Subpart I - Laboratory Controls

(21 CFR 211.160 – 211.176)

211.160 General requirements.

211.165 Testing and release for distribution.

211.166 Stability testing.

211.167 Special testing requirements.

211.170 Reserve samples.

211.173 Laboratory animals.

211.176 Penicillin contamination.

Your firm failed to document at the time of performance required laboratory control mechanisms (21 CFR 211.160(a)).

Your laboratory control data was not recorded contemporaneously. Five blank preventative maintenance documents were discovered during the inspection that had been pre-signed and dated to January 9, 2025, in the "Performed by" section. Additionally, your lab manager was observed on August 14, 2025 signing and backdating spectrometry analysis reconciliation records to March 6, 2025. The non-contemporaneous recording of CGMP information is a repeat observation that has been cited in multiple FDA inspections.

In your response, you state that you suspended the supervisor observed backdating documents, commit to performing a third-party review of the extent of the backdating practices, and commit to re-training staff on procedures.

Your response is inadequate. Your response does not include an assessment or commitment to determine the extent of documentation deficiencies throughout your firm and their impact on the integrity of data you provide to drug manufacturers. You also do not propose any global actions to address the data integrity culture at your firm, identify the root cause of continued documentation and data integrity deficiencies, implement adequate controls, or create an environment that prioritizes the handling of data with integrity.

Your customers rely on the integrity of your laboratory data to make decisions regarding drug quality. It is important to maintain strict control ensuring that all laboratory data is retained and that any additions or modifications of information are authorized and appropriately documented.

You lacked appropriate sampling and testing to ensure the (b)(4) water used as a component in your drug products is suitable for the intended use, including in drug products intended for

wound treatment in children. Specifically, you did not perform adequate testing for bacteria, fungi, and objectionable microorganisms on your (b)(4) water (e.g., Burkholderia cepacia complex (BCC), Pseudomonas species, etc.). In addition, neither of your test methods have been validated to demonstrate that they are equal to or superior to the compendial methodology. For example, you used (b)(4), a (b)(4) based microbiological test method, but you did not demonstrate that it was equivalent to or better than USP <62>. Your sampling plan was also not representative of daily use in manufacturing; it relied on a (b)(4) sampling point, despite your having (b)(4) points of use, vessels, and stages of treatment.

(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 is integral to ensuring oversight of ongoing state of control and suitability of water for use in manufacturing operations.

Inadequate design, control, and/or maintenance of (b)(4) water systems have led to contamination with BCC and other water-borne opportunistic pathogens.

You lacked adequate controls to assure the reliability of microbiological testing results. For example:

A. Numerous non-viable dark particles were observed in **(b)(4)** plates used for microbiological analyses in your laboratory.

B. Non-viable dark particles were observed on filter **(b)(4)** used for **(b)(4)** microbiological testing.

C. Media plates prepared in-house did not consistently possess smooth surfaces needed to ensure maximum contact of test articles to facilitate the growth of any microbiological organisms present.

D. Analysts did not consistently ensure filter **(b)(4)** on media plates during microbiological testing needed to ensure maximum contact of filter **(b)(4)** to facilitate the growth of any microbiological organisms present.

In your response, you indicate you discontinued use of, and discarded, the implicated filter **(b)(4)** lot associated with the observed particulate matter and are attempting to identify an alternate vendor. You also performed a retrospective review of **(b)(4)** testing data, and you do not identify any similar instances of air bubbles being observed during testing. You conclude any incidence of failing to ensure filter **(b)(4)** on media plates during testing are "rare" and do not impact product quality.

Your response is inadequate. You do not holistically assess microbiological laboratory conditions and practices and their impact on the reliability of microbiological test results. Your retrospective review protocol to identify instances of **(b)(4)** filter **(b)(4)** during testing is

insufficient as it relies on documentation of events that were not being recorded by your analysts. Additionally, the conclusion of the retrospective review stating there was no impact on product quality lacks scientific justification, in that contact between the filter **(b)(4)** and the media is essential for the growth and identification of any microbiological organisms on the filter **(b)(4)**.

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In your response, you state that you suspended the supervisor observed backdating documents, commit to performing a third-party review of the extent of the backdating practices, and commit to re-training staff on procedures.

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Your customers rely on the integrity of your laboratory data to make decisions regarding drug quality. It is important to maintain strict control ensuring that all laboratory data is retained and that any additions or modifications of information are authorized and appropriately documented.

Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

You failed to appropriately establish and validate your gas chromatographic (GC) method for assay testing of **(b)(4)** in your finished drug products. Also, you failed to validate your GC method for determining **(b)(4)** and volatile impurities in your **(b)(4)** raw material. In addition, you failed to test your **(b)(4)** raw material for the presence of **(b)(4)** and volatile impurities.

In your response, you state that you will discontinue using the unvalidated methods and intend to establish and validate new GC testing methods. You also state your firm will implement **(b)(4)** testing for your **(b)(4)** raw material and conduct impurity testing for every lot of **(b)(4)** per your updated release requirements.

Your response is inadequate because you failed to conduct a risk assessment evaluating the impact of using unvalidated methods and did not address testing of finished product retains that may have been manufactured using untested or inadequately tested raw materials.

Analytical methods must be validated to demonstrate they are suitable for their intended use and equivalent or better than applicable United States Pharmacopeia compendial methods. Verifying the accuracy, sensitivity, specificity, and reproducibility of your test methods is essential to ensuring that manufactured drug products meet established specifications for chemical and microbial attributes.

Your firm lacked appropriate spore population verification on in-house prepared biological indicators (BIs) used in your **(b)(4)** sterilization **(b)(4)** process. You used these BIs for verifying sterilization effectiveness and as a batch release specification for **(b)(4)** drug products.

You validated your method for preparing BIs for your **(b)(4)** process in 2015 and included a target specification for **(b)(4)** spores of **(b)(4)** colony forming units (CFU). However, you have failed to perform quantitative verification of the spore population for these BIs since the initial validation. Instead, your firm has relied on a combination of vendor certificates for the initial spore count, theoretical calculations, and qualitative (growth/no growth) testing after **(b)(4)** with the final prepared BIs to evaluate sterilization effectiveness. Your procedure for preparing BIs states that population verification is not required because the preparation method was validated. However, validation of a preparation method does not eliminate the need for ongoing verification.

In your response, you state that you have subsequently performed verification studies on recent BI preparations, and you commit to implementing ongoing verification. You also state that there is no impact to finished products because your **(b)(4)** parameters are set to ensure the reproducibility of the **(b)(4)** process.

Your response is inadequate because you did not assess the impact of the lack of quantitative verification of your BIs. Your assertion of **(b)(4)** process reproducibility assumes the BIs consistently contained adequate spore populations, which you have not demonstrated.

Without quantitative verification, you cannot determine whether "no growth" results after **(b)(4)** are due to an effective sterilization cycle or are because the BIs are lacking sufficient viable spore population.

You failed to demonstrate that your sample preparation methods are suitable for testing drugs or to account for how these methods could affect test results. For example, you use **(b)(4)** to prepare samples of your **(b)(4)** tablets and **(b)(4)** tablets for high-performance liquid chromatography analysis. However, **(b)(4)**, which can lead to inaccurate results showing OOS levels for **(b)(4)** content.

In your response, you acknowledge that you did not fully meet the test method validation requirements, and that you will review and re-validate **(b)(4)** of your test methods assaying for **(b)(4)** in **(b)(4)** of your formulations. You commit to updating your analytical method validation master plan to incorporate all current test method validation requirements. You also commit to reviewing all other test methods used to assay your other OTC drug products.

