U.S. FOOD & DRUG ADMINISTRATION

To: File STN BL 125742/0 – COVID-19 mRNA Vaccine

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Sponsor: BioNTech Manufacturing GmbH in partnership with Pfizer, Inc.

Product: COVID-19 mRNA Vaccine (BNT162/PF-07302048), COMIRNATY™

Indication: Prevention of COVID-19 in adults ≥16 years of age

Subject: **Original Biologics License Application (BLA) STN 125742/0** Review Memorandum – BioNTech Manufacturing GmbH in partnership with Pfizer, Inc.: to provide for review of the responses to the 483 Inspectional Observations issued during the July 19 – 23, 2021, Pre-License Inspection (PLI) of Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC (referred to as Pfizer Andover; FEI: 1222181). Pfizer Andover was previously authorized for manufacture of BNT162b2 drug substance for the COVID-19 mRNA vaccine in Building (b) (4) ((b) (4)) and Building (b) (4) ((b) (4) (b) (4) under Emergency Use Authorizations (EUAs) 27034.0 and 27034.76, respectively.

Review Recommendation

Review of the firm's responses (Amendment STN 125742/0.25 and Amendment STN 125742/0.60) to the Form FDA 483 confirmed that the proposed corrective actions for Observation Nos. 2 – 13 appear to be acceptable and may be evaluated during the next routine inspection. Regarding Observation No. 1, the firm's response to this Observation was evaluated by the Product Office in a separate memorandum (dated

August 12, 2021, from Anissa Cheung) and found to be adequate for follow up during the next inspection.

Summary

The Center for Biologics Evaluation and Research (CBER) and Office of Regulatory Affairs conducted a PLI of Pfizer Andover from July 19 – 23, 2021, in support of the review of original BLA STN 125742/0. Pfizer Andover was previously authorized to manufacture BNT162b2 drug substance for the COVID-19 mRNA vaccine under EUAs 27034.0 and amendment 27034.76 for (b) (4) (b) (4)

The inspection team consisted of Kathleen R. Jones (KRJ), Ph.D., Biologist, Lead Inspector, CBER/DMPQ/MRBI, Ekaterina Allen (EA), Ph.D., CSO, CBER/OCBQ/DMPQ/MRBII, Anissa Cheung (AC), CSO, CBER/OVRR/DVP, and Debra M. Emerson (DME), CSO, ORA/OMPTO/OBPO/BPIS. At the conclusion of the PLI, a thirteen-item Form FDA 483, List of Inspectional Observations, was issued to the firm.

On July 30, 2021, Pfizer submitted a written response (Amendment STN 125742/0.25) that outlined the proposed corrective actions to address each inspectional observation. The firm's responses to Observation Nos. 2b, 2c, 6, and 9c were also discussed during a teleconference on August 17, 2021. Additional updates and commitments from the teleconference were submitted by the firm via email on August 17, 2021 and received under Amendment STN 125742/0.60 on August 18, 2021. The information provided in Amendments STN 125742/0.25 and STN 125742/0.60 was reviewed, summarized, and assessed in this memorandum by Christian D. Lynch (CDL), CSO, CBER/OD/BOS. Where applicable, initials of inspection team members were incorporated if the inspector/investigator provided comments regarding the appropriateness of the firm's response to a specific observation.

Review of the information contained in the preceding responses revealed that the corrective actions appear to be acceptable and may be evaluated during the next routine inspection.

Review of Pfizer's Responses to the FDA Form 483 Observations

Pfizer's response to the FDA Form 483 observations was submitted on August 2, 2021, in Amendment STN 125742/0.25. A summary of the original 483 Observations (in italics), Pfizer's responses (in regular text), and reviewer (CDL)/inspector/investigator comments (in bold/italics) is provided below:

Observation No. 1 (written by AC)

1. *There is insufficient data to support product quality prior to the release of BNT162b2 drug substance (DS) batch* (b) (4) *manufactured at* (b) (4) (b) (4) *Pfizer Andover on* (b) (4) *was derived from in* (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).

Reviewer's Comments (CDL): ***The firm's response to this observation was reviewed by the Product Office in a separate memorandum and found to be "adequate" with corrective actions*** (b) (5), (b) (7)(E) ***For more information regarding this assessment, please refer to the August 12, 2021, memorandum from Anissa Cheung.***

Observation No. 2 (written by DME)

2. *There is inadequate quality oversight in that:*

Pfizer's Response

The firm's response acknowledged that manufacture of BNT162b2 DS is controlled principally by (b) (4) validated computerized systems:

- (b) (4) located in Building (b) (4) (b) (4) of the Andover Manufacturing Facility
- (b) (4), located in Building (b) (4) (b) (4).

For (b) (4), phase parameters are entered (b) (4) and (b) (4) (b) (4) per batch record instructions. (b) (4) utilizes the input parameters to execute phase parameters as designed. The firm also confirmed that (b) (4) records all entries and actions performed. Per (b) (4), the batch summary report, which includes the batch alarm report and (b) (4) manipulation reports, is reviewed by both Operations and Quality Assurance (QA) during executed batch record review.

Regarding (b) (4), the firm confirmed that all recipes within this recipe-based system are reviewed and approved by Subject Matter Experts (SMEs) and QA in accordance with (b) (4) Operators are responsible for loading approved recipes per batch record instructions. Per (b) (4),

Operations personnel are required to review (b) (4) manipulations (such as temporary changes to running batch active steps as per (b) (4)), the (b) (4) event log, and the batch alarm report. The firm also noted that (b) (4) requires that QA review the associated (b) (4) manipulations, the (b) (4) event log, and the batch alarm report as part of the executed batch record review process. The firm acknowledged that QA does not review the (b) (4) Batch Summary Report as part of its executed batch record review "in all instances"; however, QA does review the Batch Summary Report in certain scenarios (e.g., when the report is linked to an investigation or during impact assessment reviews).

a. *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.*

Pfizer's Response

The firm's response reiterated that (b) (4) governs QA review of batch related operating parameters and monitoring data. The firm also confirmed that the (b) (4) batch alarm report for each batch is attached to the executed batch record. As noted above, any (b) (4) manipulation, the (b) (4) event log, and the batch alarm report that is generated during batch processing must also be documented in the executed batch record for QA review. Additionally, the firm reiterated that QA is 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. Although the firm claimed that the established batch record review process described above ensures full QA oversight of batch execution and any associated eventful operations (such as deviations and alarms), they committed to revise (and enhance) (b) (4) to include additional instructions for (b) (4) system review (which includes the (b) (4) Batch Summary Report) as part of the executed batch record review process. The due date for this action item is September 30, 2021.

