Subpart C - Buildings and Facilities

(21 CFR 211.42 – 211.58)

211.42 Design and construction features.

211.44 Lighting.

211.46 Ventilation, air filtration, air heating and cooling.

211.48 Plumbing.

211.50 Sewage and refuse.

211.52 Washing and toilet facilities.

211.56 Sanitation.

211.58 Maintenance.

Your firm failed to have buildings used in the manufacture, processing, packing, or holding of drug products with adequate space for the orderly placement of equipment and materials to prevent mixups and contamination (21 CFR 211.42(b)).

Your drug manufacturing facility lacked adequate controls. For example:

A. Material storage
Investigators observed approximately **(b)(4)** truck trailers on your property used for the storage of components, finished products, and other items. These trailers were not climate controlled, and you were unable to accurately describe the contents of the trailers due to your inadequate inventory management system. Furthermore, **(b)(4)**, an API in your drug products, was stored outdoors and exposed to the elements.

B. Pest control
Pest traps inside your raw material storage area were covered with filth and insects, and reports from your pest control service provider showed an ongoing pest issue.

In your response, you state a procedure will be developed for managing inventories, including the dispositioning of nonconforming material in your warehouse and shipping trucks. You also state your pest control procedure will be improved and followed effectively.

Your response is inadequate. You fail to demonstrate adequate controls over your inventory, including materials stored in trailers outside your facility. You also fail to comprehensively evaluate the scope and product quality risk of your pest control issue.

Your firm's packaging and labeling operations are performed without adequate controls to prevent mix-ups and cross-contamination. For example, our investigators observed employees performing manual packaging and labeling operations on the floor of the manufacturing room. Investigators also

noted that multiple drug products were packaged simultaneously without adequate separation and spacing. The drug products were also packaged without the use of batch records.

Our investigators also observed that your reserve samples were improperly stored, commingled with expired products, and lacked routine monitoring.

In your response, you state that you implemented procedures for dispensing and issuing packaging materials. Your response also includes plans to expand your warehouse. Your response is inadequate because you failed to address the interim plans to prevent labeling mixups in your current packaging area while you remediate your lack of adequate facility spacing. You also do not describe how you intend to ensure that the procedural updates are effective.

Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas (21 CFR 211.42(c)(10)).

Significant deficiencies were identified with aseptic processing controls in your **(b)(4)** and restricted access barrier system (RABS) processing lines used to aseptically manufacture sterile drug products for the U.S. market.

Cleaning and Disinfection

You used **(b)(4)** extensively to rinse critical, interior surfaces and aseptic processing equipment in your **(b)(4)** and RABS lines after production. This **(b)(4)** was fed from **(b)(4)** cleaning use points inside your **(b)(4)** and RABS through excessively long (up to approximately **(b)(4)**) deadlegs from your **(b)(4)** loop. Deadlegs in **(b)(4)** systems are known to cause stagnation of **(b)(4)** and excessive microbial growth.

Between June 2023 and September 2025, routine testing of **(b)(4)** cleaning use points in your ISO 5 **(b)(4)** and RABS resulted in at least 47 microbial recoveries, including 14 that exceeded your action limit. Your routine monitoring samples repeatedly recovered gram-negative, biofilm-forming, **(b)(4)** organisms including *Sphingomonas*, *Methylobacterium*, *Bradyrhizobium*, and *Ralstonia* species. Investigations for at least two incidents associated with microbial recoveries identified the design of your **(b)(4)** cleaning use point piping as the most likely root cause. However, your corrective action and preventive action (CAPA) plans have failed to comprehensively address the identified deficiencies in your **(b)(4)** system design.

Furthermore, post-production environmental monitoring (EM) samples taken within your ISO 5 **(b)(4)** and RABS between June 2023 and September 2025 have resulted in repeated recoveries of gram-negative **(b)(4)** organisms including *Sphingomonas, Methylobacterium*, and *Cupriavidus* species.

This sampling identified a worrisome adverse trend in your RABS in late 2023 in which **(b)(4)** gaskets and **(b)(4)** were found to be contaminated with gram negative microbes. Significantly, too-numerous-to-count (TNTC) levels were present on RABS **(b)(4)** gaskets in

multiple instances during this period. Your investigations acknowledged that equipment design (including **(b)(4)** gaskets) and maintenance, in combination with cleaning (e.g., residual **(b)(4)** from cleaning), caused the deviation.

