Subpart D Equipment

(21 CFR 211.63 – 211.72).

211.63 Equipment design, size, and location.

211.65 Equipment construction.

211.67 Equipment cleaning and maintenance.

211.68 Automatic, mechanical, and electronic equipment.

211.72 Filters.

Your firm 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 211.63).

Your firm utilizes **(b)(4)** as a component to manufacture your over-the-counter (OTC) drug products. However, you failed to design and control your **(b)(4)** to ensure reliable production of **(b)(4)**. The system was unsuitable to ensure both chemical and microbiological quality attributes.

For example, your **(b)(4)** design did not ensure **(b)(4)**. Notably, the system consistently failed to meet the **(b)(4)** specification. The performance qualification report for your **(b)(4)** included over **(b)(4)** of **(b)(4)**-sampling data, showing that most samples failed USP **(b)(4)** standards. Despite obtaining failing data, you approved the qualification study in **(b)(4)**. Subsequent **(b)(4)** data obtained from August 2023 through August 2025 showed that nearly all your **(b)(4)** samples continued to fail the **(b)(4)** specification for **(b)(4)**. You used **(b)(4)** from this **(b)(4)** in the manufacture of finished drug products.

Your **(b)(4)** also had numerous points within the system that can harbor **(b)(4)**, dead-legs), including some points-of-use located in the drug production area. Your firm was aware of the presence of dead-legs in the system.

Deficient **(b)(4)** design can foster the development of biofilms, resulting in significant sporadic spikes in microbial levels of **(b)(4)** used for formulation and cleaning. Examples of gram-negative bacteria found in your **(b)(4)** include Pseudomonas aeruginosa and Serratia marcescens (a family *Yersiniaceae* microbe).

In your response, you state that you plan to redesign your **(b)(4)** to eliminate dead-legs, add **(b)(4)** equipment, and qualify the system for the production of **(b)(4)**. Your response is inadequate. You do not address your quality unit's protracted insufficient action to address a long-standing pattern of failing test results of the **(b)(4)** utilized to make drug products.

We acknowledge your commitment to stop using **(b)(4)** from your **(b)(4)** to manufacture drug products until the system can be remediated. We also acknowledge your commitment to use purchased **(b)(4)**, in the interim.

(b)(4) must be suitable for its intended use. Systems used to produce **(b)(4)** must be adequately designed, controlled, maintained, and monitored. The monitoring program should include routine testing to ensure that appropriate chemical and microbiological limits are consistently met.

You have not demonstrated all equipment used to manufacture finished drug products is suitable for its intended use. You qualified the (b)(4) filler machine for the filling of (b)(4) in (b)(4) mL bottles following an inadequate product (b)(4) approach. For example, you filled (b)(4) mL of a (b)(4) product into (b)(4) bottles and (b)(4) mL of a (b)(4) product into (b)(4) bottles. The qualification documentation does not provide adequate scientific justification for this limited (b)(4) approach. It also does not explain how (b)(4) batch size products like (b)(4), which has a theoretical batch size of (b)(4) bottles, fits within the (b)(4) approach. The (b)(4) filler machine also failed to meet the qualification criterion for fill weight percent coefficient of variation for the (b)(4) product filled in (b)(4) mL bottles.

You have also not established whether your cleaning procedures consistently reduce chemical and microbiological residues to acceptable levels. The cleaning validation protocol was not designed to demonstrate reproducibility of the cleaning process. For example, the cleaning validation protocol required (b)(4) swab samples to be taken from different locations for each of the (b)(4) qualification runs. Your cleaning validation also did not adequately justify the decision to use a (b)(4) tank in lieu of the (b)(4) tank used to manufacture the (b)(4) drug products. For example, there is no discussion of the (b)(4) tanks' material(s) of construction and interior features (e.g., drains, ports, (b)(4)).

Your response is inadequate. You commit to requalify your (b)(4) filler machine using a "maximum batch size [of] (b)(4)" by approximately October 2026 but do not commit to reassess your protocol design (e.g., (b)(4) approach) and acceptance criteria. Additionally, you do not commit to implement interim actions to ensure drug products manufactured on the machine meet their required quality attributes. You also commit to revise your written procedure for cleaning validation activities to verify the cleaning process will consistently render surfaces suitably clean. However, you do not commit to adequately justify your various (b)(4) methodologies and to revalidate your cleaning process.

