Observation 1:

There is insufficient data to support product quality prior to the release of BNT162b2 drug substance (DS) batch FA8057 manufactured at (b) (4) (b) (4) Pfizer Andover on (b) (4) (b) (4) was derived from (b) (4) batch (b) (4), and a deviation (b) (4) was initiated due to the multiple control limit excursions during the (b) (4) of (b) (4) The (b) (4) were below the control limits and the (b) (4) between (b) (4) and overall (b) (4) (b) (4) both exceeded the control limits. The affected batch (b) (4) was manufactured with a process that deviated from the validated process parameters, and your firm planned to put this batch on stability to further assess product quality. However, DS batch (b) (4) was not put on stability until July 22, 2021. The affected DS batch was released on (b) (4) and formulated into (b) (4) drug product (DP) lots (b) (4) at (b) (4) on (b) (4). All (b) (4) DP lots were released on (b) (4).

Response to Observation 1

The Pfizer, Andover site has a robust, well documented batch release process to ensure that drug substance batches meet specification. Quality Assurance (QA) reviews the data supporting the release of each individual batch, which includes the review of both in-process data and final release data and confirms that the batch meets all release specifications.

As part of batch release per site procedure (b) (4) (b) (4), all data associated with drug substance (DS) batch (b) (4) was reviewed, including in process critical quality attributes and DS final release results. There is sufficient data to support the release, namely all release data per (b) (4) were within specification and all critical quality attributes were within the expected historical experience. DS batch (b) (4) has been enrolled on stability to monitor the drug substance over the shelf-life. (b) (4) drug product (DP) lots (b) (4) were manufactured at (b) (4) from DS batch (b) (4) and all (b) (4) drug product batches met release specifications. The (b) (4) drug product lots were released to ex-US markets on (b) (4).

There are (b) (4) quality reviews performed by Quality Assurance to determine acceptability of the batch. (b) (4) investigation that is associated with a batch, if applicable, is assessed for any potential quality impact to that respective batch. Then, as part of the batch disposition process, a (b) (4) review of all associated deviations is conducted to determine if there is any impact to product quality. This (b) (4) assessment is performed pursuant to procedure (b) (4) (b) (4).

The deviations documented in Investigation (b) (4) did not impact DS batch (b) (4). Critical quality attributes specific to the mRNA were reviewed for DS batch (b) (4) and include the following:

(b) (4)

(b) (4)

In addition to DS (b) (4) data listed above, Pfizer reviewed the batch release data for the DP lots associated with DS batch (b) (4), and all data is within specification and within historical experience. (b) (4) (b) (4) is the DP critical quality attribute that is most directly linked to the DS. The (b) (4) (b) (4) for the (b) (4) DP lots is as follows:

Table 2 (b) (4) (b) (4) for DP Lots

(b) (4)

Investigation (b) (4) was initiated on (b) (4) to document a deviation to executed batch record (b) (4), during (b) (4) for drug substance batch (b) (4). During execution it was determined that there were (b) (4) deviations that led to the (b) (4) being outside of the control limits. A (b) (4) was added to bring the (b) (4) to within the control limit. The final (b) (4) (b) (4) (b) (4) was also exceeded. The impact of these deviations is described below.

During DS manufacturing, control of (b) (4). The ranges studied for

parameters in the lab qualification studies were focused on manufacturing capability and did not establish the point of failure or account for all possible deviations. However, the investigation for this batch shows all performance and quality attributes were within drug substance specification at release. Results for the batch in question are listed in Table 1.

(b) (4)

Investigation (b) (4) determined that there was no product quality impact. All drug substance release data for the associated drug substance batch (b) (4) are within specification and all critical quality attributes are also within the expected historical ranges.

Therefore, during the quality review performed in connection with the investigation and again in connection with the quality review performed as part of batch disposition, it was determined that the product met specification and there was no impact to product quality.

Pfizer notified FDA of the above discussed deviation associated with DS batch (b) (4) that was the subject of (b) (4) in writing on (b) (4). In that communication, Pfizer stated its intent to release the batch and process it into drug product, as the batch conformed to release specifications and the investigation determined there was no impact to product quality. Pfizer acknowledges that, in error, the communication also stated that the DS batch was enrolled on stability when, in fact, a commitment had been initiated to enroll the batch on stability no later than 30 September 2021. Pfizer's purpose in enrolling the batch on stability is to monitor the drug substance over the shelf life and not to obtain stability data for purposes of batch release disposition. Pfizer did not enroll the lot immediately because (b) (4) . Drug substance batch (b) (4) was enrolled on long-term stability on 22 July 2021. Pfizer updated its 23 June 2021 communication to FDA on 30 July 2021 to reflect the correct date that the batch was placed on stability. The initial timepoint sample was pulled and submitted for testing on 22 July 2021. The initial stability timepoint assay results are pending at the time of this response.

In addition, (b) (4) manufactured from DS (b) (4) was enrolled on long-term stability on (b) (4). The DP lots were released to ex-US markets only on (b) (4).

Action

Procedure (b) (4) (b) (4) will be revised and made effective to include the requirement that a drug substance batch be enrolled in a stability program within (b) (4)

(b) (4) from the date the determination to enroll is made. Additionally, the procedure will include a requirement for a justification as to why the batch is being enrolled on stability, including whether the stability data is required for drug substance batch release. Relevant individuals will be trained per site procedures.

Due Date
15 September 2021

Observation 2
There is inadequate quality oversight in that:

a. **The electronic data/reports from (b) (4) associated with the (b) (4), and (b) (4) (b) (4) process used in the manufacture of BNT162b2 drug substance are not reviewed by Quality during batch record review or prior to batch release.**
b. **During processing of BNT162b2 drug substance lot (b) (4), the (b) (4) were (b) (4), and the operator switched from (b) (4) The operators performed a calculation for (b) (4), and this calculation is not recorded in the batch record. The (b) (4) printout from the (b) (4) system documents (b) (4) per (b) (4) yet the batch record documents (b) (4) were performed (b) (4). The record was reviewed and approved by QA on (b) (4)**
c. **BNT162b2 drug substance lot (b) (4) was manufactured in (b) (4). The record was reviewed by Operations in (b) (4) and by Quality on (b) (4) All (b) (4) were (b) (4) There was no notation in the batch record until (b) (4) that (b) (4) exceeded the allowable (b) (4)**

Response to Observation 2

The manufacture of BNT162b2 is controlled principally by (b) (4) validated computerized systems: (b) (4) located in Building (b) (4) of the Andover Manufacturing Facility; and (b) (4), located in Building (b) (4) of the (b) (4)

For (b) (4), phase parameters are required to be input and (b) (4) per batch record instruction. The control system uses the input parameters to execute phase parameters as designed. The (b) (4) computerized system records all entries and actions performed. Per procedure (b) (4) (b) (4), the batch summary report, which includes the batch alarm report and automation manipulation reports, is reviewed by both Operations and Quality Assurance during executed batch record review.

(b) (4) is a recipe-based system for which the recipes are reviewed and approved by Subject Matter Experts (SMEs) and Quality Assurance per procedure (b) (4) (b) (4) (b) (4) (b) (4) Operators load approved recipes per batch record instruction. For (b) (4), per procedure (b) (4) (b) (4) Operations reviews (b) (4) manipulations (such as temporary changes to running batch active steps as per (b) (4) (b) (4) (b) (4), the (b) (4) event log, and the batch alarm report. Per procedure (b) (4) (b) (4) Quality Assurance also reviews the associated (b) (4) manipulations, the (b) (4) event log, and the batch alarm report, as part of the executed batch record review. The (b) (4) Batch Summary Report is not reviewed as part of the Quality Assurance executed batch record review in all instances. Rather, Quality Assurance reviews the Batch Summary Report by exception (as applicable in connection with investigation and impact assessment reviews).