Your response is inadequate in that it did not fully evaluate the scope of this deficiency and the impact to product quality. You did not commit to a retrospective review and risk assessment for all test results generated using these methods. Additionally, you have not established interim controls to use during the review and validation of your test methods.

Your firm failed to demonstrate that your test methods were appropriate to assure that your product conforms to appropriate standards of identity, strength, quality, and purity. For example, your firm performs assay for **(b)(4)** using a **(b)(4)** method. The data you provided to support equivalency of the **(b)(4)** method to the USP compendial method consisted of assay results for **(b)(4)** lot of material tested by **(b)(4)** third-party laboratories. A protocol or report describing the **(b)(4)** method and its validated state, or criteria for determining its equivalency with the USP method, was not provided. Additionally, you have not adequately qualified the third-party laboratories used to perform your analysis.

In your response, you stated that you would cease use of the **(b)(4)** method until its equivalence to the compendial method is scientifically demonstrated.

Your response is inadequate because it did not evaluate the distributed batches on which you used the **(b)(4)** method for your **(b)(4)** assay test.

Test methods must be validated to show that they are suitable for their intended use and are equivalent to or better than applicable USP compendial methods. The reproducibility of your test methods is essential to determine if your drug products meet established specifications.

Your firm failed to demonstrate that your microbiological test methods were appropriate to assure your drug products and components conform to appropriate standards of quality and purity. Specifically, you failed to conduct growth promotion testing of your microbiological media to assure suitability before use in release and stability testing of your drug products. Additionally, you lacked appropriate sampling and testing to ensure **(b)(4)** used as a component in your drug products is suitable for its intended use as you did not perform testing for *Burkholderia cepacia complex* (BCC).

In your response, you acknowledged that your firm accepted media growth promotion testing solely based on the supplier's certificate of analysis (CoA) without independent verification. You also acknowledged that your firm did not perform suitability testing and did not evaluate your **(b)(4)** system for BCC. Your firm committed to using a qualified third-party laboratory to verify the quality of growth media and to perform suitability testing, as well as initiate sampling and testing of your **(b)(4)** system for BCC. Your response is inadequate. Notably,

your response stated that a review of internal microbial limit testing data from recent years indicates that microbial detection has been achievable, demonstrating the effectiveness of the current testing process. However, as noted in this letter, your internal microbial limit testing is flawed.

The ability of microbial testing methods to detect objectionable microorganisms in the presence of each drug product must be established. Results generated using unverified or unvalidated methods may put consumers at risk.

(b)(4) is used in the formulation of your **(b)(4)** products and cleaning of production equipment. Your testing and specifications of your **(b)(4)** are inadequate. You did not test samples of **(b)(4)** for all significant quality attributes, including **(b)(4)**. You also have not established suitability of test methods, including evaluating whether your drug product formulations intrinsically inhibit microbiological growth during bioburden testing.

Your response is inadequate. We acknowledge your commitment to implement **(b)(4)** testing of **(b)(4)** samples. However, in your response to this violation and several others you noted that the basis of your procedures is to comply with local regulatory requirement(s) despite manufacturing drug products intended for distribution to the United States. It is incumbent upon your firm to ensure it complies with all applicable U.S. statutory and regulatory requirements prior to distributing drug products to the U.S. market.

You also commit to revalidate your **(b)(4)** system over a period of **(b)(4)** and determine whether you need to adjust your routine sampling schedule based on the results. You currently test the **(b)(4)** loop **(b)(4)**. You do not provide scientific justification for limiting the validation of your **(b)(4)** system to a **(b)(4)** period or for your sampling schedules for the **(b)(4)** loop **(b)(4)**.

We acknowledge your commitment to conduct "bioburden suitability studies" on bulk samples to assess any potential growth inhibition of the drug products. However, you do not explain how these studies will be performed, nor do you commit to provide this information to FDA in a future response.

Appropriate bioburden controls must be implemented to provide assurance that your subsequent terminal sterilization processes will be successful.

Your firm lacked appropriate testing to ensure finished drug products conform to appropriate standards of identity, strength, quality, and purity. For example, the United States Pharmacopeia (USP) monograph for (b)(4) suppositories includes specific testing for identification and (b)(4) determination, but your finished product release specifications did not include these required tests. Your firm manufactured and distributed approximately (b)(4) batches of (b)(4) suppositories since March 2022 without adhering to USP testing standards. Additionally, your finished product release specifications

for (b)(4) suppositories did not include the specific identification testing required in the USP monograph.

You failed to establish that your test methods and specifications are scientifically sound and appropriate or that they are equivalent to or better than the current USP compendial methods.

In your response, you acknowledge comparing your product specifications against USP and CGMP requirements to identify testing gaps for remediation. You then revised your product specifications to meet analytical requirements and shared the updated specifications with your third-party laboratories. You also state you are implementing a "risk-based confirmatory testing plan across relevant product lines."

Your response is inadequate. You fail to provide an adequate timeline for transferring testing to contract laboratories. Additionally, you propose to continue risk-based retroactive testing in-house despite acknowledged testing deficiencies. Furthermore, you continue manufacturing and releasing products without having fully remediated your laboratory deficiencies.

You lacked appropriate sampling and testing to ensure your drug products conform to appropriate standards of identity, strength, quality, and purity. For example, you failed to establish adequate procedures for finished drug product sampling to ensure adequate representation of each batch. Also, there were multiple instances where required finished drug product samples were either not taken or taken but not appropriately tested.

Furthermore, your firm failed to demonstrate that your microbiological test methods were appropriate. Specifically, you could not provide evidence to demonstrate method suitability for microbiological tests used to test samples from your water system and finished drug products.

In your response, you state that the laboratory technician pulled samples primarily based "by memory" and that you will send retains for testing. You also state your "investigation is underway" and due to resource issues, you will address this after implementing related CAPA regarding the microbiological testing deficiencies.

Your response is inadequate. You do not provide sufficient detail or adequate evidence of corrective actions (e.g., protocol or procedure). You also do not provide a timeline for verification of the methods or describe your plans for testing in the interim. Furthermore, you do not address whether a retrospective impact assessment would be performed for previously distributed drug products that are still within expiry.

The ability of microbial testing methods to detect objectionable microorganisms in the presence of each drug product must be established and validated. Results generated using unverified or unvalidated methods may put consumers at risk.

During our inspection, we observed the preparation and reading of bacterial endotoxin tests and identified numerous deficiencies:

- Failure to completely discharge the micropipette solution during preparation of water for injection samples, which may compromise the accuracy and reproducibility of the test results.
- Transfer of gel-clot sample tubes from the incubator to the waste container in a single rapid motion during microbiological analysis, without the crucial pause required to inspect the firmness of the gel for endotoxin detection.
- The analyst responsible for the (b)(4) verification of the gel-clot assessment was unable to adequately observe or verify the process due to the primary microbiologist's rapid assessment. Despite this basic deficiency, the secondary analyst signed off on the verification.
- Inadequate documentation practices when recording sample results of bacterial endotoxin tests for water for injection, including non-contemporaneous documenting of negative sample results and assigning a passing result to a positive control sample prior to the actual observation and confirmation of the result.

In your response, you state that you revised various procedures, provided associated training, retested reserve samples of potentially impacted drug products, and purchased new equipment to increase laboratory automation.

Your response is inadequate due to its limited scope, which primarily addressed the specific deficiencies identified during the FDA inspection. You did not conduct a comprehensive evaluation to determine if similar deficiencies exist in other laboratory operations or address additional opportunities for laboratory equipment automation.