Your non-dedicated manufacturing equipment was not designed and maintained appropriately to prevent potential cross-contamination of drug products.

For example, **(b)(4)** were not designed and maintained to ensure that the **(b)(4)** consistently closes tightly, to prevent backflow of bulk drug powder into the **(b)(4)** duct. Residues were observed in the **(b)(4)** duct of **(b)(4)**.

Numerous drug substance residues, including **(b)(4)**, were recovered upon swabbing of **(b)(4)**. Your **(b)(4)**, are used to manufacture multiple drug products, including **(b)(4)** therapeutics such as **(b)(4)**.

In addition, junctions on the **(b)(4)** duct had degraded seals and were covered with tape.

In your response, you state you will replace the **(b)(4)** on **(b)(4)** to prohibit backflow into the **(b)(4)** ducting and replace the **(b)(4)** ducting on **(b)(4)** for ease of cleaning and sanitization. You further state you are identifying all batches of U.S. product within expiry from these **(b)(4)** and have initiated testing reserve samples for possible cross-contamination.

Your response is inadequate. Your assessment is limited to testing reserve samples of each finished drug product only for the presence of the preceding drug substance processed on the same non-dedicated equipment, instead of testing each reserve sample for all drug substances processed on the equipment. You do not adequately address how you intend to maintain this equipment to ensure the integrity of the seals.

Equipment used in pharmaceutical manufacturing operations should be designed to protect drug products from contamination. Air flow over dirty surfaces can cause contamination of the drug being processed in a **(b)(4)**. Robust design, cleaning, and maintenance of this and other equipment are critical to prevent cross-contamination.

Contamination is generally not uniformly distributed. Data obtained from retrospectively testing a small proportion of a batch (e.g., reserve samples for the presence of previous active ingredient) is limited in its ability to retrospectively assess the extent of contamination in other portions of a batch. The lowest or highest results obtained from testing a small sample size is unlikely to reveal the true range of minimum and maximum contamination level that exists in a batch exposed to the contamination hazards identified at your firm. Consequently, the range of variability of contamination levels in batches produced by your firm remain characterized by substantial residual uncertainty.

Because of the limitations of retrospective testing in gaining a representative understanding of the entire lot, testing reserve samples alone is insufficient to determine the scope of the contamination issues and mitigate the associated risks. Further evaluation and scientific rationale are needed in your firm's risk assessment to reflect the nature of cross-contamination events and determine the degree of cross-contamination risk that may be posed to portion of marketed batches.

Your firm has not demonstrated that the **(b)(4)** water that you use as a component is suitable for aqueous-based drug product manufacturing and, at a minimum, meets the United States Pharmacopeia (USP) **(b)(4)** Water monograph and appropriate microbial limits.

Your legacy **(b)(4)** water system included two dead legs that create stagnant areas, fostering biofilm development and microbial contamination. This risk is compounded by your documented history of water system and drug product microbial failures which include

TNTC results. These fundamental design deficiencies posed contamination risks to all products manufactured using this water.

In your response, you acknowledge that your facility experienced significant water system deficiencies that required comprehensive remediation efforts and installation of a new **(b)(4)** water system capable of producing water suitable for its intended purpose. Your response also includes corrective actions such as decommissioning your legacy system, implementing controlled data collection forms, retraining staff on good documentation practices, updating water monitoring SOPs and conducting an impact analysis of products manufactured prior to the improvements.

Your response is inadequate. Although you commit to decommissioning the legacy system after validating your new water system, your response does not provide supportive documentation to demonstrate that the new water system is validated for its intended use. Additionally, your response lacks adequate details to ensure that your sampling, testing, and monitoring procedures can meet USP **(b)(4)** Water monograph requirements.

Pharmaceutical water must be suitable for its intended use and routinely tested to ensure ongoing conformance with appropriate chemical and microbiological attributes.

Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

You failed to adequately clean and maintain your nondedicated drug manufacturing equipment. For example, our investigator observed visible stains within the (b)(4) duct of a (b)(4) (PD/(b)(4)-01) and visible residues on a capsule filling machine (PD/CFM-03) that were documented as clean and had undergone drug product changeover cleaning. Your analytical testing of these stains and residues confirmed the presence of multiple active pharmaceutical ingredients (APIs) with values exceeding your allowable limit.

