Warning Letters - Active Pharmaceutical Ingredient

Failure to investigate all critical deviations.

FDA documented that approximately 20 percent of bioreactor runs attempted between January 2022 and July 2024 were rejected for contamination or other quality failures. This rate is excessive and calls into question the state of control of your process. You failed to conduct adequate investigations into critical deviations, including multiple microbiological contamination events recorded in this timeframe. For example:

A. Two lots of **(b)(4)** and three lots of **(b)(4)** were out-of-specification (OOS) for appearance due to the presence of **(b)(4)** particles and were not adequately investigated.

B. Three in-process high-pressure events associated with product leakage during the transfer of bulk **(b)(4)** through a **(b)(4)** to **(b)(4)** L shipping bags were not adequately investigated.

Your investigations failed to identify all potential contributing causes, did not consider the conclusions of an engineering study that contradicted your assigned root cause for the OOS appearance events, and did not document all investigational activities, including the collection of at least one sample found in a storage room by FDA investigators.

In your response, you reference numerous corrective actions and preventive actions (CAPAs) initiated to address the inadequate investigations into the microbiological contamination and the in-process high-pressure events including:

- "… additional quality oversight of significant deviations…,"
- implementation of "… an investigation job aid" for **(b)(4)** technology items that help determine product impact,
- and revising your procedure governing appearance testing of APIs to ensure the observation of particles will result in an investigation that includes particle characterization.

Your response is inadequate. You did not provide the completed investigations alluded to in your response, identify the root cause(s), justify each CAPA, or explain how the effectiveness of the CAPA will be determined. You also did not address the impact of excessive **(b)(4)** particles in your drug substances potentially reducing the ability of **(b)(4)** to successfully remove objectional microbiological contamination.

Failure to demonstrate that your manufacturing process can reproducibly manufacture an API meeting its predetermined quality attributes.

You repeatedly deviated from your validated manufacturing process for the production of **(b)(4)**. For example:

A. You performed **(b)(4)** of the **(b)(4)** during **(b)(4)** of the **(b)(4)** bioreactor runs while the manufacturing process was validated with **(b)(4)**. You identified the **(b)(4)** process as

increasing the risk of microbiological contamination events in an investigation into a March 2024 in-process contamination event.

B. Your manufacturing personnel were observed to use a written work instruction (Pre-Job Briefing) describing itself as "… not a GMP document/process…" to deviate from your validated manufacturing procedure by replacing the **(b)(4)** with **(b)(4)** L shipping bag to control the frequency of high-pressure and in-process leaking events. The **(b)(4)** manufacturing process described in the electronic batch record used by manufacturing personnel was validated using a **(b)(4)** to process the transfilling of all **(b)(4)** L shipping bags used in a batch.

In your response, you commit to executing a protocol intended to identify additional CAPA to increase control of upstream processing and thereby reduce the incidence of microbiological contamination events. In addition, you commit to prohibiting the practice of replacing the **(b)(4)** with **(b)(4)** L shipping bag during the manufacture of **(b)(4)**. You also state the Pre-Job Briefing document was used incorrectly to implement the change to the validated manufacturing process and commit to identify and correct any other manufacturing instructions that rely on a Pre-Job Briefing document to deviate from the validated manufacturing process.

Your response is inadequate. There is no indication you initiated an investigation into your deviating from the validated manufacturing process by replacing the **(b)(4)** filling bags on multiple occasions. In addition, there is no retrospective review of batch records for batches within expiry, to identify any other process deviations performed without the appropriate corresponding documentation including risk assessment(s). You did not provide your rationale for ending the practice of replacing the **(b)(4)** for **(b)(4)** L shipping bag during the manufacture of **(b)(4)**. Furthermore, you did not identify an alternative control strategy to address the high-pressure events that resulted in the in-process product leakage events. You also did not investigate or describe your CAPA to address your QU's roles in these deviations from validated manufacturing processes.

When significant variability is observed in a drug manufacturing process or in its input materials, it is essential for executive management to support and implement effective actions to promptly address the source(s) of the variation and ensure a continued state of control.

Failure to have equipment of the appropriate design and suitability for their intended use for the manufacture of APIs.

Your firm used equipment unsuitable for its intended use in microbiologically controlled manufacturing environments. For example:

A. Mobile carts used in the setup of **(b)(4)** units required operators to get down to the floor and manually lock and unlock the cart brakes despite previously determining equipment proximity to the floor as a contributing root cause in microbiological contamination events.

B. **(b)(4)** used to establish temporary sterile boundaries for tubing continue to be used despite being identified in a June 2023 microbial contamination event investigation as possessing a "design flaw" that may allow microbial ingress.

In your response, you commit to removing all brakes from the **(b)(4)** carts, assessing potential design improvements to the carts, and you note supplemental contamination control training to manufacturing personnel. You explain the previous documented description of a design flaw in the **(b)(4)** was incorrect, and the problem is a "design limitation" that requires specific instruction to fully mitigate the risk of microbiological contamination. You also commit to verification of the **(b)(4)** usage by a second operator.

Your response is inadequate. You disregarded your previous conclusion that equipment and personnel proximity to the floor is a contributing root cause in microbiological contamination events and state the design of the mobile carts is "… fit for purpose when used per the SOP and in a manner consistent with manufacturing training." You do not commit to reassess manufacturing equipment to ensure it is of appropriate design to minimize the risk of microbial contamination. You do not describe the **(b)(4)** "design limitation" or explain why this "design limitation" was not previously mitigated. You also do not discuss how the revised instructions for usage and verification will mitigate the risk associated with their use.

Failure of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP.

Your facility is subdivided into "Blocks" sharing walls and hallways. Your facility experienced a significant fire in Block **(b)(4)** on December 5, 2022. Additional areas affected included Block **(b)(4)**, where your firm stored **(b)(4)** finished API lots. You moved your APIs after they were exposed to improper storage conditions and identified **(b)(4)** lots of **(b)(4)** API and **(b)(4)** lots of **(b)(4)** API as impacted by the fire in your incident report. Although these lots were impacted by the fire, your quality unit (QU) released **(b)(4)** lots of **(b)(4)** API and **(b)(4)** lot of **(b)(4)** API for distribution to the U.S. market.

In your response, you propose to update your procedure for handling of incidents and deviations. You also attempt to recreate the worst-case condition for finished drugs stored in Block **(b)(4)** at the time of the fire by placing **(b)(4)**, and you conclude there was no product impact.

Your response is inadequate. Your response attempts to justify that your drugs, exposed to improper conditions, are acceptable. Drugs that have been subjected to improper storage conditions, including extremes in temperatures and smoke, are considered adulterated and are not suitable for distribution in the U.S. supply chain. Further, you do not commit to initiate a market action against the lots your incident report identifies as "impacted and degraded".

Your firm utilized a contract manufacturing organization (CMO), **(b)(4)**, to perform manufacturing, processing, and packaging activities on your behalf. You received drugs from

this CMO and declared your firm as the manufacturer on import records. Additionally, you registered your firm with the FDA **(b)(4)**. **(b)(4)** is not registered as a drug manufacturer with the FDA.

A written agreement with your CMO, provided during the inspection, describes the responsibilities of your firm in the manufacturing of **(b)(4)**. For example, Jagsonpal personnel are responsible for supervising the manufacturing and analysis of **(b)(4)** and assuring your CMO adheres to CGMP.