Observation 2a

The electronic data/reports from (b) (4) associated with the (b) (4), and (b) (4) process used in the manufacture of BNT162b2 drug substance are not reviewed by Quality during batch record review or prior to batch release.

Response to Observation 2a

Executed batch record review per procedure (b) (4) governs QA review of batch related operating parameters and monitoring data. The (b) (4) batch alarm report is attached to the executed batch record. Any (b) (4) manipulation, the (b) (4) event log, and the batch alarm report that is generated during a batch is documented in the executed batch record for QA review. QA is also part of the review and approval process for the (b) (4) recipe build, which includes the review and approval of alarm setpoints and alarm criticality. The established batch record review program ensures full QA oversight of batch execution and any associated eventful operations, such as deviations and alarms. As an enhancement, QA batch record review procedure (b) (4) (b) (4) will be revised to include a full review of the batch summary report.

Actions

Procedure (b) (4) will be revised and made effective to include additional instructions for automation system review as part of the executed batch record review process, which will include the (b) (4) Batch Summary Report. Relevant individuals will be trained according to site procedures.

Completion Date
30 September 2021

Observation 2b

During processing of BNT162b2 drug substance lot (b) (4), the (b) (4) were (b) (4), and the operator switched from (b) (4) for (b) (4). The operators performed a calculation for (b) (4), and this calculation is not recorded in the batch record. The (b) (4) printout from the (b) (4) system documents (b) (4) yet the batch record documents (b) (4) were performed (b) (4). The record was reviewed and approved by QA on 7/15/2021.

Response to Observation 2b

For BNT162b2 drug substance lot (b) (4) were performed in the (b) (4). During processing, (b) (4) were (b) (4) and operators accordingly switched from (b) (4) per site procedure (b) (4) (b) (4) *in* (b) (4) (b) (4). To account for the (b) (4), the operators and engineering determined an appropriate amount for (b) (4). This calculation was not documented in the batch record. Investigation (b) (4) was initiated on (b) (4) to address the documentation discrepancy. Although not documented in the batch record, the (b) (4) calculation that is missing from the batch record was reconstructed using data documented in (b) (4) (data for (b) (4) and the executed batch record at the time of execution. During Operations and Quality Assurance batch record review per (b) (4) (b) (4) the correct (b) (4) was confirmed using the (b) (4) data and the executed batch record for (b) (4) have been confirmed to meet all acceptance criteria as documented in the executed batch record as part of batch record review.

The (b) (4) for (b) (4) was documented in the executed batch record. In (b) (4) operation mode, (b) (4) remains running in the background but is not controlling the additions. While (b) (4) therefore continued to log (b) (4) data for additions (b) (4), that data is rendered extraneous data in (b) (4). Once operators take manual control of the (b) (4), the primary GMP source data is the executed batch record.

Action
Procedure (b) (4) (b) (4) *in* (b) (4) (b) will be revised and made effective to further clarify instructions for implementing (b) (4) operations and to document the (b) (4) calculation within the batch record. Relevant colleagues will be trained per site procedures.

Completion Date
15 September 2021

Action
Manufacturing batch record (b) (4) will be revised and made effective to clarify that once switching to (b) (4) data documented in the batch record, and not the data in (b) (4), is the data to be evaluated for acceptance criteria.

Completion date
15 September 2021

Action
Investigation (b) (4) was initiated on (b) (4) for the documentation discrepancies noted above. This investigation was closed on (b) (4).

Completion Date
Complete

Updated Action as of 17 August 2021

As discussed with the Agency, Pfizer will conduct an evaluation to determine whether the (b) (4) has the ability to document within its system changes made from (b) (4) . The evaluation will be completed by 17 September 2021. Based on the outcome any required updates will be made.

Completion Date
17 September 2021

Observation 2c

BNT162b2 drug substance lot (b) (4) was manufactured on (b) (4). The record was reviewed by Operations in (b) (4) and by Quality on (b) (4). All (b) (4) were (b) (4). There was no notation in the batch record until (b) (4) that (b) (4) exceeded the allowable duration.

Response to Observation 2c:

Drug substance Batch (b) (4), the first batch of BNT162b2 produced in (b) (4) was manufactured in (b) (4) per master batch record 513AM version 2.0. The executed batch record was reviewed by Operations in (b) (4) and reviewed by Quality Assurance in (b) (4) At the time of batch execution, the (b) (4) was a target and not a control limit per the batch record, and therefore no further action was taken for the exceeded value.

As part of the continuous process monitoring verification program, to provide ongoing assurance that during routine production the process remains in a state of control, per (b) (4) (b) (4) (b) (4) the (b) (4) target was changed to a control limit in master batch record 513AM version 3.0, effective date, (b) (4) . As part of the (b) (4) process verification monitoring, the parameter was noted as (b) (4) . Investigation (b) (4) was initiated on (b) (4) (b) (4) to assess and document impact and on (b) (4) a notation was made in the executed batch record for (b) (4), referencing the investigation. The investigation was closed on (b) (4).

Pfizer will continue to monitor BNT162b2 drug substance manufacturing process through its (b) (4) process monitoring verification program and manage validated parameter changes through the change control process.

Action
No action is required.

Completion Date
Not applicable

Observation 3:

The following deviation investigations were found deficient. Deviation (b) (4) (b) (4) (b) ((COVID): (b) (4) (b) (4) and (b) (4) (b) (4) (b) ((COVID): (b) (4) (b) (4) (b) (4) was found in (b) (4) during its visual inspection (b) (4). On both occasions the (b) (4) was cleaned and released into manufacture. No (b) (4) sampling of (b) (4) and no cleaning verification was performed or is required after re-cleaning.

Response to Observation 3

Procedure (b) (4) (b) (4) defines the process by which visual inspection of the wetted surfaces of process equipment for cleanliness is conducted. All visual inspection outcomes are assessed as described in the procedure. As per the procedure, identification of (b) (4) observed in equipment" results in a failed visual inspection. If the visual inspection fails due to the presence of (b) (4) an investigation is initiated per procedure (b) (4) (b) (4) and a team of Subject Matter Experts (SMEs) consisting of Quality Assurance (QA), EMU (Engineering, Maintenance and Utilities) and Operations are notified. This SME team conducts a preliminary assessment

which typically includes a review to: (1) confirm that the qualified cleaning cycle ran as expected; (2) determine if any mechanical failures occurred; (3) determine the duration between the completion of the cleaning cycle and identification of the (b) (4); and (4) qualitatively determine the (b) (4) (b) (4) (b) (4) Based on the review of data collected above, QA will document in the investigation if operations can proceed or not.

Investigations (b) (4) (initiated (b) (4)) and (b) (4) (initiated (b) (4)) were initiated per procedure following the detection of (b) (4). SME preliminary assessments were performed for both investigations resulting in QA endorsement to proceed with manufacturing operations. Documentation of the preliminary assessment was deficient and procedure (b) (4) will be updated to provide a more standard approach for both performing and documenting the SME preliminary assessment.

The dirty hold time established as part of the cleaning performance qualification (CPQ) was reviewed. In both occurrences of (b) (4), the amount of time the (b) (4) was in the system was (b) (4) than the maximum dirty hold time. As a result, (b) (4) sampling of the (b) (4) was not deemed a requirement by the SME team. For investigation (b) (4) (initiated (b) (4)) recleaning of the (b) (4) was performed because the amount of time the (b) (4) was present in the system was (b) (4). Procedure (b) (4) (b) (4) states that stored (b) (4) is given a (b) (4) expiration from the date it is dispensed. While this instruction is specific to (b) (4) dispensed (b) (4), the SME team performing the preliminary assessment leveraged this instruction and directed Operations to reclean the (b) (4). A cleaning verification was not considered a requirement because the amount of time the (b) (4) was in the (b) (4) was (b) (4) than the qualified maximum dirty hold time established for the (b) (4). For the occurrence documented in investigation (b) (4) (initiated (b) (4)), recleaning of the (b) (4) was not considered a requirement as the amount of time the (b) (4) was present in the system was (b) (4). (b) (4) was again leveraged by the SME team to make this determination. A (b) (4), approximately (b) (4), was observed in the (b) (4), which was (b) (4) prior to commencement of manufacturing operations.