In your response, you provide investigations into these findings, including a retrospective review of analytical and stability data for all drug products previously manufactured on the pieces of equipment mentioned above. Your investigations attribute the root cause of the cleaning deficiencies to procedural gaps in the cleaning instructions for the (b)(4) and the capsule-filling machine. You state that you plan to revise your cleaning procedures and cleaning checklists.

Your response is inadequate because your review of analytical data and cleaning procedures fails to scientifically demonstrate that your drug products are free of contaminants from the visibly dirty equipment. Your response lacks information about reserve sample testing of drug products released to the U.S. market and within expiry, that were manufactured on these

pieces of non dedicated equipment, for cross-contamination potential posed by all previously manufactured drug products.

You failed to adequately maintain your equipment. For example, during the inspection, our investigators observed white particle buildup on manufacturing equipment surfaces used to produce **(b)(4)** spray drug products distributed to the U.S. market. They observed that the source of the particles was the **(b)(4)** which is made of **(b)(4)**. They saw particles along the conveyor that transports container-closure components (e.g., **(b)(4)**) to the filling operations. You purchased equipment nearly one year before our inspection that included a design upgrade (e.g., **(b)(4)**) for your existing **(b)(4)**. However, you continued manufacturing using the deteriorating **(b)(4)** that was actively generating particles. This demonstrates a failure in your maintenance program to implement timely equipment upgrades necessary to correct and prevent contamination hazards.

Your response is reactive and inadequate because your CAPA was not timely. You did not propose meaningful corrective actions until a regulatory inspection identified violations that had occurred over an extended period.

An effective equipment management program requires a proactive lifecycle approach with systematic monitoring, maintenance, and timely replacement to ensure continued process capability. Pharmaceutical quality systems must integrate equipment performance data, maintenance trending, and risk assessment to drive timely CAPA.

You failed to adequately clean and maintain your filling rooms and tube filling equipment used to manufacture your (b)(4) and (b)(4) over-the-counter (OTC) drug products. For example, our investigators observed the following:

- The presence of mold and dirt on the walls in your filling and sealing rooms.
- Soiled and stained air handling units.
- Unidentified product buildup inside your (b)(4) manufacturing vessel and tube filling equipment.
- More than one drug product was found on the packaging line.

In addition, your firm did not have validated cleaning procedures, including written equipment usage and cleaning logs to demonstrate that your drug product manufacturing equipment was adequately cleaned and maintained.

In your response, you state that you revised your cleaning procedures and logbooks and commit to retrain your staff on cleaning practices and procedures. You also state that cleaning and sanitization of the filling and sealing rooms was conducted and building maintenance will be performed. Your response is inadequate because you failed to provide supporting data to demonstrate that your cleaning practices are sufficient to remove contaminants from the product surfaces of your drug product manufacturing equipment. You also failed to provide any documentation that the above-mentioned activities occurred.

Furthermore, you failed to assess the impact of your inadequate cleaning processes on products that are currently on the market and within expiry.

It is essential that your facility and equipment are cleaned, and sanitary conditions are maintained, to ensure ongoing suitability for drug manufacturing, and to protect drug products from contamination.

Your firm 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. Your firm also failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess. Additionally, your firm also failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. (21 CFR 211.63 and 211.100(a) and 211.67(a)).

Inadequate Equipment

You use (b)(4) as a component to manufacture your sterile and non-sterile OTC drug products. Your (b)(4) system is inadequately designed and maintained for its intended use. For example, your ambient non-circulating (b)(4) system included dead legs which could foster the development of biofilms. When not in use, stagnant (b)(4) remained in the sampling hose and distribution system. You use (b)(4) from this system to manufacture your drug products.

In your response, you state that you removed the dead legs and revised your procedure for hose storage. You also state that you will continuously operate your (b)(4) system, record maintenance events, and increase sampling frequency. Your response is inadequate because you failed to replace the unsuitable (b)(4) system observed during the inspection with a new appropriately designed system. You also failed to provide corresponding plans for system validation. Additionally, you lack plans for maintenance, control, and appropriate testing and monitoring for (b)(4), as well as appropriate microbiological tests.

The (b)(4) system must be adequately designed for its intended use and properly maintained and controlled. It is essential that (b)(4) is routinely tested to ensure ongoing conformance with appropriate chemical and microbiological attributes.