However, you did not adequately ensure that process validation was completed by your CMO, that master production instructions were complete, and that compendial methods used to analyze your product were appropriately verified as suitable for their intended use.

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer. You are responsible for the quality of your drugs regardless of agreements in place with your contract facility. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act to ensure safety, identity, strength, quality, and purity. See FDA's guidance document *Contract Manufacturing Arrangements for Drugs: Quality Agreements* at https://www.fda.gov>media>download.

Your firm's quality systems are inadequate.

Our inspection documented approximately 84 open and past due deviation investigations existed as of June 21, 2024. For example:

A. QE-000270 (187 days past due)
B. QE-004069 (179 days past due)
C. QE-004896 (129 days past due)
D. QE-023790 (45 days past due)

Multiple past due investigations also lacked procedurally required extensions to the due date.

The procedure governing deviation handling requires non-significant deviations be closed within **(b)(4)** and significant deviations be closed within **(b)(4)**. The procedure further requires a documented and approved request for extension in the event a deviation investigation cannot be closed within the specified timeframe.

In your response, you identify four contributing root causes: excessive personnel attrition of trained investigators, process knowledge gaps amongst newer investigators, prioritization of investigations associated with lots pending release, and inconsistent communication of "deviation performance metrics."

Your response is inadequate. Although you identified CAPA, for each contributing root cause, you did not provide sufficient detail for their implementation. You commit to adding resources to your "Compliance Engineer and QA team to sustain the deviation quality system…" and assess this action "… against adherence to performance metrics and the **(b)(4)** planning exercises for resource allocation." You also commit to reassigning existing personnel and to bring in subject matter experts to assist with addressing the investigation backlog but do not explain how this will impact other operations, how these personnel will be trained to conduct specific aspects of the investigations, and how their performance will be monitored and assessed.

Failure of your quality unit to exercise its responsibility to ensure the intermediates manufactured at your facility are in compliance with CGMP.

Several original batch production records were found torn in your scrapyard. The investigator asked to review the batch records associated with the torn documents. Your management then provided a second set of these batch records in question. During the inspection, no explanation was provided regarding how there could be two sets of original batch production records or who authorized the disposition of these documents.

In addition, batch production records are not completed contemporaneously. Batch records were observed to be stored in the Quality Assurance (QA) department while manufacturing operations were ongoing. Production tasks performed by operators were recorded later by the production supervisor, who was overseeing five production rooms at the same time.

In your response, you state that some of the batch production record pages were damaged by chemical spillages and the pages were replaced by the QA department. The damaged pages were

not returned to QA and were sent to the scrapyard. You explain that your production supervisor fills out the batch production records because your operators lack proficiency in English. You also state that several production staff members were unable to attend work due to illness, which is why one production supervisor had to oversee and record operations in multiple areas.

Your response is inadequate. You failed to provide supporting evidence of any incident or deviation regarding chemical spills on CGMP documents. You also do not address your practice of tearing CGMP documents and its potential impact, including ensuring accurate results were reported when the batch production records were recreated. In addition, there is no assurance that CGMP activities are adequately performed and documented, given that the records are not in a language understood by your employees executing such activities.

Complete and accurate batch production and control records must be contemporaneously documented to ensure that manufacturing processes are consistently followed and

reproducible. Additionally, incomplete manufacturing records deprive you of the ability to adequately investigate deviations.

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.

Failure of your quality unit to exercise its responsibility to ensure the API and intermediates manufactured at your facility are in compliance with CGMP.

Your quality unit failed to ensure adequate document control over paper and electronic records. Your quality unit was not exercising its basic responsibilities for oversight and control of the adequacy and reliability of all CGMP data at your facility. In addition, your quality unit failed to ensure that employees involved in CGMP operations for APIs understand and adhere to data integrity principles. For example:

- Your quality unit failed to ensure that batch production records were prepared with complete information relating to the manufacture and control of each lot of API produced. You manufactured and released lots of APIs without creating or maintaining batch manufacturing records. Your quality unit failed to identify this deviation and did not investigate until our investigators cited it as a CGMP deficiency.
- You distributed multiple lots of the API (b)(4) without documenting review and release by the quality unit.
- Your quality unit kept two separate logbooks for the issuance of lot numbers which showed that two batch manufacturing records were issued for the same lot numbers. In addition, we observed two API batch records in use, in production, with neither an assigned control number nor any documentation that they had been issued by the quality unit.
- Your quality unit engaged in deficient data integrity practices. For example:
  o Your quality unit failed to control your process for replacing controlled documents. Your quality unit replaced original CGMP documents consisting of numerous pages of executed batch production records and a laboratory-testing record in which original pages were discarded or destroyed without a documented investigation. Your quality assurance manager stated that you do not maintain the original pages. We found blank forms used to replace controlled records in the production department with no indication that they had been issued by the quality unit.
  o Your quality unit allowed your production operators to retroactively complete CGMP information in batch production records for production steps performed by the previous (b)(4). Your quality unit did not start an investigation until this data integrity failure was pointed out during our inspection. We observed your (b)(4) production personnel – who had not performed or witnessed the previous (b)(4) operations – in the production office non-contemporaneously documenting CGMP information, such as weights and measures of components, solvents, and temperatures, on API batch records for operations performed by the previous (b)(4).

Your response dated August 21, 2025, acknowledges multiple deficiencies in your documentation practices, including inconsistencies in batch manufacturing record issuance, missing quality assurance review, uncontrolled forms, and inadequate documentation oversight. You acknowledge that your quality unit is responsible for preparing, reviewing, and approving master production and control records, and for ensuring their accuracy, distribution, and reconciliation.

You responded that you recovered approximately half of the original API batch manufacturing records. You stated that you will update your procedures to include a batch manufacturing record closure checklist and mandatory reconciliation of these records to ensure they are not lost. Additionally, you stated that you failed to document the release of lots because you do not have enough quality assurance personnel to review batch production records and release batches.

You stated that you misclassified replacement of CGMP documents as administrative corrections, and you did not have procedures requiring an investigation when you replaced these documents. You stated your procedures will be updated to require original document retention and documented deviation investigations for all replacements.

Your response is inadequate. You do not sufficiently address and reconcile all missing batch records. You do not provide results of any comprehensive retrospective evaluation, nor do you provide any testing data and release documentation.

You do not provide a plan or procedures to holistically improve your document lifecycle controls, issuance traceability, and quality unit release processes. You do not provide results from comprehensively investigating past incidents of non-contemporaneous documentation, nor have you reconciled existing batch manufacturing records for completeness and release by the quality unit.

You do not perform a comprehensive retrospective review of the replaced CGMP document pages. You do not provide any indication of the relevance of the original pages that were not maintained. You do not provide adequate revised procedures to ensure that original data will be recorded contemporaneously and indelibly.

Complete and accurate batch production and control records must be contemporaneously documented to ensure that manufacturing processes are consistently followed and are reproducible. Additionally, incomplete manufacturing records deprive you of the ability to adequately investigate deviations.

Reliability of data is fundamentally compromised when there is a failure to contemporaneously record and/or maintain complete and accurate records of testing conditions and results. Furthermore, the lack of reliable data compromises the ability of your quality unit to exercise its function of ensuring compliance to applicable standards.