You failed to sufficiently address the underlying cause of residual **(b)(4)** in a timely manner, instead relying on personnel to **(b)(4)** dry any observed moisture.

In your response, you commit to corrective actions including **(b)(4)** sanitization of **(b)(4)** cleaning use point piping and **(b)(4)** of the **(b)(4)** used in ISO 5 cleaning. Additionally, you explain your process of **(b)(4)**-drying your **(b)(4)** and RABS with **(b)(4)** drying of residual **(b)(4)** during visual inspection by operators. You also commit to implementing **(b)(4)** disinfection of the **(b)(4)** in your **(b)(4)** and RABS.

Your response is inadequate because your corrective actions fail to address the fundamental, self-identified design flaw in your **(b)(4)** supply lines" that lead to each of your **(b)(4)** and RABS processing lines for cleaning. You also fail to holistically address residual **(b)(4)** from cleaning your **(b)(4)** and RABS units across your site. The residual **(b)(4)** issue poses a significant risk to barrier/**(b)(4)** system control (e.g., interference with decontamination cycle efficacy) and can potentially lead to drug product contamination.

(b)(4) Integrity Testing

You failed to adequately maintain equipment to assure aseptic conditions. Your **(b)(4)** integrity testing program for **(b)(4)** was found to be deficient. For example:

- Your **(b)(4)** integrity testing program for **(b)(4)** permitted **(b)(4)** to fail acceptance criteria during pressure decay testing **(b)(4)** times before requiring replacement. Your translated procedure states, "All **(b)(4)** that fail the leak test (pressure drop test) may be retested. If the **(b)(4)** fails more than **(b)(4)** times, it must be replaced."
- When **(b)(4)** failed leak testing, retesting was often not performed the same day but at a later date. As a result, you manufactured drug products using **(b)(4)** that had failed leak testing without confirming their integrity. For example, **(b)(4)** on line **(b)(4)** failed to meet acceptance criteria on July 1, 2025, and did not pass testing until July 19, 2025. In the 18-day period between these tests, your production schedule indicated you manufactured at least **(b)(4)** batches of drug products.
- You lacked raw **(b)(4)** testing data. During the inspection, you were unable to locate raw **(b)(4)** integrity testing data from **(b)(4)** for line **(b)(4)**.
- Instead of reviewing raw **(b)(4)** testing data, your quality assurance unit relied on forms containing transcribed information.

In your response, you commit to enhancing your **(b)(4)** integrity testing program through procedural updates requiring additional quality oversight, defining actions following test failures including not permitting production to proceed "following an invalid or failed test," and implementing quality review of visual and **(b)(4)** testing results.

You indicate that inappropriate acceptance criteria programmed into your **(b)(4)** integrity testing device caused many of the failures. You also assert, "[T]here has been no impact to any released batches or the overall control of sterility assurance at the site."

Furthermore, your response states that in your operators' experience, pressure decay failures are generally not indicative of non-integral **(b)(4)**, and they instead relied upon visual inspection.

Your response calls into question the reliability of your **(b)(4)** integrity testing program. Visual inspections, on their own, are insufficient to monitor **(b)(4)** integrity. Visual **(b)(4)** examinations provide far lower detectability than, and cannot be substituted for, **(b)(4)** integrity testing devices. It is essential that your firm use **(b)(4)** integrity testing devices that are capable of reliably detecting sub-visible breaches in **(b)(4)** integrity.

You also failed to perform retrospective evaluation of potentially impacted products and processes. In response to the uninvestigated **(b)(4)** integrity failures, you concluded there was no quality impact to released batches or overall contamination risk at the site. However, you appear to have limited your review only to examples cited during the inspection.

Additionally, you failed to assess equipment management across your site to identify other potentially impacted critical equipment that may affect aseptic conditions. You should give continual attention to the integrity of critical equipment. This includes comprehensive maintenance procedures that establish adequate integrity testing and proactive replacement before breakdown.

