b) (4) warehouse has the size of (b) (4) The stored materials are placed on (b) (4) are installed on the (b) (4) For the temperature mapping, a total of (b) (4) monitoring probes were distributed throughout the warehouse, including the worst-case locations on the (b) (4) (b) (4) For (b) (4) monitoring, (b) (4) monitoring probes are positioned throughout the warehouse.
(b) (6), (b) (7)(C) stated that (b) (4) temperature mapping studies were conducted:

(b) (4)

I requested and audited the data for temperature mapping, which is documented in (b) (4) "Performance Qualification Report for (b) (4) (b) (4) dated 1/21/2021. For each study, the temperature was monitored for (b) (4) The firm also conducted the (b) (4) (b) (4) The temperature was set at (b) (4) and alarm limits were set at (b) (4) The locations of the monitoring probes were adequately identified in the report. I reviewed the temperature (b) (4) (b) (4) and checked the (b) (4) The firm also identified the (b) (4) (b) (4) Based on the mapping study, (b) (4) monitoring probe locations are determined (b) (4) I also reviewed the attached deviation reports and the audit trail report. I had no issues with the documents I reviewed.

The (b) (4) substances such as (b) (4) are stored in a (b) (4) (b) (4)

Qualification of the freezer (b) (4)
(Written by ZW)

The freezer (b) (4) has (b) (4) working (b) (4) is installed (b) (4) (b) (4) appears to have adequate space and is organized. The stored materials are placed on (b) (4) Per (b) (6), (b) (7)(C) the temperature is monitored and controlled by (b) (4) a (b) (4) facility (b) (4) system.

I reviewed the qualification document for the freezer (b) (4) with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) She stated that (b) (4) temperature readings (b) (4) and the most recent requalification/temperature mapping was performed in (b) (4) as documented in (b) (4) "Combined revalidation/requalification report for the (b) (4) (b) (4) (b) (4) approved on (b) (4) The freezer (b) (4) has a temperature set at (b) (4) (b) (4) According to (b) (6), (b) (7)(C) (b) (4) monitoring probes were distributed in the mapping study and the testing period (b) (4) was (b) (4)
The monitoring probes were placed as follows:

(b) (4)

The study identified the (b) (4) The firm also conducted the (b) (4) I audited the (b) (4) temperature (b) (4) I had no issues.

The emergency power backup system for the freezer (b) (4) and other facilities will be discussed later in this report.

(b) (4) *Building for the storage of the finished products, "Freezer Farm"*
(Written by ZW)

I conducted the inspection of the (b) (4) Building on 6/28/2021 (**Exhibit ZW-1**). The (b) (4) is a (b) (4) building located on the (b) (4) side of the campus. On the way to the (b) (4) I noticed (b) (4) approximately (b) (4) (b) (4) (b) (6), (b) (7)(C) stated that the firm purchases the (b) (4) from (b) (4) to ensure the uninterrupted supply. The (b) (4) is (b) (4) at the (b) (4) and added to the (b) (4) (more discussion later in this report).

To enter the (b) (4) building, I needed to go through a (b) (4) door, which is locked and opened only to the authorized personnel (b) (4) I noted there were (b) (4) at the entrance.

Mr. Jan Dams, Senior Project Manager and Mr. Abo Steels, Team Lead assisted me during the inspection. They answered questions and provided documents. Mr. Luc Van Steenwinkel, the site head, was also present during the walk-through inspection. Currently, the (b) (4) Building is a (b) (4) facility for the COVID BNT162b2 vaccine. I noted that there are adequate spaces for the equipment such as (b) (4) ultra-freezers and the storage (b) (4) arranged in an organized fashion for inspection and cleaning (**Exhibit ZW-1**). The (b) (4) area appeared clean, and no cracks were noted between the doors and frames. The (b) (4) and mouse traps were also found in the (b) (4) area as a pest control measure. The firm uses an external contractor for the pest control, per Mr. Dams.

According to Mr. Dams, there are approximately (b) (4) authorized people working in the (b) (4) Building. I asked what procedures have been taken to ensure the security of the freezers which are (b) (4) Mr. Steels stated that the firm has several procedures such as:

(b) (4)

For the training, Mr. Steels stated that each new hire is required to take training based on his or her job responsibilities and they are not allowed to go to places beyond their job description. I randomly picked one employee, (b) (6), (b) (7)(C) from the (b) (6), (b) (7)(C) and requested to audit her training records and training materials. I noted that (b) (6), (b) (7)(C) is a (b) (4), (b) (6), (b) (7)(C) Her training records show that she has had (b) (4) on-job trainings (OJT) and (b) (4) SOP trainings since February 2021. The GMP training slides (b) (4) (b) (4) instructed employees (b) (4) I had no issues with the training documents I reviewed.

Freezer Farm
(Written by ZW)

According to Mr. Steels and Mr. Dams, there are currently approximately (b) (4) ultra-freezers (b) (4) (**Exhibit ZW-1)** in the (b) (4) Building, and (b) (4) freezers (b) (4) (b) (4) I noted that all the freezers appear new. Per Mr. Steels, the firm started the purchase of freezers in (b) (4) 2020 and qualifications of freezers in (b) (4) 2020. The (b) (4) Building is also called “Freezer Farm”. It has a size of (b) (4) (b) (4)

Per Mr. Steels, each freezer has a (b) (4) attached to the freezer and this (b) (4) is equivalent to that displayed on the (b) (4) found in the (b) (4) (b) (4) The freezer temperature is also displayed (b) (4) Mr. Steels stated that each freezer is monitored for temperature through a (b) (4) called (b) (4) and the temperature reading is taken every (b) (4)

My audit of the freezer qualification started with a randomly selected freezer (b) (4) (b) (4) from the floor. Mr. Steels showed me, (b) (4) the current temperature, and the temperature for the last five days, of this freezer, managed on the (b) (4) I noted there are (b) (4) with a difference around (b) (4) Mr. Steels explained that there are (b) (4) (b) (4) respectively. The (b) (4) on the (b) (4) represents the worst case, normally (b) (4) than the (b) (4) (b) (4) based on the temperature mapping study and real-time monitoring.

I then requested to review the temperature monitoring for the month January and February 2021, and I noted there are two temperature excursions on 1/14/2021 and 2/4/2021. Mr. Steels explained that the temperature excursion on 1/14/2021 is due to the loading of the vaccine Lot (b) (4) This lot was unloaded, and freezer was cleaned on 2/4/2021, resulting in another excursion. I reviewed the records without discrepancies noted. This freezer was cleaned on (b) (4) 2/4/2021. Mr. Steels stated that the (b) (4) freezer is maintained at (b) (4) When the vaccine vials, which are kept (b) (4) after packaging, are loaded to the freezer, the freezing process takes approximately (b) (4) Lot (b) (4) is currently stored in the freezer (b) (4) Mr. Steels stated that the turnover is approximately (b) (4) because of high demand. No issues were identified.

Freezer qualification and temperature mapping
(Written by ZW)

The qualification procedures and acceptance criteria are described in the document (b) (4) "Form: performance qualification protocol", and in (b) (4) (b) (4) "FORM: Template System Acceptance and Release Report (SARR)", respectively. The temperature mapping is performed for (b) (4) freezers. The freezer has (b) (4) and (b) (4) temperature monitoring probes are placed in the (b) (4) (b) (4) The freezer temperatures should stay within predetermined working temperature (b) (4) The freezer is monitored for (b) (4) I randomly selected the following three freezers (Table ZW2) and reviewed temperature mapping data:

Table ZW2. Qualification of the ultra-freezers

Freezer	Mapping date (b) (4)
(b) (4)	(b) (4)

The qualification study has (b) (4) data sets (b) (4) plus audit trail) for each freezer. I noted that the temperatures stay within the specifications during the (b) (4) tests. For the (b) (4) test, (b) (4) temperature monitoring probes show the temperature increases up to (b) (4) When the (b) (4) the temperature drops to (b) (4) Per Mr. Steels, the freezers, (b) (4) generally (b) (4) I had no issues with the documents I reviewed.

I also selected randomly and inspected a cleaned freezer (b) (4) that is ready to receive vaccines. After the door opens, there are (b) (4) (b) (4) The freezer appeared to be in good conditions and no ice build-up was observed. According to Mr. Steels, each freezer, when fully loaded, should take (b) (4) pizza boxes (195 vaccine vials per box) (b) (4) (b) (4)

Temperature monitoring probe calibration
(Written by ZW)

I requested and reviewed the calibration documents for the temperature monitoring probes. (b) (6), (b) (7)(C) stated that the probe calibration is performed (b) (4) and all the temperature monitoring probes are calibrated (b) (4) I randomly selected the calibration reports of the following three probes:

- (b) (4) calibrated on 3/16/2021
- calibrated on 5/12/2021
- calibrated on 5/28/2021

There are (b) (4) temperature set points such as (b) (4) and the failure limits are the set point (b) (4) I reviewed all three reports and noted that the observed temperature outputs are at most (b) (4) from the set points. I had no issues.

(b) (4) *and Alarm system*
(Written by ZW)

(b) (6), (b) (7)(C) and Mr. Abo Steels explained to me the alarm system for the (b) (4) using (b) (4) The procedures for the alarm handling are governed with SOP (b) (4) "Handling of alarms (b) (4) effective date

10/13/2020. Mr. Abo stated that the alarm system is on the (b) (4) and the (b) (4) alarm messages are sent to the responsible person. According to the procedure, the alarm message is (b) (4) (b) (4) The working temperature for the (b) (4) is (b) (4) When the temperature increases to (b) (4) or beyond for (b) (4) the alarm system will be activated. Per (b) (6), (b) (7)(C) the (b) (4) (b) (4) window will avoid false alarms and gives operators enough time to perform regular activities such as (b) (4)

The firm performed the validation for the alarm system and the report is documented in Document ID: (b) (4) "Verificatie test plan/rapport (b) (4) alarmen op/ALERT", with approval date 2/3/2021. It appears that all the pre-determined parameters were met.