Failure to ensure all production deviations are reported and evaluated, and that critical deviations are investigated, and the conclusions are recorded.

Multiple production deviations went unaddressed until our investigators informed facility personnel of the issues. For example:

A. An **(b)(4)** line used for aseptic processing was observed to be touching the floor during **(b)(4)** setup activities. The batch record specifically includes an instruction for personnel to ensure production lines do not contact the floor.
B. An operator was observed to touch their gown and hairnet with their hands and then handle sterile manufacturing equipment without sanitizing their hands.
C. The **(b)(4)** located between the **(b)(4)** L **(b)(4)** and a **(b)(4)** L shipping bag was observed to be oriented **(b)(4)** during processing of **(b)(4)** lot **(b)(4)**. The batch record specifically instructs personnel to orient the **(b)(4)**.

In your response, you commit to conducting additional training for all facility personnel and to revise your **(b)(4)** contamination control training to include additional instructions on when to use **(b)(4)** and when gowning changes are appropriate. You also commit to making procedural changes associated with equipment management and using additional resources for operational coaching and oversight.

Your response is inadequate. You do not provide your investigation(s) into the objectionable behaviors, assess your training program, or assess your oversight of setup and manufacturing operations.

Failure to test the identity of each batch of incoming production material.

Based on the records and information you provided, you failed to conduct an identity test on the raw materials used for manufacturing of your API during **(b)(4)**, e.g., **(b)(4)**.

Without adequate testing, there is no scientific evidence to assure that your raw materials conform to appropriate specifications before release.

Failure to test the identity of each lot of incoming production material.

Your incoming raw material used to manufacture API intended for the U.S. market was not adequately tested. For example, you did not test the **(b)(4)** used as a raw material in the production of **(b)(4)** for identity.

Your response is inadequate. You state that you "initiated the activity" to test **(b)(4)** for identity. However, you do not address whether all other raw materials are tested for identity or how you will prevent this deviation from recurring with new raw materials.

You manufacture APIs that were distributed to **(b)(4)** in the United States. Based on the records and information you provided, you have not demonstrated that you are adequately

testing each shipment of each lot of incoming materials. Specifically in response to our request, you state that you do not perform identity testing on each shipment of each lot of incoming material before they are released for use in drug manufacturing.

Without adequate testing, you do not have scientific evidence that incoming materials conform to appropriate specifications prior to use in the manufacture of your drugs. As a manufacturer, you have a responsibility to sample, test, and examine incoming materials before use in production to assure adequate quality.

Failure of your quality unit to establish a system to release or reject raw materials, intermediates, packaging, and labeling materials.

The records and information you provided demonstrate that your quality unit (QU) did not effectively exercise its responsibilities to oversee the quality of your drug manufacturing operations. Specifically, your QU did not establish an appropriate system to approve or reject incoming materials.

Your QU is responsible for fully exercising its authority and responsibilities.

An adequate QU overseeing all elements of CGMP is necessary to consistently ensure drug quality. FDA considers the expectations outlined in ICH Q7 when determining whether API are manufactured in conformance with CGMP, including sections on quality oversight.

Access to Information During Inspection

On March 15, 2024, the FDA arrived at the registered address, B-1124, RIICO Ind. Area, Phase-III, Bhiwadi Dist., Alwar, Rajasthan, 301019, India, to conduct an inspection and was refused entry by individuals present at this address.

On March 20, 2024, the FDA was permitted to enter the facility at the registered address to conduct an inspection; however, access to requested documents was limited during the inspection. For example, complete analytical data, equipment logbooks, and change control documents were not provided upon request because, according to your representatives, the facility was in **(b)(4)** status. Representatives from Jagsonpal and your CMO were present during these requests.

When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be deemed adulterated under section 501(j) of the FD&C Act.

Failure to record all quality-related activities at the time they are performed.

Your quality unit (QU) failed to ensure the integrity of CGMP records. For example, during the inspection, a member of your management stated that two of your operators admitted to falsifying temperature data for a drying oven that was not turned on during the manufacture of a **(b)(4)** batch, which later failed to meet the residual solvents specification. In addition, an

Assistant Manager in Production, an Assistant Manager in Quality Assurance, and a Quality Control Manager admitted to participating in the preparation of a "backdated calculation sheet" that was given to our investigator.

Your documentation practices were not indicative of a facility that is in compliance with CGMP.

Your response is inadequate. You state that you plan to hire a consultant to identify data integrity gaps and prepare and implement an action plan by June 30, 2025, approximately ten months from the conclusion of the inspection, which documented serious questionable data integrity practices. In addition, you state that you removed some of the employees involved in these incidents from CGMP-related activities, but you do not explain what was done to prevent the other employees involved in these activities from further data integrity deviations. Finally, you do not fully evaluate the scope of data integrity lapses at your firm, including by interviewing current and former employees and comprehensively reviewing data records.

Significant findings in this letter indicate that your QU is not fully exercising its authority and/or responsibilities. Your firm must provide the QU with the appropriate authority and sufficient resources to carry out its responsibilities and consistently ensure drug quality.

Failure to clean equipment and utensils to prevent contamination or carry-over of a material that would alter the quality of the APIs beyond the official or other established specifications.

FDA documented rust-like residues inside **(b)(4)** non-dedicated **(b)(4)** used in the production of **(b)(4)**. In addition, FDA documented bare footprints inside another **(b)(4)** used in the production of **(b)(4)**. Each **(b)(4)** was labeled that it had been cleaned and was ready for use.

Inadequately cleaned and maintained manufacturing equipment can lead to potential cross-contamination that could compromise your API's quality and safety.

Your response is inadequate. You state that you reviewed the quality of the products manufactured in the impacted equipment since February 2024, but you do not describe how you conducted this review, nor the reason you limited your review to this timeframe. In addition, you do not adequately explain how you will prevent the failure to clean equipment after personnel enter inside it from recurring. Finally, you state that personnel entering inside equipment should "wear cloth shoe cover after removing shoe," but failing to wear suitable clothing, including appropriate footwear, poses an unacceptable risk to the product.

You failed to have adequate procedures for the cleaning and maintenance of manufacturing equipment and facilities. Our inspection found manufacturing equipment labeled as "Cleaned" and found the following deficiencies. For example:

• **(b)(4)** #B-**(b)(4)**-404 in Production Block-**(b)(4)** was documented on the equipment usage log as "Cleaned as per SOP" on September 5, 2024; however, excessive **(b)(4)** colored

residues were observed inside the **(b)(4)** later this same day. This **(b)(4)** is used to manufacture **(b)(4)**.

• **(b)(4)** #BI/**(b)(4)** in Room #**(b)(4)** used to manufacture **(b)(4)** intermediate, was documented on the equipment usage log as "Cleaned as per SOP" on August 30, 2024; however, **(b)(4)** was observed on the inside and outside of the equipment's product discharge area.

In addition, buildings used in the manufacture of key starting materials and intermediates used in the production of APIs are not maintained in a good state of repair. For example, the ceiling above **(b)(4)** located outside Production Block-**(b)(4)** was observed to be heavily stained, and with cracks and fallen plaster. These **(b)(4)** are used to manufacture **(b)(4).**

In your response, you state that the equipment used in the **(b)(4)** processing areas is dedicated and the **(b)(4)** found on the equipment surfaces corresponds to the same compound, therefore, no cross-contamination is expected. You acknowledge there was insufficient oversight in ensuring compliance with cleaning procedures and inadequate monitoring of cleaning intervals. In addition, you state that daily sanitation procedures were not adequately enforced to prevent material accumulation, but they will be reinforced. You also state that an immediate corrective action was to repair and restore the ceiling outside Production Block-**(b)(4)**.