Action

Procedure (b) (4) (b) (4) will be revised and be made effective to provide a more standardized approach to the preliminary assessment that SMEs are required to perform when determining potential impact to manufacturing equipment post identification of a (b) (4) (b) (4). Specifically, the revision will include the requirement to assess and document the assessment of (b) (4)

Completion Date

31 August 2021

Action
A study will be conducted to determine the conditions under which cleaning verification will be required following identification of (b) (4). The study will include an evaluation of the potential impact of the (b) (4) contribution to (b) (4) and therefore on the requirement for performing cleaning verification.

Completion Date
30 November 2021

Action
Based on the outcome of the study, procedure (b) (4) (b) (4) will be revised and be made effective to ensure the key factors that must be considered as part of the assessment are documented and to include additional instructions on how to perform and document the assessment of risk when a visual failure for (b) (4) is identified. Relevant individuals will be trained according to site procedures.

Completion Date
30 December 2021

Observation 4

Per (b) (4) (b) (4) (b) (4) cleaning validation has not been performed on the (b) (4) (Building (b) (4) (b) (4) The (b) (4) is stored in a (b) (4) and as a result, a (b) (4) trend occurred in (b) (4) ((b) (4) noted by identification of (b) (4)

Response to Observation 4

The design and use of the Building (b) (4) (b) (4) (b) (4) requires storage of both the (b) (4) in between manufacturing batches. As such, the opportunity to collect (b) (4) samples for (b) (4) is limited. Additionally, the ability to collect (b) (4) from the surface of the (b) (4) (b) (4) is impractical as the (b) (4) (b) (4) would need to be dismantled. As a result, the (b) (4) system is subjected to cleaning verification via in-process monitoring rather than the cleaning cycle being validated via execution of a cleaning performance qualification protocol.

The (b) (4) is subject to routine process monitoring controls which ensure, among other things, detection of (b) (4). As per these controls, a trend for (b) (4) was noted and investigation (b) (4) was initiated on (b) (4). The investigation determined that the most probable root cause for the (b) (4)

(b) (4) trend was that certain areas of the (b) (4) were not being (b) (4) The root cause for this inadequate (b) (4) of the (b) (4) with (b) (4) was identified to be an (b) (4) which resulted in a (b) (4) being unexposed to the (b) (4) . The storage in (b) (4) was not fully effective because of the lack of (b) (4) . Additionally, because of the (b) (4) . Investigation (b) (4) which was closed on (b) (4) , contained corrective and preventative actions including:

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

The above actions were implemented on (b) (4) and documented within change control (b) (4)

Following the implementation of the above actions, a supplemental validation protocol (b) (4) (b) (4) (b) (4) was executed to demonstrate the effectiveness of the corrective and preventative actions taken. The protocol monitored the (b) (4) BNT162b2 drug substance batches that were manufactured post-remediation. Results of the monitoring are summarized in validation report (b) (4) (b) (4) The summary concluded that the manufacturing process steps in scope of the study effectively maintained (b) (4) control following mitigation and determined that no additional mitigation was warranted. The (b) (4) results for all samples from the batches in scope of the supplemental validation protocol were (b) (4) .

As of 12 July 2021, (b) (4) data from (b) (4) operations is available for (b) (4) batches of BNT162b2 drug substance manufactured in (b) (4) since implementation of the corrective and preventative actions identified. The (b) (4) data from these batches demonstrates that the equipment continues to operate as expected and that no indication of a (b) (4) trend has been observed since implementation of the corrective and preventative actions.

The ability to perform cleaning performance qualification on manufacturing equipment is directly related to how the equipment is used in the drug substance manufacturing process. In instances where the manufacturing process requires equipment to be stored in a (b) (4) between batches, the ability to execute cleaning performance qualification testing is diminished and additional controls are evaluated and/or implemented in order to verify that the

manufacturing equipment is maintained in a clean state. In-process analytical testing is built into the manufacturing process to monitor the effectiveness of the batch-to-batch storage operation with the (b) (4) storage solution.

Because the equipment design and manufacturing process requires (b) (4) to be stored in (b) (4), typical cleaning performance qualification analysis cannot be obtained. Instead, the manufacturing process includes a series of samples that are obtained to ensure the equipment is maintained in a state of control regarding cleaning status.

Following manufacturing operations, the (b) (4)

Action
An effectiveness check (b) (4) (child action record to (b) (4) was initiated on 28 July 2021 to document the effectiveness of the (b) (4) mitigation strategy implemented per change control (b) (4) Sample results from (b) (4) operations of BNT162b2 batches manufactured from (b) (4) were reviewed.

The data confirms the processing step is appropriately stored, effectively monitored, and is operating as expected.

Completion Date
Complete

Observation 5

Cleaning of reusable product-contact parts using (b) (4) is not validated. Cleaning verification of such parts is inadequate as it is limited to testing of (b) (4) . Verification of surface and (b) (4) testing is not performed routinely.

Response to Observation 5

Andover Cleaning Master plan (b) (4) (b) (4) takes into consideration that operator dependent processes like (b) (4) are less controllable and repeatable than equipment system parameter dependent processes and therefore are to be verified and not validated as a cleaning procedure. The Cleaning Master Plan highlights that where cleaning by (b) (4) does occur, the strength of the process requires a combination of stringent development studies, specific procedural instructions including disassembly of equipment, operator training and assessment, and inclusion of analytical and visual verification of acceptable cleanliness.

A development cleanability assessment was executed using BNT162b2 Vaccine process residues to understand both the characteristics of the process residues that are intended to be cleaned as well as determine the cleaning capabilities of the (b) (4) procedure used by operations personnel. The assessment concluded that the (b) (4) operation was capable of cleaning the process residues from equipment surfaces and that the BNT162b2 Vaccine process residues are able to be visually detected on processing equipment within the (b) (4) . The development cleanability assessment included representative materials of construction (MOCs) for equipment used in BNT162b2 Vaccine manufacturing and used worst-case cleaning conditions to appropriately challenge the (b) (4) procedure used by operations personnel.

Procedure (b) (4) (b) (4) (b) (4) governs execution of (b) (4) activities within the manufacturing suite and is used by operations to (b) (4) . Procedure (b) (4) requires operations personnel to collect (b) (4) testing (b) (4) performance of a (b) (4) cleaning to a specified acceptance criterion of (b) (4) , the procedure requires a visual inspection of all parts that have been (b) (4) following procedure (b) (4) (b) (4) to an acceptance criterion of (b) (4) . If the (b) (4) is not within specification and/or the (b) (4) visual inspection fails per procedure (b) (4) an investigation is initiated per site procedure (b) (4) (b) (4) All personnel performing (b) (4) analysis and visual inspection are required to complete and pass a skills-based training for these operations and retrain on any modifications to the governing procedure as necessary.

Lastly, verification of the effectiveness of the (b) (4) operation, including (b) (4) testing, is performed on a (b) (4) basis. Periodic monitoring is performed on equipment cleaned via (b) (4) under the formal cleaning monitoring program

governed by standard operating procedure (b) (4) (b) (4) Cleaning monitoring provides ongoing assurance that the (b) (4) cleaning process is operating as expected to predetermined acceptance criteria. Cleaning Monitoring includes (b) (4) , as well as visual inspection. The acceptance criteria are pre-established and includes (b) (4) .

Cleaning monitoring of the (b) (4) (b) (4) operation was executed in March 2021. All results obtained from this monitoring activity, including (b) (4) analysis, were within the specified acceptance criteria.