Protective Equipment Materials

You failed to implement other adequate equipment control systems to prevent contamination during aseptic processing. Our investigators observed particles shedding from **(b)(4)** material in aseptic areas. For example, loose, visible fibers were observed on and dislodging from **(b)(4)** covers during **(b)(4)** installation within critical aseptic filling areas. Fibers also were observed on tubing in two locations in line **(b)(4)**. Subsequently, unused **(b)(4)** covers were inspected and observed to have loose fibers indicating the material itself was the source of contamination. You use the material is used to protect **(b)(4)** and the end of sterile tubing.

Furthermore, this is an ongoing issue. Your customer reported your previous non-pharmaceutical grade **(b)(4)** material as a source of particulate contamination. In response, you introduced your current **(b)(4)** material across your **(b)(4)** and RABS processing lines without evaluating its particle generating characteristics.

In your response, you explain the **(b)(4)** seams on the **(b)(4)** are the apparent source of visible fibers and they appear to be statically charged. You also indicate you are working with your supplier to address this issue while taking interim controls including awareness training, visual checks of equipment at risk of fibers, removal of observed fibers with sterile lint-free wipes, and the exchange of equipment when fibers are observed attached to product contact surfaces.

Your response is inadequate. You limited your retrospective batch review to only the two batches observed to be exposed to loose fibers during the inspection. Your response also fails to assess the particles generated by the **(b)(4)** material to determine their characteristics (e.g., size). Additionally, your response fails to support the adequacy of visual inspection as an interim control or to review quality indicators for particle related issues (e.g., complaints, deviations). Finally, your response did not address your failure to evaluate particle generation in the replacement material when you implemented a change control for **(b)(4)** in response to a particle generation complaint. This is a quality oversight failure.

Aseptic processing operations should be designed and executed to minimize exposure of sterile articles to potential contamination hazards in the manufacturing operation. Flaws in the design of cleanrooms and aseptic processing lines or improper execution of aseptic operations can enable entry of contaminants into the critical (ISO 5) processing area and lead to product contamination.

(b)(4) technology represents a significant advance over traditional operational designs. However, all technologies have failure modes that require ongoing, vigilant monitoring and maintenance to ensure a state of control, including **(b)(4)**. A strong quality system is essential to oversee design and construction of aseptic processing lines and supporting utilities, and to ensure ongoing proper operational control to safeguard against contamination hazards throughout the facility lifecycle.

Your firm failed to maintain buildings used in the manufacture, processing, packing, or holding of drug products in a good state of repair (21 CFR 211.58).

You failed to adequately maintain your facility in a good state of repair. Specifically, we observed the following deficiencies during the inspection:

- Gaps were observed in the protective wall, covering the original underlying wall surface in the (b)(4) machine room, thus creating areas that are difficult to clean.
- An unknown brown-yellow material was visible in the wall gaps located near the (b)(4) equipment, indicating potential contamination risks in the manufacturing environment.
- A ceiling vent was improperly secured with transparent tape in the tablet room, demonstrating substandard facility maintenance practices.
- The walls of the room housing the (b)(4) were unfinished and not cleanable.

In your response, you state that you immediately halted all manufacturing operations and promptly took corrective actions to address the specific deficiencies. You also indicated that you would not resume manufacturing operations until all repairs were completed, and the rooms met the required standards for cleanliness and maintenance.

Your response is inadequate. You did not provide a systemic and comprehensive CAPA plan to ensure that your facility is and remains in a good state of repair.

It is essential that your facility be in a good state of repair to prevent contamination and to ensure its ongoing suitability for drug manufacturing.

Inadequate Design of Facility and Equipment

Your firm is a contract manufacturer of sterile injectable drug products produced primarily through aseptic processing including, but not limited to, products for (b)(4) use. (b)(4) of your aseptic processing lines are described as "(b)(4) restricted access barrier systems." However, (b)(4) of these processing lines (b)(4) are not restricted access barrier systems (RABS). They lacked fundamental RABS design elements, such as (b)(4), that are essential for reducing or eliminating direct gowned personnel intervention into the critical (ISO 5) area during batch manufacturing.

(b)(4) are (b)(4) foundational elements of RABS design and control, minimizing contamination risk from the surrounding cleanroom environment. Without these basic features, your processing lines (b)(4) cannot be categorized as RABS.