Your response is inadequate. Although you indicate cross-contamination may not be expected, product carryover and unknown impurities may form as a result of product build up on unclean equipment. You also do not acknowledge why personnel signed off on equipment usage logs as equipment being clean when it was not clean. In addition, no evidence of the ceiling repair was provided.

Failure to clean equipment and utensils to prevent contamination or carry-over of a material that would alter the quality of the intermediates and API beyond the official or other established specifications.

Your firm manufactures **(b)(4)** API intended for the U.S. market. You lacked adequate procedures for cleaning and maintenance of manufacturing equipment. FDA documented an unidentified **(b)(4)** residue, apparent rust, and unidentified liquids inside or on product contact surfaces of various non-dedicated process equipment used in the production of **(b)(4)**. Each was marked as cleaned and ready for use. Additionally, investigators observed discolored and scratched **(b)(4)** containers for use in **(b)(4)** operations.

In your response, you state that you have cleaned equipment and have updated cleaning and maintenance procedures. You also commit to using **(b)(4)** storage for **(b)(4)**.

Your response is inadequate in that it fails to comprehensively address cleaning and maintenance deficiencies or how you will attempt to develop any system to proactively

address these issues. Furthermore, you did not perform an assessment of residues and liquids in process equipment that you had identified as clean.

Inadequately cleaned and maintained manufacturing equipment can lead to potential cross-contamination that could compromise your API's quality and safety.

Data Integrity Remediation

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

Failure of your quality unit to ensure that quality-related complaints are investigated and resolved.

Inadequate root cause determination

Your firm failed to adequately determine the root cause of approximately 22 complaints since 2020 related to metal contamination in your APIs. For example, your investigation into a complaint of black particles in **(b)(4)** API identified this was the first lot manufactured after a facility modification. You stated some particles may have not been removed completely during equipment cleaning but concluded "no exact root cause identified." You also stated the particles were metallic in nature and were beyond the detection limit of your metal detector used to remove metallic particles in your API. However, our inspection determined you did not have a "**(b)(4)**" to adequately qualify your metal detector's performance for **(b)(4)** particles, even though most of your manufacturing equipment is composed of **(b)(4)**.

We also note your investigation determined the contamination to be technically unavoidable particles. You referenced an industry standard on technically unavoidable particles in excipients as applicable. According to this guideline, technically unavoidable particles are inherent to the product and are not foreign contamination introduced by incomplete cleaning. Not only is this standard not applicable to your active ingredient manufacturing process, it also specifies that appropriate evaluation of materials of construction and particle mitigation strategies are required. Based on your investigation indicating a cleaning deficiency as a likely root cause, you do not have evidence to support that the metallic particles present are inherent to the manufacturing process. Your firm remains responsible for establishing and following adequate cleaning procedures.

In your response, you state you have now obtained a "**(b)(4)**" and determined the metal detector is working satisfactorily. You then concluded there is "no impact on the performance of the metal detector."

Your response is inadequate. The current performance of the metal detector does not provide adequate assurance that previous API lots met established safety and quality standards. Also, your conclusion that your metal detector works adequately stands in contrast to customer complaints indicating contamination with metallic particles. Additionally, your investigation fails to adequately assess whether your manufacturing equipment's design and materials are suitable for API production without introducing contamination risks. Furthermore, you lack an adequate evaluation of your cleaning procedures and in-process controls to prevent the presence of metal particles in your API.

Ineffective corrective actions and preventive actions (CAPAs)

Your firm failed to implement effective CAPAs after receiving numerous complaints of foreign material contamination of your APIs. For example, a customer reported foreign material contamination involving eight lots of **(b)(4)** API. Your investigation found CAPAs were implemented for similar complaints prior to the manufacture of the complaint lots. However, our inspection found approximately 28 additional complaints reporting foreign material contamination after you completed your investigation.

Inadequate investigations can result in unidentified root causes, ineffective CAPAs, and recurring problems that compromise your ability to manufacture safe and effective APIs.

We also note that during our review we found the risk assessment included in your complaint investigation is not scientifically sound, as you ranked this **(b)(4)** API complaint as an unlikely failure with the lowest probability of occurrence despite repeated similar complaints.

In your response, you state you hired a third-party consultant to evaluate contamination, investigations, risk assessments, and CAPAs related to foreign material contamination.

Your response is inadequate. You do not provide sufficient evidence of a comprehensive evaluation of potential contamination sources and process controls.

You failed to adequately investigate a complaint of **(b)(4)** particles in the intermediate, **(b)(4)**, Stage-**(b)(4)**, batch **(b)(4)**. The root cause was attributed to improper cleaning/usage of the **(b)(4)** bag. A CAPA to change the **(b)(4)** bag more frequently (i.e., after **(b)(4)** batches instead of **(b)(4)** batches) was proposed.

The complaint investigation was deficient because it did not extend to other batches, as required by your procedure, and it failed to identify other potential causes of the **(b)(4)** particles. Despite CAPA implementation of more frequent **(b)(4)** bag changes, the **(b)(4)** in Production Block – **(b)(4)** was observed during the inspection to be in disrepair, with the interior lining worn and corroded. The **(b)(4)** is located outdoors, exposed to the outside environment, and was also observed to contain heavy rust and a dead insect. Your management acknowledged the condition of the equipment and environmental conditions were not evaluated as potential source(s) of the contamination.

In your response, you acknowledge your procedure for handling complaint investigations, but did not account for environmental conditions, which likely contributed to the complaint. You provided an addendum investigation report extending the investigation to other batches and including environmental conditions. You also state that the **(b)(4)** equipment will be upgraded and enclosed to create a controlled environment.

Your response is inadequate. You do not commit to conduct a retrospective review of all complaints to ensure they were adequately investigated, extended to other batches, and considered environmental conditions, if necessary.

Failure to design and construct buildings and facilities used in the manufacture of your API in a manner to minimize potential contamination, facilitate appropriate cleaning, maintenance, and operations.

You produce higher-risk APIs in an inadequate facility including one that lacks appropriate separation for high pharmacological activity or toxic materials including **(b)(4)** drugs. During the inspection, our investigator observed your facility was in a state of disrepair, with manufacturing areas open to the outdoor environment with inadequate protection of materials. Our investigator also observed that **(b)(4)** drugs were manufactured in a common area.

For example, your firm stated that "all the operations are conducted under one roof in **(b)(4)** Block Annex without proper segregation" and that "**(b)(4)** Block Annex manufacturing facility is in the process of demolish." Of note, FDA collected batch indicating you produced drugs during this time period.

In your response you indicate that your facility is undergoing renovations. Your response is inadequate because you did not provide sufficient details of how your facility design will prevent contamination of drug substances from the open environment, as well as cross-contamination of non-toxic drug substance from highly toxic components.

It is expected that buildings used in the manufacture of APIs are designed and constructed to minimize potential contamination.

Failure to properly maintain buildings and facilities used in the manufacture of API.