Softbox qualification
(Written by ZW)

Inside the (b) (4) Building and before entering the (b) (4) section, are the shipping lines for the vaccine products. The vaccine vials, packaged in the flat "pizza box", 195 vials per box, are shipped as a bundle of (b) (4) pizza boxes in the (b) (4) Softbox, or (b) (4) bundles in the (b) (4) Softbox. There are (b) (4) shipping lines: (b) (4) lines for the (b) (4) Softbox and (b) (4) for the (b) (4) Softbox. I observed (b) (4) Softbox shipping lines were in operation during my walk-through inspection. The pizza boxes in bundles are kept in a (b) (4) the storage ultra-freezer and the Softbox. I observed an operator picked up the bundle with the (b) (4) and placed the bundle inside the Softbox, and then added the dry ice to fill the Softbox. Each shipping line has (b) (4) dry ice (b) (4) (b) (4) operator checked the packaging conditions, and the logger. More discussions later in this report) on top of the payload and closed the Softbox. (b) (4) operator attached the shipping label and the Softbox was placed in a shipping ready area.

Softbox is a packaging thermal container manufactured by a UK based company called Softbox Systems. I reviewed the following documents (Table ZW3) to evaluate the qualification of the most often used Softbox (for (b) (4) pizza boxes) as a shipper to maintain the temperature at (b) (4) for no less than (b) (4) Because of the time constraint, I did not request and review the (b) (4) Softbox qualification.

Table ZW3. Softbox qualification

Doc ID	Document	Approval date	Authorship	Summary
(b) (4)	Thermal performance qualification protocol,	10/14/20	Pfizer	A total of (b) (4) shipments in Softbox will be executed from (b) (4) (b) (4) (b) (4) The

Doc ID	Document	Approval date	Authorship	Summary
	transportation of ULT product from (b) (4) (b) (4) using a passive dry ice thermal container			minimum load will each consist of (b) (4) (b) (4) representing the worst case. The shipper will be transported via (b) (4) and the Softbox shipper should maintain (b) (4) temperatures for a minimum of (b) (4) One temperature monitoring device (TMD) is packed with each shipper and the temperature reading is taken at (b) (4) intervals, with alarm set outside (b) (4)
(b) (4)	(b) (4) Thermal performance qualification **report**, transportation of ULT product from (b) (4) (b) (4) using a passive dry ice thermal container	10/30/20	Pfizer	The total transition time is (b) (4) (b) (4) and TMD shows the Softbox shipper maintain the temperature between (b) (4) During my in-depth review of this document after the inspection, I noted that there is no data for (b) (4) (b) (4) as planned in the protocol (b) (4) However, more studies show that the Softbox maintains the temperature for more than (b) (4) See doc (b) (4) below.
(b) (4)	Technical assessment for OQ data on Softbox (b) (4) ULT for transport of (b) (4) products	1/20/21	Pfizer	The firm performed (b) (4) (b) (4) (b) (4) The firm demonstrated that the SoftBox is capable to maintain the temperatures between (b) (4) (b) (4) for up to (b) (4) The Softbox is (b) (4) (b) (4) mimicking the worst case, (b) (4) However, I noted that the (b) (4) temperature, indicated here between (b) (4) may not represent the worst case, as the product may be kept in places where temperature excursions beyond (b) (4) may occur. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) stated that the firm has performed another study for (b) (4) (b) (4) temperature profile, and provided the document (b) (4) (b) (4) see below.

Doc ID	Document	Approval date	Authorship	Summary
(b) (4)	(b) (4) ULT dry-ice shipper (b) (4) (b) (4) temperature control packaging system (b) (4) (b) (4) temperature control profile	2/1/21	(b) (4)	This study shows the Softbox shipper maintains (b) (4) for approximately (b) (4) under the (b) (4) temperature conditions.
(b) (4)	(b) (4) shipping study report summary for project BNT162b2	6/16/21	Pfizer	The firm stated that this document evaluates the impact of the (b) (4) on the drug product utilizing a worst-case (b) (4) (b) (4) drug products from batch (b) (4) (b) (4) are included in the study. This is a (b) (4) study. Test samples are exposed to (b) (4) (b) (4) After the (b) (4) shipment, the firm performed the tests including but not limited (b) (4) (b) (4) (b) (4) (b) (4) The results are within specifications.
(b) (4)	(b) (4) testing of a (b) (4) ULT dry-ice shipper	8/4/20	(b) (4)	(b) (4) performed the (b) (4) of the Softbox shipper. The Softbox was (b) (4) load. (b) (4) tested the Softbox with the following elements: (b) (4) (b) (4) On completion, the Softbox shows (b) (4) (b) (4) (b) (4)
(b) (4)	(b) (4) ULT dry-ice shipper (b) (4) (b) (4) temperature control packaging system (b) (4) temperature profile	7/15/20	(b) (4)	This document has instructions on how to pack the Softbox. (b) (4) (b) (4) is added to the Softbox (b) (4) The document also defines the (b) (4) (b) (4) profile as (b) (4)

During my inspection, I noted that each Softbox was packed with (b) (4) pizza boxes, while for the Softbox qualification, (b) (4) is used with (b) (4) dry ice. My concern was, if (b) (4) pizza boxes are shipped, (b) (4) dry ice may have to be used, then the cooling capability might be compromised. (b) (6), (b) (7)(C) stated that that is not the case. The Softbox is always filled with (b) (4) dry ice, as in the qualification study. If (b) (4) pizza boxes are shipped, (b) (4) will be (b) (4) During my review of the Softbox photos (**Exhibit ZW-1**, (b) (4)), I noted that the dry ice (b) (4) is (b) (4) to the Softbox. No issues were identified.

Shipping control strategy
(Written by ZW)

(b) (6), (b) (7)(C) gave a presentation about the shipping process (Exhibit ZW-3). She stated that each Softbox shipper is packed with a logger, which is linked to the Controlant Platforms for live temperature monitoring and GPS tracking. Controlant tracks the movement of the Softbox the moment it leaves the Puurs facility until reaching the final destination. The critical data such as the temperature and location can be seen real time. Any excursions will be notified (b) (4) The logger also has a (b) (4) If the Softbox is (b) (4) (b) (4) Controlant will be notified. Controlant is a contractor located in Iceland (Holtasmari 1, 201 Kopavogur, Iceland). No issues were identified.

Dry ice (b) (4)
(Written by ZW)

(b) (6), (b) (7)(C) explained to me that each shipping line is equipped with (b) (4) (b) (4) dry ice (b) (4) to ensure the (b) (4) dry ice supply. (b) (4) has a capacity of (b) (4) (b) (6), (b) (7)(C) also stated that the firm has (b) (4) (b) (4) can also (b) (4) dry ice (b) (4) in case that all the (b) (4) fail.

Emergency power backup system
(Written by ZW)

I requested and reviewed the emergency power backup system. Because of the temperature sensitive nature of this vaccine, the uninterrupted power supply for the ultra-low temperature freezers should be assured. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) assisted me in the review process. (b) (6), (b) (7)(C) stated that at the Pfizer Puurs site, there are (b) (4) power sources: (b) (4) (b) (4) (b) (4) supplies the electricity regularly to the plant. In case of (b) (4) power failure, (b) (4)

(b) (6), (b) (7)(C) explained that the (b) (4) is a (b) (4) (b) (4) When there is (b) (4) power failure, the (b) (4) (b) (4) so there is no interruption of the power supply. The (b) (4) are linked to the (b) (4) ensure (b) (4) at any moment.

(b) (6), (b) (7)(C) stated that there are (b) (4) for the freezer farm and the most recently (b) (4) qualified in June 2021. When (b) (4) power fails, the (b) (4) I selected (b) (4) (Table ZW4) to review their qualification documents (preventive maintenance work orders and qualification report, particularly if the response time is within the specified time frame when there is power failure (or shutdown)):

Table ZW4. (b) (4) qualification (b) (4)

I found no discrepancies from the documents I reviewed.

(b) (4)
(Written by ZW)

On the first day of the inspection on 6/24/2021, I conducted the inspection of the (b) (4) (b) (4) facility, (b) (4) with Inspectors Fontan, Cheung and Jackson. (b) (4) (b) (4) are required to enter (b) (4) (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) explained the manufacturing processes from formulation, (b) (4) (b) (4) filling to vial inspection and packaging. I observed the formulation process/lipid nanoparticle (LNP) formation, the formulation booth (b) (4) and the filling process (b) (4) I revisited the (b) (4) on 6/30/2021 with Inspector Fontan and observed the (b) (4) and the (b) (4) (b) (4) process using the (b) (4) (b) (4) No issues were identified.