Additionally, your processing lines (b)(4) were designed as traditional aseptic filling lines surrounded by barrier (b)(4) under (b)(4) high efficiency particulate air (HEPA) systems. These processing lines required manually intensive operations during equipment setup and throughout routine production, and did not provide appropriate separation and protection of the ISO 5 areas. For example, we observed the following regarding these aseptic processing lines:

- Excessive and high-risk manual interventions required during operations on your aseptic processing lines created unacceptable hazards to product sterility. For instance, barrier (b)(4) lines (b)(4) required hundreds of interventions, including numerous lubrications of (b)(4) and conveyor belts with (b)(4), during the production of a batch.
- Product contact equipment on multiple lines was poorly protected or otherwise exposed to contamination hazards. For example:
  o Barrier (b)(4) on opposite sides of processing line (b)(4) remained (b)(4) to the surrounding environment for almost (b)(4) during installation of the stopper bowl assembly.
  o (b)(4) manifold set up on line (b)(4) required personnel to break first pass air to the critical areas of the production line with their arms, head, and upper body, and lasted nearly (b)(4).
  o The design of the stopper bowl component required personnel to break first pass air with (b)(4) and forearms during installation on production lines (b)(4).
  o Product tubing extended above and over open vials and filling operations of line (b)(4).

Your aseptic processing cleanroom layout, filling equipment design, protection of ISO 5 areas, and the number and complexity of personnel interventions during setup and filling operations are deficient. These basic design deficiencies and manually intensive interventions affect multiple processing lines and compromise your ability to maintain aseptic conditions.

Inadequate Environmental Monitoring

You also failed to ensure adequate environmental monitoring (EM) of classified areas used for aseptic production of sterile injectable drug products. For example:

- EM of critical filling equipment (b)(4) did not ensure each of the (b)(4) were periodically assessed for microbiological quality.

- Your EM program for ISO 5 non-viable particulate monitoring was deficient. You failed to demonstrate that your sample collection apparatus (using tubing (b)(4) long with (b)(4) bends) provides meaningful and representative samples.

Inadequate Unidirectional Airflow

The qualification of airflow in critical areas demonstrated further inadequacies in the suitability and design of aseptic processing lines (b)(4). Dynamic airflow studies demonstrated that airflow patterns failed to adequately protect the aseptic processing line, including exposed sterile product and product contact equipment, from significant contamination hazards.

Your dynamic smoke studies did not demonstrate unidirectional airflow protection of the production line while barrier (b)(4) were (b)(4). The study showed air moving at a sharp angle toward (b)(4) vents, leaving critical areas of your aseptic processing line potentially unprotected.

Furthermore, design flaws in production equipment led to poor aseptic practices and ergonomics that compromised unidirectional airflow. For example:

- The (b)(4) assembly design required personnel to grip the (b)(4) with (b)(4), touching the critical portions of the (b)(4) through which the (b)(4) during assembly.
- Personnel blocked first pass air to (b)(4) with their forearms and (b)(4) during installation of the (b)(4) assembly.

Your response emphasizes aseptic processing controls measured by environmental and personnel monitoring recovery rates, numbers of media filled units produced, and sterility tests performed. Furthermore, in your response you also commit to reconfiguring line (b)(4), tightening EM specifications for ISO 5 non-viable particulate monitoring to account for tubing length, eliminating the need for (b)(4) lubrication, and ensuring all (b)(4) are monitored. You also acknowledge the high-risk aseptic line setup activities and have implemented improvements including maintaining (b)(4) protection of equipment for a longer period, changing sequence of setup activities, and improving operator ergonomics.

Your response is inadequate as the retrospective review does not overcome fundamental design flaws. Rather than implementing more extensive changes to the aseptic processing operation, you are attempting to partially mitigate significant aseptic processing line hazards. Overall, your response fails to address how you will ensure adequate aseptic processing operations and collect meaningful data to support your aseptic processes.

We acknowledge that you also have temporarily suspended manufacture and release of aseptically filled product from all (b)(4) production lines pending a third-party consultant review.

Your aseptic manufacturing processes should be designed, and operations executed, to prevent contamination hazards to your sterile product. Flaws in the design of cleanrooms and aseptic processing lines, or improper execution of aseptic operations, can promote influx of contamination into the critical processing area.