Reviewer's Response (CDL and DME): ***The firm's commitment to revise (b) (4) to include additional instructions for (b) (4) system review (which includes the (b) (4) Batch Summary Report) is considered an acceptable response for enhancement of their executed batch record review process.***

b. *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 (b) (4).

Pfizer's Response

The firm's response confirmed that during processing of BNT162b2 DS lot (b) (4) were performed via (b) (4). As (b) (4) values were (b) (4) the operators switched from (b) (4) (in accordance with (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) however, the firm acknowledged that this calculation was not documented in the batch record. On (b) (4), investigation (b) (4) was initiated to address the documentation discrepancy. Although not documented in the batch record, the (b) (4) calculation that was missing from the batch record was reconstructed using data documented in (b) (4) and the executed batch record at the time of execution. During Operations and Quality Assurance batch record review (per (b) (4)), the correct (b) (4) was confirmed using the (b) (4) data and the executed batch record for (b) (4). The firm also confirmed (as part of batch record review) that (b) (4) met all acceptance criteria as documented in the executed batch record.

The firm's response noted that the (b) (4) process for (b) (4) was documented in the executed batch record. The firm also clarified that during (b) (4) continues to run in the background (though it is not controlling the additions). Consequently, (b) (4) continued to log (b) (4) data for additions (b) (4) during this event; however, the firm noted that this "data is rendered extraneous data in (b) (4) The firm also confirmed that after operators take manual control of the (b) (4), the primary source data is the executed batch record.

In response to this Observation, the firm committed to revise (b) (4) to include clarified instructions for implementing (b) (4) operations and documenting (b) (4) calculations within the batch record. The firm also committed to revise (b) (4), to include clarification that after operations are switched to (b) (4), only the data captured in the batch record should be used for evaluation against established acceptance criteria. The due date for both action items is September 15, 2021.

Reviewer's Comments (CDL and DME): ***Initial review of this response found it to be deficient in that it failed to address that*** (b) (4)

can: (1) display that a (b) (4) was (b) (4) when it was performed (b) (4); and (2) generate extraneous data (a potential data integrity issue) after operators switch from (b) (4) to (b) (4) control for (b) (4). During the teleconference on August 17, 2021, FDA discussed these concerns with the firm and asked what actions would be taken to correct the concerns prior to the next inspection. The firm acknowledged our concerns and agreed to submit an updated response for this observation. In Amendment STN 125742/0.60, the firm committed to conduct an evaluation to determine whether (b) (4) can document (internally) any change from (b) (4) mode and cease recording of data (following a change to (b) (4) mode). The firm's updated response is considered acceptable and the Agency recommends (b) (5), (b) (7)(E) (b) (5), (b) (7)(E).

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).*

Pfizer's Response

The firm's response indicated that DS Batch No. (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 by QA in (b) (4). The firm noted that 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.

To provide assurance that the routine production process remains in a state of control, the (b) (4) was changed to a control limit (per (b) (4) in master batch record 513AM, version 3.0 (Effective date: (b) (4)). As part of the (b) (4) process verification monitoring outlined in (b) (4), the (b) (4) for batch No. (b) (4) was noted as (b) (4)

On (b) (4), investigation (b) (4) was initiated to assess and document the impact to batch No. (b) (4). The firm confirmed that on (b) (4), a notation was made (in the executed batch record for (b) (4)) referencing this investigation. The firm's response also noted that this investigation was closed on (b) (4); however, no information was provided regarding the outcome of the investigation.

The firm's response confirmed that they will continue to monitor the BNT162b2 DS manufacturing process via the (b) (4) process manufacturing verification program and the change control process (for management of validated parameter changes).

No additional action items were reported for this observation.

Reviewer's Comments (CDL and DME): ***Initial review of the firm's response found it to be deficient in that no corrective actions were noted regarding the failure of Operations and QA to identify that the (b) (4) exceeded the target (b) (4)) during production of batch No. (b) (4) . During the teleconference on August 17, 2021, the firm was asked if any corrective actions had been initiated regarding QA oversight of the batch record review process. The firm initially reiterated much of the information regarding the (b) (4) target and the subsequent switch to a control limit; however, after FDA clarified that our general concern with this response was the lack of corrective actions regarding QA oversight of batch record review, the firm acknowledged that no corrective actions had been initiated. FDA recommended that the firm consider ways to enhance their (b) (4) process verification monitoring and batch record review process. The firm acknowledged our recommendation and agreed to evaluate potential enhancement of these processes prior to the next routine inspection.***

Observation No. 3 (written by EA)

3. *The following deviation investigations were found deficient. Deviation (b) , (b) (4) (b) (4) (COVID): (b) (4) (b) (4)) and (b) (4) , (b) (4) (b) (4) (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.*

Pfizer's Response

The firm's response indicated that (b) (4) , defines the visual inspection process to evaluate wetted process equipment surfaces for cleanliness. In brief, all visual inspection outcomes are assessed as described to include identification of (b) (4) observed in equipment" (which results in a failed visual inspection). If the visual inspection fails due to the presence of (b) (4) , an investigation is initiated per (b) (4) , and a team of Subject Matter Experts (SMEs) comprised of QA, Engineering, Maintenance, and Utilities (EMU), and Operations is notified. The SME team then 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 then document in the investigation whether operations can proceed or not.