Qualification of the (b) (4)
(Written by ZW)

One of the critical processes in BNT162b2 manufacturing is the formulation process in which (b) (4) and this process is performed using the (b) (4) (b) (4)

(b) (4)

I interviewed (b) (6), (b) (7)(C) for the qualification of the (b) (4). He stated that the (b) (4) The (b) (4) is manufactured by (b) (4) and the (b) (4) is developed by (b) (4). The (b) (4) consists of (b) (4) To verify/qualify (b) (4) the firm uses (b) (4) such as (b) (4) I reviewed the following documents without issues noted (Table ZW5):

Table ZW5. Qualification of the (b) (4)

Doc ID	Document	Date	Summary
(b) (4)			

(b) (6), (b) (7)(C) stated that it takes about (b) (4) The (b) (4) have to be (b) (4) I asked (b) (6), (b) (7)(C) how the (b) (4) is monitored for each (b) (4) (b) (6), (b) (7)(C) stated that each (b) (4) is connected to a (b) (4) and then I requested and reviewed the (b) (4) documents. The (b) (4) calibration is performed by (b) (4) (b) (4) I requested the initial calibration of the (b) (4) The (b) (4) were initially calibrated in May 2020 and it appears that the (b) (4) and the certificate was issued to (b) (4) I reviewed the certificates without concerns. The illustrated service procedures can be seen in **Exhibit ZW-2**. I had no issues with the documents I reviewed.

(b) (4)
(Written by ZW)

The firm utilizes a number of (b) (4) (b) (4) I requested and reviewed the following qualification documents (Table ZW6) without concerns.

Table ZW6. Qualification of the (b) (4)

Doc ID	Doc title	Date	Summary
(b) (4)			

Compressed air
(Written by ZW)

I noted that the compressed air is used to (b) (4) during the (b) (4) I requested to review the qualification of the compressed air. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) assisted me with reviewing the documents and answered my questions. He stated that the firm monitored the compressed air (b) (4) by monitoring the (b) (4) I reviewed the

Doc ID: (b) (4) "System acceptance and release report: compressed air (b) (4) of (b) (4) (machine ID (b) (4) , the approval date 9/25/2020. This report documents the verification activities, such as (b) (4) (b) (4) I also requested and reviewed the (b) (4) maintenance records from January 2021 to June 2021. The maintenance log shows the testing results for (b) (4) (b) (4) I asked about (b) (4) and was told it is considered to be similar to (b) (4) I compared the testing results against the specifications without issues noted.

(b) (6), (b) (7)(C) stated that the (b) (4) is also used (b) (4) (b) (4) Because of the time constraint, I did not request and review the (b) (4) qualification documents.

(b) (4) *Sterilization*
(Written by LF)

I discussed the (b) (4) sanitization with (b) (6), (b) (7)(C) (b) (4) (b) (4) No concerns were noted.

Water purification system
(Written by ZW)

The firm (b) (4) water system for purified water and water-for-injection (WFI) for the (b) (4) facility. I conducted the walk-through inspection on 7/2/2021, and met (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) stated that there are (b) (4) (b) (4) water is processed with the (b) (4) (b) (4) I checked these (b) (4) and examined piping configuration for any possible (b) (4) without concerns. The equipment appeared in good maintenance conditions without leakages or wetness on the floor. I also inquired about the (b) (4) and the shelf life and found no issues. The water quality is monitored with (b) (4) I noted the (b) (4) on the (b) (4) as (Table ZW-7) and they met both USP and internal specifications for the purified water (b) (4)

Table ZW7. (b) (4) of the purified water (b) (4)

The monitoring data are (b) (4) (b) (4) are also equipped with the (b) (4) (b) (4) I asked about the (b) (4) (b) (4) (b) (6), (b) (7)(C) stated the purified water is (b) (4) I randomly selected and audited three (b) (4) records for the (b) (4) (b) (4) without issues. Per (b) (6), (b) (7)(C) the (b) (4) has been (b) (4) and it will occur (b) (4) (b) (4)

The WFI facility is housed in (b) (4) WFI is generated by the (b) (4) process and stored in a (b) (4) I inspected the (b) (4) and the (b) (4) and they appear in good working condition. WFI is kept at (b) (4) (b) (4) I also inspected the (b) (4) of the (b) (4) (b) (4) and found no issues.

At the user point in the (b) (4) room of (b) (4) I noted the (b) (4) (b) (4) (b) (6), (b) (7)(C) stated that if the required WFI (b) (4) has not yet been reached the (b) (4) When the required WFI (b) (4) has been reached, the (b) (4) At the user point, the WFI (b) (4) is (b) (4) (b) (4) before use.

I have no issues with the purified water. See below for the WFI qualifications.

WFI Qualification
(Written by ZW)

I requested and reviewed the (b) (4) "Initial environmental control qualification report for WFI in (b) (4) (b) (4) approved on 7/14/2020. The protocol for the qualification was approved on 5/15/2020. (b) (4) (b) (4) The specifications are as follows:
(b) (4)

The firm performed the (b) (4) performance qualification in June 2020 and the samples were collected (b) (4) I reviewed the testing results, and they met the specification.

I had no issues with the (b) (4) water purification system.

Cleaning Validation
(Written by LF)

I reviewed the cleaning program with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and Bojan Wijremblewski, SME, Cleaning Validation.

The cleaning validation program is governed by SOP- (b) (4) V (b) (4) effective February 24, 2020. The SOP is attached in **Exhibit LF- 6**. (b) (4) a cleaning validation, a cleaning procedure needs to be in place that can be validated. The procedure must be in at least draft form and must include the following:

(b) (4)

If a new analytical method is required, the (b) (4)
(b) (4)

Cleaning validation studies are divided into initial validation, verification, revalidation and routine requalification. Initial validation, verification, and revalidation are triggered by a change control. The routine requalification is based on (b) (4) (b) (4) For product (b) (4) monitoring, a (b) (4) approach is used. The (b) (4) is based on (b) (4) (b) (4) (b) (4) which is used for the cleaning studies. (b) (4) (b) (4)

(b) (4)

Initial cleaning validation is performed for (b) (4) (b) (4) (b) (4) If this cannot be confirmed a complete cleaning validation is performed. For a list of all the products manufactured on filling line (b) (4) including the category of product, and allowable (b) (4) see **Exhibit LF-7.**

The (b) (4) is required to be implemented (b) (4) cleaning validation. The (b) (4) used for validation may be (b) (4) (b) (4) The (b) (4) is part of the microbiological cleaning validation covered in (b) (4) 'Rationale: Cleaning validation: Microbiological cleaning validation approach", approved 29 Apr 2020. This document describes equipment storage conditions, specific manufacturing area cleaning procedures, preventive measures, (b) (4) analytical methods used and (b) (4) approach for potential microbial contamination after cleaning and during storage. The storage conditions for formulation equipment (b) (4) are summarized below:

Equipment	Storage Conditions
Formulation materials (b) (4)	-Stored in Grade (b) (4) (b) (4)
(b) (4)	-Stored in Grade (b) (4) (b) (4) -Stored in Grade (b) (4)

(b) (4) (b) (4) During a walkthrough of the (b) (4) filling area, I observed the storage of cleaned equipment used for filling the BNT162b2 COVID vaccine in (b) (4) designated for the COVID vaccine in Room (b) (4) The (b) (4) used for (b) (4) was (b) (4) Room (b) (4)

Twelve documents were reviewed related to the cleaning validation of equipment used for the manufacture of the BNT162b2 COVID 19 Vaccine in (b) (4) (b) (4)

The (b) (4) of (b) (4) is performed (b) (4) (b) (4) The (b) (4) are replaced with (b) (4) during the execution of the (b) (4) The (b) (4) Cleaning Sequence consists of (b) (4)

(b) (4)

(b) (4)

The (b) (4) are performed in (b) (4) and the (b) (4) are performed in (b) (4) (b) (4) area (Room (b) (4)). See **Exhibit LF-8** (b) (4) Photo.

All the product contact parts for the (b) (4) remain in place for (b) (4) The product contact parts are made of (b) (4) Multiple (b) (4) tests are performed on the (b) (4)

(b) (4)

(b) (4) The (b) (4) cleaning was performed for (b) (4) successful repetitions.

Most of the equipment that is used for the (b) (4) of BNT162b2 is (b) (4) as indicated in the list below. (b) (4) during these tests. (b) (4) (b) (4) is used in production.

The table below summarizes the cleaning validation testing required for the (b) (4) (b) (4) equipment.

Equipment	Stage/ Production use	Type Cleaning	Test Runs	(b) (4)
(b) (4)				

Equipment	Stage/ Production use	Type Cleaning	Test Runs	(b) (4)
(b) (4)				

The (b) (4) samples taken were (b) (4) with (b) (4) The cleaning validation executed to date, met the required limits, however (b) (4) is still ongoing. Refer to **Discussion Item LF-1**. **See Exhibit LF-9**, (b) (4) memo and **Exhibit LF-10**, (b) (4)

Microbiological Cleaning Validation
(Written by LF)

Microbiological cleaning validation testing is performed (b) (4) (b) (4) protocols. The equipment listed below was chosen to verify that endotoxin and bioburden can be (b) (4) (b) (4) using the current cleaning procedures.

Equipment	Type Cleaning/Location	Test Runs	Sampling
(b) (4)			

Equipment	Type Cleaning/Location	Test Runs	Sampling
(b) (4)			

Bioburden (b) (4) were taken at (b) (4) with (b) (4) Bioburden acceptance criteria for the testing is (b) (4) The endotoxin limit is (b) (4) The microbiological cleaning validation executed to date, met the required limits, (b) (4) (b) (4) Refer to **Discussion Item LF-1**. See **Exhibit LF-11**, Microbiological cleaning memo.