Your firm's response also includes evaluation of retrospective sterility testing data. It should be noted that a sterility test, while a critical quality control for aseptically processed products that purport to be sterile, cannot be solely relied upon as justification to release drug product batches. The test is only the last in a series of design provisions and controls intended to protect the consumer from distribution of an unsafe batch.

Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

You did not establish an adequate system for monitoring environmental conditions on the "(b)(4)' aseptic filling line. For example:

- You did not conduct viable monitoring of the air and surfaces in ISO 5 areas where an operator was continuously present removing fallen bottles.
- You did not place the non-viable particle monitoring (NVPM) probes in representative ISO 5 areas where the product and primary components were exposed. Our investigators noted the following:
  o The NVPM probe closest to the (b)(4) was located approximately (b)(4) above the level of the (b)(4).
  o The NVPM probe nearest to the sterile cap (b)(4) was located approximately (b)(4) above the level of the (b)(4).
- Your operators routinely placed mobile NVPM devices in locations different from those specified in your procedures to monitor the ISO 5 areas. As such, NVPM data may not accurately represent the critical areas in operation.

In your response, you commit to upgrade your "(b)(4)" aseptic filling line and perform a Quality Risk Assessment for NVPM in Suite (b)(4).

Your response is inadequate. While you commit to conducting a Quality Risk Assessment for NVPM to identify, assess, and mitigate all gaps, you have not provided any updates on the status of risk assessment. Vigilant and responsive environmental monitoring programs should be designed to provide meaningful information on the state of control of your aseptic processing environment. Operations that include highly manually intensive aseptic activities warrant a more extensive environmental and personnel monitoring program, including but not limited to, heightened emphasis on well-timed sampling to appropriately monitor batch manufacturing conditions.

Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).

A. Your firm failed to validate and assess the effectiveness, distribution, and reproducibility of (b)(4) decontamination to ensure it can safely achieve a state of control in aseptic rooms against objectionable microorganisms.

For example, your firm utilized (b)(4) as an (b)(4) decontamination of aseptic filling lines (b)(4). Your investigation reported several instances of spore-forming bacteria during (b)(4), in ISO 7 areas.

The identified bacteria included species such as Paenibacillus provencensis/shunpengii/urinalis, Bacillus infantis, Niallia circulans complex, Metabacillus halosaccharovorans, Peribacillus simplex, Bacillus subtilis group and Bacillus cereus group. The root cause was identified as an "inadequate process for (b)(4) sanitization," which was "unclear and may be causing the growth of spore forming bacteria in Grade B." Additionally, the same (b)(4) decontamination cycle showed positive biological indicators (BIs) on aseptic lines (b)(4) during (b)(4) periods ((b)(4)). The results indicate the (b)(4) decontamination process is ineffective.

In your response, you state the BIs were used for informational purposes only and not as an evaluation of the (b)(4) decontamination process. You acknowledge the title of the SOP "(b)(4) Sanitization – Decontamination of rooms at Bulk Production" is misleading and the use of (b)(4) is not implemented as a routine decontamination process. You corrected the title to be "Disinfection of grade A and B areas within Bulk Production with (b)(4)." You state that you will collaborate with your vendor to perform a mapping study to verify the effectiveness of the disinfection process.

Your response is inadequate. You do not provide evidence the (b)(4) decontamination process provides adequate surface coverage of all areas on the aseptic line, is compatible with materials, and ensures that residual (b)(4) that may remain on equipment does not affect product quality. Critical cleaning and sanitization agents must be validated. A mapping study is not validation of the disinfectant. Validation requires documented evidence that the disinfection process consistently removes or inactivates known or possible pathogens.

B. Our investigators observed walls and floors of numerous ISO 8 production rooms were sticky and left visible (b)(4) residue when wiped by the hand. The investigators additionally noted fibers from disposable coveralls stuck to the walls in one of the production rooms. Such residual contamination can compromise product sterility and safety potentially resulting in patient harm.

In your response, you state that your Quality Control Microbiology (QCM) group discovered the sticky floors and walls (b)(4). Your deviation investigation concluded that the probable root causes were a build-up of new cleaning disinfectants and a possible interaction with materials in the facility. Your CAPA included wiping surfaces with (b)(4) after cleaning.