According to the firm's response, investigations (b) (4) and (b) (4) (initiated on (b) (4) and (b) (4), respectively) were both initiated in accordance with (b) (4) following detection of (b) (4). As part of these investigations, the firm reviewed the dirty hold time established as part of the cleaning performance qualification (CPQ). In both events, the amount of time the (b) (4) was in the system was (b) (4) than the maximum dirty hold time. Consequently, (b) (4) sampling of the (b) (4) was not deemed to be a requirement by the SME team. Regarding investigation (b) (4), recleaning of the (b) (4) was performed as the amount of time the (b) (4) was present in the system was (b) (4). The firm noted that per (b) (4), 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 that performed the preliminary assessment leveraged this instruction and directed Operations to reclean the (b) (4). A cleaning verification was not performed as 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 investigation (b) (4), recleaning of the (b) (4) was not performed 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. The firm also reported that a (b) (4) (approximately (b) (4) was observed in (and subsequently (b) (4)) the (b) (4) prior to commencement of manufacturing operations.

The SME preliminary assessments performed for these investigations resulted in QA endorsement to proceed with manufacturing operations; however, the firm acknowledged that documentation of these assessments was deficient and committed to revise procedure (b) (4) to include a more standardized approach for performing and documenting the SME preliminary assessment of the potential impact to manufacturing equipment following a (b) (4) (b) (4) (b) (4) (b) (4). Specific revisions to the SOP will include the requirement to assess and document the following: (b) (4) The due date for this action item is August 31, 2021.

A study will also be conducted to determine which conditions will trigger cleaning verification following identification of (b) (4) This study will include an

evaluation of the potential impact of (b) (4) and the requirement for cleaning verification. Based on the outcome of the study, the revision of (b) (4) will also include additional instructions for utilizing key factors when performing and documenting risk assessment. The due date for this action item is November 30, 2021.

Reviewer's Comments (CDL): ***The firm's commitment to revise*** (b) (4) ***to include a more standardized approach for assessing and documenting the potential impact to manufacturing equipment following a*** (b) (4) (b) (4) ***appears to be an adequate enhancement of their investigational procedures.***

Observation No. 4 (written by KRJ)

4. *Per* (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)

Pfizer's Response

The firm's response indicated that the design and use of the Building (b) (4) (b) (4) (b) (4) requires storage of both the (b) (4) between manufacturing batches. Consequently, the opportunity to collect (b) (4) samples for (b) (4) is limited. The firm also noted that 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 subject to cleaning verification via in-process monitoring rather than the cleaning cycle being validated (via execution of a cleaning performance qualification protocol).

The firm confirmed that (b) (4) is subject to routine process monitoring controls which ensure, among other things, detection of (b) (4) . The (b) (4) trend referenced in the observation was detected with these controls and subsequently evaluated as part of investigation (b) (4) (initiated on (b) (4)). The investigation determined that the most probable root cause for the (b) (4) trend was certain areas of the (b) (4) not being (b) (4) . The root cause for the inadequate (b) (4) of the (b) (4) was identified as an (b) (4) , which resulted in a (b) (4) being unexposed to the (b) (4) The firm also reported that as the (b) (4) was subjected (per procedure) to a (b) (4)

(b) (4). Based on the findings of this investigation, the following corrective and preventive actions were implemented:

(b) (4)

The preceding actions were implemented on (b) (4), as outlined in change control (b) (4). A supplemental validation protocol, (b) (4), was then executed by the firm to demonstrate the effectiveness of the corrective and preventive actions. As part of this protocol, the firm monitored the (b) (4) BNT162b2 DS batches that were manufactured post-remediation. Results of the (b) (4) monitoring for all samples from these batches were reported as (b) (4) (per validation report (b) (4)). Based on these results, the firm concluded that the manufacturing process steps within the scope of the study effectively maintained (b) (4) control with no additional mitigation warranted.

The firm also reported that an effectiveness check (child action record to (b) (4)) was initiated on July 28, 2021, to document the effectiveness of the (b) (4) mitigation strategy implemented per change control (b) (4). For this evaluation, the firm reviewed sample results from (b) (4) operations in (b) (4) for (b) (4) batches of BNT162b2 DS manufactured from (b) (4). Following review of these data, the firm concluded that the equipment continues to operate as expected and no indication of a (b) (4) trend has been observed since implementation of the corrective and preventive actions.

<u>Reviewer's Comments (CDL and KRJ):</u> Although the results from the effectiveness check appear to confirm that the corrective actions implemented in response to the (b) (4) ***trend have been effective in maintaining*** (b) (4) ***control of*** (b) (4)**,**
(b) (4), (b) (5), (b) (7)(E)

<u>Observation No. 5 (written by EA and KRJ)</u>

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.*

Pfizer's Response

The firm's response indicated that the Andover Cleaning Master plan ((b) (4)) takes into consideration that operator dependent processes like (b) (4) are less controllable and repeatable when compared with equipment system parameter dependent processes (and thus are to be verified and not validated as a cleaning procedure). The Cleaning Master Plan also highlights that when cleaning by (b) (4) is required, 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.

According to the firm, a development cleanability assessment was executed using the BNT162b2 vaccine process residues to understand both the characteristics of the process residues that are intended to be cleaned and determine the cleaning capabilities of the (b) (4) procedure used by operations personnel. The firm's assessment concluded that the (b) (4) operation can clean the process residues from equipment surfaces and that the BNT162b2 vaccine process residues can be visually detected on processing equipment within the (b) (4) . The development cleanability assessment included representative materials of construction (MOCs) for equipment used to manufacture BNT162b2 vaccine and used worst-case *cleaning* conditions to appropriately challenge the (b) (4) procedure ((b) (4)) used by operations personnel.