It is imperative that your organization conducts a more thorough and systemic review of all laboratory processes, testing methodologies, equipment capabilities, and documentation practices to ensure compliance with CGMP and prevent recurrence of similar issues in the future.

Your firm failed to perform method validation (or verification, as appropriate) of test methods to ensure they were suitable for their intended use. Your senior leadership confirmed multiple test methods used for incoming API and drug product testing of quality attributes, such as **(b)(4)** content, identification, and specific rotation, have not been validated, verified, or appropriately transferred.

In your response, you provide a retrospective gap assessment evaluating the adequacy of your method validation/verification studies for API and drug product test methods for the U.S. market. You also acknowledge certain methods had not been validated or verified, and that you have already completed some of the pending studies. The response includes planned completion dates for remaining validation/verification studies (May 31, 2025 for API methods; April 30, 2025 for finished drug products). Additionally, you commit to perform an

impact assessment of the drug products distributed to the U.S. market after completion of relevant method validation/verification studies. We acknowledge you completed an interim impact assessment for all drug products in the U.S. market.

Your response is inadequate. Your gap assessment does not adequately address the lack of reference to method validation or verification studies for all appropriate methods, such as your in-house **(b)(4)** testing and in-house elemental impurities testing for **(b)(4)** tablets USP **(b)(4)** mg and **(b)(4)** mg. Also, your interim impact assessment does not scientifically justify the reliability of your test results in the absence of appropriate method validation/verification studies. System suitability controls and calibration controls for test methods are not an adequate substitute for method validation/verification studies.

Method validation and verification studies are necessary to support reliable determination of identity, strength, quality, purity, and potency of drugs. Without evaluating the validity of methods, you lack the basic assurance that your laboratory data accurately reflects drug product quality.

Your firm failed to demonstrate that your microbiological test methods were appropriate to assure that your product conforms to appropriate standards of identity, strength, quality, and purity. Specifically, you could not provide evidence of method suitability for microbiological testing performed by your third-party laboratory. The ability of microbial testing methods to detect objectionable microorganisms in the presence of each drug product must be established.

In your response, you provide the documentation from your third-party laboratory showing that system suitability has been conducted on all liquid drug products to ensure the recovery of any objectionable organism in your finished product.

Your response is inadequate. The system suitability protocols for the methods specified in USP <60> and USP <62> lacked the final step to confirm the identity of the recovered microorganisms in the tests. As a result, the methods were not confirmed as suitable.

Your firm did not establish appropriate specifications or test your sterile over-the-counter (OTC) (b)(4) drug products to monitor impurities at release and throughout expiry. For example:

- You did not perform impurity testing prior to release and during stability for (b)(4).
- You did not establish scientifically justified specifications to monitor impurities during stability testing of drug products containing Naphazoline Hydrochloride or Tetrahydrozoline Hydrochloride active pharmaceutical ingredient (API).

In your response, you state that the impurity limits were established based on your customer's requirements and that no limits were included for release testing. You provide your customer's health hazard evaluation (HHE) which concluded that the presence of Impurity (b)(4) at stability levels of up to (b)(4)% of the labeled (b)(4) content would not

pose any safety risk for those that use the products according to directions. The Agency disagrees with the HHE assessment and concludes that the presence of impurity levels at (b)(4)% may pose a risk to patient safety at the recommended dosage. It is your responsibility to ensure that appropriate specifications are established to monitor impurities throughout the expiry period.

Your response is inadequate. You lack adequate scientific rationale for the current impurity specifications of your drug products. A similar deficiency for the lack of impurity specifications for release and stability testing for (b)(4) API containing products was also identified during the 2016 inspection. However, this deficiency has not been fully addressed to date. Additionally, your risk assessment does not include an evaluation of reserve samples of potentially impacted product batches distributed to the United States.

Drug product batches must be tested for identity, strength, quality, and purity prior to release. Insufficient release and stability testing to appropriately detect impurities in your drug products could potentially impact product quality and patient safety.

Your firm failed to demonstrate that your test methods were appropriate to assure that your product conforms to appropriate standards of identity, strength, quality, and purity. For example, your test methods and specifications are based on the Chinese Pharmacopeia (ChP). However, you failed to establish that these test methods and specifications are scientifically sound and appropriate, or that they are equivalent to or better than the current United States Pharmacopeia (USP) compendial methods.

In your response, you state that you will compare the differences in testing methods for **(b)(4)** and **(b)(4)** between the ChP and the USP, and then conduct validation on the revised methods. However, your response is inadequate because you fail to comprehensively assess the appropriateness of the methods and specifications used during system suitability and for the testing of other components and finished drug products.

Test methods must be validated to show that they are suitable for their intended use, and equivalent to or better than applicable USP compendial methods. The reproducibility of your test methods is essential to determine if your drug products meet established specifications.

Without appropriate test methods, you do not have scientific evidence to support whether your drug products meet their established specifications through their labeled expiry.

During our inspection, we observed the preparation and reading of bacterial endotoxin tests and identified numerous deficiencies:

- Failure to completely discharge the micropipette solution during preparation of water for injection samples, which may compromise the accuracy and reproducibility of the test results.

- Transfer of gel-clot sample tubes from the incubator to the waste container in a single rapid motion during microbiological analysis, without the crucial pause required to inspect the firmness of the gel for endotoxin detection.
- The analyst responsible for the (b)(4) verification of the gel-clot assessment was unable to adequately observe or verify the process due to the primary microbiologist's rapid assessment. Despite this basic deficiency, the secondary analyst signed off on the verification.
- Inadequate documentation practices when recording sample results of bacterial endotoxin tests for water for injection, including non-contemporaneous documenting of negative sample results and assigning a passing result to a positive control sample prior to the actual observation and confirmation of the result.

In your response, you state that you revised various procedures, provided associated training, retested reserve samples of potentially impacted drug products, and purchased new equipment to increase laboratory automation.

Your response is inadequate due to its limited scope, which primarily addressed the specific deficiencies identified during the FDA inspection. You did not conduct a comprehensive evaluation to determine if similar deficiencies exist in other laboratory operations or address additional opportunities for laboratory equipment automation.

It is imperative that your organization conducts a more thorough and systemic review of all laboratory processes, testing methodologies, equipment capabilities, and documentation practices to ensure compliance with CGMP and prevent recurrence of similar issues in the future.

Your firm failed to perform method validation (or verification, as appropriate) of test methods to ensure they were suitable for their intended use. Your senior leadership confirmed multiple test methods used for incoming API and drug product testing of quality attributes, such as **(b)(4)** content, identification, and specific rotation, have not been validated, verified, or appropriately transferred.

In your response, you provide a retrospective gap assessment evaluating the adequacy of your method validation/verification studies for API and drug product test methods for the U.S. market. You also acknowledge certain methods had not been validated or verified, and that you have already completed some of the pending studies. The response includes planned completion dates for remaining validation/verification studies (May 31, 2025 for API methods; April 30, 2025 for finished drug products). Additionally, you commit to perform an impact assessment of the drug products distributed to the U.S. market after completion of relevant method validation/verification studies. We acknowledge you completed an interim impact assessment for all drug products in the U.S. market.

Your response is inadequate. Your gap assessment does not adequately address the lack of reference to method validation or verification studies for all appropriate methods, such as

your in-house **(b)(4)** testing and in-house elemental impurities testing for **(b)(4)** tablets USP **(b)(4)** mg and **(b)(4)** mg. Also, your interim impact assessment does not scientifically justify the reliability of your test results in the absence of appropriate method validation/verification studies. System suitability controls and calibration controls for test methods are not an adequate substitute for method validation/verification studies.