(b) (4) The cleaning validation for the (b) (4) parts consisted of (b) (4) testing to demonstrate the (b) (4) with the same limits used for (b) (4) The cleaning validation was successful and validated a (b) (4) of (b) (4) The cleaned (b) (4) parts are (b) (4)

In addition, verification tests were performed for the (b) (4) (b) (4) (b) (4) The testing verified that the (b) (4) (b) (4) on the equipment is (b) (4) (b) (4) samples were taken from (b) (4) No concerns were noted.

Sterilization Validation
(Written by LF)

Sterilization validation summaries for all direct product-contact equipment were reviewed. Processing equipment is sterilized (b) (4) (b) (4) are validated by performing (b) (4) (b) (4) The (b) (4) process is validated to show (b) (4)

(b) (4) The product (b) (4) are sterilized (b) (4) (b) (4) (b) (4) test locations are chosen according to (b) (4) (b) (4) (b) (4)

For the (b) (4) type, there are (b) (4) however, (b) (4) were determined to be (b) (4) (i.e., no worst-case (b) (4) could be determined). (b) (4) validation run was performed for (b) (4) with a minimum of three validation runs for the (b) (4) type.

In addition, three (b) (4) validation runs were successfully performed to confirm that the (b) (4) after the (b) (4) Requalification of the (b) (4) of the (b) (4) type is performed (b) (4) (b) (4)

The bulk drug product is sterile filtered (b) (4) (b) (4) The bulk drug product (b) (4) is filtered using (b) (4) (b) (4) filters (b) (4) The (b) (4) sterilizing filters are (b) (4) using a (b) (4) (b) (4)

(b) (4)

(b) (4) Filter integrity tests are performed on (b) (4) (b) (4) when I observed part of the set up during a walkthrough on July 1, 2021. (b) (4) (b) (4) (b) (4)

In addition, a (b) (4) bioburden sample is collected from (b) (4) (b) (4) Bioburden is also tested during (b) (4) (b) (4) See **Exhibit LF-4** for a picture of the (b) (4) (b) (4)

The (b) (4) sterilization process is controlled by a (b) (4) (b) (4)

(b) (4) The (b) (4) is set up according to SOP- (b) (4) ver. (b) (4) The (b) (4) phases consist of:

(b) (4)

During (b) (4) various (b) (4) are (b) (4) for certain durations.

For the validation, (b) (4) (b) (4) were placed in (b) (4) locations including (b) (4) (b) (4) (b) (4) The acceptance criteria are listed in the table below. A (b) (4) analysis is also performed evaluating the attained (b) (4) for the (b) (4) and the results of the (b) (4) instruments.

Previously, (b) (4) was validated and used for the BNT162b2 process (Mar 2019 and Sep 2020). The (b) (4) was updated per change control (b) (4) (b) (4) and change existing (b) (4) (b) (4) This change control referred to (b) (4) An additional change control (b) (4) (b) (4) included (b) (4) This was in preparation to (b) (4) (b) (4) (b) (4)

(b) (4) Integrity of these filters are controlled by (b) (4) integrity testing. (b) (4) was used for the (b) (4) when I observed part of the set up during a walkthrough on July 1, 2021. (b) (4) was transferred from (b) (4) (b) (4)

Seven sterilization validation documents were reviewed for the (b) (4) in (b) (4) for (b) (4) of (b) (4) (b) (4)

Sterilization Validation Summary of Formulation Equipment at Puurs:

Validation	Testing performed	Acceptance Criteria	Acceptance Criteria Met
(b) (4) (b) (4) *Revalidation* (b) (4)	(b) (4) Revalidation Performed Sep 2020	(b) (4)	Yes
(b) (4) (b) (4) *Revalidation* (b) (4)	(b) (4) Revalidation Performed Jan 2020		Yes
(b) (4)	(b) (4) Revalidation Performed Feb 2021 Reports Mar/Jun 2021		Yes

No Concerns were noted.

Stoppers
(Written by LF)

I discussed the stopper processing with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C). The (b) (4) (b) (4) area has (b) (4) stopper processor (b) (4) in room (b) (4) that is dedicated to the (b) (4) area. The stopper processor has (b) (4) stopper (b) (4) and (b) (4) of these are dedicated to BNT162b2 and the (b) (4) stoppers. There are also (b) (4) stopper processors in the (b) (4) (b) (4) (b) (4) (b) (4) During validation, the stopper processors are evaluated for (b) (4) (b) (4) (b) (4) No concerns were noted.

(b) (4) *Sterilization*
(Written by LF)

(b) (4)
(b) (4) The direct product contact parts of the
(b) (4)
(b) (4) If the analysis concludes that the revalidation runs are not reproducible a failure investigation will be performed, and corrective actions will be taken. Ten validation documents were reviewed for the (b) (4)
(b) (4)
sterilization.

The sterilization/depyrogenation validation studies to support the BNT162b2 process at Puurs are summarized below.

Depyrogenation/Sterilization at Puurs (b) (4)

Validation	Testing performed	Acceptance Criteria	Acceptance Criteria Met
Vial Depyrogenation (b) (4)	(b) (4) Last revalidation June 2020	(b) (4)	Yes
Stopper Depyrogenation and Sterilization (b) (4) (b) (4)	(b) (4)		Yes
	(b) (4) Jun 2020		Yes
(b) (4) *Decontamination-* (b) (4) (b) (4)	(b) (4) Revalidation Aug 2020		Yes

Validation	Testing performed	Acceptance Criteria	Acceptance Criteria Met
		(b) (4)	
(b) (4) *Sterilization* (b) (4)	(b) (4)		Yes
(b) (4) *Sterilization* (b) (4)			Yes

No Concerns were noted.

(b) (4) *Sterilization*
(Written by LF)

(b) (4)
(b) (4) The direct product contact parts (b) (4)
(b) (4) are cleaned and sterilized
(b) (4)

(b) (4)
(b) (4) the following
actions must be performed (b) (4)

(b) (4)

The decontamination is performed via a (b) (4) comprised of a (b) (4) located in the clean room (b) (4) During the decontamination, (b) (4) (b) (4) (b) (4) The decontamination (b) (4) consists of (b) (4) (b) (4)

(b) (4)

The sterilization of the (b) (4) is a (b) (4) process. The (b) (4) is regulated on (b) (4) During the sterilization (b) (4) the (b) (4) has to (b) (4) (b) (4) (b) (4) During validation, a worst-case (b) (4) The worst-case (b) (4) used the following parameters:

(b) (4)

(b) (4) (b) (4) The PQ protocol (b) (4) (b) (4) attached in **Exhibit LF-12** contains a system description and diagrams. (b) (4) (b) (4)

Seventeen validation documents were reviewed for the (b) (4) in support of vial depyrogenation, (b) (4) decontamination, stopper depyrogenation, (b) (4)

(b) (4) sterilization. The sterilization/depyrogenation validation studies to support the BNT162b2 process at Puurs are summarized below.

Depyrogenation/Sterilization at Puurs for (b) (4)

Validation	Testing performed	Acceptance Criteria	Acceptance Criteria Met
Vial Depyrogenation (b) (4)	(b) (4) Initial qualification June 2020 (3 runs) using 2mL vial	(b) (4)	Yes
Stopper Depyrogenation and Sterilization (b) (4) (b) (4)	(b) (4) Requalification performed (b) (4)		Yes
	(b) (4) Requalification performed (b) (4)		Yes
(b) (4)	(b) (4) Testing performed September 2020		Yes
	(b) (4) (b) (4) Study Oct 2020		Yes
	(b) (4)		Yes

Validation	Testing performed	Acceptance Criteria	Acceptance Criteria Met
(b) (4)	(b) (4)	(b) (4)	
	Testing performed July and August 2020 (b) (4)		
	(b) (4) September 2020 (b) (4)		Yes
	(b) (4) (b) (4) August 2020 (b) (4) performed August 2020		Yes
	(b) (4) executed August and Sept 2020 (b) (4)		Yes
(b) (4)			

(b) (4)

No concerns were noted.

MATERIALS SYSTEM

Supplier Management
(Written by SJ)

Management of suppliers is performed according to SOP (b) (4) version (b) (4) *Supplier Management* effective December 14, 2020. The supplier management process includes selection, qualification, use and ongoing performance review of all vendors in the supply chain. The supplier management process also includes the management of Quality/Technical Agreements, quality risk assessment for all suppliers of production materials and or providers of outsourced services within a QMS-process.

SOP (b) (4) Supplier Qualification and Re-Assessment effective 28 April 2021 describes the initial qualification and requalification of suppliers of production materials. The initial qualification requires a quality risk assessment, audit, and quality agreement. The Pfizer site must first determine if the supplier is on the supplier list per SOP- (b) (4) A quality risk assessment is performed per SOP (b) (4) then an audit of the supplier which is a (b) (4) is performed according to SOP (b) (4) Suppliers are assigned one of (b) (4) in the qualification process: (b) (4) (b) (4) A supplier is (b) (4) when there is a quality risk assessment, onsite audit, and a quality agreement between the supplier and Pfizer.

The list of raw materials for BNT162b2 drug product contained (b) (4) material numbers. The supplier qualification history for each raw material supplier associated with the material number was reviewed from the (b) (4) system which manages the raw material supplies. (b) (6), (b) (7)(C) presented the process flow for the supplier qualification. (b) (6), (b) (7)(C) presented each supplier status as it pertains to the risk assessment, frequency of the onsite audits, last onsite audit date prior to the manufacture of the PPQ batches and the quality agreement between the supplier and Pfizer. All suppliers for BNT162b2 drug product met the requirements for qualified status.