Lack of process validation

In addition to inadequate facility and process design, you lacked adequate qualification of equipment and validation of processes used to manufacture your drug products. The “current

validated" sterilization manufacturing process provided in your response is fundamentally flawed as evidenced by:

- insanitary conditions in your facility;
- use of a (b)(4) not sufficient for sterile (b)(4);
- reliance on a manually intensive process;
- lack of batch sterility testing (your firm performed "CFU testing").

Also, you lacked other basic elements of a reliable sterile manufacturing operation needed to support a validated process.

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately to ensure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established. Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality are necessary to ensure that you maintain a stable manufacturing operation throughout the product lifecycle.

Lack of cleaning validation

You manufacture sterile and non-sterile OTC drug products and cosmetics on non-dedicated manufacturing equipment in a shared area. You failed to conduct cleaning validation studies to demonstrate that your cleaning, disinfection, and sterilization practices, as applicable, are adequate to remove contaminants and residues from your drug product manufacturing equipment.

Your procedure for cleaning production equipment used to manufacture (b)(4) drug products, "Special Cleaning Procedure For Other Equipment," relies on (b)(4) (e.g., (b)(4)) as the "sterilization" agent. While (b)(4) can be an effective disinfectant, your procedure lacks critical elements such as validated contact times, concentration verification, residue removal, and demonstration that the cleaning process consistently achieves the sterility assurance levels required for sterile drug products.

Inadequate removal of active ingredients and residues from manufacturing equipment during cleaning can result in cross-contamination of the drug products.

Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

Your firm failed to adequately validate your equipment cleaning process to demonstrate its effectiveness to prevent potential cross-contamination between your OTC drug products and non-pharmaceutical products. You manufactured your OTC (b)(4) drug products on non-

dedicated equipment, e.g., your (b)(4) tank. This equipment was also used to manufacture (b)(4) including, but not limited to, (b)(4) that is intended for (b)(4).

Inadequate removal of residues from manufacturing equipment during cleaning can lead to contamination of drug products subsequently manufactured on the non-dedicated equipment. It is unacceptable as a matter of CGMP to manufacture drugs using the same equipment that you use to manufacture non-pharmaceutical products due to the risk of cross-contamination.

In your response, you state that you will develop and implement a site-wide cleaning validation master plan including, but not limited to, identifying equipment and establishing analytical methods and acceptance criteria. You also state you will determine worst-case products and most difficult to clean manufacturing surfaces based on solubility, potency, toxicity, and cleanability.

Your response is inadequate because you do not provide a risk assessment for the drug products manufactured on shared equipment potentially impacted by inadequate cleaning. In addition, your target timeline for completing cleaning validations is not until August 2026, you do not provide your interim plan to ensure that your non-dedicated equipment is adequately cleaned prior to manufacturing your drug products.

You have not demonstrated that your cleaning practices are adequate to remove contaminants from the shared equipment used to manufacture multiple drug products. Your 2018 cleaning validation study failed to use the identified worst-case drug product, making it inadequate to ensure cleaning effectiveness. You also did not re-evaluate your cleaning validation program when introducing new drug products on shared manufacturing equipment, and you lack routine cleaning verification. Inadequate removal of drug residues during cleaning can cause cross-contamination in subsequently manufactured drugs on the same equipment.

In your response, you state that the results of your cleaning verification studies from 2019 to 2024 demonstrate that your cleaning processes are effective. You state that you have engaged an independent third-party consultant to review your cleaning validation program and cleaning practices.

Your response is inadequate because your cleaning validation and verification program does not adequately evaluate the effectiveness of your cleaning procedures. Your cleaning verification lacks the ability to detect cross-contamination from carryover.

Your cleaning validation program for non-dedicated manufacturing equipment, used for multiple drug products, is inadequate. It does not include the equipment used in tablet manufacturing, such as Intermediate Bulk Container (IBC) tanks **(b)(4)** tanks, product transfer hoses and **(b)(4)** hoses. Additionally, your firm lacks equipment usage logs and cleaning documentation, to ensure that the equipment is adequately cleaned and to prevent carry-over contamination from a prior batch during production campaigns.

In your response, you acknowledge that the cleaning validation is not reflective of your current operations, because you continued to purchase new equipment and add new drug products to your operations. You stated that you recognize that the cleaning validation needs a comprehensive revision.