Method validation and verification studies are necessary to support reliable determination of identity, strength, quality, purity, and potency of drugs. Without evaluating the validity of methods, you lack the basic assurance that your laboratory data accurately reflects drug product quality.

Your visual inspection program was inadequate to ensure your sterile injectable drug products were essentially free of visible particulates. For example,

Inadequate Personnel Capabilities

Your probability of detection of particulates using (b)(4) visual inspection was inadequate. You conducted Knapp studies for (b)(4)-mL and (b)(4)-mL vials and demonstrated that personnel were often not able to achieve a probability of detection of 70% for certain critical particulates larger than 150 microns (e.g., dark fibers, light fibers, glass, and (b)(4)).

Inadequate Procedures and Particle Characterization

- You incorrectly categorized critical defects as major and subsequently approved products that passed acceptable quality limits (AQL) testing. After completion of our inspection, you submitted Field Alert Reports for (b)(4) different products manufactured on (b)(4) different product lines where major particulates were recategorized as critical with subsequent AQL failures.
- Your written procedures allowed multiple re-inspections for visual particulates, and you acknowledged that up to (b)(4) re-inspections may be performed in support of batch release.

Furthermore, since 2023 you failed to conduct thorough investigations of trends in product quality glass defects that adequately remediate your visual inspection program and include adequate support for your product quality impact conclusions.

Your response included further details pertaining to a September 2023 deviation for adhered glass defect from a specific vial vendor. Your clarification further acknowledges that your visual inspection program did not adequately assess this defect type.

Although you stopped using the glass supplier and determined the defect had no impact on your batches, your investigation failed to assess the full scope, including the number of vials procured and used, and the impact on your entire product portfolio.

Additionally, adhered glass defects represent a recurring problem inadequately detected by your visual inspection program and not properly addressed through CAPA. For example, you produced (b)(4) batches of (b)(4) in July and August 2024. Your quality unit approved them for release, but later you identified internal adhered glass defects in these batches.

Further, you initiated CAPA 11768 following our inspection to assess 28 AQL failures related to visual inspection. You identified six as needing CAPA improvement.

Your response acknowledges serious deficiencies in your visual inspection program, as you have halted all visual inspection activities and hired a third-party consultant to completely remediate your process. You also commit to retrospective evaluation of all deviations for the previous three years, re-inspection of all retained samples for batches associated with adhered glass AQL failures, procedural changes to particle characterization/classification including performing retrospective trending and review, enhanced personnel training, and limiting the number of re-inspections to (b)(4) prior to batch disposition. Your response omits an assessment of products currently in commerce. You continue to lack assurance that distributed products are essentially free of visible particulate matter.

Visual detection of particulates is a probabilistic process that depends on, among other things, ensuring that visible particulates can be reproducibly detected by trained personnel with appropriate visual acuity. At a minimum, personnel should reliably be capable of detecting particulates of 150 microns or greater at a 70% probability of detection. Furthermore, written procedures governing 100% inspections for visual particulates should clearly define the number of times re-inspection may be performed. You should limit and justify re-inspections. Generally, FDA does not recommend more than one re-inspection in an attempt to release a batch with atypical defect levels1.

Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. Your firm also failed to establish laboratory controls that include scientifically sound and appropriate specifications designed to ensure conformance with appropriate standards of identity, strength, quality, and purity. (21 CFR 211.113(b) and 211.160(b))

Your firm manufactures OTC drug products, including (b)(4) that are labeled as sterile and indicated for use (b)(4). Based on records and information you provided, you did not demonstrate that your (b)(4) are rendered sterile by an appropriate manufacturing process. Your production records do not indicate that you use aseptic processing or (b)(4) sterilization to render your (b)(4) sterile.

Furthermore, you did not provide evidence that you performed sterility testing using a validated method and provided microbiological test results with specification of "total number of bacterial colonies ≤ (b)(4) CFU/g." Sterile products introduced to the U.S. market

must meet United States Pharmacopeia (USP) <71> Sterility Tests. Microbiological contamination of products labeled as sterile could pose a serious hazard to patients.

Failure to establish appropriate product specifications and scientifically sound testing procedures (21 CFR 211.160(b)).

A. Your high-performance liquid chromatography (HPLC) analyses for (b)(4) Assay Content lacked an appropriate determination of system suitability, as outlined in USP <621>, before sample injections. Your quality approved test method, Quality Specification and Operating Procedures for Testing (b)(4), is not scientifically sound in that your Quality Control (QC) analysts are instructed to generate a chromatographic standard curve "(b)(4)." This method of calculation from the standard curve has the practical effect of masking system drift and performance issues that affect the quantitative accuracy of batch-specific test results, because the frequency is conducted "(b)(4)."

In your response, you commit to revising the frequency of establishing a standard curve (linear solution test) from "(b)(4)" to "at the same time with each sample test." However, your response is inadequate because you have not committed to ensuring that standard curves (linear solution tests) performed "at the same time with each sample test" are extended to include gas chromatography (GC), which is used to determine (b)(4) Assay Content.

B. Your firm lacked sufficient controls over GC and HPLC data acquisition systems that are used to test assay label claims for drug products before release. Specifically, Excel worksheets used to perform chromatogram calculations were not retained, and access accounts to the GC and HPLC workstations were shared by job title and were not attributable to the individual analyst. The inspection documented the deletion of several recent Excel spreadsheets that were used to perform suitability and assay calculations. Your QC Supervisor/Manager confirmed that the Excel spreadsheets that were relied upon to generate the finished product quality standards, had not been validated, controlled, retained, or quality verified for data integrity before they were used for product release. Further, this individual was the only analyst who performed testing, yet maintained administrative privileges within the system. When further questioned on this practice, the QC Supervisor/Manager identified that the administrative role was the only primary access point to the Gas Chromatography data acquisition software for OTC (b)(4) product release and stability testing.

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 perform method validation (or verification, as appropriate) of test methods to ensure they were suitable for their intended use. Your senior leadership confirmed multiple test methods used for incoming API and drug product testing of quality attributes, such as (b)(4) content, identification, and specific rotation, have not been validated, verified, or appropriately transferred.

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Your response is inadequate. Your gap assessment does not adequately address the lack of reference to method validation or verification studies for all appropriate methods, such as your in-house (b)(4) testing and in-house elemental impurities testing for (b)(4) tablets USP (b)(4) mg and (b)(4) mg. Also, your interim impact assessment does not scientifically justify the reliability of your test results in the absence of appropriate method validation/verification studies. System suitability controls and calibration controls for test methods are not an adequate substitute for method validation/verification studies.

Your firm failed to demonstrate that your test methods were appropriate to assure that your product conforms to appropriate standards of identity, strength, quality, and purity. For example, your test methods and specifications are based on the Chinese Pharmacopeia (ChP). However, you failed to establish that these test methods and specifications are scientifically sound and appropriate, or that they are equivalent to or better than the current United States Pharmacopeia (USP) compendial methods.

In your response, you state that you will compare the differences in testing methods for (b)(4) and (b)(4) between the ChP and the USP, and then conduct validation on the revised methods. However, your response is inadequate because you fail to comprehensively assess the appropriateness of the methods and specifications used during system suitability and for the testing of other components and finished drug products.

Test methods must be validated to show that they are suitable for their intended use, and equivalent to or better than applicable USP compendial methods. The reproducibility of your test methods is essential to determine if your drug products meet established specifications.

Without appropriate test methods, you do not have scientific evidence to support whether your drug products meet their established specifications through their labeled expiry.