Material control
(Written by ZW)

I reviewed the firm's procedures for the incoming materials with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and Ms. Annelien Everaert, Quality Lead Operation. SOP-(b) (4) "Check of raw materials batch record", effective date 3/25/2021, is one of the SOPs that handles the incoming materials. Briefly, the firm uses a checklist to check the conformity such as (b) (4) (b) (4) This SOP also has instructions on how to enter the information into the (b) (4)

I requested to review the (b) (4) documents for (b) (4) particularly the batch (b) (4) which was used in the validation batches for this application. (b) (6), (b) (7)(C) stated that the (b) (4) was supplied by (b) (4) and the (b) (4) was performed at (b) (4) I reviewed the following documents without discrepancies noted:

- (b) (4) Receipt- (b) (4) dated 10/16/2020
- (b) (4) for release of raw materials (batch record), dated 12/2/2020
- SOP- (b) (4) Receipt (b) (4) approved 5/20/2020 (version (b) (4))

(b) (4)

I also requested and reviewed one randomly selected lot of the glass vials, lot (b) (4) to evaluate the procedures for (b) (4) of the containers. The checklist used is Form (b) (4) and the glass vial supplier is (b) (4) with COA. The firm checked (b) (4)
I reviewed the following documents without issues:

- Form- (b) (4) Checklist for release of (b) (4) devices, dated 10/26/2020
- SOP (b) (4) Inspection of vials, approved 2/11/2021 (version (b) (4))

PRODUCTION SYSTEM

Manufacturing codes
(Written by ZW)

(b) (6), (b) (7)(C) presented to me the SOP (b) (4) for batch number assignment (effective date Aug. 24, 2020). (b) (6), (b) (7)(C) stated the batch numbers are (b) (4) and used in the (b) (4) The batch number for each material has (b) (4)

(b) (4) The materials can be (b) (4) (b) (4) For the finished product, the batch number starts with two letters, followed by four digits, such as (b) (4) (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) stated (b) (4) she is able to (b) (4) (b) (4) but not the (b) (4)

Process Validation
(Written by AC)

To support EUA for BNT162b2, (b) (4) process validation approach was executed (b) (4) (b) (4) Pfizer named this (b) (4) validation as (b) (4) Performance Qualification (PPQ) (b) (4) (b) (4) under EUA in the US. (b) (4) PPQ required (b) (4) (b) (4) (b) (4) The first PPQ DP batch generated at Puurs was lot # (b) (4) at (b) (4) (b) (4) and the lot was filled and finished at the (b) (4) line. During (b) (4) process validation at Puurs, an additional (b) (4) PPQ DP batches (also called process validation lots, PV) were manufactured (b) (4) (b) (4) and filled/finished in (b) (4) fill lines (b) (4) to demonstrate that the process at Puurs can consistently produce drug product (DP) lots of acceptable quality through the above-mentioned manufacturing steps (**Exhibit AC-2**).

Due to the (b) (4) DP batch (b) (4) an additional PPQ run with a (b) (4) was performed (b) (4) (b) (4) (b) (4) (b) (4) No adverse effects on product quality are anticipated (b) (4) No additional sampling or (b) (4) were performed during the process validation of the (b) (4) DP batch (b) (4) In addition, no (b) (4) was included in this validation run (b) (4) (b) (4)

All PPQ batches were executed according to the defined protocols and evaluated with predetermined acceptance criteria. Additional sampling was performed during the PPQ lots, (b) (4) to gather additional product data. Validation of (b) (4) was included in the design of process validation protocol. However, (b) (4) PPQ lot from (b) (4) was challenged with the worst-case cumulative holds (b) (4) (**Exhibit AC-3**). Additional discussion

on the validation of (b) (4) is included in the section of Discussion with Management. All required process controls including process parameters and (b) (4) limits were met for all PPQ lots. Although deviations were raised during process validation, all of them were adequately addressed. Some deviations led to initiation of investigations and CAPA was implemented if needed.

Pfizer also performed a process validation study to validate the (b) (4) (b) (4) in the DP manufacturing process. (b) (4) was executed in this validation study. The firm emphasized that it is not a common practice to (b) (4) during the DP manufacture; however, it is just a (b) (4) procedure to (b) (4) Pfizer is planning to (b) (4) to validate (b) (4) (b) (4) The validation protocol includes the (b) (4) (b) (4)

The approved validation master plan for the COVID-19 vaccine DP (b) (4) Protocol) stated that (b) (4) lots are included in stability studies (**Exhibit AC-4**). However, (b) (4) PPQ batches (b) (4) (b) (4) were not put on stability, leaving (b) (4) PPQ batch with the (b) (4) (b) (4) put on stability. The firm explained that the stability studies were monitored by St. Louis, Chesterfield site, so they (b) (4) with David Cirelli (Research Fellow Analytical R&D) from Andover, (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and Paul Rohlfing (Executive Director Vaccine CMC) to address this issue. David and (b) (6), (b) (7)(C) explained that a (b) (4) (b) (4) DP PPQ batch generated at the Kalamazoo site was put on stability and another (b) (4) DP PPQ batch from Puurs was also put on stability, therefore based on the firm's practice of (b) (4) in validating the process, Pfizer believed that sufficient stability data will be generated from the (b) (4) PPQ batches from different manufacturing (b) (4) since all (b) (4) have (b) (4) The number of PPQ batches put on stability study are further discussed under the section of Discussion with Management.

Reprocessing/Rework Process
(Written by AC)

An SOP-(b) (4) version (b) (4) Carrying out rework processes was used to guide the firm doing the reprocessing of (b) (4) A total of (b) (4) (b) (4) was observed at the (b) (4) during (b) (4) The (b) (4) rework (b) (4) included (b) (4) For the (b) (4) reprocessing step, the firm (b) (4) process validation plan for the formulation of COVID-19 vaccine. The (b) (4) step will (b) (4) (b) (4) The outcomes of this validation study support

(b) (4) step has no significant impact on final product quality. Additional information on (b) (4) was reviewed in the BLA and the assessment is discussed in the BLA review memo.

Media Fills
(Written by SJ)

SOP (b) (4) version (b) (4) *Media Fill* effective June 22, 2021 is a general procedure which describes that the purpose of the media fill is to evaluate the capabilities of aseptic processing activities. This procedure details that media fill process validation is performed for (b) (4) (b) (4)

Initial validation consists of a minimum of three (b) (4) successful media fills, performed on (b) (4) (b) (4) (b) (4) Routine requalification of each different aseptic/line is completed on a (b) (4)

Revalidation (b) (4) (b) (4) (b) (4) is performed (b) (4) (b) (4) Revalidation (b) (4) should occur in the case of a (b) (4) (b) (4) (b) (4) that concludes the need for requalification.

Media fill study design is documented in the Master Batch Record and in the media fill protocol. (b) (4) is the medium utilized in media fill qualification. Interventions performed during (b) (4) aseptic production are simulated during the media fill qualification studies. Interventions incorporated into the media fill batch record represent all the allowed interventions during (b) (4) production activities. All media fills are observed and documented by a qualified observer which is a representative of the Quality Authority.

SOP (b) (4) also details the media fill (b) (4) (b) (4) (b) (4) This SOP also describes the media fill evaluation, the criteria for pass/fail when contamination is detected and media fill investigation.

BNT162b2 drug product is filled (b) (4) the (b) (4) was installed and qualified for use in the year 2020, while the (b) (4) was installed and

qualified for use in 2014. Three media fills were conducted (b) (4) as part of the (b) (4) qualification for (b) (4) filling runs and three media fills for (b) (4) filling.

Exhibit SJ-1 is a copy of all media fills conducted on filling line (b) (4) to support BNT162b2 (BLA 125742) drug product. The list gives details as to (b) (4) (b) (4) (b) (4) The list of media fills provided by the firm, showed there were no contaminated media fill units. The (b) (4) validation on (b) (4) for (b) (4) run (b) (4) consisted of (b) (4) The number of vials filled for (b) (4) did not meet the criteria of greater than (b) (4) vials. A root cause analysis was initiated as Deviation (b) (4) see **Exhibit SJ-2.** The root cause for this deviation was identified as a failure of the (b) (4) (b) (4) The media fill validation and the root cause investigation were discussed with (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) explained that even though Media Fill (b) (4) did not meet the requirement for greater than (b) (4) vials, all vials from the batch were (b) (4) and met the requirement for sterility/no growth. In addition, the (b) (4) media fill (b) (4) run on (b) (4) represented the worst case as (b) (4) media fill was the last batch filled after a (b) (4) run greater than (b) (4) other media fill batches were also filled (b) (4) final batch of the (b) (4)

Media Fill Protocol and Report for the Introduction of a New Vial Filling Line (b) (4) (b) (4) *and COVID 19 Vaccine*, (b) (4) were reviewed, and no objections noted, see **Exhibit SJ-3.** The report describes the results for the introduction of a liquid filling process on a new line, all media fills were specific for COVID 19 vaccine.
In addition to the overall protocol and summary, *Media Fill Report for the COVID 19 Vaccine Product-Specific Media Fill on the* (b) (4) *Vial Filling Line* (b) (4) (b) (4) were reviewed, and no objections were noted see **Exhibit SJ-4.**

Media fill batch records for (b) (4) and the filling section of the batch record for PPQ batch (b) (4) were reviewed. The media fill batch record review included evaluation of (b) (4) (b) (4)

The media fill batch record (b) (4) and the filling section of a commercial COVID 19 vaccine mRNA batch (b) (4) batch of a (b) (4) on (b) (4) were reviewed. The aseptic operations performed (b) (4) were executed per the media fills records reviewed. It should be noted that (b) (4) is not simulated as part of the media fills and hence was not reviewed during media fill review. (b) (4) (b) (4) is performed at the (b) (4) and is not performed (b) (4) The media fills are designed to incorporate the use of the same (b) (4) which is also used in the COVID 19 mRNA vaccine commercial batches and was used in the COVID 19 vaccine PPQ batches. No

objections were noted with the media fill design and simulation of aseptic filling operation.