Your response is inadequate. You have not provided sufficient details about your updated cleaning validation and associated procedures. You also did not provide a risk assessment of the quality of your distributed drugs, which are potentially contaminated because of your inadequate cleaning practices.

You lacked the cleaning validation studies required by your written procedures for OTC drug products. You failed to demonstrate your cleaning practices are adequate to remove potential contaminants and to prevent product carry over in shared equipment (for example, fillers and small utensils used for formulation) used to manufacture your OTC drug products.

Inadequate removal of residues from manufacturing equipment during cleaning can lead to the contamination of drug products subsequently manufactured on nondedicated equipment.

In your response, you commit to conducting cleaning verifications for the removal of residues left by cleaning chemicals and organic materials. Specifically, you commit to completing a cleaning validation by the end of Q4 of 2025.

Your response is inadequate. You fail to provide specific details, such as predetermined acceptance criteria, cleaning frequency, and procedures and acceptable holding time limit for dirty equipment, supported by cleaning validation. Furthermore, you fail to assess the impact of your inadequate cleaning processes on product that is currently on the market and within expiry. Of note, cleaning deficiencies were discussed with your firm in a previous FDA inspection.

You manufacture over-the-counter (OTC) drug products, **(b)(4)** Hand Sanitizer Foam, both alcohol and alcohol-free formulas, using the same equipment that you use to manufacture non-drug products, including industrial cleaning detergents and disinfectants such as Bowl Cleaner, a strongly acidic (pH <2) toilet cleaner, and **(b)(4)**.

In your response, you commit to maintaining cleaning records for all shared equipment and performing additional cleaning validation. However, your response is inadequate. Under CGMP, it is unacceptable to manufacture drug products using the same equipment you use to manufacture non-pharmaceutical products due to the risk of cross-contamination. Inadequate removal of active ingredients and product residues from surfaces of non-dedicated manufacturing equipment can lead to contamination of drug products subsequently manufactured on that equipment.

Further, we acknowledge your commitment in your August 4, 2025, response to cease production of all benzalkonium chloride-containing drug products at this facility for the U.S.

market. We acknowledge your intent to delist your **(b)(4)** product line by September 30, 2025.

Your cleaning procedures lack sufficient detail to ensure repeatability between operators. We observed cleaning deficiencies and variability between operators, including wiping technique, using the same cleaning cloths for multiple areas, and failure to clean on top of the overhead light casings of the filling line.

Further, the disinfection efficacy studies for **(b)(4)** did not adequately address all materials of the filling line, including but not limited to, **(b)(4)** (filling equipment), **(b)(4)** and **(b)(4)**, and **(b)(4)** hose).

In addition, your **(b)(4)** room decontamination validation is deficient (e.g., biological indicator locations are not adequately justified).

Your response is inadequate. You commit to conduct a comprehensive review and assessment of cleaning and disinfection practices; however, you fail to investigate the impact on the products in the U.S. Market. In addition, a retrospective review for only extraneous chromatographic peaks is not sufficient to determine if deficient cleaning practices contribute to finished product that does not meet established specifications.

Our investigators observed significant contamination in multiple **(b)(4)** ducts of non-dedicated **(b)(4)** used in the preparation of **(b)(4)** for finished drug products manufactured at your facility. While filters were installed to prevent contamination, inadequate cleaning and maintenance processes rendered them ineffective. Swab samples collected from the **(b)(4)** ducts by your firm during the inspection, specifically from areas after the **(b)(4)**µ high efficiency particulate air (HEPA) filters, detected residues from multiple previously manufactured drug products and too numerous to count (TNTC) microbial contamination. Furthermore, you lacked documented cleaning procedures for the sections of the **(b)(4)** ducts located between the **(b)(4)**µ HEPA air filter and the cleaning **(b)(4)**. Air flow over dirty surfaces can facilitate contamination of the drug being processed in **(b)(4)**. Robust design, cleaning, and maintenance of this and other equipment are critical to prevent cross-contamination.

In your response, you provide an impact assessment, limited reserve sample testing results, and assurance of low microbiological contamination risk. You identify multiple potential root causes of the air handling unit (AHU) contamination and propose corrective actions and preventive actions (CAPAs). Reserve sample results confirmed cross-contamination; however, you deem the risk to drug product safety low based on your retrospective maximum allowable carry-over (MACO) calculations and additional testing results.