Your high-performance liquid chromatography (HPLC) analyses for (b)(4) Assay Content lacked an appropriate determination of system suitability, as outlined in USP <621>, before sample injections. Your quality approved test method, Quality Specification and Operating Procedures for Testing (b)(4), is not scientifically sound in that your Quality Control (QC) analysts are instructed to generate a chromatographic standard curve "(b)(4)." This method of calculation from the standard curve has the practical effect of masking system drift and

performance issues that affect the quantitative accuracy of batch-specific test results, because the frequency is conducted "(b)(4)."

In your response, you commit to revising the frequency of establishing a standard curve (linear solution test) from "(b)(4)" to "*at the same time with each sample test*." However, your response is inadequate because you have not committed to ensuring that standard curves (linear solution tests) performed "*at the same time with each sample test*" are extended to include gas chromatography (GC), which is used to determine (b)(4) Assay Content.

B. Your firm lacked sufficient controls over GC and HPLC data acquisition systems that are used to test assay label claims for drug products before release. Specifically, Excel worksheets used to perform chromatogram calculations were not retained, and access accounts to the GC and HPLC workstations were shared by job title and were not attributable to the individual analyst. The inspection documented the deletion of several recent Excel spreadsheets that were used to perform suitability and assay calculations. Your QC Supervisor/Manager confirmed that the Excel spreadsheets that were relied upon to generate the finished product quality standards, had not been validated, controlled, retained, or quality verified for data integrity before they were used for product release. Further, this individual was the only analyst who performed testing, yet maintained administrative privileges within the system. When further questioned on this practice, the QC Supervisor/Manager identified that the administrative role was the only primary access point to the Gas Chromatography data acquisition software for OTC (b)(4) product release and stability testing.

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 establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Your firm also failed to conduct appropriate laboratory testing, as necessary, for each batch of drug product required to be free of objectionable microorganisms (21 CFR 211.160(b) and 21 CFR 211.165(b)).

Your firm is a contract testing laboratory that conducts testing of various application and nonapplication drug products for your customers. You failed to conduct appropriate testing to ensure that the results your firm provided to customers were accurate and scientifically sound.

Lack of Adequate Documentation

Your firm lacks significant CGMP documentation for your microbiological testing. For example, you routinely failed to document specific attributes of each test such as:

- equipment number

- sample size
- media batch number
- sample dilutions
- incubation temperatures
- name/signature of performing analyst

According to your personnel, your firm also lacked adequate equipment logs to track usage and maintenance.

Your response is inadequate. You commit to performing a comprehensive review of your testing operations and records. Based on the outcome of the review, your firm plans to update the affected data and test forms. You did not provide specific details on the records, equipment, and data that will be evaluated, nor did you commit to conducting a full retrospective review of test results provided to your customers.

Additionally, you indicate that going forward you will meet standards for laboratory studies. Please note that appropriate regulatory requirements for laboratories conducting testing for drug product manufacturers are 21 CFR parts 210 and 211 and Section 501(a)(2)(B) of the FD&C Act.

Laboratory investigations cannot be performed when systems, procedures, and documentation are deficient.

Complete and accurate records are necessary to ensure that test methods are consistently followed and reproducible. Additionally, complete test records are necessary to reliably conduct record reviews and adequately investigate deviations and drug product failures.

Lack of Appropriate Media Qualification

You lack adequate controls to ensure the reliability of your microbiological testing results. For example, the media used to test your customers drug products was inadequately qualified. You lacked screening for inhibitory properties of your incoming lots of (b)(4).

In your response, you commit to reviewing your tests and methods to identify gaps and implement the appropriate remediation.

Your response is inadequate because you did not commit to pausing testing until assessments are complete, nor did you implement any interim corrective actions. Furthermore, your firm did not provide a plan to re-assess results that have been communicated to customers.

Your firm failed to conduct adequate release testing of all your drug products prior to distribution. Specifically, you did not test your drug products for identity, assay, impurities, or microbiological attributes.

In your response, you state that you are now performing release testing. Your response is inadequate because you failed to adequately detail the tests, methods, and specifications for your over-the-counter (OTC) drug products to ensure your finished products meets appropriate standards prior to release and distribution.

Full release testing, including strength and identity testing of the active ingredient, must be performed before drug product release and distribution. Without adequate testing, you do not have adequate scientific evidence to assure that your drug products conform to appropriate specifications before release.

Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. You also failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.160(b)) and (21 CFR 211.166(a)).

Finished Product Testing

Your finished product testing for release of ophthalmic drug product batches did not include adequate analytical testing to determine the identification or assay of the active ingredient, hydroxypropyl methylcellulose (Hypromellose).

Your response and subsequent updates are inadequate. You commit to updating your finished product specifications. However, you reference an internally-developed, non-specific method for assay (strength) without providing adequate documentation and scientific justification to support its use. In contrast, a method is available in the USP that employs a reference standard and spectrophotometric measurements to determine Hypromellose assay.

Stability Program

Your firm lacked an adequate stability program to support the (b)(4) expiration date. For example:

- Your firm did not establish appropriate tests and specifications for your ophthalmic drug products to monitor the active ingredient identity or assay at release and throughout expiry. Your stability program did not include an adequate test for assay of the active ingredient, hydroxypropyl methylcellulose (Hypromellose). In place of the USP assay, your firm used an in-house method based on loss-on-drying without scientific justification.
- Your firm did not follow your Operational Procedure, Control, Testing, and Release of Drug Products, which requires placement of samples from one commercial batch of each product on the stability program each year, and testing at (b)(4) intervals. Your

2023 batch was delayed in its entry to your stability program and your 2024 testing was not initiated. A similar pattern of non-compliance was noted during your 2018 inspection.

Your response is inadequate. You reference stability studies from batches made in 2013 and 2016 to justify reduced stability testing intervals. You fail to provide a root cause or an adequate CAPA to address the failure to follow your own stability procedure.

Drug product batches must be tested for identity, strength, quality, and purity prior to release. Without sufficient release and ongoing stability testing, defective drug products that may pose a risk to consumers are unlikely to be detected.

Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications designed to assure drug products conform to appropriate standards of identity, strength, quality, and purity. Your firm also failed to have, for each batch of drug product, an appropriate laboratory determination of satisfactory conformance to final specifications for drug products prior to release (21 CFR 211.160(b) and 211.165(a)).

Your firm manufactures various topical over-the-counter (OTC) drug products, including those containing the active ingredient benzoyl peroxide. There is a known degradation mechanism of benzoyl peroxide, under certain conditions, to form benzene, a known carcinogen. Your firm failed to establish scientifically sound and appropriate finished product specifications and failed to conduct benzene testing on your OTC topical drug products prior to release. For example, you manufactured and released at least (b)(4) lots of the (b)(4) 2.5% benzoyl peroxide acne lotion without testing for benzene. FDA laboratory analysis of one lot of (b)(4) 2.5% benzoyl peroxide acne lotion your firm manufactured and distributed yielded excessive benzene levels of more than 20 parts per million (ppm). You failed to ensure that your drug products do not contain unacceptable benzene impurity levels.

During the inspection, you informed our investigator that a retain sample of the FDA-tested lot as well as other lots manufactured of the (b)(4) 2.5% benzoyl peroxide acne lotion were sent to a contract testing laboratory (CTL) to conduct impurity and assay testing.

In your response, you mention that you will use a CTL to conduct benzene testing on the above-mentioned drug product. However, it is not clear if benzene testing will be performed on all lots prior to release. Your response also states that you are not aware of any FDA guideline on benzene testing, but FDA has alerted drug manufacturers of products at risk for presence of benzene that they should be testing those drug products for benzene.