Your response is inadequate. You did not provide the deviation investigation for the evaluation and identification of the (b)(4) residue and a risk assessment of contamination to the drug product. Furthermore, you did not provide an assessment of your cleaning validation with regard to the new cleaning agents.

Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. Your firm also failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas (21 CFR 211.113(b) & 211.42(c)(10)).

Cleaning, Decontamination, and Maintenance

You failed to adequately clean, decontaminate, and maintain your (b)(4) used for aseptic drug product manufacturing. For example, our investigator observed multiple instances of deterioration and damage to the (b)(4) used for manufacturing sterile (b)(4) drug products. These instances of deterioration and damage were not adequately addressed through your cleaning, decontamination, and maintenance programs. For example, our investigator observed:

- discolored (b)(4) gloves
- excess sealant adjacent to the (b)(4)
- various discolorations of undetermined origin (e.g., possibly dried drug product residue) on interior equipment surfaces
- a notably discolored plastic utensil within the (b)(4) environment
- deteriorated gasket seals

Additionally, your personnel failed to follow established (b)(4) decontamination procedures. Numerous creases were observed in (b)(4) glove (b)(4) during decontamination cycles, despite your procedure requiring (b)(4) to be "free of creases." Incomplete exposure of interior surfaces to (b)(4) compromises decontamination effectiveness and places the (b)(4) environment at risk.

Regarding maintenance, our investigator observed multiple instances of tape applied to multiple "false covers" which are used to maintain a sealed environment during the (b)(4) decontamination cycle. The use of tape is an insanitary practice and your firm could not explain the presence of this tape. Maintenance and change management procedures should prevent such practices that may compromise equipment or introduce contamination risks.

Your preventive maintenance schedules lack timeframes for critical equipment, such as, gaskets on (b)(4) gloves. It is unacceptable to only belatedly change critical equipment (e.g., gloves, gaskets) when a leak occurs. This solely reactive approach to maintenance fails to safeguard against a critical failure mode in (b)(4) technology.

The integrity of equipment should receive daily attention through comprehensive preventive maintenance procedures that establish adequate integrity testing, cleaning and disinfection methods, and proactive replacement before breakdown or degradation.

Notably, you experienced (b)(4) glove breach events during the manufacturing of three different batches of (b)(4) drug products, creating a risk of contamination. One of the breach events included a six-millimeter hole that was closed with a "cable tie" after which processing continued. This practice is unacceptable as it does not sufficiently mitigate the breach in (b)(4) associated with a loss of glove integrity. You released these products but later recalled them after our inspection.

Environmental Monitoring

Your environmental monitoring program is deficient as it fails to adequately monitor the aseptic processing line. For example, critical areas within the (b)(4) lack continuous non-viable particle

monitoring. Instead, you rely on a single monitoring probe oriented away from critical areas where open processing occurs. Your inadequate and limited monitoring deprive you of sufficient meaningful data for determining risk to product during batch operations.

Your response is inadequate because your CAPA was not timely. You do not propose meaningful corrective actions until a regulatory inspection identified violations that had occurred over an extended period. Furthermore, it is unclear if your CAPA commitment to simply update your written procedure to "minimize creases" in your (b)(4) gloves will ensure surface exposure of all gloves to the (b)(4) decontaminating agent.

Aseptic processes need to be designed to minimize exposure of sterile articles to potential contamination hazards. A suitable monitoring system is critical to maintain appropriate environmental conditions throughout your (b)(4) and cleanrooms. Prompt detection of an emerging problem is essential to preventing contamination of your aseptic production operations. Vigilant and responsive environmental monitoring programs should be designed to provide meaningful information on the state of control of your aseptic processing environment.

Equipment as a Route of Contamination

The design of the aseptic processing line used to manufacture over-the-counter (b)(4) drug products was inadequate. Line (b)(4) is a traditional filling line consisting of an ISO 5 area (b)(4) and a surrounding ISO 7 area. The line involves manually intensive (b)(4) interventions, and the HEPA filter layout leaves approximately 10-centimeter gaps due to overhead lights in between the filters that appear to affect unidirectional airflow.