Action
A pre-approved protocol will be executed to generate a larger data set, inclusive of (b) (4) sampling, to further support verification of the (b) (4) operation performed in (b) (4)(b) (4). The protocol will verify (b) (4) cleaning operations performed on (b) (4) equipment used in (b) (4) (b) (4) using all testing, as required, in the (b) (4) verification. The results obtained from the executed protocol will be summarized in a formal summary report by the completion date. If the data from the study indicates a change in cleaning monitoring frequency is needed, then a subsequent commitment will be initiated.

Completion Date
The study will be completed by 30 November 2021.

Observation 6

Cleaning efficacy studies are inadequate (Building (b) (4) (b) (4) in that the firm has not demonstrated consistent efficacy with (b) (4) and a contact time of (b) (4). (b) (4) (b) (4) **(Building (b) (4) (b) (4) demonstrates efficacy on all surfaces, however,** (b) (4) (b) (4) (b) (4) **(Building (b) (4) (b) (4) (b) (4) demonstrates a lack of efficacy on all surfaces except (b) (4) with a contact time of (b) (4).**

Response to Observation 6

(b) (4) disinfectant efficacy studies were performed to qualify disinfectants for use in (b) (4) facilities, including (b) (4) These are summarized in report (b) (4) (b) (4) The studies include surfaces and (b) (4) that are representative of Building (b) (4) (b) (4) and support the

contact times applied to Building (b) (4) (b) (4) The (b) (4) independent studies, which included (b) (4) different surfaces and challenged (b) (4) different (b) (4), showed that a greater than a (b) (4) reduction could be achieved with a (b) (4) contact time for (b) (4).

A comprehensive review of the Building (b) (4) including (b) (4) (b) (4) disinfectant efficacy program was conducted over the last several years and as a result a contemporaneous study employing improved study design and methodologies was executed and is summarized in report (b) (4) (b) (4) This study was executed including surfaces and (b) (4) that are representative of Building (b) (4) (b) (4) (b) (4) This study also demonstrated efficacy of a (b) (4) contact time for (b) (4), consistent with the studies supporting the same for Building (b) (4) (b) (4) Combined data from multiple reports support a (b) (4) contact time for (b) (4) for both facilities.

Actions
No action required.

Completion Date
Not applicable

Observation 7

The ISO-(b) (4) are not monitored to the ISO (b) (4) standards. Specifically,

- **a. (b) (4) monitoring is not routinely performed.**
- **b. (b) (4) monitoring limit is set a (b) (4) instead of (b) (4).**
- **c. (b) (4) (Building (b) (4) (b) (4) (b) (4) (b) (4)) is within an ISO (b) (4) room.**

Response to Observations 7a, 7b, and 7c

The Building (b) (4) Andover (b) (4) (b) (4) (b) (4) were classified and qualified as ISO (b) (4) during the execution of the Environmental Monitoring Qualification (EMQ) per validation protocol (b) (4) The objective of the EMQ was to classify and qualify that each of the current Clean Environmental Areas (CEAs) of the (b) (4) can meet and maintain the air and surface environmental quality levels for Good Manufacturing Practices (GMP) based on use for a (b) (4) drug substance facility. The EMQ was designed to demonstrate that the facility met United States Pharmacopeia (USP) and International Organization for Standardization (ISO) (b) (4) requirements. Per ISO (b) (4), ISO-(b) (4) in (b) (4) met the air quality levels requirement for (b) (4) that includes (b) (4) monitoring for (b) (4) conditions. (b) (4) quality levels are not specified per ISO (b) (4)

(b) (4) quality levels for (b) (4) are not applicable to a (b) (4) drug substance facility. The (b) (4) are routinely monitored for (b) (4) and meet the air quality levels of ISO (b) (4) requirements.

Actions for 7a, 7b, and 7c
All ISO-(b) (4) in the (b) (4) will be classified as (b) (4), removing the ISO(b) (4) designation. Procedures (b) (4) (b) (4) (b) (4) and (b) (4) (b) (4) (b) (4) will be revised and made effective to reflect the (b) (4) classification for a (b) (4) drug substance facility. Relevant individuals will be trained according to site procedures.

Completion Date
15 September 2021

Observation 8:

Routine monitoring of the compressed air of Building (b) (4) (b) (4) does not adequately represent all points of use. Only (b) (4), specifically (b) (4), listed in (b) (4) (b) (4) are routinely monitored.

Response to Observation 8

At the present time, there are no specific regulatory guidance or requirements around the number of compressed air points of use to be sampled or the frequency of samples, but there are recommendations. For example, the ISPE Good Practice Guide recommends testing every (b) (4) on a rotating basis from representative sample locations.

Procedure (b) (4) (b) (4) (b) (4), describes the routine monitoring program for the compressed air system. As part of the routine monitoring program, (b) (4) are representative sample locations of the compressed air system with a sampling frequency of (b) (4) which is based on Validation Protocol (b) (4) (b) (4).

Per Validation Protocol (b) (4) Section 5.1, the sample site selection followed a (b) (4) approach. The (b) (4) approach was based on (b) (4)

(b) (4)

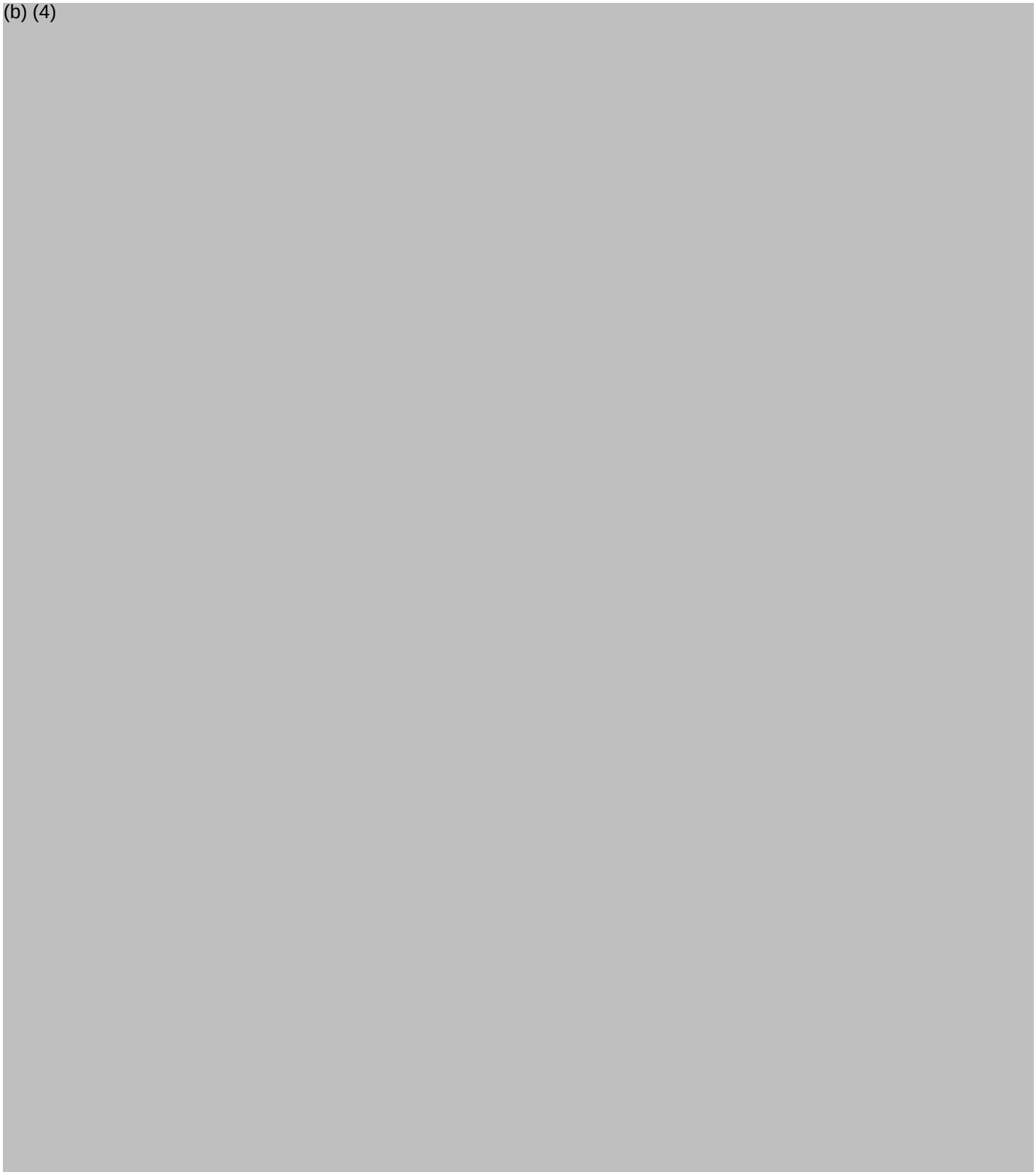
Representative sample location (b) (4) were selected as the routine monitoring points after performance qualification based on (b) (4) being at the beginning of the compressed air distribution and (b) (4) being at the end of the distribution as described in Procedure (b) (4)