Your response is inadequate because it does not detail any retrospective risk assessments (e.g., the actions that you will take) should any of the lots sent to your CTL for testing yield unacceptable benzene impurity levels. Further, your response lacks information that your CTL is qualified to test your drug products for benzene.

211.165 Testing and release for distribution

Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

You did not ensure drug products manufactured at your facility were evaluated for all critical quality attributes. You did not test **(b)(4)** drug products for identity and strength of the active ingredient **(b)(4)**, and particulate and foreign matter. Additionally, you did not evaluate the preservative content of **(b)(4)** drug product.

Your response is inadequate. We acknowledge your commitment to validate an analytical test method for **(b)(4)** assay and to implement **(b)(4)** assay testing for future batch release and retrospective testing of reserve samples of **(b)(4)** drug products. However, you do not commit to re-evaluate your batch release criteria to identify all critical quality attributes and establish appropriate batch release criteria.

Your firm contract manufactures an over-the-counter **(b)(4)** drug product. You failed to adequately test batches of your finished drug product for the identity and strength of your active ingredient (e.g. **(b)(4)**) before release and distribution. Your specification procedures only discuss appearance, color, and weight checks prior to batch release.

Full release testing, which includes strength and identity testing of the active ingredient, must be performed before drug product batch release and distribution. Without adequate testing, you do not have adequate scientific evidence to assure that drug product batches conform to appropriate specifications before release.

Your firm failed to adequately determine the appropriate laboratory testing necessary for your **(b)(4)** over the counter (OTC) drug products. For example, you did not perform testing for identity and strength of the active ingredients prior to drug product release and distribution. This is a repeat observation from the 2016 inspection.

In your response, you indicate your intent to conduct active ingredient testing for retain samples of batches that have been distributed to the United States and to develop a risk assessment. However, your response is inadequate because you do not propose a comprehensive corrective action and preventive action plan to ensure that appropriate testing is conducted prior to drug product release. In addition, you do not indicate further actions that your firm will pursue for distributed drug products if test results are found to be outside specification.

Full release testing, including strength and identity testing of the active ingredients, must be performed before drug product release and distribution. Without adequate testing, you do not have adequate scientific evidence to ensure that your drug products conform to appropriate specifications before their release.

Your firm manufactures OTC drug products, including **(b)(4)**. Your response to our request for records and other information under section 704(a)(4) indicated that you did not conduct adequate finished product testing on drug products shipped to the United States market.

Testing is an essential part of CGMP to ensure that the drug products you manufacture conform to all pre-determined quality attributes appropriate for their intended use. Drug products must be tested for identity and strength of the active ingredient, prior to release and distribution. Without adequate testing, you do not have adequate scientific evidence to assure that your drug products conform to appropriate specifications before release.

Based on the records and information you provided, you did not demonstrate you conducted adequate finished drug product testing on your drug products before releasing them for distribution.

Full release testing, including strength and identity testing of the active ingredient, must be performed before drug product release and distribution. Without adequate testing, you do not have adequate scientific evidence to assure your drug products conform to appropriate specifications before release.

Your firm manufactures topical over-the-counter (OTC) drug products, including drug products that contain the active ingredient minoxidil. You failed to establish adequate release testing procedures or specifications for your OTC drug products, and accordingly released batches of drug products for distribution without conducting adequate testing to confirm critical quality attributes.

In your response, you state that your finished product testing will be performed by a contract laboratory. Your response is inadequate. You did not describe how you will ensure that your finished products meet appropriate quality standards prior to release. You also did not consider a detailed risk assessment addressing the potential effects of releasing drug product to the market without established specifications to ensure their identity, strength, quality, and purity.

Full release testing, including strength and identity testing of the active ingredient, must be performed before drug product release and distribution. Without adequate testing, you do not have adequate scientific evidence to assure that your drug products conform to appropriate specifications before release.

Your firm failed to adequately determine the appropriate laboratory testing necessary for your **(b)(4)** over the counter (OTC) drug products. For example, you did not perform testing for identity and strength of the active ingredients prior to drug product release and distribution. This is a repeat observation from the 2016 inspection.

In your response, you indicate your intent to conduct active ingredient testing for retain samples of batches that have been distributed to the United States and to develop a risk assessment. However, your response is inadequate because you do not propose a

comprehensive corrective action and preventive action plan to ensure that appropriate testing is conducted prior to drug product release. In addition, you do not indicate further actions that your firm will pursue for distributed drug products if test results are found to be outside specification.

Full release testing, including strength and identity testing of the active ingredients, must be performed before drug product release and distribution. Without adequate testing, you do not have adequate scientific evidence to ensure that your drug products conform to appropriate specifications before their release.

Your firm manufactures OTC drug products, including **(b)(4)**. Your response to our request for records and other information under section 704(a)(4) indicated that you did not conduct adequate finished product testing on drug products shipped to the United States market.

Testing is an essential part of CGMP to ensure that the drug products you manufacture conform to all pre-determined quality attributes appropriate for their intended use. Drug products must be tested for identity and strength of the active ingredient, prior to release and distribution. Without adequate testing, you do not have adequate scientific evidence to assure that your drug products conform to appropriate specifications before release.

Your firm failed to perform appropriate testing on your drug products prior to release for distribution. Your facility management stated to our investigator that testing for identity and strength of each active ingredient prior to release had not been performed for approximately **(b)(4)** batches manufactured for the U.S. market.

Full release testing, including for identity, strength, and purity, must be performed prior to batch release and distribution. Without adequate finished product release testing, you do not have scientific evidence that each batch of drug product conforms to appropriate specifications before release.

In your response, you state that exported products are manufactured using the same process and formulation as domestic products. As a result, the internal quality standards for export products are based on those for domestic sales products, which does not require testing for identity or quantity of active ingredients.

Your response is inadequate. You state that your internal quality standards and operating procedures for export products will be revised to include the identity or quantity of active ingredients. Both identity and quantity of active ingredients testing are required to be performed prior to release. You fail to assess the risk of drugs products that were released to the U.S. market without adequate testing. In addition, you do not discuss your plan to perform validation (or verification, as appropriate) of your test methods.

Your firm failed to adequately test batches of your drug products before release and distribution. You stated your firm does not perform finished product testing.

In your response, you state you contracted a third-party laboratory to perform full release testing, and you implemented finished product specifications, Certificates of Analysis (COAs), and a standard operating procedure (SOP) for identity, strength, purity, and microbial testing.

Your response is inadequate. You do not provide sufficient details about the test methods and specifications you implemented for your over-the-counter (OTC) drug products to ensure each batch of your finished products met appropriate standards before release and distribution. Also, you do not commit to performing retrospective testing of your drug product retains (reserve samples) for batches already distributed in the U.S. market.

Drug product batches must be tested for identity, strength, quality, and purity before release. Without sufficient release testing, defective drug products that may pose a risk to consumers are unlikely to be detected.

Your firm contract manufactures an over-the-counter (b)(4) drug product. You failed to adequately test batches of your finished drug product for the identity and strength of your active ingredient (e.g. (b)(4)) before release and distribution. Your specification procedures only discuss appearance, color, and weight checks prior to batch release.

Full release testing, which includes strength and identity testing of the active ingredient, must be performed before drug product batch release and distribution. Without adequate testing, you do not have adequate scientific evidence to assure that drug product batches conform to appropriate specifications before release.

Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Your firm failed to conduct, for each batch of drug product, appropriate laboratory testing, as necessary, required to be free of objectionable microorganisms (21 CFR 211.165(a) and 211.165(b)).