Your response is inadequate. Cross-contamination is not uniform, and testing of limited reserve samples alone cannot ensure products are contaminant-free. While MACO is helpful in validated cleaning scenarios, it cannot apply where cleaning has not been performed, or

exposure is inconsistent. Additionally, the denominators utilized for batch size in your MACO calculations are inconsistent with the size of your **(b)(4)** bowls. The MACO limits outlined in your response were not adequately justified and fully encompass the contamination risk to drug product. Immediate remediation, effective cleaning protocols, and comprehensive testing are essential to resolve this serious CGMP violation.

Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment; and failed to perform operations within specifically defined areas of adequate size; and failed to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.67(b) and 21 CFR 211.42(c)).

During our inspection, we observed inadequate cleaning and inadequate contamination control throughout your manufacturing facility where sterile drug products are assembled and packaged.

For example, our investigators found **(b)(4)** and **(b)(4)** inside your **(b)(4)** chambers which sterilize your drug product ampoules. During the inspection, your firm confirmed that the chamber cleaning procedure involved **(b)(4)** the **(b)(4)** chambers **(b)(4)** to remove **(b)(4)**. However, we noted multiple instances of your operators' failure to appropriately document **(b)(4)** during a period when multiple U.S. batches were being sterilized. Additionally, you did not test the **(b)(4)** used in your **(b)(4)** process for chemical or microbiological specifications. Unsuitable **(b)(4)** quality could introduce **(b)(4)**, **(b)(4)**, and bioburden – further compromising chamber cleanliness and sterilization efficacy.

FDA investigators observed **(b)(4)** residue on air vents, walls, and equipment surfaces in your main production area, packaging lines, ampoule rinsing room, and equipment washroom, despite cleaning logs documenting these areas had been cleaned. FDA investigators also observed broken **(b)(4)** on **(b)(4)** with sterilized ampoules next to assembly lines where these ampoules are **(b)(4)**.

Your contamination control practices were also inadequate. FDA investigators observed personnel wearing face masks improperly in violation of your gowning procedures. Your quality notification QN 201162939 documented a bioburden excursion in non-sterile **(b)(4)** product showing **(b)(4)** CFU with *Streptococcus pneumoniae* identified, a significant opportunistic pathogen commonly found in the nose and throat.

Multiple environmental monitoring (EM) excursions also occurred in your filling areas. These contamination control failures are particularly worrisome if your **(b)(4)** do not ultimately undergo terminal sterilization on the **(b)(4)**, including the **(b)(4)**. When terminal sterilization is not applied to the finished product, robust aseptic processing control becomes critical to ensuring product sterility.

Notably, robust manufacturing design and control to prevent contamination also applies if **(b)(4)** are not intended to be sterile, when appropriate based on their indication. Such products must be free of microbes that may be objectionable in view of their intended use.

Your response states that you engaged an independent third-party expert to review and redesign your cleaning validation program and committed to implementing cleaning validation for equipment and product-contact surfaces. You identified the **(b)(4)** residue as **(b)(4)** used in certain **(b)(4)** and stated you evaluated chromatography data to confirm the absence of cross-contamination to other products. You conducted a risk assessment of your cleaning program and concluded that existing process controls at various manufacturing stages would detect and reject products containing residues, contaminants, or microorganisms beyond acceptable limits.

Your response is inadequate. Your commitment to implement cleaning validation does not address products currently in distribution manufactured under the conditions documented during the inspection. Your conclusion that existing controls would robustly detect contamination is contradicted by the nature of the customer complaints received by your firm, particularly given the extent of contamination, debris, gowning violations, and EM excursions documented during the inspection. Additionally, your identification of the **(b)(4)** residue and review of chromatography data do not address why your cleaning procedures failed to prevent its accumulation.

Inadequate removal of debris and residues from manufacturing equipment during cleaning can lead to contamination of drug products subsequently manufactured on the equipment. In addition, inadequate operational controls to prevent contamination can jeopardize patient safety by potentially compromising the sterility of products designed to **(b)(4)**.

Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality of purity of the drug product beyond the official or other established requirements and you failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(a) and (b))).