Table 1 contains the (b) (4) action quality levels for compressed air. Table 2 contains the results from (b) (4) sample (b) (4) from routine monitoring that started after the performance qualification and indicates that the compressed air system is in a state of control. The data results show that (b) (4) sample (b) (4) (b) (4) met (b) (4) quality levels.

Table 1 (b) (4) Quality Levels for Compressed Air

ISO Class	Water / Oil Detection	TAP Action Level		Active Air Action Level
		0.5µm	5.0µm	
		Particles/ m^3	Particles/ m^3	cfu/m^3
(b) (4)				

(b) (4)



Action
Procedure (b) (4) (b) (4) (b) (4) , will be revised and made effective to require that all (b) (4) locations are tested each (b) (4) . Relevant individuals will be trained according to site procedures.

Completion Date:
31 August 2021

Observation 9

The environmental program (EM) program in (b) (4)(b) (4 is deficient in ensuring that the cleanrooms are operating in a state of environmental control:

- **a. No prospective EM performance qualification (PQ) of classified areas or PQ of (b) (4) was performed to ensure EM specifications in operation are met.**
- **b. Routine monitoring of ISO(b) (4) area is performed on a (b) (4) basis.**
- **c. During a walkthrough on 7/22/2021, the door to the Control Room (b) (4) was observed opened to manufacturing (b) (4) (b) (4) (ISO(b) (4) through the duration of the walkthrough. Room (b) (4) is classified as controlled not classified and is not monitored.**

Response to Observation 9

Observation 9a

No prospective EM performance qualification (PQ) of classified areas or PQ of (b) (4) was performed to ensure EM specifications in operation are met.

Response to 9a

The environmental monitoring performance qualification (EMPQ) of (b) (4)(b) (4 was performed per procedure (b) (4) (b) (4) (b) (4)(b) (4) (b) (4) (b) (4) which includes the (b) (4)(b) (4 sample locations, the action levels, as well as the required (b) (4) identifications. EM results were documented on form (b) (4) All results met criteria of no action level excursions and were approved by Quality Assurance on 24 December 2020, prior to performing GMP operations.

As part of EMPQ, (b) (4) days of sampling Room (b) (4) and (b) (4) under (b) (4) conditions were performed from (b) (4) per site procedure (b) (4)

This was followed by (b) (4) of sampling Room (b) (4) and (b) (4) under (b) (4) conditions from (b) (4) per site procedure (b) (4) (b) (4) conditions were achieved in the ISO(b) (4) production room (b) (4) by allowing personnel into the room to (b) (4) (b) (4) operational equipment.

Additional sampling of Room (b) (4) and (b) (4) under (b) (4) conditions was performed between 28 December 2020 – 02 January 2021 per site procedure (b) (4)

Although EMPQ (b) (4), and additional sampling was performed in (b) (4), the site acknowledges that there was no activity in the (b) (4) at the time of sampling; therefore, EMPQ of (b) (4) was not performed under true (b) (4) conditions.

The EMPQ was performed per effective start-up and environmental monitoring procedures. All results were below action levels and one result was above the alert level. Release of (b) (4)(b) (4) for GMP use was documented in change control (b) (4)

As part of the review of change control (b) (4) it was noted by the site that the EMPQ was not executed via a pre-approved protocol, as required in procedure (b) (4) and a summary report was not written. However, all elements of EMPQ were completed per site procedure and all samples met acceptance criteria of no action levels as required by site procedure (b) (4)

Investigation (b) (4) was initiated on 30 June 2021 to document and investigate this deviation from site procedure (b) (4) The investigation concluded a root cause related to an isolated human error for not performing the EMPQ via a preapproved protocol. There was no impact as all EM sampling requirements were performed per effective cGMP procedures. A summary report, (b) (4) was written and approved on 23 July 2021.

There is no product quality impact resulting from the failure to perform the EMPQ of (b) (4) (b) (4) per protocol as all required performance qualification elements were met.

Action
A summary report, (b) (4) was written and approved on 23 July 2021.

Completion Date
Complete

Action
Procedure (b) (4) will be revised and made effective to define (b) (4) conditions under which to execute the (b) (4) portion of

EMPQ and require appropriate documentation of (b) (4) activities within the EMPQ Protocol and Final Report. Relevant individuals will be trained according to site procedures.

Completion Date:
31 August 2021

Action
An environmental monitoring qualification of (b) (4) and (b) (4) will be performed in (b) (4) (b) (4) under predefined (b) (4) conditions.

Completion Date:
15 September 2021

Observation 9b

Routine monitoring of ISO (b) (4) area is performed on a (b) (4) basis.

Response to 9b

The Environmental Monitoring Performance Qualification (EMPQ) for (b) (4) (b) (4) controlled classified production areas was executed from 16 December 2020 to 21 December 2020 and followed by increased sampling from 28 December 2020 to 02 June 2021. Routine EM began on 04 January 2021 at a frequency defined in procedure (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

Routine EM data from 04 January 2021 to 30 June 2021 was assessed and found all samples reported results within quality levels (below alert or action levels) for all test types (b) (4) collected from (b) (4) (b) (4) ISO (b) (4) areas:

- Total samples collected: (b) (4)
- Count of Alert Level Results: 0
- Count of Action Level Results: 0.

To evaluate the current sampling frequency for the (b) (4) (b) (4) ISO (b) (4) classification, increased sampling will be executed at a frequency of (b) (4) for a (b) (4) period. The data will be evaluated and an appropriate sampling frequency for the (b) (4) (b) (4) ISO (b) (4) areas will be determined and implemented as applicable.

Action
Implement protocol for increased sampling to (b) (4) period of (b) (4) (b) (4) ISO (b) (4) areas. The data will be evaluated and an appropriate sampling frequency for the (b) (4) (b) (4) ISO (b) (4) areas will be determined and implemented as applicable.

Completion Date
The study protocol will be developed, and the study execution will be completed by 15 December 2021.

Observation 9c

During a walkthrough on 7/22/2021, the door to the Control Room (b) (4) was observed opened to manufacturing (b) (4) (b) (4) (ISO(b) (4) through the duration of the walkthrough. Room (b) (4) is classified as controlled not classified and is not monitored.

Response to Observation 9c

During the inspection, it was communicated in error that the (b) (4)(b) (4) control room (b) (4) was classified as Controlled Not Classified (CNC). Control room (b) (4) is classified as an ISO(b) (4) area.

(b) (4)(b) (4) control room (b) (4) and adjacent room (b) (4) have the same ISO(b) (4) classification and a neutral pressure differential; therefore, the room air cascade and air quality should not be impacted. Pfizer acknowledges is that the ancillary room doors should not be left open.

Environmental monitoring of (b) (4) (b) (4) control room will be performed at a frequency of (b) (4) for a (b) (4) period. The data will be evaluated, and an appropriate sampling frequency will be determined and implemented as applicable.