Your firm failed to adequately test your over-the-counter (OTC) **(b)(4)** drug products for strength (assay) of each active ingredient prior to release and distribution. You also failed to ensure adequate microbiological testing for each batch of your **(b)(4)** and **(b)(4)** drug products prior to release.

Drug product batches must be tested for identity, strength, quality, and purity prior to release. Testing is an essential part of ensuring that the drug products you manufacture conform to all predetermined quality attributes and are appropriate for their intended use. Without adequate testing, you lack basic data to support that each drug product batch conforms to appropriate specifications before release.

In your response, you state that you will develop test methods or identify a contract testing laboratory to ensure product integrity and revise your product release standard operating

procedures (SOPs) to require assay for active ingredients and microbiological testing "clearance."

Your response is inadequate. Because you lack adequate testing of each batch of your drug products, you do not know whether they conform to all appropriate finished product specifications and are suitable for release to consumers.

You released finished drug products without adequate testing. For example, you did not perform adequate microbiological monitoring and chemical testing on your finished drug products. Further, you did not adequately validate the method you use for assay testing your bulk **(b)(4)** containing drug products.

Your response states that you do not "produce any products that are drugs." Your response is inadequate because your drug products are subject to CGMP requirements. Further, your response does not indicate that you will test your finished drug products to ensure they meet appropriate specifications.

You released finished drug products without adequate testing. For example, you did not perform adequate microbiological monitoring and chemical testing on your finished drug products. Further, you did not adequately validate the method you use for assay testing your bulk **(b)(4)** containing drug products.

Your response states that you do not "produce any products that are drugs." Your response is inadequate because your drug products are subject to CGMP requirements. Further, your response does not indicate that you will test your finished drug products to ensure they meet appropriate specifications.

Drug product batches must be tested for identity, strength, and purity prior to release. Testing is essential to ensure that the drug products you manufacture conform to all predetermined quality attributes appropriate for their intended use. Without adequate finished product release testing, you do not have scientific evidence that each batch of drug product conforms to appropriate specifications before release.

Your firm manufactures over-the-counter (OTC) drug products including sterile (b)(4). Based on the records and information you provided, you did not demonstrate that you adequately test your OTC finished drug products prior to release for distribution to the United States.

In your initial response, you state that you test each batch of your finished drug products before release. On June 23, 2025, FDA specifically requested that you provide the test data; however, in response to this request, you failed to provide the requested information to demonstrate that your finished products are tested prior to release.

Full release testing, including for identity, strength, and impurities, must be performed prior to drug release and distribution. Without adequate testing, there is no scientific evidence to assure that your drug products conform to appropriate specifications before release.

Your firm manufactures over-the-counter drug products such as **(b)(4)**. You failed to conduct adequate finished product release testing for each batch of your drug product including, but not limited to, testing the identity and strength of the active ingredient, **(b)(4)**, and testing for objectionable microorganisms.

In your response, you state that you developed and will validate the titration and Fourier-transform infrared spectroscopy test methods, used for the **(b)(4)** assay and identification. You also state that you will investigate microbiological testing options for your finished drug products prior to release.

Your response is inadequate because it lacks sufficient details regarding specific tests for each finished drug batch and fails to include a risk assessment or retrospective review of products released without appropriate testing.

Without adequate finished product release testing, you do not have scientific evidence that each batch of drug product conforms to appropriate specifications before release.

Your firm failed to conduct adequate release testing of all your drug products prior to distribution. Specifically, you did not test your drug products for identity, assay, impurities, or microbiological attributes.

In your response, you state that you are now performing release testing. Your response is inadequate because you failed to adequately detail the tests, methods, and specifications for your over-the-counter (OTC) drug products to ensure your finished products meets appropriate standards prior to release and distribution.

Full release testing, including strength and identity testing of the active ingredient, must be performed before drug product release and distribution. Without adequate testing, you do not have adequate scientific evidence to assure that your drug products conform to appropriate specifications before release.

Your firm manufactures an over-the-counter (OTC) **(b)(4)** drug product. Your firm failed to conduct adequate finished product release testing for each batch of your drug product, including but not limited to, testing the identity and strength of the active ingredient, **(b)(4)** and testing for objectionable microorganisms.

In your response, you state that you developed and validated an updated test method, and updated release specifications, for the labeled active ingredient, **(b)(4)**. You also state that you will perform all appropriate USP <61> and <62> testing for your finished drug products. Your response is inadequate as you did not provide sufficient details regarding the specific tests to be performed for each batch of finished drug product. You also did not consider a risk assessment or retrospective review of products that have been released without appropriate testing.

Without adequate finished product release testing, you do not have scientific evidence that each batch of drug product conforms to appropriate specifications before release.

Your firm manufactures over-the-counter (OTC) **(b)(4)** drug products. You did not test your drug products for the strength of each active ingredient prior to release and distribution. You also failed to conduct adequate microbiological testing for each batch of your OTC **(b)(4)** drug products. For example, your certificates of analysis (COAs) for **(b)(4)** batch **(b)(4)** and **(b)(4)** batch **(b)(4)** lacked active ingredient assay values and results for specified microorganisms.

Full release testing, including for identity, strength, impurities, and microbiological limits, must be performed prior to drug product release and distribution.

Your firm failed to conduct adequate finished product release testing for each batch of your drug products including, but not limited to, testing the identity and strength of the active ingredient, **(b)(4)**, and testing for objectionable microorganisms.

For example, your firm manufactures **(b)(4)**, an over-the-counter (OTC) topical pain relief drug product. The only tests you perform on the finished product are for viscosity, pH, and color. Your firm stated your OTC drug product lacks a final product specification and does not follow recognized standards.

Appropriate testing is an essential part of ensuring that the drug products you manufacture conform to CGMP. Without adequate finished product release testing, you do not have scientific evidence that each batch of drug product conforms to predetermined specifications before release.

Your firm failed to conduct, for each batch of drug product, appropriate laboratory testing, as necessary, required to be free of objectionable microorganisms. Your firm also failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity ((21 CFR 211.165(b) & 21 CFR 211.160(b)).

Your firm manufactures drug products such as **(b)(4)**, intended for **(b)(4)**. You failed to conduct adequate finished product testing for each batch of your drug product. For example, you released your finished drug product **(b)(4)** without testing for critical microbial attributes (e.g., total count, absence of objectionable microorganisms).

Furthermore, you failed to establish scientifically sound and adequate specifications for microbial limits for your drug products. For example, we reviewed your established microbiological limits for total aerobic plate count and note that they are set **(b)(4)** times greater than the United States Pharmacopeia (USP) <61> *Microbiological Examination Of Nonsterile Products: Microbial Enumeration Tests* limit of 10^2 cfu.

In your response, you state that you will conduct the microbial rapid test system validation accordance with USP <1223> *Validation of Alternative Microbiological Methods* requirements and the manufacturer's specifications. You also note that you will verify system suitability for the specific product type and that you will maintain comprehensive raw data documentation for all tested batches.

Your response is inadequate because it lacks sufficient detail regarding tests for each finished drug batch and fails to include a risk assessment or retrospective review of products released without appropriate testing.

Adequate microbial specifications and testing methods to detect objectionable microorganisms in the presence of each drug product must be established. Without testing each batch prior to release, you did not have scientific evidence that all **(b)(4)** drug product batches were free of objectionable microbial contamination.