The firm also noted that verification of the effectiveness of the (b) (4) operation (to include (b) (4) testing) is performed on a (b) (4) basis. Additionally, periodic monitoring is performed on equipment cleaned via (b) (4) under the formal cleaning monitoring program. This program is governed by (b) (4)

Cleaning monitoring provides ongoing assurance that the (b) (4) cleaning process is operating as expected in accordance with predetermined acceptance criteria. Cleaning Monitoring includes (b) (4) , as well as visual inspection. The acceptance criteria are pre-established and include the following: (b) (4)

(b) (4)

The firm confirmed that the most recent cleaning monitoring of the (b) (4) (b) (4) operation was executed in March 2021. Although all results obtained from this monitoring activity (including (b) (4) were within specified acceptance criteria, the firm committed to execute a pre-approved protocol 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) This protocol will verify (b) (4) cleaning operations performed on dirty equipment utilized in (b) (4) (b) (4) using all testing required in the (b) (4) verification. The results obtained from the executed protocol will be summarized in a formal summary report by November 30, 2021. Per the firm, if the data from the study indicate that a change in cleaning monitoring is needed, a subsequent commitment will be initiated.

Reviewer's Comments (CDL): ***Execution of a pre-approved protocol to compile a larger data set (inclusive of*** (b) (4) ***sampling) to further support verification of the*** (b) (4) ***operation performed in*** (b) (4) (b) (4) ***appears to be an acceptable response for this observation. It is recommended that*** (b) (4), (b) (5), (b) (7)(E)

(b) (4), (b) (5), (b) (7)(E)

Observation No. 6 (written by KRJ)

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) *; (Building* (b) (4) *) demonstrates efficacy on all surfaces, however,* (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)

Pfizer's Response

The firm indicated that (b) (4) disinfectant efficacy studies were performed to qualify disinfectants for use in (b) (4) facilities (including (b) (4)). These studies are summarized in report (b) (4) The firm also confirmed that the efficacy studies included 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) . Per the firm, results from the (b) (4) independent studies, which included (b) (4) different surfaces and challenged (b) (4) different (b) (4) , showed that a greater than (b) (4) reduction could be achieved with a (b) (4) contact time for (b) (4)

The firm also acknowledged that a comprehensive review of the Building (b) (4) disinfectant efficacy program (including (b) (4) (b) (4) was conducted over the last several years. Following this review, a contemporaneous study employing improved study design and methodologies was executed and summarized in (b) (4). Per the firm, results from this study "also demonstrated efficacy of a (b) (4) contact time for (b) (4) consistent with studies supporting the same for Building (b) (4) (b) (4)." The firm concluded that the combined data from the multiple studies/reports support a (b) (4) contact time for (b) (4) in both facilities. Consequently, no corrective actions were reported for this observation.

<u>Reviewer's Comments (CDL and KRJ):</u> During the teleconference on August 17, 2021, CBER reported that discrepancies were noted between (b) (4) (approved on April 28, 2021), and (b) (4) effective April 30, 2015. Specifically, the (b) (4) report indicated that (b) (4) was effective with a contact time of (b) (4) while (b) (4) noted that (b) (4) was not effective with a contact time of (b) (4) (except on (b) (4). The firm acknowledged these discrepancies; however, they also noted that the (b) (4) study was performed by (b) (4) on the coupons (versus (b) (4) of the coupons as per (b) (4)). The firm (b) (4) that (b) (4) the (b) (4) on the coupons allowed for evaporation and appeared to be the preferred method for conducting these studies (when compared with (b) (4). The firm also referenced an additional study (b) (4) that was performed with improved design and methodologies for Building (b) (4) (including (b) (4) (b) (4) by (b) (4) on the coupons. As noted above, results from this study demonstrated that (b) (4) is effective with a (b) (4) contact time (which is consistent with the studies supporting the same for Building (b) (4) (b) (4)).

It should be noted that an additional discrepancy was discovered (post-inspection) regarding the effectiveness of (b) (4) against (b) (4) on (b) (4) flooring and (b) (4) wall surfaces. Specifically, (b) (4) reported that (b) (4) demonstrated effectiveness with a contact time of (b) (4), while (b) (4) noted that (b) (4) was not effective with a contact time of (b) (4). During the August 17, 2021, teleconference, FDA confirmed that the contradictory information regarding (b) (4) was also due to study methodology (b) (4) Based on the clarified information regarding studies (b) (4), the firm's response is

considered acceptable (b) (5), (b) (7)(E)
(b) (5), (b) (7)(E)

Observation No. 7 (written by KRJ)

7. *The ISO-*(b) (4) *are not monitored to 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) *is within an ISO*(b) (4) *room.*

Pfizer's Response

The firm's response indicated that the Building (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 this EMQ was to demonstrate that each of the current Clean Environmental Areas (CEAs) in (b) (4) could meet and maintain the air and surface environmental quality levels for Good Manufacturing Practice (GMP) based on use for a (b) (4) DS facility. The EMQ was also designed to demonstrate that the facility met United States Pharmacopeia (USP) and International Organization for Standardization (ISO) (b) (4) requirements. Per the firm, results from the EMQ showed that the ISO-(b) (4) in (b) (4) met air quality level requirements (per ISO (b) (4) for (b) (4) monitored under (b) (4) conditions. Regarding (b) (4) levels, the firm stated that (b) (4) quality levels are not specified per ISO (b) (4) quality levels for (b) (4) are not applicable to a (b) (4) drug substance facility." The firm also reported that "the (b) (4) are routinely monitored for (b) (4) and meet the air quality levels of ISO (b) (4) requirements."

Despite the above referenced ISO(b) (4) qualification and routine monitoring of the (b) (4), the firm acknowledged that all ISO-(b) (4) in (b) (4) will have the ISO(b) (4) designation removed and be re-classified as (b) (4) Additionally, (b) (4) and (b) (4) will be revised to reflect the new (b) (4) classification of these units for a (b) (4) DS facility. The due date for the preceding action items is September 15, 2021. Affected individuals will also be retrained in accordance with site procedures.

Reviewer's Comments (CDL and KRJ): ***Given that the*** (b) (4) ***in*** (b) (4) ***are utilized for DS (upstream) operations in ISO*** (b) (4) ***areas, the firm's commitment to remove the ISO*** (b) (4) ***designation and re-classify these units as*** (b) (4) ***" is considered acceptable.***

Observation No. 8 (written by KRJ)

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) (b) (4) *are routinely monitored.*

Pfizer's Response

The firm's response noted that at the present time, no specific regulatory guidance documents (or requirements) exist regarding the number of compressed air points of use (POUs) to be sampled or the frequency of sampling. However, the firm did reference recommendations such as the ISPE Good Practice Guide, which recommends testing every (b) (4) on a rotating basis from representative sample locations.