Action
A protocol for increased sampling to (b) (4) will be implemented for a (b) (4) period of (b) (4) (b) (4) control room. The data will be evaluated and an appropriate sampling frequency for the (b) (4) (b) (4) ISO(b) (4) areas will be determined and implemented as applicable.

Updated Action as of 17 August 2021
As discussed with the Agency, an appropriate routine EM strategy for all ancillary ISO(b) (4) rooms in (b) (4) (b) (4) including room (b) (4), will be established. A protocol for increased sampling to (b) (4) will be implemented for a (b) (4) period of the (b) (4)(b) (4) ISO(b) (4) ancillary rooms. The data will be evaluated and sample type and sampling frequency for the (b) (4) (b) (4) ISO(b) (4) areas will be determined and implemented, as applicable.

Completion Date
The study protocol will be developed, and the study execution will be completed initiated by 15 December 2021.

Action
Procedure (b) (4) (b) (4) (b) (4) (b) (4) will be revised and made effective to ensure all doors to ancillary rooms, including (b) (4) , are not left open. Additionally, attention activators will be applied to doors within (b) (4) to remind personnel to close doors behind them. Relevant individuals will be trained according to site procedure.

Completion Date
31 August 2021

Observation 10

On (b) (4) the HVAC supplying (b) (4) was shut down for preventative maintenance, which resulted in pressure differential of room (b) (4) to drop to (b) (4) relative to the outside non-controlled non-classified corridor at 2:25 AM. The room was not cleaned until (b) (4) and environmental monitoring (EM) of the room was not performed to ensure that the room returned to ISO state until (b) (4) . Between (b) (4) the room was used for processing of drug substance batches (b) (4) , all of which were processed into drug product and released to US and international markets.

Clean status of the room is not verified or documented in the batch record. The firm allows up to (b) (4) of HVAC shutdown time until an additional cleaning needs to be performed. There is no data to support that (b) (4) room continuously meets its EM specification for any time after HVAC shutdown. No product impact assessment was performed.

Response to Observation 10

Heating, ventilation, and air conditioning (HVAC) systems that supply the cGMP manufacturing areas are qualified per procedure (b) (4) During the initial HVAC qualification, each HVAC unit is required to undergo multiple tests per Standard ISO-(b) (4) , which includes a (b) (4) test. This test is designed to identify the time frame required for each HVAC unit to reduce the (b) (4) concentration by (b) (4) after being exposed to a source of (b) (4) challenge. HVAC (b) (4), serving (b) (4) , (b) (4) passed the particulate testing in under (b) (4) , and all other HVAC qualification tests demonstrating ISO standards were achieved.

Based on historical data documented in assessment (b) (4) allowance is made for a loss of air flow for up to (b) (4) prior to requiring an additional facility sanitization.

A Closure Risk Assessment (CRA) was performed (and was effective 31 December 2020) per (b) (4) with the purpose to document and understand the operational details and environmental controls around the final (b) (4) unit operations and related processing steps performed within (b) (4) In-process monitoring is employed to detect the entry of (b) (4) contaminants into the manufacturing process. During the production of each batch, samples are taken at pre-defined points from (b) (4) .

On (b) (4) the HVAC unit serving (b) (4) was shutdown at approximately (b) (4) to perform planned maintenance. The planned maintenance was performed (b) (4) to (b) (4) and (b) (4) of terminal HEPA filters. Temperature and relative humidity inside (b) (4) stayed within specification throughout this period. The HVAC unit was returned to service and all pressure cascades and air change rates were re-established at (b) (4) . A facility sanitization was performed at (b) (4) prior to the HVAC shutdown, per procedure (b) (4)(b) (4) No personnel were present within the suite and no manufacturing operations were occurring during the HVAC shutdown. Closed operations within (b) (4) began at approximately (b) (4) No additional sanitization was required because of the loss of airflow on (b) (4) per procedure (b) (4) which allows for a loss of air flow up to (b) (4) prior to requiring an additional facility sanitization. Subsequent, routine facility sanitization was performed on (b) (4)

For the reasons noted below, there is no product impact to batches (b) (4) Per procedure (b) (4) manufacturing operations occurring with an audible HVAC alarm require a comment in the executed Manufacturing Batch Record (MBR) that is in process at the time of the alarm. Per procedure (b) (4) executed MBRs are reviewed by Quality Assurance. Batch records (b) (4) did not contain comments for loss of air flow as there was no processing at the time of the loss of air flow.

The associated drug substance batches produced from (b) (4) met all in process and release specifications, and disposition criteria including (b) (4) as outlined in procedures (b) (4)(b) (4) and (b) (4) (b) (4) and were dispositioned with a status of released.

Action
A study to assess the return to environmental specification per procedure (b) (4) will be initiated following an HVAC unit Shutdown in (b) (4) . The study will be initiated by 28 October 2021.

Completion Date
28 October 2021

Action
Based on the results of the study, if required, procedure (b) (4) (b) (4) , will be revised and made effective to specify actions, such as facility sanitization and/or environmental monitoring in response to alarms. Relevant individuals will be trained per site procedures.

Completion Date
25 November 2021

Action
An interim control to assess for product impact following a HVAC shutdown of greater than a (b) (4) duration until the study has been completed and will be documented per planned temporary change (b) (4) This interim control was approved on 30 July 2021.

Completion Date
Complete

Action
(b) (4)(b) (4 manufacturing batch records will be revised and made effective to document the confirmation of the clean status of (b) (4) (b) (4

Completion Date
15 September 2021

Observation 11

Standard operating procedures are not followed. For example,

a. On 7/22/2021 during observation of (b) (4) **operations, cleaning of** (b) (4) **, and dispensing of drug substance, the following was observed in deviation from** (b) (4) (b) (4) (b) (4) **,** (b) (4) **and** (b) (4) (b) (4) (b) (4)

- **An alarm went off (b) (4) due to operator (b) (4) to introduce a (b) (4) . (b) (4) prohibits work in a (b) (4) if it is in alarm condition.**
- **(b) (4) operators were (b) (4) over the (b) (4) of the (b) (4) blocking the (b) (4) .**
- **(b) (4) did not cover all surfaces of the (b) (4) and was (b) (4) contact time required per (b) (4)**

b. (b) (4) cleaning of the (b) (4) in (b) (4) was not performed in the (b) (4) of July 2021 in deviation from (b) (4)

Response to Observation 11

Observation 11a

On 7/22/2021 during observation of (b) (4) operations, cleaning of (b) (4) , and dispensing of drug substance, the following was observed in deviation from (b) (4) (b) (4) (b) (4) (b) (4) and (b) (4) (b) (4) (b) (4)

- **An alarm went off (b) (4) due to operator (b) (4) to introduce a (b) (4) . (b) (4) prohibits work in a (b) (4) if it is in alarm condition.**
- **(b) (4) operators were (b) (4) over the (b) (4) of the (b) (4) blocking the (b) (4) .**
- **(b) (4) did not cover all surfaces of the (b) (4) and was (b) (4) set contact time required per (b) (4)**

Response to Observation 11a

At the time of the alarm conditions on 22 July 2021, no work was being performed in (b) (4) . All aseptic connections required for the (b) (4) were made by the operator within (b) (4) prior to the alarm condition created when the (b) (4) were transferred into the (b) (4). Per procedure (b) (4) (b) (4) (b) (4) were (b) (4) with (b) (4) prior to transfer into the (b) (4). The alarm condition was triggered by the operator (b) (4) to introduce the (b) (4) into the (b) (4) and the alarm cleared once the (b) (4) was (b) (4) . Once the (b) (4) were in the (b) (4) and the alarm was cleared, the operator followed procedure (b) (4) by allowing the items introduced to sit undisturbed for a minimum of (b) (4) within the (b) (4) before proceeding with putting the (b) (4) .