Failure to Clean Equipment

You have not demonstrated that your cleaning practices are adequate to remove contaminants from the nondedicated equipment used to manufacture your prescription drug products, including **(b)(4)** tablets and **(b)(4)** tablets. Multiple pieces of manufacturing equipment, including the **(b)(4)** and the Tablet Press, were observed to have drug product residue and oxidized metal surfaces, which were documented as being clean and were released by your quality unit. Additionally, the dedicated **(b)(4)** equipment showed visible product residue, oxidized metal, and foreign material, despite being cleaned and released by your quality unit.

Similar equipment cleaning deficiencies were cited during your previous FDA inspections, indicating that your cleaning procedures are insufficient to prevent contamination that could alter the safety, identity, strength, quality, or purity of your drug products.

Additionally, your firm's voluntary recall of **(b)(4)**mg **(b)(4)** tablets due to **(b)(4)** mg tablets being found inside the bottle could be associated to inadequate line clearance of equipment prior to use.

In your response, you state that you have implemented a new procedure requiring the use of a flashlight to detect residues or surface abnormalities not visible to the naked eye, and you provided training on the revised procedures.

Your response is inadequate because you do not provide evidence that your cleaning methods are appropriate and effective, nor do you assess the impact of your inadequate cleaning processes on drug product that is currently on the market and within expiry.

Failure to Maintain Equipment

You failed to adequately maintain your equipment. For example, the metal detection equipment MFG-1276 was found to be nonfunctioning during the inspection. Your preventive maintenance procedures were also inadequate, focusing only on the metal detector's physical appearance rather than its operational functionality.

Additionally, your executed metal detector qualification protocol did not include the qualification of the metal detector MFG-1276.

These equipment maintenance failures compromise your ability to detect and prevent contamination. Notably, a metal screw was found in a sealed bottle of **(b)(4)**mg, lot **(b)(4)**.

In your response, you stated that you halted all packaging activities and did not resume packaging operations until the metal detectors had been repaired, and preventive maintenance had been performed.

Your response is inadequate because you did not commit to completing the equipment qualification for the metal detector or describe how you will periodically requalify it. Additionally, you did not commit to conducting a retrospective risk assessment for batches that were processed while the metal detector was not functioning properly.

Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance of automatic, mechanical, electronic equipment, or other types of equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product (21 CFR 211.68(a)).

You failed to adequately inspect and maintain your AHUs to ensure air filters would be effective at preventing contamination. The procedure for HEPA filter integrity and particle

count testing did not clearly define the quality unit's role in verifying the condition of critical AHU components, such as **(b)(4)** ducts, **(b)(4)**µ HEPA filters, and **(b)(4)**µ filters, during preventive maintenance, including assessing accumulated residues, filter integrity, and overall cleanliness. The lack of oversight led to insufficient monitoring of the filter replacement process during routine maintenance, preventing the detection of potential filter failures, air leakage, and contamination risks from compromised HEPA filters and ducting, which remained unaddressed and uninvestigated. These deficiencies demonstrate your failure to maintain a robust program to assure the proper performance of equipment essential to the manufacturing, processing, and holding of your drug products.

In your response, you note damage to the **(b)(4)** filters was confirmed by the original equipment manufacturer and potentially increased pressure differentials. You propose monitoring pressure differentials to determine when cleaning or replacement of filters is needed.

Your response is inadequate. While you acknowledge damage to the **(b)(4)** and propose periodic pressure differential monitoring, you fail to address the root cause or assess risks to airflow and cross-contamination identified during this inspection.

Concerns with CGMP records

A large amount of torn CGMP records were discovered in at least 15 plastic waste bags during the inspection, including analytical balance printouts and worksheets containing manufacturing and testing data.

During the inspection and in subsequent correspondence, you provided supporting documentation asserting that the CGMP records observed in plastic waste bags did not affect product quality. You identified several root causes for these issues, including insufficient clarity in good documentation practices and data integrity protocols, inadequate SOP provisions requiring the attachment of defective or illegible printouts with appropriate annotations, employee misinterpretation of existing procedures, and inadequate controls over raw data sheets for primary packaging materials.

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture.

Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Your laboratory equipment lacked sufficient controls to prevent and detect deletion or manipulation of your laboratory's electronic raw data. For example, your ultraviolet-visible (UV-vis) and infrared (IR) spectroscopy equipment was found to lack audit-trail functionality, and your analysts were able to alter and delete data, files, and folders. This is a repeat observation from your 2016 inspection.