The firm also indicated that (b) (4) outlines the routine monitoring program for the compressed air system. As part of this program, (b) (4) were designated as representative sample locations with a sampling frequency of (b) (4) (based on Validation Protocol (b) (4) : (b) (4) . Per (b) (4) (Section 5.1), the sample site selection followed a (b) (4) approach that was based on (b) (4)

The firm also confirmed that (b) (4) (b) (4)

Following the compressed air PQ, the firm implemented routine monitoring at (b) (4) (b) (4) sample (b) (4) (b) (4) (b) (4) . Monitoring results are compared against the following quality levels:

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

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

Results from routine monitoring of (b) (4) sample valve locations (b) (4) showed that all samples met (b) (4) quality levels for the period from March 7, 2019 – May 7, 2021. Based on these results, the firm concluded that the compressed air system in Building (b) (4) is operating in a state of control (based on only (b) (4) sample locations); however, they also acknowledged that (b) (4) will be revised to include a requirement that all (b) (4) locations be tested each (b) (4) The due date for this action item is August 31, 2021. Relevant individuals will also be trained in accordance with site procedures.

Reviewer's Comments (CDL): ***The firm's commitment to revise*** (b) (4) ***to include a requirement for*** (b) (4) ***sampling of all*** (b) (4) ***is considered an acceptable response for enhancement of their monitoring program.***

Observation No. 9 (written by EA)

9. *The environmental program (EM) program in* (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.*

Pfizer's Response

The firm's response indicated that the environmental monitoring performance qualification (EMPQ) of (b) (4) was performed in accordance with (b) (4) The EMPQ included (b) (4) days of sampling ((b) (4)) in Room (b) (4) and (b) (4) under (b) (4) conditions. This was followed by (b) (4) days of sampling ((b) (4)) in Room (b) (4) and (b) (4) under (b) (4) conditions. All sampling was performed per (b) (4), Environmental Monitoring Program for Building (b) (4) (b) (4) which includes (b) (4) sample locations, action levels, and required (b) (4) identifications. The firm also confirmed that the (b) (4) conditions referenced above were achieved in production Room (b) (4) (ISO by allowing personnel into the room to

(b) (4) (b) (4) operational equipment.

Results from the EMPQ (captured on (b) (4)) showed that all samples met acceptance criteria (with no action level excursions and only one result above the alert level) and were approved by QA on December 24, 2020 (prior to performing operations). Additional sampling of Room (b) (4) and (b) (4) was performed from December 28, 2020 – January 2, 2021, under (b) (4) conditions (and in accordance with site procedure (b) (4)). Release of (b) (4) (b) (4) for use was documented in change control (b) (4) .

Although it was reported that the EMPQ included (b) (4) , and additional sampling of (b) (4) , the firm acknowledged that the EMPQ of the (b) (4) was not performed under true (b) (4) conditions as there was no activity in the (b) (4) at the time of sampling. The firm also acknowledged that during review of change control (b) (4) , it was revealed that the EMPQ was not executed with a pre-approved protocol (as required per (b) (4)) or summarized in a final report. On June 30, 2021, investigation (b) (4) was initiated to document and investigate the deviation from (b) (4) . The root cause for this event was identified as an isolated human error with no impact to the EMPQ or product quality (as all sampling was performed in accordance with established procedures). A summary report, (b) (4) , was written and approved on July 23, 2021.

In response to the observation, the firm committed to revise (b) (4) to include defined (b) (4) conditions that should be executed during the (b) (4) portion of an EMPQ. (b) (4) will also be revised to include appropriate documentation requirements to capture (b) (4) activities within the EMPQ protocol and final report. The action due date for the revisions to (b) (4) is August 31, 2021. The firm also committed to perform an EMPQ of (b) (4) and (b) (4) (in (b) (4) (b) (4) under predefined (b) (4) conditions by September 15, 2021.

Reviewer's Comments (CDL): ***The firm's commitment to revise*** (b) (4) ***and perform an EMPQ of*** (b) (4) ***(in*** (b) (4) ***under predefined*** (b) (4) ***conditions appears to be acceptable response for this observation.***

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

Pfizer's Response

The firm's response indicated that the EMPQ for (b) (4) controlled classified production areas was executed from December 16 – 21, 2020 (with increased sampling conducted from December 28, 2020 – June 2, 2021). The firm also confirmed that routine EM was initiated on January 4, 2021, at a frequency defined in (b) (4) (b) (4) (b) (4)

Analysis of the routine EM data from January 4 – June 30, 2021, revealed that all samples (b) (4) total) had results within quality levels (below alert or action levels) for all test types (b) (4) collected from (b) (4) ISO areas.

In response to the observation, the firm committed to implement a protocol for increased sampling (at a frequency of (b) (4)) for a (b) (4) period in the (b) (4) ISO areas. Results from this study will be evaluated to determine an appropriate sampling frequency for the (b) (4) ISO areas. The target date for completion of this study is December 15, 2021. Relevant individuals will also be trained on any sampling changes in accordance with established site procedures.

<u>Reviewer's Comments (CDL):</u> The firm's commitment to conduct an increased sampling study in the (b) (4) ISO areas is considered an acceptable response to address the concerns regarding EM in these areas. It is recommended that (b) (5), (b) (7)(E)

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 through the duration of the walkthrough. Room (b) (4) is classified as controlled not classified and is not monitored.*

<u>Pfizer's Response</u>

The firm's response acknowledged that a communication error occurred during the inspection regarding classification of control room (b) (4) Specifically, it was communicated (in error) that (b) (4) control room (b) (4) is a Controlled Not Classified (CNC) area. The firm's response clarified that control room (b) (4) is actually classified as an ISO area. The firm also noted that as (b) (4) control room (b) (4) and adjacent room (b) (4) have the same ISO classification and a neutral pressure differential, the room air cascade and air quality should not be impacted. The firm also acknowledged that the doors to ancillary rooms should not be left open.