Investigation (b) (4) was initiated on 26 July 2021 regarding the alarm condition of the (b) (4) that was observed on 22 July 2021. The root cause was determined to be procedure (b) (4)

(b) (4) (b) (4) lacks instructions on how to proceed when the (b) (4) needs to be (b) (4) to add/remove items from a (b) (4).

As an additional improvement, the site will assess minimizing the number of items transferred into the (b) (4) to only what is required for open product manipulation. Enabling the (b) (4) operations portion of the (b) (4) activities to occur outside of the (b) (4) will eliminate the need to (b) (4) to bring in equipment such as (b) (4), thus preventing the triggering of an alarm condition within the (b) (4).

Investigation (b) (4) was initiated on 27 July 2021 to document the deviations to procedure (b) (4) pertaining to (b) (4) operator (b) (4) over the (b) (4) of the (b) (4) and insufficient work surface sanitization of (b) (4) observed on 22 July 2021.

Colleagues and contractors are trained on training material (b) (4) as a pre-requisite to open product manipulations in critical environments and are requalified (b) (4) by completing training material (b) (4), (b) (4) Both training materials, (b) (4), require the learner to demonstrate proper aseptic technique and pre-use/post-use sanitization of the (b) (4) per procedure (b) (4) The operator who performed the work surface sanitization of (b) (4) and (b) (4) operations within the (b) (4) was trained on procedure (b) (4) and training material (b) (4).

Procedure (b) (4) states "In (b) (4), do not (b) (4) the (b) (4). This will disrupt the (b) (4)." Based on an interview with the operator, the root cause of this observation was human error of omission. The operator was aware of the requirement to not (b) (4) the (b) (4) of the (b) (4) and was purposefully keeping his arms up while working within the (b) (4); however, while the (b) (4) was running, the operator was (b) (4). Enabling the (b) (4) activities to occur outside of the (b) (4) will minimize the time an operator will spend (b) (4) within the (b) (4), thus reducing the risk of deviation to procedure (b) (4) (b) (4) the (b) (4).

For work surface sanitization of the (b) (4), procedure (b) (4) specifies to saturate unit surfaces with (b) (4) and leave undisturbed for (b) (4), however it does not require that the work surface must remain wet for the full (b) (4) contact time. Additionally, as a control for batch-to-batch processing, (b) (4) requires (b) (4) a (b) (4) work surface sanitization and (b) (4) sanitization of the (b) (4).

The operator who performed the sanitization of the (b) (4) was interviewed regarding the observation of not covering all surfaces of the (b) (4) with (b) (4). The operator's recollection was that procedure (b) (4) was followed and that all surfaces of the (b) (4) were covered with (b) (4). The operator completed re-training on (b) (4) on 29 July 2021 prior to performing additional operations within the (b) (4).

There is no impact to product quality for the batch that was processed on 22 July 2021. The drug substance (b) (4) sample results for the (b) (4) product (b) (4) for batch (b) (4) passed testing in (b) (4)

Action
Investigation (b) (4) was initiated on 26 July 2021 for the documentation discrepancies noted above. This investigation was closed on 29 July 2021.

Completion Date
Complete

Action
The current method used to perform (b) (4) operation will be evaluated to minimize the type of equipment/materials that are brought into the (b) (4) for this operation. (b) (4) and batch records (b) (4) and (b) (4) will be revised and made effective, as appropriate, based on the evaluation. Relevant individuals will be trained according to site procedures.

Completion Date
15 September 2021

Action
Procedure (b) (4) (b) (4) (b) (4) , will be revised and made effective to clarify section 9.1.6 regarding Alarm Condition and include instructions for what to do if the (b) (4) needs to be (b) (4) when adding/removing materials from (b) (4). Relevant individuals will be trained according to site procedures.

Completion Date
31 August 2021

Action
The operator who performed final (b) (4) operation within the (b) (4) and sanitization of the (b) (4) was retrained on the entirety of procedure (b) (4) (b) (4) (b) (4) , according to site procedures. The re-training was completed on 29 July 2021.

Completion Date
Complete

Action
Training materials (b) (4) ,(b) (4) (b) (4) and (b) (4) ,(b) (4) (b) (4) will be reviewed to ensure all key aseptic technique elements from (b) (4) (b) (4) (b) (4) , are included. Training materials (b) (4) will be revised and made effective to include the instructions for (b) (4) the (b) (4) (b) (4) of the (b) (4) as part of the proper aseptic technique demonstration. Additional aseptic technique elements will be added, as needed, based on the review. The revisions to the training material will be completed by 30 September 2021 and will be used for Aseptic Technique Fundamentals for Manufacturing Qualification and Requalification moving forward, according to site procedures.

Completion Date
30 September 2021

Observation 11b

(b) (4) cleaning of the (b) (4) in (b) (4) (b) (was not performed in the (b) (4) of July 2021 in deviation from (b) (4)

Response to Observation 11b

Investigation (b) (4) was initiated on 22 July 2021 to document the deviation to procedure (b) (4) for not performing the (b) (4) cleaning of the outside surfaces of the equipment in (b) (4)(b) (4 during (b) (4) of July 2021. The surfaces of equipment were cleaned upon discovery per procedure (b) (4) on 22 July 2021. Procedure (b) (4) currently requires log sheet review for completeness and accuracy (b) (4) , as needed. A retrospective review of the sanitization logbook was conducted to ensure no other (b) (4) cleanings for (b) (4)(b) (4 had been missed.

There is no potential impact to product quality as in-process controls and environmental monitoring ensure the bioburden/endotoxin levels stay within limits. There were no environmental or HVAC alarm excursions reported for (b) (4)(b) (4 during the timeframe in scope.

Action
Procedure (b) (4) (b) (4) will be revised and made effective to remove the terminology "as needed" and change the requirement of review of the sanitization log sheets from (b) (4) . Relevant individuals will be trained on revised procedure (b) (4) according to site procedures.

Completion Date
31 August 2021

Observation 12

The following deficiencies were observed within buildings used to produce BNT162b2 drug substance:

a. In Building (b) (4) **preparation area:**
- (b) (4) **was observed on multiple walls.**
- (b) (4) **was observed in the hallway.**
- (b) (4) **were observed with dust and debris on the** (b) (4) **and streaking/raised residue down the sides and bottom of multiple** (b) (4) **.**

b. In Building (b) (4) (b) (4) (b) (4)
- (b) (4) **was observed on multiple walls inside room** (b) (4) **.**
- (b) (4) **was observed in room** (b) (4)

c. Residue was observed on the sides and base of multiple sample pass throughs to include (b) (4) **preparation,** (b) (4) (b) (4) **and** (b) (4) **.**

d. A gap to the outside was observed on the side of the mobile platform at the receiving dock in Building (b) (4)

Response to Observation 12

Pfizer Andover is committed to ensuring facilities, equipment and utilities are well maintained. Site procedure (b) (4) describes the procedures used to perform preventive and corrective maintenance activities and to manage and document these activities within the Computerized Maintenance Management System (CMMS). This procedure covers the requirements for establishing and executing equipment maintenance tasks and schedules applicable to equipment, instruments, utilities, facilities and systems, and the documentation, review, and approval of maintenance records in CMMS in accordance with procedure (b) (4)

In addition, periodic self-inspection programs are in place for the GMP manufacturing areas and associated mechanical spaces as described in responses for 12a and 12b. These inspection programs include the identification of facility defects on walls and floors. Defects identified during the inspection process are repaired using corrective maintenance. Corrective work orders to repair surface defects are evaluated and prioritized based on risk. Facility inspection and maintenance are continuous processes.

The periodic inspections and corrective maintenance process maintain the facility walls and floors in a state of control.