You failed to maintain your drug manufacturing facility in a good state of repair. Specifically, our investigator observed the following deficiencies in the (b)(4) production building during the inspection:

- Water condensation from (b)(4)-216 on the (b)(4) floor was actively falling onto the catwalk and subsequently dripping onto the working space for (b)(4)-207, resulting in standing water around that (b)(4).
- Water from the bottom of (b)(4)-203, (b)(4)-204, and (b)(4)-209 on the (b)(4) floor was dripping onto the production floor and the outer surfaces of (b)(4)-204.

- You placed (b)(4) drums below the water drips and (b)(4) sheeting on the catwalk to shield the (b)(4) from overhead dripping water.

In your response, you attribute the condensation to degraded (b)(4) and a failure in your preventive maintenance program to monitor (b)(4) integrity. You state that you placed batches manufactured during the inspection on hold and conducted microbiological testing on these batches as part of your risk assessment. You commit to repairing and replacing the degraded (b)(4), conducting engineering changes to minimize overhead drips, installing permanent drip barriers, and updating the preventive maintenance program to include routine inspections.

Your response is inadequate because you lack sufficient data to substantiate your conclusion of "no confirmed impact to product quality." Your investigation does not include retain sample testing or assessing the duration of your facility's state of disrepair to determine the scope of potentially affected batches. While you conduct manufacturing operations in (b)(4) systems, your response does not account for the fact that equipment had damaged gaskets and a corroded and damaged (b)(4) which can compromise the integrity of (b)(4) systems.

It is your responsibility to ensure sustainable corrective actions to maintain your manufacturing facility in a good state of repair.

Your firm manufactures **(b)(4)** APIs, such as **(b)(4)** for use in human and animal drug compounding. You failed to adequately maintain your equipment and facility in an adequate state of repair, creating conditions that could contaminate your APIs and compromise drug quality. For example, our investigator observed extensive corrosion on the bottom pipe connections of **(b)(4)** tank **(b)(4)**, located in equipment workshop **(b)(4)**, where you manufacture **(b)(4)**. Additionally, the investigator observed numerous water leaks in the ceiling of the warehouse and production and packaging areas. Due to these leaks, water puddled on the ground in the drug warehouse, the Class D area of workshop **(b)(4)** where drugs are packaged, and in the **(b)(4)** water distribution system area.

In your response, you describe corrective actions you performed with photos of repairs to equipment and exterior roofs. You also outline a preventive maintenance program for equipment. Your response is inadequate because it lacks sufficient detail describing the repairs performed and adequate evidence of corrective actions taken to address facility deficiencies. You also do not provide a comprehensive assessment of your preventative maintenance program, nor do you adequately describe whether you evaluated all buildings and equipment for leaks and poor conditions. Additionally, your response lacks a risk assessment to determine whether excess moisture adversely impacted the quality of any APIs.

Moisture exposure can cause chemical reactions that degrade API potency and purity. Furthermore, water leaks create ideal conditions for microbial growth which can contaminate APIs.

Failure to ensure that equipment is maintained.

Your firm failed to adequately maintain the (b)(4) used to manufacture (b)(4) API for the U.S. market. Our investigator documented (b)(4) in the (b)(4) manufacturing workshop in various levels of disrepair, including cracked, taped, and deteriorating (b)(4) gaskets, rust-like residues on product-contact surfaces such as (b)(4), and cracked (b)(4) inside one of the (b)(4). These findings directly contradict your firm's own cleaning and preventive maintenance records, which had documented the condition of all these (b)(4) as "ok." Additionally, our investigator observed wet paint on one of your (b)(4) while production activities were ongoing.

In your response, you acknowledge the deteriorated condition of your equipment and attributed the deficiencies to inadequacies in your cleaning program and absence of a lifecycle management program for your equipment. You also acknowledge that your inaccurate recordkeeping stemmed from "insufficient inspection rigor." As corrective action, you have initiated physical repair of all equipment and a complete overhaul of procedures for cleaning, maintenance, inspection, and gasket management.

Your response is inadequate because your investigation does not extend to testing residues found in your equipment or retain samples to assess the potential impact on product quality. Furthermore, your response fails to explain the inability of your quality system, despite having numerous checklists and procedures already in place, to identify and proactively address these obvious equipment maintenance issues.

It is your responsibility to ensure your equipment maintenance program is comprehensive and includes appropriate assessment of equipment failures and their impact to product quality.

Failure to demonstrate that your manufacturing process can reproducibly manufacture an API meeting its predetermined quality attributes and failure to adequately validate written procedures for the cleaning and maintenance of equipment.

Process Validation

You failed to appropriately validate your processes prior to release and distribution of your API. Specifically, you manufactured and distributed two batches of semaglutide API to the U.S. market despite having conducted no process validation.

Without adequate process validation, your firm lacks basic assurance that you can reproducibly deliver products that meet specifications. See FDA's guidance document for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download

In your response, you acknowledge that you have not initiated process validation for semaglutide API that you repackage and relabel. You compared the critical process

parameters with the planned process validation lots and concluded that releasing these products without process validation was low risk.

Your response is inadequate. Your risk assessment lacks sound scientific testing data to conclude low impact of using non-validated processes on APIs already distributed to the United States. Additionally, you failed to provide a complete process validation protocol for review. Your CAPAs lacked metrics for effectiveness of bringing your operations into compliance with CGMP.

Cleaning Validation

You lacked adequate cleaning validation studies that demonstrate your cleaning procedures for your manufacturing equipment are effective. For example, your cleaning procedure requires calculation of a maximum allowed carry over limit based on API toxicity. However, you did not establish a maximum allowed carryover limit in your cleaning validation study for the equipment used to manufacture peptide APIs, including semaglutide and tirzepatide. Furthermore, your cleaning validation study did not provide justification for the swab sampling locations, nor did it contain results from the swab sample testing as required by the same cleaning procedure.

Inadequately cleaned and maintained manufacturing equipment can lead to potential cross-contamination that could compromise your API quality and safety.

In your response you commit to drafting and executing a new cleaning validation protocol during your next production campaign in the original API workshop to include chemical residue testing on both direct and indirect product surfaces. Your response is inadequate because you did not provide a systemic CAPA for the deficiencies related to the misalignment between your cleaning procedure requirements and your cleaning validation study.

Process Validation

You failed to appropriately validate your processes and adequately qualify the equipment used to manufacture your drugs. Specifically, you have not completed process validation for commercial size lots of your APIs. For example, you rely on studies conducted on development lot sizes for **(b)(4)** API intermediates manufactured utilizing different equipment than that used for commercial production.

In your response, you state that you compared commercial lots to the smaller development validation lots, found no significant variations, and will perform commercial size process validations. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant **(b)(4)** of a manufacturing process must be designed

appropriately to assure the quality of raw material inputs, in-process materials, and finished APIs. Process qualification studies determine whether an initial state of control has been established.

Successful process performance qualification (PPQ) studies incorporating the use of appropriately qualified equipment and validated test methods are necessary prior to commercial distribution. Thereafter, ongoing vigilant oversight of process performance and drug quality is necessary to ensure you maintain a stable manufacturing operation throughout the drug lifecycle. Failure to implement adequate analytical method validation practices can result in insufficient understanding of process variables or failure to detect a drift in capability, which increases the risk of drug quality defects.