In response to the observation, the firm committed to implement a protocol for increased sampling (at a frequency of (b) (4) for a (b) (4) period in the (b) (4) (b) (4) control room. Results from this study will be evaluated to determine an appropriate sampling frequency for the (b) (4) (b) (4) ISO (b) (4) areas. The target date for completion of this study is December 15, 2021. (b) (4) (b) (4) will also be revised to ensure that all doors to ancillary rooms (including (b) (4) are not left open. Attention activators will also be applied to doors within (b) (4) (b) (4) to remind personnel to close doors behind them. The due date for the SOP revision and application of attention activators is August 31, 2021. Relevant individuals will be trained on the preceding revisions in accordance with established site procedures.

<u>Reviewer's Comments (CDL and EA):</u> The firm's commitment to conduct an increased sampling study in the (b) (4) (b) (4) ***control room is considered an acceptable response to address the concerns regarding the EM program in this area. It is*** (b) (5), (b) (7)(E)

During the teleconference on August 17, 2021, the firm was asked about their EM strategy for the ancillary ISO (b) (4) ***rooms in*** (b) (4) (b) (4) ***(including the*** (b) (4) ***control room). The firm indicated that an updated response would be submitted for this observation. In Amendment STN 125742/0.60, the firm committed to implement a protocol for increased sampling (at a frequency of*** (b) (4) ***) for a*** (b) (4) ***period in the*** (b) (4) (b) (4) ***ISO*** (b) (4) ***ancillary rooms. The compiled data will be evaluated to determine an appropriate routine EM strategy (to include sample types and frequency) for all the ancillary ISO*** (b) (4) ***rooms in*** (b) (4) (b) (4) ***(including the*** (b) (4) ***control room). The due date for completion of the increased sampling study is December 15, 2021. The firm's updated response is considered acceptable to address the observation*** (b) (5), (b) (7)(E) (b) (5), (b) (7)(E)

<u>Observation No. 10 (written by EA)</u>

10. On (b) (4) *the HVAC supplying* (b) (4) (b) (4) *was shut down for preventive 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 (b) (4) 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.

Pfizer's Response

The firm's response confirmed that the heating, ventilation, and air conditioning (HVAC) systems that supply the manufacturing areas are qualified per (b) (4) During initial qualification, each HVAC unit is required to undergo multiple tests per ISO-(b) (4) . This includes a (b) (4) test, which 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. The firm reported that HVAC (b) (4), which serves (b) (4) (b) (4) passed particulate testing (in under (b) (4) as well as all other HVAC qualification tests, thus demonstrating that ISO (b) (4) standards were achieved.

The firm also noted that (b) (4) , includes an allowance for a loss of air flow for up to (b) (4) prior to requiring an additional facility sanitization. The firm confirmed that this allowance is based on historical data documented in (b) (4)

A Closure Risk Assessment (CRA) was also performed (and became effective on December 31, 2020) per (b) (4) to document and understand the operational details and environmental controls around the (b) (4) unit operations (and related processing steps performed within (b) (4) (b) (4) The assessment noted that 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 also taken at pre-defined points from (b) (4)

(b) (4)

Regarding the events surrounding the observation, the firm noted that a facility sanitization was performed at (b) (4) on (b) (4), per (b) (4), Scheduling, Frequency and Order of Sanitizing for (b) (4). No personnel were present within the suite and no manufacturing operations occurred during the HVAC shutdown. The HVAC unit serving (b) (4) was then 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) Closed operations within (b) (4) were initiated at approximately (b) (4). The firm noted that this event did not require additional sanitization as the loss of airflow did not exceed the (b) (4) allowance outlined in (b) (4). The firm also confirmed that the subsequent facility sanitization was performed on (b) (4).

According to (b) (4), audible HVAC alarms that occur during manufacturing operations require a comment to be entered in the Manufacturing Batch Record (MBR) that is in process at the time of the alarm. Regarding batch Nos. (b) (4), the firm noted the QA review of the MBRs (per (b) (4)) revealed that no comments were entered in the respective MBRs as no operations were being conducted at the time of the loss of air flow. The firm also noted that DS batch Nos. (b) (4) met all in process and release specifications (including (b) (4) as outlined in (b) (4) and were subsequently dispositioned with a status of released. Based on the preceding information, the firm concluded that there was no product impact to batch Nos. (b) (4) following the (b) (4).

In response to the observation, the firm committed to initiate a study (by October 28, 2021) to assess the return to environmental control specification(s) per (b) (4) (b) (4) (b) (4) Depending on the results of the study, (b) (4) may be revised to include specific actions, such as facility sanitization and/or EM, that will be required in response to future alarm events. An interim control to assess product impact following an HVAC shutdown greater than (b) (4) in duration was also approved on July 30, 2021 and will be documented per planned temporary change (b) (4). Additionally, (b) (4) MBRs will be revised by September 15, 2021, to capture confirmation of cleaning status in this suite.

Reviewer's Comments (CDL): ***The firm's commitment to revise (b) (4) to include specific actions for future alarm events is considered an acceptable response for this observation.***

Observation No. 11 (written by EA)

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) and (b) (4):

i. 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.

ii. (b) (4) operators were (b) (4) over the (b) (4) of the (b) (4) blocking the (b) (4).

iii. (b) (4) did not cover all surfaces of the (b) (4) and was (b) (4) (b) (4) contact time required per (b) (4).

Pfizer's Response

The firm's response confirmed that at the time of the alarm conditions on July 22, 2021, no work was being performed in (b) (4). The firm also noted that all aseptic connections required for the (b) (4) were completed by the operator within (b) (4) prior to the alarm event. In accordance with (b) (4) (b) (4), the (b) (4) were (b) (4) with (b) (4) prior to transfer into the (b) (4). The firm acknowledged that the alarm condition was triggered by the operator (b) (4) to introduce the (b) (4) into the (b) (4) however, once the (b) (4) were in the (b) (4) and the (b) (4) was (b) (4), the alarm cleared. The firm also noted that the introduced items remained undisturbed for the required (b) (4) within the (b) (4) (per (b) (4)) before the operator attached the (b) (4).