In your response, you commit to performing audit-trail reviews for active ingredient assays before batch release. However, your response is inadequate because your commitment does not include the review of other electronic laboratory data associated with component and finished-product testing. Furthermore, you fail to provide review procedures designed to ensure data accuracy and integrity.

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture.

Your firm lacked sufficient controls over your liquid chromatography (LC) and gas chromatography (GC) instrument used to test drug products prior to release. Specifically, your firm did not appropriately control administrative privileges for file modification and deletion using your Agilent OpenLab software data system.

During the review of analytical system audit trails for final release testing of finished OTC drug products, our inspection found that your firm does not review audit trails and raw analytical data captured by these analytical instruments. You do not have written procedures to review electronic data or integration to ensure data reliability for batch release.

Your quality system does not adequately ensure the adequacy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. Without complete and accurate records, you cannot assure appropriate decisions regarding batch release, drug product stability, and other matters that are fundamental to ongoing assurance of quality.

Your response acknowledges that your firm failed to appropriately set up the instrumentation software used for data collection and analysis of OTC drug products. You also acknowledge that your firm failed to review audit trails and establish an SOP requiring review of computer-generated data during batch release testing. You commit to taking corrective actions, including updating user access and permissions for all lab instruments and creating a new SOP requiring review of raw data and audit trails prior to batch release.

Your response is inadequate because it lacks an independent review including, but not limited to, an assessment of drug product impact and whether a retrospective review is warranted based on the drug product impact assessment. Your response also did not provide adequate details of management oversight to ensure effectiveness of the corrective actions implemented.

Your laboratory equipment, used to generate analytical data for finished drug product release and stability testing, lacked restricted access and sufficient controls. Specifically, your firm did not have proper controls in place to prevent the deletion or record manipulation of your laboratory's electronic raw data. For example, our investigator documented numerous examples of deleted electronic raw data files. Additionally, your analysts had administrative rights capable of altering and deleting data, files, and folders on your chromatographic systems, including the date and time of tests.

We also note that you did not ensure retention of complete electronic raw data for all laboratory instrumentation and equipment. For example, our investigators documented several electronic data results that were not available for review.

In your response, you acknowledge the lack of document control and state that you have initiated change controls to reduce DI gaps identified during the inspection. Your response is inadequate because you failed to include a comprehensive review of each piece of equipment and the impact of the significant adverse pattern of data that has been discarded or lost. Your impact assessment commitment is also limited to missing **(b)(4)** test data and stability.

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture.

Your Production and QU did not review electronic raw data and audit trails to ensure data integrity prior to batch release. Your operators obtained and printed a passing result after multiple production filter integrity tests failed. Your operators did not record or print the failing results. For example:

- On August 8, 2024, two operators performed four post-use sterilizing filter integrity tests for (b)(4) batch (b)(4). The four tests included three failing results and the final passing result. Your operators only reported the passing result.
- On July 25, 2024, two operators performed nine filter integrity tests associated with (b)(4), bulk batch (b)(4). The nine tests included five failing results, three aborted tests, and the final passing result. Your operators only reported the passing result.

In your response, you acknowledge the deficiency and commit to perform a full audit trail review of your production equipment. You also indicate that you are completing the investigations into anomalous filter integrity tests.

Your response is inadequate as you do not provide details of the investigation outcome or explain whether effective corrective actions and preventive actions (CAPAs) have been implemented. Further, you do not provide the scope and time period of the retrospective review to ensure all batches potentially affected are part of the assessment.

Your firm lacked adequate system security and access controls over your laboratory equipment used to test drug products prior to release. For example, your firm utilized a common username and password to access high performance liquid chromatography (HPLC) equipment used for impurity testing of drug products. Additionally, analysts had administrator privileges to modify and delete data. Our investigators also found multiple deleted gas chromatography (GC) analytical sequences in the recycle bin, including sequences used for system suitability and stability analysis.

In your response, you state your employee violated your procedure and training by deleting sequence files without informing the supervisor or quality assurance (QA). You also state a

software update allowed users to bypass “User-Security Access Restrictions” and that you have disabled the automatic software update function. You also state that you have implemented security parameters to enhance access controls to electronic data files.

Your response is inadequate. You do not provide adequate details of management oversight to ensure effectiveness of the corrective actions implemented. You also lack a comprehensive assessment of all electronic and paper-based documentation systems to ensure their adequacy.