Cleaning Validation

You lacked cleaning validation studies that demonstrate your cleaning procedures are adequate. For example, you previously identified the need to implement a cleaning validation based on your internal deviation report, yet our investigator observed that you lack cleaning validation.

In addition, our investigators observed manufacturing equipment labeled "Cleaned" that contained liquid with a **(b)(4)** floating substance or residue on product-contact surfaces.

In your response you indicate that you plan to perform cleaning validation for your drugs and perform hold time studies. Your response is inadequate because you did not provide supportive documentation or your interim plans for drug production while you complete corrective and preventive actions.

Inadequately cleaned and maintained manufacturing equipment can lead to potential cross-contamination that could compromise your API's quality and safety. Cleaning procedures should consider solubility, cleaning difficulty, and residue limits, while reproducible and effective for the removal or obliteration of previous lot identification and protection of clean equipment from contamination prior to use. Furthermore, the use of dedicated production areas should be considered for higher-risk material of an infectious nature or high pharmacological activity or toxicity (e.g., certain steroids or (b)(4) agents) where cleaning and inactivation alone are not sufficient controls.

Failure to have originals or copies of records readily available and promptly retrievable during the retention period.

You failed to ensure adequate document control over paper and electronic records. For example, you provided a written statement on firm letterhead admitting to backdating a QC lab document and you signed a declaration confirming commercial drugs shipped to the US were not supported by appropriate original data.

In your response, you acknowledge a lack of original data and that you will improve your document management system. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

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.

Failure to design a documented, on-going stability testing program to monitor the stability characteristics of API and to use the results to confirm appropriate storage conditions and retest or expiry dates.

Based on the records and information you provided, your firm failed to perform routine stability testing to demonstrate that the quality attributes of your APIs remain acceptable throughout the labeled expiry period. For example, your firm did not provide sufficient stability test data for **(b)(4)**, or other APIs manufactured at your facility.

Without an appropriate stability program, you lack adequate scientific evidence to support that your APIs meet established specifications and retain their quality attributes throughout their labeled expiry.

Your firm's stability program is inadequate. For example, your firm does not have adequate data to support the retest date for drugs shipped to the United States.

In your response, you acknowledge the deficiencies of your stability program and propose corrective actions including addition of stability indicating analysis. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

Without an adequate stability program, you cannot ensure that your APIs meet established specifications and all pre-determined quality criteria throughout the APIs' assigned shelf-life.

Failure of your quality unit to ensure that there is stability data to support retest or expiry dates and storage conditions of API.

Based on the records and information provided for stability, you did not demonstrate the quality attributes of your API lots remain acceptable throughout the labeled expiry period.

You experienced numerous power failures in your stability chambers over the past two years. These failures extended for up to 40 hours. You also lack data loggers to monitor and document actual conditions in the event of a failure or power loss.

Your response is inadequate. You acknowledge your stability program is inadequate. You commit to update your stability procedure regarding power failures and conduct a study to "determine the trend of temperature and humidity in the powered-off condition and make it

part of equipment qualification." You do not provide your study protocol or risk assessment "regarding electrical connection, power supply, power surge & voltage disruption."

Failure to have a system for evaluating suppliers of critical materials.

Your firm's supplier qualification procedure stated corrective action is required when a supplier's rejection rate exceeds **(b)(4)**% during incoming inspection. However, it did not incorporate mechanisms for re-evaluation of an approved supplier when quality deficiencies or complaints are detected after initial qualification.

This deficiency in your supplier qualification procedure allowed you to continue using materials from qualified suppliers after you determined their materials were found defective. For example, your firm received repeated customer complaints about particles in your APIs that you concluded most likely originated from your supplier of **(b)(4)** drums and lids. Despite notifying the supplier of these quality issues and continuing to receive customer complaints, your firm failed to implement timely corrective actions, such as qualifying alternate suppliers, enhancing supplier oversight, or discontinuing use of defective materials from this supplier.

An adequate supplier qualification program includes ongoing monitoring of supplier performance beyond incoming inspection and prompt implementation of corrective actions when quality issues are identified at any point in the manufacturing process.

In your response, you provide an updated supplier qualification procedure that accounts for quality issues identified during manufacturing and customer complaint investigations. You also state you have suspended the use of your drum supplier, and you are qualifying additional suppliers.

Your response is inadequate. You do not provide quality data for the new supplier, which you state was providing **(b)(4)**% of your drums prior to the inspection. Furthermore, you lack a comprehensive root cause analysis of your supplier qualification system's failure to identify and respond to ongoing quality issues.

Failure to demonstrate that your manufacturing process can reproducibly manufacture an API meeting its predetermined quality attributes.

Based on the records and information you provided, your firm failed to conduct process validation for the **(b)(4)** APIs manufactured at your facility. These APIs are for use in further processing to produce sterile drug products and for pharmaceutical compounding operations.

Process validation evaluates the soundness of design and state of control of a process throughout its life cycle. Each significant stage of a manufacturing process must be designed appropriately and assure 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 is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

Without adequate process validation, your firm lacks basic assurance that you can reproducibly deliver products that meet specifications.

Based on the records and information you provided, your firm has not conducted process validation for the Glucagon-Like Peptide-1 Receptor Agonist (GLP-1) API Semaglutide manufactured at your site.

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 and 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 is necessary to ensure that you maintain a stable manufacturing operation throughout the product lifecycle.

Without adequate process validation, your firm lacks basic assurance that you can reproducibly deliver products that meet specifications.

Failure to adequately investigate and document out-of-specification results and implement appropriate corrective actions.

Your firm manufactures APIs for incorporation into application drug products, including those intended for use in **(b)(4)** drug products for parenteral administration. You failed to adequately investigate multiple out-of-specification (OOS) results and laboratory incidents during the testing of various samples, including raw materials, starting materials, and stability samples.

Since 2023, your firm has experienced approximately 1,500 laboratory incidents involving OOS results and other significant analytical events (e.g., equipment failures). There were numerous examples where your investigations were inadequate, and often lacked thorough root cause analysis, and appropriate corrective actions and preventive actions (CAPAs). In addition, your firm frequently failed to investigate these laboratory incidents as "OOS results," as specified by your own procedures. Several laboratory incidents without conclusive laboratory root causes lacked sufficient or no manufacturing investigations.

For example, your firm initiated a laboratory incident in which test results from two sample preparations of a stability sample for **(b)(4)** crude failed to meet specification limits for an "unknown peak." Your firm retested these sample preparations in their original vials and in

new sample vials. The results of all four retests were also OOS for an "unknown peak." Subsequently, you performed a third test with fresh sample preparations and after receiving passing results, your firm invalidated all earlier test results.

Your investigation concluded that the unknown peaks "could be due to sample solution contamination during preparation." However, the investigation lacked scientific and thorough root cause analysis, failing to identify the contaminant, its origin, or the cause of its presence within your samples. Because you did not determine a definitive laboratory error, your investigation should have included a manufacturing investigation. Additionally, your corrective action of providing "refresher training for personnel on good laboratory practice" contradicted the investigation's own initial finding that the analyst was trained and qualified to perform the HPLC test according to your procedure.

We note that this batch of **(b)(4)** remains within U.S. distribution and is only one example out of numerous inadequate investigations observed during our inspection.