On July 26, 2021, investigation (b) (4) was initiated for the alarm condition observed within (b) (4). The root cause for this event was identified as a lack of instructions (in (b) (4)) regarding how to proceed when the (b) (4) needs to be (b) (4) to add or remove items from a (b) (4). As a corrective action, the firm committed to revise (b) (4) (Section 9.1.6 regarding alarm condition) to include instructions for what to do if the (b) (4) needs to be (b) (4) when adding or removing items from a (b) (4) The firm also committed to assess the procedure for final (b) (4) to determine whether the

number of items transferred into the (b) (4) can be minimized to only those required for open product manipulation. (b) (4)

(b) (4)

will be revised (as appropriate) based on the results of the assessment. The due date for the preceding action items is September 15, 2021.

The firm indicated that an additional investigation (b) (4) was initiated on July 27, 2021, to document the deviations to (b) (4) regarding aseptic technique and insufficient work surface sanitization of (b) (4). The operator that performed the work surface sanitization of (b) (4) and (b) (4) operations within the (b) (4) for this event was trained on the appropriate SOPs ((b) (4) and (b) (4) at the time of the deviation. The affected operator was also interviewed and confirmed that he was aware of the requirement to not (b) (4) the (b) (4) of the (b) (4) (per (b) (4); however, as the (b) (4) was running, he (b) (4)
(b) (4)
(b) (4)

As a corrective action for this event, (b) (4) will be reviewed to ensure that all key aseptic technique elements from (b) (4) are included. (b) (4) will also be revised to include instructions to not (b) (4) the (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 firm's review. The due date for these revisions is September 30, 2021.

Regarding work surface sanitization of the (b) (4), (b) (4) specifies that unit surfaces be saturated with (b) (4) and remain undisturbed for (b) (4) however, this SOP does not require that the work surface 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 of the (b) (4). The operator involved in the work surface sanitization event was interviewed and confirmed that (b) (4) was followed and that all surfaces of the (b) (4) were covered with (b) (4). As a corrective action for this event, the affected operator was re-trained on (b) (4) on July 29, 2021, prior to performing any additional operations within the (b) (4)

The firm also noted that (b) (4) samples from the (b) (4) product (b) (4) for batch No. (b) (4) (in-process at the time of the deviation event) met all specifications. Based on these results and the investigations, the firm concluded that there was no product impact for batch No. (b) (4)

Reviewer's Comments (CDL): ***The firm's commitment to revise*** (b) (4) ***to include updated instructions for demonstration of proper aseptic technique in*** (b) (4) ***is considered an acceptable response to address the aseptic behavior and events noted in this observation.***

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

Pfizer's Response

The firm's response indicated that investigation (b) (4) was initiated on July 22, 2021, to document the deviation to (b) (4) regarding failure to perform the (b) (4) cleaning of the outside surfaces of the equipment in (b) (4) during (b) (4) in July 2021. Following identification of this deviation, all equipment surfaces in (b) (4) were cleaned (on July 22, 2021) in accordance with (b) (4). (b) (4) also requires (b) (4) review of the log sheet for completeness and accuracy ("as needed"). A retrospective review of the sanitization logbook confirmed that no other (b) (4) cleanings for (b) (4) had been missed. The firm also confirmed that no environmental or HVAC alarm excursions were reported for (b) (4) during the (b) (4) timeframe. Based on this information, the firm concluded that there was no impact to product quality as all in-process controls and environmental monitoring samples were within limits.

In response to this observation, the firm committed to revise (b) (4) to include removal of the terminology "as needed" and change the requirement for review of the sanitization log sheets from (b) (4). The due date for this action item is August 31, 2021.

Reviewer's Comments (CDL): ***The firm's commitment to revise*** (b) (4) ***to include an updated requirement for*** (b) (4) ***review of sanitization log sheets is considered an acceptable response for this observation.***

Observation No. 12 (a, c, and d written by DME; b written by EA)

12. The following deficiencies were observed within buildings used to produce BNT162b2 drug substance as noted below:

Pfizer's Response

The firm indicated that the Andover site is committed to ensuring facilities, equipment, and utilities are well maintained. Site (b) (4) – Maintenance Procedure, describes the procedures used to perform preventive and corrective

maintenance activities and manage and document these activities within CMMS. The firm noted that this procedure also 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 (b) (4)).

The firm also confirmed that periodic self-inspection programs are in place for the manufacturing areas and associated mechanical spaces as described in the responses for 12a and 12b below. These inspection programs include the identification of facility defects on walls and floors. Defects identified during the inspection process are repaired using corrective maintenance procedures. Corrective work orders to repair surface defects are evaluated and prioritized based on risk.

a. In Building (b) (4) preparation area:

i. (b) (4) was observed on multiple walls.

ii. (b) (4) was observed in the hallway.

iii. (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).

Pfizer's Response

The firm indicated that (b) (4) , provides standard expectations for quarterly self-inspections of the external condition of the equipment, general physical appearance inside manufacturing spaces, and associated mechanical spaces. According to the firm, the last self-inspection of (b) (4) was performed on June 7, 2021, and documented in report (b) (4) .

The firm also confirmed that (b) (4) , requires (b) (4) cleaning of all equipment exteriors with disinfectant. After the disinfectant contact time is achieved, the exterior of piece of equipment is wiped with ethanol to remove any residual cleaning agent. (b) (4) , Section 5.8, instructs operators to perform workspace clearance (b) (4) formulation. Workspace clearance (b) (4)

(b) (4) Remediation of the observed residues on the exterior surfaces of (b) (4) was completed on July 28, 2021, and documented as part of work order Nos. 1593895, 15593897, 1593908, and 1593910, respectively. The firm also committed to revise (b) (4), to include more robust instructions for cleaning of equipment exteriors and removal of residual disinfectant. Additionally, the firm committed to revise (b) (4) to include the following:

- Requirement for workspace clearance upon (b) (4) formulation.
- More robust instructions for (b) (4) and surrounding surfaces.
- Requirement for inspection of (b) (4) and surrounding areas to ensure they are free of dust, debris, and residual raw material (b) (4) formulation.