Environmental Monitoring
(Written by SJ)

SOP (b) (4) *Routine EM Program* (b) (4) and SOP (b) (4) *Routine EM Program* (b) (4) describes the types of environmental monitoring, sampling locations, frequency and the alert and action limits for classification rooms. The firm performs active air sampling, passive air sampling, surface monitoring and particle monitoring. The Grade (b) (4) monitoring includes the active air sampling by (b) (4) passive air sampling utilizing (b) (4) Surface sampling also includes (b) (4) monitoring which is managed under SOP (b) (4) Particle monitoring for non-viable particulates is described in SOP (b) (4). (b) (4) are equipped with a (b) (4) (b) (4) consisting of particle counters that are controlled (b) (4) (b) (4)

Environmental monitoring frequency, alert and action limits for (b) (4) are provided in the tables below:

Frequency and Limits for (b) (4) **Grade** (b) (4) **Area** (b) (4)

Grade (b) (4)				
Test	**Performer**	**Frequency**	**Alert limit**	**Action limit**
(b) (4)				

Frequency and Limits (b) (4) **Grade** (b) (4) **Areas**

Grade (b) (4) **Rooms**				
Test	**Performer**	**Frequency**	**Alert limit**	**Action limit**
(b) (4)				

Grade (b) (4) Rooms				
Test	**Performer**	**Frequency**	**Alert limit**	**Action limit**
(b) (4)				

Frequency and Limit (b) (4) **Grade** (b) (4) **Areas**

Grade (b) (4)				
Test	**Performer**	**Frequency**	**Alert limit**	**Action limit**
(b) (4)				

Frequency and Limit (b) (4) **Grade** (b) (4) **Areas**

Grade (b) (4)				
Test	**Performer**	**Frequency**	**Alert limit**	**Action limit**
(b) (4)				

Frequency and Limit for (b) (4) **Grade** (b) (4) **Area** (b) (4)

(b) (4)			
Test	Performer	Frequency	Action Level
(b) (4)			

(b) (4)			
Test	Performer	Frequency	Action Level
(b) (4)			

Frequency and Limits (b) (4) **Grade**(b) (4) **Areas**				
Test	Performer	Frequency	Alert level	Action level
(b) (4)				

Frequency and Limits (b) (4) **Grade** (b) (4) **Rooms**				
Test	**Performer**	**Frequency**	**Alert level**	**Action level**
(b) (4)				

Frequency and Limits (b) (4) – Grade (b) (4)

Grade (b) (4)		**– Grade** (b) (4)	**– Grade**(b) (4)	
Test	**Performer**	**Frequency**	**Alert level**	**Action level**
(b) (4)				

Grade (b) (4) **– Grade** (b) (4) **– Grade** (b) (4)				
Test	**Performer**	**Frequency**	**Alert level**	**Action level**
(b) (4)				

Frequency and Limit (b) (4)

Material transfer from the (b) (4) **to grade** (b) (4)				
Test	**Performer**	**Frequency**	**Alert level**	**Action level**
(b) (4)				

ECO = environmental monitoring team

In addition to the review of the environmental monitoring SOPs mentioned above the rationale for environmental monitoring sampling locations in (b) (4) (b) (4) and the EM trends for (b) (4) from March 2020 to March 2021 were reviewed. No adverse trends were identified in the Grade (b) (4) Review of EM trends in (b) (4) Grade (b) (4) and (b) (4) areas including the Grade (b) (4) area from April 2020 – April 2021 revealed no objectionable trends. It should be noted that the same sampling and the same number of sampling sites as documented in the EM rationale were monitored during the PPQ batch (b) (4)

A list of environmental monitoring excursions prepared by the firm was presented for review. The list included the investigation number, room classification and of the organism identification. There was a total of ten excursions, none of the excursions were identified in in the Grade (b) (4) areas. All ten excursions were in the Grade (b) (4) areas, no mold organism was identified and although the individual excursions reached the action limit, no adverse trend was identified.

Disinfectant Efficacy
(Written by SJ)

The list of disinfectants used in the Grade (b) (4) areas of (b) (4) and (b) (4) (b) (4) are as follows:

(b) (4)

I reviewed disinfectant efficacy study (b) (4) Performance Qualification Protocol and Result, approved by Quality on August 30, 2019. The study results show that the use of (b) (4) technique met acceptance criteria of (b) (4) (b) (4) (b) (4)

Disinfectant efficacy study (b) (4) QA approved on December 23, 2016 describes the qualification of (b) (4) method on surfaces found in Puurs Belgium manufacturing site. (b) (4) efficacy met the criteria for (b) (4) The disinfectant efficacy study (b) (4) approved by QA December 23, 2016 describes the qualification of (b) (4) for (b) (4) using the (b) (4) method and surfaces. (b) (4) met the acceptance criteria of (b) (4)

Disinfectant efficacy study (b) (4) describes the (b) (4) for (b) (4) describes the efficacy study for (b) (4) (b) (4) for (b) (4) and (b) (4) describes the (b) (4) for (b) (4) All test results met the criteria for the category for which the study was performed. No objectionable conditions were noted for the studies reviewed.

Visual inspection and automated inspection machines
(Written by LF)

Filling lines (b) (4) use automated vial inspection machines (b) (4) which undergo multiple phases of validation including (b) (4) (b) (4) followed by phase 1 and phase 2 performance qualifications (PQs). The phase 1 PQ tests determine the machine performance by:

(b) (4)

The goal of the phase 1 testing is to identify (b) (4) (b) (4) (b) (4) can be seen in **Exhibit LF-13**. 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. Multiple PQ documents were presented and reviewed. :

(b) (4) filling line inspects vials using the (b) (4) and the (b) (4) (b) (4) The (b) (4) filling line also uses (b) (4) inspection machine, however the (b) (4)

The (b) (4) used for (b) (4) filling line (b) (4) (b) (4) is a (b) (4) inspection machine that can (b) (4) (b) (4) (b) (4) The PQ protocol described the inspection stations that are used for the COVID-19 vaccine inspection which occur in the following order:

Stations	Detection
(b) (4)	

The (b) (4) used for (b) (4) filling line (b) (4) (b) (4) is a (b) (4) used for (b) (4) (b) (4) It consists of (b) (4) (b) (4) (b) (4) Vials are (b) (4) (b) (4) Any rejected vials are (b) (4) and are rejected. Any non-tested vials (usually due to (b) (4) are also rejected.

AQL testing performed during validation for the (b) (4) consisted of a sample size of (b) (4) vial requiring critical defects (b) (4) major defects (b) (4) and minor defects (b) (4)

Visual Inspection
(Written by LF)

On June 24, 2021, we (LF, AC, SJ, ZW) witnessed filling on (b) (4) in Room (b) (4) The filling of Batch (b) (4) was in progress. The (b) (4) automated visual inspection machine was processing vials at a speed of (b) (4) I requested the Electronic Batch Record (EBR) results for the inspection of batch (b) (4) The parts of the batch record provided included the verification (set up) process for the (b) (4) inspection machine and the (b) (4) the AQL sampling performed, and the end verification performed for the (b) (4) (b) (4) I was also provided the EBR reports for the inspection. The (b) (4) report included a summary of the following results for the Batch:

- (b) (4)
- Incoming total vials: (b) (4)
- Inspected vials: (b) (4)
- % good: 96.3%

- Total rejected: (b) (4) (3.7%)
- Rejected categories summarized in the report included:
  (b) (4)
- (b) (4)

The (b) (4) record report from the EBR was also requested for Batch (b) (4) The (b) (4) report included (b) (4) (b) (4) total rejected vials at (b) (4) total rejected vials at the (b) (4) (b) (4) (b) (4) The (b) (4) for Batch (b) (4) was (b) (4) which was deemed acceptable. No concerns were noted.

Production in (b) (4)
(Written by LF)

We (ZW and LF) observed operator (b) (6), (b) (7)(C) perform the (b) (4) (b) (4) Room (b) (4) on June 30, 2021. The (b) (4) (b) (4) was performed using a (b) (4) (b) (4) (b) (4) the operator confirmed (b) (4) in the EBR. This information is (b) (4) transferred into the batch record (b) (4) (b) (4)

The (b) (4) room is also used for the (b) (4) Extensive cleaning of all surfaces and floors in the room is required (b) (4) A picture of the (b) (4) is attached in **Exhibit LF-10**.
No concerns were noted.

In process bioburden and endotoxin results
(Written by LF)

In process bioburden and endotoxin results for (b) (4) was requested as a pre-request prior to the start of the inspection. (b) (4) was provided for lots made from October 30, 2020 to May 21, 2021 (b) (4) The complete list is provided in **Exhibit LF-14**. Information was provided from the manufacturing steps listed below and the results were all within the action limits except for Lot (b) (4) manufactured on November 12, 2020. The deviation related to this excursion was reviewed and found acceptable. Refer to the Deviation section under Quality Systems. No concerns noted.