Observation 12a

In Building (b) (4) **preparation area:**
- (b) (4) **was observed on multiple walls.**

- (b) (4) **was observed in the hallway.**
- (b) (4) **were observed with dust and debris on the** (b) (4) **and streaking/raised residue down the sides and bottom of multiple** (b) (4) **.**

Response to Observation 12a

Procedure (b) (4) provides standard expectations for the self-inspection of the external condition of the equipment, general physical appearance inside manufacturing spaces and associated mechanical spaces. Per procedure, the facility self-inspections are executed on a quarterly basis. In (b) (4) the last self-inspection of this area was performed on 07 Jun 2021 and documented in report (b) (4) (b) (4) (b) (4) (b) (b) (4) .

Procedure (b) (4) requires cleaning of the exterior of all equipment with disinfectant (b) (4) . After the contact time is achieved, the exterior of equipment is wiped with ethanol to remove residual cleaning agent. Procedure (b) (4) (b) (4) Section 5.8 instructs operators to perform workspace clearance (b) (4) formulation. Workspace clearance (b) (4)

Action
Repairs of (b) (4) in Building (b) (4) Preparation Area were documented under work orders 1592463 and 1592462 and completed on 22 July 2021. There were no defects observed in the drug substance manufacturing (b) (4) (b) (4) .

Completion Date
Complete

Action
Repairs to the (b) (4) in the Clean Not Classified (CNC) corridors, (b) (4) were documented under work orders 1593616 and 1593622 and completed on 28 July 2021.

Completion Date
Complete

Action
Procedure (b) (4) (b) (4) (b) (4) , will be revised and made effective to include instructions for personnel to (1) identify any defects/damage that occur or are observed between routine

inspections and (2) how to escalate facility maintenance issues. Relevant individuals will be trained according to site procedures.

Completion Date
10 September 2021

Action
Remediation of observed residues (residual disinfectant) on (b) (4) exterior surfaces for (b) (4) were documented under work Orders 1593895, 15593897, 1593908 and 1593910 respectively, and completed on 28 July 2021.

Completion Date
Complete

Action
Procedure (b) (4) (b) (4) (b) (4) will be revised and made effective to provide more robust instruction for the cleaning of equipment exteriors and removal of disinfectant residue. Relevant individuals will be trained according to site procedures.

Completion Date
30 September 2021

Action
Procedure (b) (4) (b) (4) will be revised and made effective to require workspace clearance upon (b) (4) formulation. More robust instruction for (b) (4) and surrounding surfaces will be included. Additionally, the procedure will be revised to require inspection of (b) (4) and surrounding area to ensure it is free of dust, debris, and residual raw material (b) (4) formulation. Relevant individuals will be trained according to site procedures.

Completion Date
10 September 2021

Observation 12b

In Building (b) (4) (b) (4) (b) (4)

- (b) (4) **was observed on multiple walls inside room** (b) (4) **.**
- (b) (4) **was observed in room** (b) (4)

Response to Observation 12b

Procedure (b) (4) (b) (4) (b) (4) (b) (4), provides the standard expectations of self-inspections that are required to ensure issues are escalated and resolved when observed. Per procedure (b) (4) these self-inspections occur (b) (4). In (b) (4) the last self-inspection was performed on 14 July 2021 and documented in work order 1528780. Operations personnel are performing self-inspections as required per procedure (b) (4)

Action
Repair of a single wall defect observed on a wall in (b) (4) was documented under work order 1593834 and was completed on 29 July 2021.

Completion Date
Complete

Action
Repair to a (b) (4) in (b) (4) was documented under work order 1592483 and was completed on 23 July 2021.

Completion Date
Complete

Action
Procedure (b) (4) (b) (4) (b) (4) (b) (4), will be revised and made effective for the following updates/clarification: Update Andover Production Operations responsibility section to include the requirement that manufacturing is responsible for escalating facility/equipment issues when they are observed to ensure issues are resolved in between GMP100 inspections. Relevant individuals will be trained according to site procedures.

Completion Date
08 September 2021

Action
Preventive maintenance (PM) plans will be implemented in the site maintenance system to assess the need for repair of wall and floor surface defects in (b) (4) (b) (4) on a (b) (4) basis. Frequency of assessment will be re-assessed at (b) (4).

Completion Date
08 September 2021

Observation 12c

Residue was observed on the sides and base of multiple sample pass throughs to include (b) (4), (b) (4) and (b) (4).

Response to Observation 12c

Procedure (b) (4) (b) (4) (b) (4) Sections 9.1.3 and 11.9 requires disinfecting of all sample pass throughs on a (b) (4) frequency. The residue observed on the inside surfaces of sample pass throughs was found to be residual disinfectant (b) (4).

Action
A Special Sanitization Request (SSR) was issued and completed on 27 July 2021 (b) (4) which removed the residual disinfectant.

Completion Date
Complete

Action
Procedure (b) (4) (b) (4) will be revised and made effective to provide more robust instruction for the sanitization of sample pass through interior surfaces and removal of disinfectant residue. Relevant individuals will be trained according to site procedures.

Completion Date
30 September 2021

Observation 12d

A gap to the outside was observed on the side of the mobile platform at the receiving dock in Building (b) (4)

Response to Observation 12d

Procedure (b) (4) establishes procedures for the control of insect, bird, rodent, vermin and wildlife at the Pfizer Andover, MA facilities. Building (b) (4) pest control is governed by procedure (b) (4)

Section 5.11 (Pest Control Device Inspections and Locations) indicates the pest control provider is responsible in sub-sections 5, 6, 7, 8 and 9 to "note any adverse conditions observed in the vicinity of the device." In addition, under Section 5.11 sub-section 10: "Any conditions and observations are noted on the inspection report. The IFM (Integrated Facilities Management) QA

Pest Control Specialist, or designee will initiate and track work orders to address any deficiencies."

The last inspection for the control devices associated with location (b) (4) was completed on 28June2021. The inspection frequency is (b) (4). No adverse conditions were noted with respect to the loading dock door at location (b) (4). No pest control issues were identified during this inspection and no adverse trends have been identified.

Action
Repair of the gap identified on loading dock door at location (b) (4) was documented under work order 1591632 and completed on 23 July 2021.

Completion Date
Complete

Action
Procedure (b) (4) will be revised and made effective with the following update: Update Section 5.11 (Pest Control Device Inspections and Locations) to add a step for the pest control provider to inspect doors and similar openings for adverse conditions which may lead to pest infiltration. All adverse conditions will continue to be documented in the pest control report. The Pest Control Specialist or designee will continue to initiate work orders to address any deficiencies. Relevant individuals will be trained according to site procedures.

Completion Date
31 August 2021

Observation 13:

During (b) (4) activities observed on 7/22/2021, an operator was observed to (b) (4) and subsequently (b) (4) material from a full and previously opened container of (b) (4). The previously opened container of (b) (4) had a lid which was not fully closed, the (b) (4) within the container was not closed, and there was no documentation as to when the container had been initially opened.

Response to Observation 13:

Per procedure (b) (4) (b) (4) (b) (4), partial containers returned to warehouse after sub-division must be closed, sealed, and contained.

Per procedure (b) (4) (b) (4), each container received will be given a unique reference number (Sub-batch). This allows the

(b) (4) Inventory and (b) (4) system to provide full transaction history for each sub-batch. The (b) (4) system keeps a record of every transaction performed on a sub-batch and can produce a transaction history report for each container on when it was opened, and by whom. Review of the transaction history report for the container of (b) (4) (Batch (b) (4), Sub-batch (b) (4)) observed on (b) (4) indicates the container was initially opened for subdivision on (b) (4) The transaction history provided by the (b) (4) Inventory and (b) (4) system negates the need for (b) (4) labeling of containers.

Action
An inspection of the 23 partial containers stored in the Andover (b) (4) warehouse (b) (4) was completed on 27 July 2021 to ensure containers were closed and (b) (4). All containers were found closed and (b) (4) with (b) (4). No additional corrective action is required.

Completion Date
Complete

Action
Procedure (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) will be revised and made effective to provide clear instructions for acceptable methods of container closure following sub-division or sampling and process for escalating observations of unexpected conditions. Relevant individuals will be trained according to site procedures.

Completion Date
31 August 2021