The firm reported that repairs to the (b) (4) observed in the Building (b) (4) Preparation Area were completed on July 22, 2021 and documented as part of work order Nos. 1592463 and 1592462. The firm also confirmed that no defects were observed in DS manufacturing (b) (4) (b) (4) and (b) (4) Repairs to the (b) (4) in the Clean Not Classified corridors (b) (4) were completed on July 28, 2021 and documented as part of work order Nos. 1593616 and 1593622.

The firm also committed to revise (b) (4), to include instructions for personnel to identify any defects/damage that occur or are observed between routine inspections and escalate facility maintenance issues. The due date for this action item is September 10, 2021.

<u>Reviewer's Comments (CDL):</u> As the facility was repaired and the firm committed to revise relevant SOPs to include updated instructions for identifying and escalating facility maintenance issues, the response to this observation is considered acceptable.

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

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

ii. (b) (4) *was observed in room* (b) (4)

<u>Pfizer's Response</u>

The firm's response indicated that (b) (4), (b) (4) (b) (4) provides the standard expectations

for (b) (4) self-inspections that are required to ensure that issues are escalated and resolved when observed. According to the firm, the last self-inspection of (b) (4) was performed on July 14, 2021 and documented as part of work order No. 1528780. The firm claimed that Operations personnel are performing self-inspections as required per (b) (4).

The firm confirmed that repair of the (b) (4) in (b) (4) was completed on July 23, 2021 and documented as part of work order No. 1592483. The firm also committed to revise (b) (4) to include an update of the Operations responsibility section to clarify that Manufacturing personnel are responsible for escalating facility/equipment issues when observed to ensure that these issues are resolved between GMP100 inspections. Preventive maintenance (PM) plans will be also implemented in the site maintenance system to assess, on a (b) (4) basis (b) (4), the need to repair wall and floor surface defects in suites. The frequency of this assessment will be re-assessed at (b) (4). The due date for the preceding action items is September 8, 2021.

Reviewer's Comments (CDL): ***As the facility was repaired and the firm committed to revise (b) (4) to include updated responsibilities for escalating facility/equipment issues, the response to this observation is considered acceptable.***

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

Pfizer's Response

The firm's response indicated that (b) (4), Sections 9.1.3 and 11.9, requires (b) (4) disinfection of all sample pass throughs. The firm acknowledged that the residue observed on the inside surface of the sample pass throughs was determined to be residual disinfectant (b) (4). In response to this observation, a special sanitization request (SSR) was issued and completed on July 27, 2021, ((b) (4)) to remove the residual disinfectant. The firm also committed to revise (b) (4), to include more robust instructions for sanitization of sample pass through interior surfaces and removal of residual disinfectant. The due date for this action item is September 30, 2021.

Reviewer's Comments (CDL): ***The firm's response is acceptable.***

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

Pfizer's Response

The firm's response indicated that (b) (4), outlines the procedures for control of insect, bird, rodent, vermin, and wildlife at the Pfizer Andover, MA facilities. As noted in Section 5.11 (Pest Control Device Inspections and Locations), 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." Section 5.11, sub-section 10, also states that "any conditions and observations are noted on the inspection report. The Integrated Facilities Management (IFM) QA Pest Control Specialist, or designee, will initiate and track work orders to address any deficiencies."

The firm noted that the last (b) (4) inspection for the control devices associated with location (b) (4) was completed on June 28, 2021. According to the firm, no adverse conditions (or pest control issues) were noted with respect to the loading dock door at location (b) (4). A review of previous inspections was also conducted and revealed no adverse trends associated with site pest control.

The firm confirmed that the gap identified on the loading dock door at location (b) (4) was repaired on July 23, 2021 and documented as part of work order No. 1591632. The firm also committed to revise (b) (4) to include addition of a step in Section 5.11 (Pest Control Device Inspections and Locations) that requires the pest control provider to inspect doors and similar openings for adverse conditions that could lead to pest infiltration. All adverse conditions will continue to be documented in the pest control report. Additionally, the Pest Control Specialist or designee will continue to initiate work orders to address any deficiencies. The due date for revision of (b) (4) is August 31, 2021.

Reviewer's Comments (CDL): ***As the dock door was repaired and the firm committed to revise*** (b) (4) ***to include addition of a step for inspection of doors (and other openings), the response to this observation is considered acceptable.***

Observation No. 13 (written by DME)

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.*

Pfizer's Response

The firm's response noted that per (b) (4) , partial containers returned to the warehouse after sub-division must be closed, sealed, and contained.

The firm also noted that (b) (4) (b) (4) , requires that each received container be assigned a unique reference number (sub-batch), which allows the (b) (4) Inventory and (b) (4) system to provide full a transaction history (and report) for each sub-batch. The firm noted that the transaction history report includes information such as open date (and operator) and negates the need for (b) (4) labeling of containers. Regarding the event noted in the observation, review of the transaction history report for the container of (b) (4) (Batch (b) (4) , Sub-batch (b) (4)) observed on July 22, 2021, revealed that this container was initially opened for subdivision on July 21, 2021.

On July 27, 2021, the firm inspected 23 partial containers stored in the (b) (4) warehouse (b) (4) for compliance with (b) (4) . Results from the inspection showed that all containers were closed and all (b) (4) were (b) (4) . The firm also committed to revise (b) (4) , to include clear instructions for acceptable container closure (following sub-division or sampling) and escalating observations of unexpected conditions. The due date for this action item is August 31, 2021.

> ***Reviewer's Comments (CDL and DME):*** ***The firm's commitment to revise*** (b) (4) ***to include clear instructions for acceptable container closure and escalation of unexpected conditions is considered an acceptable response for enhancement of their raw material management program.***