In your response, you provided updated procedures and a risk assessment regarding the investigations identified by our investigator, concluding that the laboratory incidents posed no risk to patients and had no impact on product quality. However, your response contains inconsistencies. For example, you state that you reviewed the incidents and concluded that "none of the batches were released to market by repeating the analysis using a new sample solution preparation." However, you also provided summarized data tables with column headers labeled "justification for repeat analysis using new sample solution preparation." Your response is inadequate. Your response lacked evidence that your firm has remediated your systems to better evaluate whether suspected laboratory causes are valid and investigate potential manufacturing causes where laboratory errors have not been clearly established.

Inadequate investigations can result in unidentified root causes, ineffective CAPAs, and recurring problems that compromise your ability to manufacture safe and effective APIs.

Failure to ensure that all specifications, sampling plans, test procedures are scientifically sound and appropriate to ensure that your raw materials, intermediate and API, conform to established standards of quality and purity.

Your firm tests your raw materials, starting materials, and finished APIs using methods developed in-house. However, your firm failed to validate (or verify if compendial testing is used) multiple test methods that you use.

In your response, you commit to validating and/or verifying your test methods. You provided an example of a newly completed method validation for a starting material used in the production of **(b)(4)** API. However, the validation report lacks adequate data to demonstrate that the method is appropriately validated for its intended use, including insufficient robustness, precision, suitability, and other testing parameter studies.

Test methods must be validated to show they are suitable for their intended use or verified to show at least equivalence with United States Pharmacopeia (USP) compendial methods.

Failure to ensure that all specifications and test procedures are scientifically sound and appropriate to ensure that your APIs conform to established standards of quality and purity.

You failed to establish that your analytical test methods are appropriately validated and suitable for use in API release testing. For example, in 2024 your firm shipped **(b)(4)** lots of tirzepatide API (about **(b)(4)** total weight) to the U.S. market without completing analytical method validation for assay and related substances by high-performance liquid chromatography, high molecular weight aggregates by size-exclusion chromatography, and amino acid ratio by high-performance liquid chromatography. Furthermore, in 2025, your firm shipped **(b)(4)** lots of tirzepatide API drugs (about **(b)(4)** total weight) without completing method verification for the bacterial endotoxin test.

FDA is also concerned that your analytical method validation for tirzepatide API, specifically for related substance test (R-VTP-TP-11-009-024), is not adequate. The test method validation data you provided indicates poor resolution, overlapping peaks, and absence of structural identification for **(b)(4)** specified impurities. lack of comparative approach using multiple, orthogonal, high-resolution analytical methods for peptide-related impurity characterization. Your microbial limit enumeration test (R-VTP-TP-04-001-2025) validation data includes inconsistencies. For example, your test data for *Pseudomonas aeruginosa* are shown twice, and data for *Bacillus subtilis* is missing.

In your response, you acknowledge that your semaglutide and tirzepatide API drugs are in the development stage and full validation of all analytical methods has yet to be completed. You also acknowledge deficiencies in your product release procedure and failure of your quality system processes to identify and correct these non-compliant practices in a timely manner.

Your response is inadequate. Although you intend to implement a new procedure requiring your certificates of analysis to contain a statement of "Only for R&D use purpose" for "developmental drug products," you did not mention any stipulations on the acceptable quantity to be released for R&D use. Based on your invoice and shipping documents, the quantity of API drugs (as much as **(b)(4)**) shipped into the U.S. is inconsistent with quantities typically used for research and development purposes.

Failure of your quality unit to exercise its responsibility to ensure that APIs manufactured at your facility are in compliance with CGMP and failure to maintain complete traceability of APIs in commercial distribution.

Your firm is a manufacturer of peptide APIs, including Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist APIs. FDA investigators observed that your firm lacked adequate quality unit (QU) oversight for the receipt of materials, repackaging, relabeling, and related controls

for APIs. Specifically, there is no quality unit approved procedure governing the repackaging and relabeling operations for APIs sourced from external manufacturers prior to distribution to the U.S. market. For example:

- On (b)(4), your firm purchased semaglutide API (batch (b)(4)) from (b)(4), a supplier that was not on your approved supplier list. You repackaged and relabeled this batch without documentation and created a new labeled batch number, CP-030-20250711. Furthermore, on the label of the container you identified your firm, "Harbin Jixianglong Biotech Co. Ltd.," as the manufacturer of API rather than (b)(4), the firm from which you purchased the API. You also changed the manufacturing date of the API from (b)(4) to July 25, 2025, and the retest date from to (b)(4) to July 24, 2027, without appropriate supporting data. This GLP-1 API was distributed to the U.S. on August 23, 2025.
- On (b)(4), your firm purchased semaglutide API (batch (b)(4)) from (b)(4), another supplier that was not on your approved supplier list at time of purchase and release. You repackaged and relabeled this batch without documentation and created a new labeled batch number, CP-030-20250911. You changed the manufacturing date of the API from (b)(4) to September 25, 2025, and the retest date from (b)(4) to September 24, 2027. This GLP-1 API was distributed to the U.S. on October 3, 2025.

We note that on September 5, 2025, FDA implemented the Green List of Import Alert 66-80 to help address GLP-1 API drugs offered for import into the United States that appear to be adulterated or misbranded. As part of this Import Alert, GLP-1 API drugs from facilities not on the Green List would be subject to detention without physical examination upon import into the United States. Your firm was added to the Green List on September 5, 2025, based upon previously provided quality information.

However, your firm purchased GLP-1 API (semaglutide) from (b)(4), a facility that is not on the Green List of IA 66-80. You then labeled the GLP-1 API as manufactured by your firm and shipped this batch to the United States, even though it was not manufactured by a facility on the green list. FDA is concerned that identifying your firm and not the actual manufacturers may have been an attempt to circumvent safeguards associated with IA 66-80 and may pose a risk to consumers of receiving substandard GLP-1 APIs.

On February 10, 2026, FDA held a teleconference with you recommending you consider removing the two relabeled batches of semaglutide API drugs currently in distribution from the U.S. market. At the teleconference meeting, you agreed to voluntarily recall the two batches of semaglutide API drugs in current distribution in the United States.

We acknowledge that on February 19, 2026, you initiated a voluntary recall of the two semaglutide API batches distributed in the United States.

Additionally, during the inspection, our investigators discussed with your firm your decision to release and distribute at least (b)(4) batches of tirzepatide API to the U.S. market prior to

the completion of stability studies to support the (b)(4) retest date. Your firm did not have an adequate written scientific justification to support the tentative expiration date applied to these lots before distribution.

In your response, you state that due to high demand of semaglutide API in the U.S., you "occasionally purchased the product externally for resale." You acknowledge lacking appropriate procedures for the release of externally purchased products and lacking batch records for the repackaging and labeling operations.

Your response is inadequate. Although you commit to prohibiting the sale of externally procured products moving forward, you failed to address actions to be taken on the two distributed semaglutide API batches in the U.S market.