Furthermore, you did not sterilize direct product contact equipment that holds primary container and closure components for your sterile drug products. These equipment were disinfected with (b)(4), which are not sterilants. You also use (b)(4) approximately (b)(4), which is a decontaminating agent.

Your response is inadequate. You commit to turning Line (b)(4) into an (b)(4) restricted access barrier ((b)(4)RAB) filling line. However, you did not provide detailed plans for how you will redesign your filling line and conduct a risk assessment for products currently released to the U.S. Market.

Environmental Monitoring (EM)

The EM of your aseptic processing operations was inadequate. The locations identified for EM in ISO 5 and ISO 7 areas lacked scientific justification and were not sufficiently located where the aseptic operations are taking place.

The consistent and meaningful contamination level in ISO 7, along with frequent manually intensive interventions, posed a high risk to sterile products on your aseptic processing line.

Your response is inadequate. You commit to repeating the EM risk assessment and trending EM data but fail to include plans for how you will assess your line after redesign.

A vigilant, ongoing EM program is essential to detect and respond to potential product contamination hazards in your manufacturing environment in a timely manner. Loss of environmental control in an aseptic manufacturing facility can ultimately pose a serious hazard to patients.

Your firm failed to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups. Your firm also failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance. (21 CFR 211.42(c) and 21 CFR 211.63)

We observed that your facility's cleanrooms and (b)(4) system used in drug product manufacturing were in a state of disrepair.

Facility and Equipment Design and Control

Your cleanrooms (e.g., ISO 5 filling line and ISO 7 weigh and formulation rooms) were inadequately designed and maintained to facilitate adequate cleaning and proper operations. For example, excessive caulking and tape were used to repair gaps around ceiling HEPA filters, air vents, and (b)(4). Rust was observed on various pieces of equipment. Inadequate materials of construction and poor facility maintenance may create potential contamination risks.

(b)(4) System

Your firm manufactures (b)(4) used to (b)(4) your filling equipment lines and as a component in your (b)(4) drug products. However, your (b)(4) system was in a significant state of disrepair. For example, peeling insulation, excessive rust, and corrosion was observed on the (b)(4) system. In addition, leaks and pooling (b)(4) were observed at various points with at least one leaking section where (b)(4) was collecting in a bucket. These conditions can allow filth and the proliferation of microorganisms to spread throughout the manufacturing areas.

It is essential that you adequately design, control, maintain, and monitor the (b)(4) system to ensure it consistently produces (b)(4) suitable for pharmaceutical use.

Since 2019, your environmental monitoring program showed excessive microbial contamination throughout your facility, particularly in your ISO 5 filling line cleanrooms. Speciation of the isolates recovered were identified as (b)(4) microorganisms, implicating your (b)(4) system as a potential source. While you initiated CAPA and change control in 2023 and 2024 to remediate the environmental excursions, our 2025 inspection found ongoing microbial presence throughout your facility.

In your response, you commit to cleanroom reconstruction with quality assurance verification of cleanability by August 2026 and replacement of major components of your (b)(4) system by April 2027. Your response is inadequate. The proposed timelines are unacceptable to adequately address these violations, and an accelerated corrective response is required. You also do not discuss interim

measures you will take to ensure your current (b)(4) system remains integral and is capable of producing (b)(4) of appropriate quality until replacement is complete.

Your firm failed to maintain buildings used in the manufacture, processing, packing, or holding of drug products in a good state of repair (21 CFR 211.58).

Your firm did not properly maintain classified areas and cleanrooms used in the manufacture of drug products. Our investigators observed peeling paint on the ceiling as well as bubbled paint and rust at the bottom of the door in ISO 7 room (b)(4). Room (b)(4) provides access into aseptic filling line (b)(4).

These deficiencies were discussed with your management at the time of the walk-through of the aseptic areas. Management stated the peeling paint surfaces above the (b)(4) door may be caused by the surface material being incompatible with the cleaning agent used to clean the production facility. It is critical that the building is maintained to prevent exposure of sterile articles to potential contamination hazards in the manufacturing operation.

In response to this letter, provide your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

Bird droppings and feathers were observed during the inspection in the AHU area, specifically on the air purification units, **(b)(4)** ducts, a **(b)(4)** tank, a cleaning **(b)(4)**, and on the floors surrounding multiple **(b)(4)** inside your drug manufacturing facility. The conditions in your AHU area raise concerns about potential contamination affecting the air supplied to critical manufacturing equipment utilized in your drug manufacturing process.