In Process Testing (IPT) Step	Action limit
(b) (4)	
(b) (4)	

(b) (4) *Management*
(Written by LF)

The (b) (4) management program at Pfizer Puurs is described in SOP- (b) (4) ver. (b) (4) (b) (4) Management (b) (4) effective: June 18, 2021. The SOP covers management of (b) (4) for (b) (4) (b) (4)

(b) (4) are cleaned with (b) (4) The (b) (4) are decontaminated (b) (4) to (b) (4) are visually checked (b) (4) (b) (4) If a (b) (4) is discovered in a (b) (4) an immediate assessment is conducted per SOP- (b) (4) to determine immediate action and whether opening an investigation is appropriate.

The integrity of the (b) (4) is also verified using a (b) (4) (b) (4) surface monitoring is conducted for each (b) (4) In the case of any excursions, a deviation is always opened. A trend analysis is carried out (b) (4) to evaluate any (b) (4) found in the (b) (4) Preventive actions are also reviewed, and additional preventive actions are defined, if deemed necessary. No concerns were identified.

Contamination and Cross-Contamination Controls
(Written by LF)

The (b) (4) Building is a dedicated multi-product facility for vaccine manufacturing. Formulation of BNT162b2 for (b) (4) use is performed in the (b) (4) Building. Currently, the (b) (4) manufactured in the (b) (4) Formulation Area are (b) (4) the COVID vaccine (BNT162b2). (b) (4) uses (b) (4) (b) (4) In general, operations personnel are (b) (4) (b) (4) filled on filling line (b) (4) is the COVID Vaccine (BNT162b2). 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.

The following procedures pertaining to cross contamination were reviewed:

- SOP- (b) (4) MSOP: Cross contamination management ver. (b) (4) effective June 28,2021
- SOP- (b) (4) SOP: Process Design and Qualification ver. (b) (4) effective February 23, 2021
- SOP- (b) (4) MSOP: Product Introduction and Product Related Changes, ver. (b) (4) effective June 7, 2018
- (b) (4) Cross contamination risk management for COVID vaccine, (b) (4) (b) (4) manufacturing (b) (4) ver. (b) (4) effective: June 25, 2021
- (b) (4) Quality Risk Management: Potential Cross-Contamination (b) (4) Plant, ver. (b) (4) effective: June 28, 2021

SOP- (b) (4) outlines the cross-contamination assessments required based on health-based exposure limits and risk assessment, and segregation requirements based on product class. Quality Risk Management (QRM) System proactively assesses the potential risks and implements necessary controls such as:

(b) (4)

(b) (4)

Toxicologists in Pfizer's Technical Review Committee (TRC) assign the product class to each Pfizer drug substance. The TRC is a multi-disciplinary group within Global Quality Operations and Environmental and Health and Safety comprised of experts that characterize the hazards of molecules and classify them into a product class. The rules for the implementation of the segregation are listed in Appendix 1 of SOP-(b) (4) The SOP is attached in **Exhibit LF-15**. Segregation practices are evaluated based on process step such as (b) (4)
(b) (4)
(b) (4) The products are grouped based on risk, as follows:

(b) (4)

(b) (4)

Risk assessment (b) (4) Cross contamination risk management for COVID vaccine, (b) (4) manufacturing in (b) (4) listed above was reviewed. The assessment classified the COVID vaccine as (b) (4)
(b) (4)

(b) (4)

(b) (4) formulation for the COVID vaccine is performed in (b) (4) COVID vaccine filling is performed on (b) (4) Vial Filling Line (as proposed in the BLA 125742/0) and (b) (4) Vial Filling Line (b) (4)
The active ingredient in the COVID vaccine (mRNA) was determined to be (b) (4) (b) (4) The manufacturing activities in the (b) (4) area are currently broken down as follows:

(b) (4)

According to Risk assessment (b) (4) cleaning activities are finalized for COVID vaccine on the (b) (4) vial line. The risk assessment is attached in **Exhibit LF-16**.
Cleaning activities are also finalized for the COVID Vaccine (b) (4) (b) (4) on vial filling line (b) (4) Cleaning validation is (b) (4) (b) (4) Note: The (b) (4) vial line is (b) (4) (b) (4) The cleaning validation activities for (b) (4) (b) (4) the (b) (4) vial filling line and the (b) (4) line are finalized. (b) (4) (b) (4) (b) (4)

The risk assessment contains further detail regarding the (b) (4) (b) (4) amount of each drug product, (b) (4) (b) (4) There is also an assessment of risk and risk reduction for procedures performed (b) (4) (b) (4)

(b) (4) to the Grade (b) (4) filling (b) (4) is (b) (4) (b) (4)

(b) (4)
(b) (4)

(b) (4) Quality Risk Management: Potential Cross-Contamination (b) (4) ver. (b) (4) effective: June 28, 2021, listed above was reviewed. The risk assessment is attached in **Exhibit LF-17**. The (b) (4) area consists of (b) (4) (b) (4) products (b) (4) (b) (4) COVID (b) (4) (b) (4) can be formulated in the (b) (4) area.

(b) (4)

(b) (4) COVID is filled on the (b) (4) filling lines, as previously mentioned, on (b) (4) filling line (b) (4) Note: Filling on (b) (4) was authorized as part of EUA 27034 and the (b) (4) (b) (4) is (b) (4)

The manufacturing activities in the (b) (4) area are currently broken down as follows:

(b) (4)

Product contact (b) (4) COVID formulation and filling equipment are (b) (4) (b) (4) The (b) (4) filling line is used for COVID vaccine (b) (4) filling line is (b) (4) (b) (4) (b) (4)

Additional controls in place include:

- Electronic batch record (EBR) control by (b) (4) (b) (4)
- (b) (4) is only performed using (b) (4) (b) (4) COVID vaccine for formulation and filling.
- Formulation booths (b) (4) (Room (b) (4) and (b) (4) (b) (4) filling line are used in a (b) (4) (b) (4) which are documented in the EBR.
- (b) (4) after performing any processing activities (b) (4) and filling (b) (4)
- A (b) (4) of the cleaning process is performed after each cleaning and documented in the EBR.
- The (b) (4) is used on a (b) (4) basis, (b) (4) (b) (4)

No concerns were noted.

PACKAGING AND LABELING SYSTEMS
(Written by ZW)

I conducted a walkthrough of the (b) (4) packaging line on 7/2/2021. As mentioned earlier, the firm has (b) (4) packaging lines for the BNT162b2 vaccine. (b) (4) (b) (4) Because of time constraint, I did not inspect the (b) (4) (b) (4) packaging line.

I met (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) They explained the packaging process and answered my questions. Per (b) (6), (b) (7)(C) the (b) (4) packaging line currently is operating (b) (4) (b) (4) I observed that the packaging line is (b) (4) (b) (4) The filled vials are (b) (4) into the packaging (b) (4) The label is applied to each vial and checked (b) (4) for accuracy. (b) (6), (b) (7)(C) stated that the labels are (b) (4) the lot # and expiry are added (b) (4) (b) (4) The labeled vials are loaded (b) (4) square flat "pizza box", 195 vials per box. (b) (4) (b) (4) verify the count before he (b) (4) the pizza

box. (b) (4) pastes the (b) (4) label on the box and packs (b) (4) boxes (b) (4) The bundle is then placed in a (b) (4) for transport to the (b) (4) warehouse in the Building (b) (4) The (b) (4) can take up to (b) (4) (to fill one ultra-freezer). From the (b) (4) warehouse to the freezer farm, a temperature-controlled truck is used for transportation, and the deliver time takes (b) (4) I reviewed the (b) (4) on the truck from randomly selected days. No issues were noted.

LABORATORY CONTROL SYSTEM

Walkthrough of the (b) (4) Laboratory
(Written by AC)

The one analytical assay that I observed in the (b) (4) laboratory was (b) (4) (b) (4) (b) (4) The operator performed this assay for DP sample (b) (4) (b) (4) (b) (4) was qualified as the reference standard (b) (4) The reference standard can be used (b) (4) This reference is used for the generation of (b) (4) for the (b) (4) (b) (4) was used for the (b) (4) of the tested samples. The (b) (4) (b) (4) is calibrated (b) (4) and the calibration events are documented. Under the (b) (4) system, I saw that (b) (4) analysts are required to review the raw data. Only if all system/assay suitability checks fulfilled the acceptance criteria to demonstrate assay validity, the lab results can be approved. I did not identify issues of concerns regarding the execution of the assay and analyses of the raw data.

Review of Endotoxin assay
(Written by AC)

Endotoxin testing for BNT162b2 drug product (b) (4) is performed using a (b) (4) (b) (4) (b) (4) Due to (b) (4) (b) (4) step is performed (b) (4) (b) (4) The verification was performed using (b) (4) to monitor endotoxin content (b) (4) verification reports (b) (4) (b) (4) were generated to ensure the sample (b) (4) used (b) (4) with the bacterial endotoxin test for (b) (4) (b) (4) In the verification study report, the prepared samples were (b) (4) (b) (4) The

data demonstrated that the sample (b) (4) the final readout and supported that the verified (b) (4) is within the (b) (4) No issue of concern was identified for this assay.

Stability Study of BNT162b2 Drug Product
(Written by AC)

The current proposed shelf life for the BNT162b2 drug product stored at the real-time condition of -90 to -60°C is (b) (4) months. Data from the stability studies consists of (b) (4) lots (b) (4) (b) (4) lots (b) (4) and (b) (4) lots (b) (4) (b) (4) manufactured by Pfizer Puurs, Pfizer Kalamazoo, (b) (4) (b) (4) were presented during the inspection (**Exhibit AC-5**). All results, generated to date, met the acceptance criteria at the time of testing. However, results of some of the stability time points are not updated in a timely manner when this inspector reviewed their DP stability data onsite. After discussion with the Pfizer's stability team, they provided the updated stability results for the (b) (4) batches on June 29, 2021 and all updated stability results met the acceptance criteria at the time of testing.