Failure to ensure that water used in the (b)(4) manufacturing steps of a non-sterile API intended for a sterile drug product is monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

You manufacture GLP-1 APIs that were imported into the United States. These GLP-1 APIs are intended for use in sterile injectable drug products. Your firm failed to ensure that the **(b)(4)** water you used in the **(b)(4)** manufacturing steps of your APIs was suitable for its intended use. For example, your non-sterile semaglutide and tirzepatide API are intended for sterile injectable drug products, and your **(b)(4)** water system has not been evaluated for the absence of objectionable microorganisms. There is no indication that your **(b)(4)** water was tested for endotoxin during manufacturing processing. Furthermore, you failed to conduct sampling and microbial testing of the **(b)(4)** water you manually transported and stored for use in the **(b)(4)** manufacturing process of your APIs.

(b)(4) water must be suitable for its intended use and routinely tested to ensure ongoing conformance with appropriate chemical and microbiological attributes. Routine and representative monitoring of microbial counts and identification of contamination in the system and at the point of use are integral to maintaining a state of control and the suitability of water used in manufacturing operations.

In your response, you acknowledge your failure to perform a risk assessment of objectionable microorganisms and your resulting failure to evaluate the requirements for controlling objectionable microorganisms in your **(b)(4)** water system. You commit to establishing a microbial identification strategy and to adding *E. coli* testing for both the **(b)(4)** water system monitoring and to the API specification. Your response is inadequate. You did not include monitoring of additional objectional organisms as required by the United States Pharmacopeia (USP) monograph for **(b)(4)** water.

Failure to validate and verify the suitability of analytical methods.

Based on the records and information you provided, your firm failed to perform test method validation or verification for each test method used for drugs distributed to the United States.

Test methods must be validated to show that they are suitable for their intended use or verified to show at least equivalence with United States Pharmacopeia (USP) compendial methods. Method validation and verification are necessary to support reliable determinations of identity, strength, quality, purity, and potency of drugs. Without evaluating the validity of methods, you lack the basic assurance that the data provided to customers were an accurate reflection of pharmaceutical product quality and safety.

Failure to demonstrate that water used in the manufacture of your API is suitable for its intended use.

Based on the records and information you provided, you failed to demonstrate that your **(b)(4)** water system is adequately monitored to ensure that it consistently produces water suitable for use in the manufacture of APIs intended for further processing into sterile drug products.

Your **(b)(4)** water system must be adequately designed and properly maintained to minimize and control the potential for contamination. It must be suitable for its intended use and routinely tested at an adequate frequency to ensure ongoing conformance with appropriate chemical and microbiological attributes.

Failure to prepare and use master production and control records.

Your master batch record for **(b)(4)** lacked critical processing information necessary to ensure consistent manufacturing and product quality. For example, **(b)(4)** step **(b)(4)** lacked time limits; **(b)(4)** step **(b)(4)** did not specify the quantity or weight of the material to be **(b)(4)**; and **(b)(4)** step **(b)(4)** lacked time limits for **(b)(4)** the **(b)(4)**.

Without these specific parameters, you cannot adequately monitor and analyze both intra-batch and inter-batch variations to ensure manufacturing processes remain in a state of control.

In your response, you describe revisions to production records for the **(b)(4)** station. Your response is inadequate because it is limited to your updates to **(b)(4)** processes. Your response does not address updates to processes for other drugs such as **(b)(4)**. Additionally, your response lacks a historical review of batch records to look for any major process deviations.

(b)(4) cross contamination

Additionally, we observed deficient separation between **(b)(4)** and **(b)(4)** operations that creates significant risk of cross-contamination between **(b)(4)** and **(b)(4)** drugs. Your firm not only manufactures **(b)(4)** which are **(b)(4)** drugs, but your firm has also manufactured and shipped **(b)(4)** to the United States. We note that you have not manufactured **(b)(4)** for the United States since 2019, but during the 2025 FDA inspection you informed the investigator that you may resume manufacturing and shipment of **(b)(4)** to the United States in the future. We are concerned about **(b)(4)** cross contamination in drugs you may manufacture in the

future. In response to this letter, commit to not distributing **(b) (4)** to the United States unless adequate separation has been put in place.

Failure to ensure that materials are handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

Your firm did not adequately prevent contamination of materials and intermediates. For example, you stored bags of raw materials outside your facility without adequate protection. Our investigators observed multiple bags of material, containing API, that were open and exposed to the environment. These bags were observed adjacent to an area undergoing apparent construction, an activity which may generate airborne dust and debris. Moreover, when your firm prepared a fresh solution of **(b)(4)**, our investigators observed that it was visibly contaminated with unidentified brown particulate matter on the surface.

Your response states that you have moved the storage location of **(b)(4)** and that you have developed a new procedure for preparing **(b)(4)** solutions in a **(b)(4)**, rather than in open barrels, as observed during the inspection. Your response is inadequate in that your response fails to identify or provide a comprehensive description of the current storage conditions of materials. Moreover, your response fails to comprehensively evaluate your material storage practices. You do not address whether **(b)(4)** or any other materials and intermediates remain stored outside without adequate protection. Additionally, your response fails to identify the source of the contamination observed or provide any evidence that improperly stored materials were not adversely affected by their storage conditions.

The introduction of undesirable foreign matter into a raw material, intermediate, or API during production may adversely affect API quality. It is essential that API manufacturers take appropriate measures to prevent such contamination.

Failure to establish an impurity profile for identified and unidentified impurities and failure to ensure all test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and purity.

You failed to conduct a comprehensive evaluation of your manufacturing processes to identify potential impurities. For example, you did not validate your method for testing for organic impurities in **(b)(4)** API, nor did you have a specification for these impurities. Chromatograms from your unvalidated method showed unknown, unintegrated impurities that were not quantified. As a result, these peaks were not fully considered when making your release decisions.

Additionally, you failed to determine the suitability of each secondary reference standard against a primary reference standard. For example, you continued to use your 2021 standard for **(b)(4)** that was never qualified against an official reference standard.

In your response, you state that you manufactured API as per the United States Pharmacopeia (USP) monograph and therefore did not test for impurities. Your response further states that

you identified and synthesized potential impurities, and you commit to developing and validating an analytical method for organic impurities. This is unacceptable, as establishing an impurity profile for your API is expected under CGMP. Furthermore, your response is inadequate in that it fails to demonstrate whether released batches will meet your general specification for related substances, particularly given that your retrospective analysis includes up to **(b)(4)** unknown impurities.

Manufacturers are expected to establish complete impurity profiles for each API as part of the process validation effort. You are responsible for developing and using suitable methods to detect impurities when designing, and making changes to, your manufacturing processes. If you detect new or higher levels of impurities, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.

Failure to test the identity of each batch of incoming production material and appropriately qualify suppliers to rely upon their Certificate of Analysis.

You failed to conduct an identity test on each lot of raw material used in the manufacture of your API. You instead relied on the certificates of analysis (COAs) from your supplier without adequately qualifying them.

For example, you accepted **(b)(4)** raw material without performing identity testing or performing vendor qualification. Your firm justified this lack of material testing by stating **(b)(4)**, which you stored outside your facility in open bags, was "**(b)(4)**." Moreover, you had not established an appropriate procedure for specification requirements of raw materials.

Your response discusses qualifying a new vendor for **(b)(4)** and develops a new procedure for setting raw material specifications. Your response is inadequate in that it fails to perform a retrospective analysis of materials that you accepted solely based on COAs. It also fails to address your practice of allowing some materials to be accepted based solely on COAs. Without adequate testing, there is no scientific evidence to assure that your raw materials conform to appropriate specifications before release.