In your response, you explain that birds were entering the manufacturing facility through numerous gaps in the exterior walls of the facility where the AHUs are located. You outline immediate actions to identify and block entry points for birds using nets.

Your response is inadequate. While you address the entry of birds and cleaned the area, you fail to perform a thorough root cause analysis or assess similar vulnerabilities elsewhere. Furthermore, pictures of the netting you installed appear to still allow smaller animals, such as insects, access to your AHU area.

Your firm failed to maintain your facility in a good state of repair. During a 2017 FDA inspection, our investigators noted that your facility was in disrepair and had experienced flood damage to your facility and (b)(4) system. Our current inspectional findings were commensurate with findings from 2017, indicating that you have not properly remediated and maintained your facility. For example, in addition to the previously mentioned insanitary conditions:

- The first floor of your facility contained dirt residue-covered flooring as well as water damage, which resulted in inadequate maintenance of the (b)(4)-production system.
- The (b)(4) floor of your facility showed evidence of significant water damage with brown discoloration of the ceiling and walls and green mold-like residue on the ceiling in retained product storage areas.

Although you are not currently producing (b)(4) drug products for the United States (U.S.), the processing lines were previously used to produce (b)(4) for the U.S. and continue to supply other markets.

To protect drug products from potential routes of contamination, your facility must be kept in a good state of repair and sanitary conditions must be maintained.

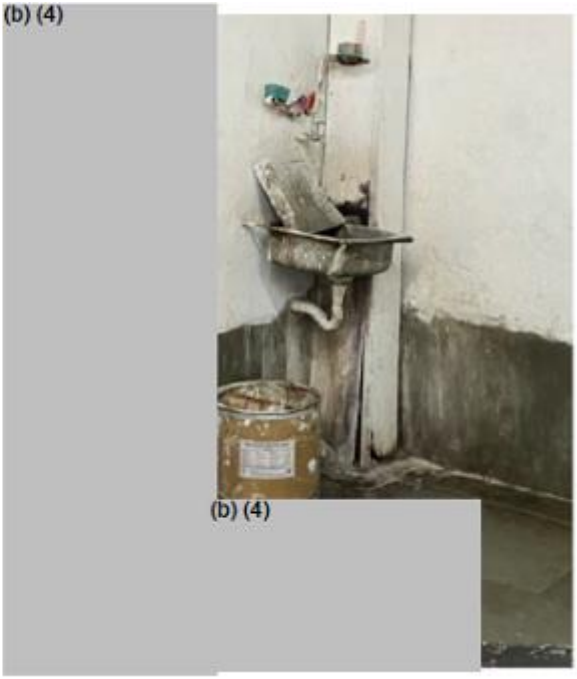
Insanitary Conditions

Your firm manufactures over-the-counter (OTC) (b)(4) drug products that are marketed to (b)(4). Your drug products are adulterated under section 501(a)(2)(A) of the FD&C Act because they were prepared, packed, and held under insanitary conditions1. Your production operations, including filling lines, are conducted in a facility that lacks adequate separation barriers from the external environment. Specifically, our investigators observed evidence of harborage areas, broken windows, insanitary production-area sinks, and significant water damage in areas where open processing lines are located and where finished drug products are stored. Further, the investigators observed the following:

- Harborage areas immediately outside the first floor of the facility where filling, packaging, and (b)(4) production operations are performed. This area consisted of discarded piping with window-grate openings to the exterior of the facility.

- A broken window precluding the protection of open processing (b)(4) lines (lower right of photo) from the outside environment surrounding the facility.

- Sinks in the production area used as a source of water for cleaning production equipment.



The insanitary conditions of your facility did not provide adequate protections of your (b)(4) manufacturing operations from potential contamination with filth.

In your response, you state that facility cleaning and repairs will be carried out before restarting production. Your response is inadequate because no other details were provided including but not limited to the scope of repairs, timeframes for completion, or photographs documenting completed remediation. Nor did you include a comprehensive evaluation of your failure to maintain your facility and equipment in a clean and sanitary condition or the potential impact to your OTC drug products.