Bioburden Test Method Verification
(Written by SJ)

Document (b) (4) Method Verification Report for (b) (4) (b) (4) in the Bioburden Test (b) (4) (b) (4) by (b) (4) on the (b) (4) (b) (4) The method verification was conducted per (b) (4) (b) (4) The method was executed with (b) (4) (b) (4) and (b) (4) using (b) (4) (b) (4) and (b) (4) using (b) (4) (b) (4) The acceptance criteria for the method verification are described as the (b) (4) from the (b) (4) product (b) (4) must be at least of (b) (4) (b) (4) The bioburden test for (b) (4) (b) (4) met all pre-established criteria hence the method was verified as acceptable.

The routine bioburden test method is described in (b) (4) version (b) (4) effective June 22, 2021. This method details the steps for routine bioburden testing via (b) (4) and results interpretation. The routine bioburden test method is in line with steps used in the bioburden method verification. No objectionable conditions were noted.

Sterility Test Method Qualification
(Written by SJ)

Document (b) (4) approved by (b) (4) January 2021 documents the (b) (4) sterility test method via (b) (4) for COVID 19 MRNA vaccine. The method verification was performed utilizing three different batches of the COVID 19 mRNA vaccine, (b) (4) (b) (4)

The results of the (b) (4) study for the COVID19 mRNA vaccine were successful in that both product and (b) (4) was comparable. (b) (4) version (b) (4) effective May 10, 2021 details the routine sterility test method for COVID-19 vaccine (b) (4) drug product in vials. This sterility test method was reviewed, and no issues were noted.

(b) (4) sterility test method was validated for the COVID-19 mRNA vaccine. Document (b) (4) approved by Quality 01 May 2021 *Validation Project Report for the Method Verification for Sterility Testing on Comirnaty* (b) (4) *Drug Product (vial) or COVID19 mRNA, BTN162b2* (b) (4) *Drug Product (Vial) using the* (b) (4) (b) (4) This (b) (4) sterility test follows the (b) (4) (b) (4) method however (b) (4) (b) (4) is utilized. The (b) (4) is a method for the detection of the presence of microorganisms (b) (4) (b) (4)

(b) (4) of the validation demonstrated the (b) (4) of the (b) (4) method for sterility testing (b) (4) The raw data to support the parameters used to define (b) (4) were as follows: (b) (4) (b) (4) were reviewed. No objections were noted.
(b) (4) validation study demonstrated that the presence of the COVID 19 mRNA vaccine product in the test sample (b) (4)

The raw data reviewed details the three batches of COVID19 mRNA vaccine were utilized in testing and the (b) (4) study was (b) (4) There were two deviation investigations during this study, the deviations were investigated, and a root cause was identified for each deviation.

The validation of the (b) (4) method with a (b) (4) (b) (4) met all specifications to be used as a (b) (4) method for COVID19 mRNA vaccine.

The (b) (4) sterility test method is described in (b) (4) version (b) (4) This method utilizes the (b) (4) and read out of results with (b) (4) as executed in the validation study.

During the inspection, I discussed sterility test failure with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) I questioned if there were any sterility test failures for COVID-19 mRNA vaccine and requested the associated deviations investigations. (b) (6), (b) (7)(C) stated there were no sterility failures at the site. I requested a signed statement that there is no sterility test failure for COVID19 mRNA batches. (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) provided a signed document attesting to no sterility failure for COVID-19 mRNA vaccines at the site see **Exhibit SJ-5**.

Sample (b) (4)
(Written by AC)

SOP- (b) (4) describes the procedure for (b) (4) COVID samples for analysis by (b) (4) Release samples are (b) (4) (b) (4) and stability samples are (b) (4) (b) (4) The protocol contains information on different sections: request of (b) (4) preparation of the accompanying documents, and preparation for (b) (4) All sections provide clear instructions, and I did not identify issues of concern on this protocol.

Sample retention program
(Written by ZW)

I reviewed the procedures for the reserved samples with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) She stated that she follows the SOP- (b) (4) for the sample retention. For each lot of the vaccine, the firm has (b) (4) groups of the retained samples: (b) (4) (b) (4)

Currently the vaccine shelf life is (b) (4) months. The (b) (4) samples are kept for (b) (4) (b) (4) and the (b) (4) samples for (b) (4) respectively. No issues were noted.

RECALL PROCEDURES

Product return and recall
(Written by ZW)

I reviewed the following recall and product return SOPs with (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) (b) (6), (b) (7)(C)

- SOP- (b) (4) "Market action management", effective date 4/21/2021 SOP- (b) (4) "Evaluation of returned goods COVID-19 vaccine", effective date 6/28/2021.

According to (b) (6), (b) (7)(C) there are no product returns or recalls since the launch of the vaccine. I reviewed the procedures without issues.

REFUSALS
(Written by LF)

We (LF, SJ, ZW, and AC) encountered no refusals during the current inspection.

No FDA Form 483 Observations was issued to the firm.

GENERAL DISCUSSION WITH MANAGEMENT

We discussed various issues with Management during the inspection which may require their attention including the following.

(Written by AC)

1. (b) (4) validation protocols were used to cover all test conditions and sampling plans needed to validate the (b) (4) supporting that the drug product manufacturing process consistently produces BNT162b2 drug product lots of acceptable quality under the commercial manufacturing range of (b) (4) (b) (4) Three batches (b) (4) manufactured at (b) (4) filling lines were included in the validation studies. All (b) (4) batches were put on stability, but (b) (4) batches was put on stability. The firm explained that the decision to put (b) (4) batch on stability was based on a (b) (4) and product (b) (4) lots produced at the Puurs and Kalamazoo sites. I advised them that in general (b) (4) (b) (4) is acceptable to be used for the design of process validation, but it is strongly recommended to get concurrence on your proposed (b) (4) from the agency prior to the execution of the study. This decision is product-specific and depends also on the level of characterization of the product. In addition, it is recommended to include at least three lots of your product in validating the worst-

case of the hold time (b) (4) The firm acknowledged these suggestions.

2. For the (b) (4) release analytical assays (b) (4) Puurs analytical laboratories, I suggested (b) (4) (b) (4) (b) (4) The firm acknowledged the suggestion.

(Written by LF)

1. Microbiological cleaning validation relating to equipment used for formulation and filling of the COVID19 Vaccine is not complete. The (b) (4) cleaning validation for the (b) (4) is also not complete. Memos provided by (b) (6), (b) (7)(C) (b) (6), (b) (7)(C) and (**Exhibit LF-11**, Microbiological cleaning validation status) and (b) (6), (b) (7)(C) (**Exhibit LF-9**, (b) (4) cleaning validation of (b) (4) were provided by the firm to summarize the status of the cleaning validation, estimated completion and next steps. During the discussion at the firm, I stated that FDA would cover the completion of these items as part of the review activities associated with BLA 125742/0.

EXHIBITS COLLECTED

LF-1a-d List of Personnel with whom We Interacted, opening and closing meeting attendees
LF-2 History of Business
LF-3 Opening Presentation
LF-4 (b) (4) and (b) (4)
LF-5 Warehouse Tour
LF-6 Cleaning Validation SOP-(b) (4)
LF-7 List of Products filled on (b) (4)
LF-8 (b) (4)
LF-9 (b) (4) memo
LF-10 (b) (4)
LF-11 Microbiological Cleaning Validation Status Memo
LF-12 PQ protocol (Doc ID: (b) (4) Sterilization of (b) (4)
LF-13 Visual Inspection (b) (4)
LF-14 In process bioburden and endotoxin results
LF-15 SOP-(b) (4) MSOP: Cross contamination management ver. (b) (4)
LF-16 (b) (4) Cross contamination risk management for COVID vaccine, (b) (4) (b) (4) manufacturing in (b) (4) ver. (b) (4)
LF-17 (b) (4) Quality Risk Management: Potential Cross-Contamination (b) (4) (b) (4) ver. (b) (4)

SJ-1 Copy of the List of Media Fills
SJ-2 Root Cause Analysis for Deviation (b) (4) associated with Media Fill (b) (4)
SJ-3 Media Fill Protocol & Report for Introduction to New Fill Line (b) (4) for COVID 19 mRNA Vaccine
SJ-4 Media Fill Protocol & Report for Introduction of COVID 19 mRNA Vaccine
SJ-5 No Sterility Test Failure for COVID 19 mRNA Vaccine Signed Statement

AC-1 COVID-19 mRNA LNP Process Flow Diagram, (b) (4)
AC-2 Drug Product Process Validation Strategy, (b) (4)
AC-3 Cumulative (b) (4) Target/Challenges, (b) (4)
AC-4 COVID-19 Vaccine, Pfizer Puurs Master Validation Plan, (b) (4)
AC-5 Summary Table of BNT162b2 Drug Product (b) (4) Stability Studies, (b) (4)

ZW-1 Photos collected, (b) (4)
ZW-2 PM (b) (4)
ZW-3 Presentation shipping qualification, (b) (4)

ATTACHMENTS

None

The signatures of the FDA representatives are on the following page(s).

Signature Page

Laura Fontan, CSO, CBER/OCBQ/DMPQ/B1

Zhongren Wu, CSO, CBER/OCBQ/DMPQ/B1

Anissa Cheung, CSO, CBER/OVRR/DVP

Susan Jackson, CSO, ORA/OMPTO/OBPO/BPIS