Your firm did not establish appropriate specifications or test your sterile over-the-counter (OTC) (b)(4) drug products to monitor impurities at release and throughout expiry. For example:

- You did not perform impurity testing prior to release and during stability for (b)(4).
- You did not establish scientifically justified specifications to monitor impurities during stability testing of drug products containing Naphazoline Hydrochloride or Tetrahydrozoline Hydrochloride active pharmaceutical ingredient (API).

In your response, you state that the impurity limits were established based on your customer's requirements and that no limits were included for release testing. You provide your customer's health hazard evaluation (HHE) which concluded that the presence of Impurity (b)(4) at stability levels of up to (b)(4)% of the labeled (b)(4) content would not pose any safety risk for those that use the products according to directions. The Agency disagrees with the HHE assessment and concludes that the presence of impurity levels at (b)(4)% may pose a risk to patient safety at the recommended dosage. It is your responsibility to ensure that appropriate specifications are established to monitor impurities throughout the expiry period.

Your response is inadequate. You lack adequate scientific rationale for the current impurity specifications of your drug products. A similar deficiency for the lack of impurity specifications for release and stability testing for (b)(4) API containing products was also identified during the 2016 inspection. However, this deficiency has not been fully addressed to date. Additionally, your risk assessment does not include an evaluation of reserve samples of potentially impacted product batches distributed to the United States.

Drug product batches must be tested for identity, strength, quality, and purity prior to release. Insufficient release and stability testing to appropriately detect impurities in your drug products could potentially impact product quality and patient safety.

Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Your firm failed to conduct, for each batch of drug product, appropriate laboratory testing, as necessary, required to be free of objectionable microorganisms. Additionally, your firm failed to conduct appropriate laboratory testing to determine whether each batch of drug product purporting to be sterile and pyrogen-free conforms to such requirements (21 CFR 211.165(a) and 211.165(b) and 211.167(a)).

You failed to conduct adequate release testing of all your drug products. For example:

- You did not conduct appropriate laboratory testing, including sterility testing, for each batch of **(b)(4)** drug product that is required to be sterile.
- You did not conduct appropriate laboratory testing of each batch of drug product, such as **(b)(4)**, required to be free of objectionable microorganisms.

In your response, you specify the microbiological media lots used to perform testing are validated. Your response is inadequate. For example, media used, sample size, incubation time and temperatures, and other elements of your test methods are inappropriate. You also do not provide sufficient details as to how you will ensure that your laboratory or your contract testing laboratories will perform adequate release testing on all OTC finished drug products. In addition to compendial methods, additional batch testing may be necessary to fully identify microbes that, based on the intended use of your non-sterile products, may be objectionable.

Moreover, you failed to perform appropriate sterility testing on your **(b)(4)** drug products prior to batch release. It is essential that you conduct sterility testing on **(b)(4)** drug products prior to making batch disposition decisions. Additionally, you do not consider a risk assessment or retrospective review of products that have been released without appropriate testing.

Full release testing, including for identity, strength, and purity, must be performed prior to batch release and distribution. Without appropriate testing, you do not have adequate scientific evidence to ensure that your drug products conform to established specifications before release.

Your firm failed to conduct, for each batch of drug product, appropriate laboratory testing, as necessary, required to be free of objectionable microorganisms (21 CFR 211.165(b)).

Your firm operates as both a contract and own label manufacturer of over-the-counter (OTC) drug products, including **(b)(4)** marketed to **(b)(4)**. Your firm released multiple batches of OTC drug products without performing appropriate microbiological release testing. For

example, on February 4, 2025, you manufactured over **(b)(4)** units of **(b)(4)** (Lot **(b)(4)**) without performing microbiological testing for release. Your quality unit (QU) approved and released this lot on **(b)(4)**, and distributed it to your customer on **(b)(4)**.

In your response you confirmed that you perform microbiological testing only at your customer's request. You also provided a justification memo which concluded "no testing required" for total aerobic microbial count, total combined yeasts/molds, and specified microorganisms based on your products being **(b)(4)**. Your response is inadequate. FDA has encountered recalls for microbial contamination in **(b)(4)** drug products. Your justification memo reveals microbial growth in your drug products. While microbial proliferation risk may be lower, microorganisms can persist in your drug products. Eliminating microbial testing of your drug products is unacceptable. CGMP regulations require written procedures be established to prevent introduction of objectionable microbiological contamination in the manufacture of drug products not required to be sterile.

You failed to ensure adequate microbiological testing for each batch of your drug products before release. For example, you failed to follow your procedure SOP L6082, "Identification of Gram-Negative Rod Bacteria and Yeast," which requires the identification of all gram-negative rods found in your samples. You had not performed the required identification of gram-negative rods recovered from your drug products since January 2025, despite seeing an increase in colony forming units (CFUs) from September 2024 through January 2025.

Testing is essential to ensure that the drug products you manufacture conform to all predetermined quality attributes appropriate for their intended use. Because you lacked adequate testing of each batch of your drug products, you do not know whether they conform to all appropriate finished-product specifications and are suitable for release to consumers.

Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods (21 CFR 211.165(e)).

You failed to adequately validate your alternative rapid microbiological test methods. You use the Neogen Soleris Next Generation System for rapid microbiological testing of your finished drug products (e.g., total aerobic counts, total counts, specified microorganisms) and failed to demonstrate that it was equivalent to or better than United States Pharmacopeia (USP) compendial methods and suitable for its intended use.

You stated that this system was validated by the manufacturer. However, your method did not meet the minimum requirements for adequate identification of objectionable microorganisms and total count quantification.

The microbiological testing methodology uses qualitative pass/fail criteria that do not ensure appropriate quantitative enumeration. The method is inadequate because it does not provide sufficient data on contamination levels, which are essential for trend analysis and evidence-based risk assessment to support quality evaluations and patient safety.

In your response, you acknowledge that you have not validated your alternative rapid microbiological test methods. You state you will fully validate methods used in your alternative rapid microbiological testing within six to eight months.

Your response is inadequate because it fails to address the fundamental gap between qualitative pass/fail criteria and appropriate quantitative enumeration.

Test methods must be validated to show that they are suitable for their intended use and equivalent to or better than applicable USP compendial methods. The reproducibility of your test methods is essential to determine whether your drug products meet established specifications for microbial attributes.

You failed to adequately validate your alternative rapid microbiological test methods. You use the **(b)(4)** system for rapid microbiological testing of your finished drug products (for example, total counts, objectionable microorganisms) and failed to demonstrate that it was **equivalent to or better than United States Pharmacopeia (USP) compendial methods and** suitable for its intended use. For example:

- Your method did not meet the minimum requirements for quantification and adequate identification of objectionable microorganisms.
  o The microbiological testing methodology employed uses qualitative pass/fail criteria that did not ensure appropriate quantitative enumeration. This approach is insufficient because it does not provide adequate quantitative data regarding contamination levels, which are essential for trend analysis and evidence-based risk assessment to support patient safety determinations. This is highlighted in the OOS investigation referenced in the violation mentioned above.
  o You failed to demonstrate that the **(b)(4)** system is appropriate for detecting *Burkholderia cepacia* complex (BCC), a contamination risk in nonsterile **(b)(4)** drug products.
- You stated that this system was validated by the manufacturer, but you failed to verify the manufacturer's validation or perform appropriate validation studies on the instrument installed at your facility.
- The validation studies you provided deviated from compendial methods by excluding challenge organisms and reducing sample volumes without providing adequate scientific rationale.

In your response, you state that your alternative rapid microbiological test methods are adequately validated. You also state that you performed a risk analysis and "found there is a low risk to the end user." Your response does not adequately address how you intend to ensure that your method is validated for its intended use.

Test methods must be validated to show that they are suitable for their intended use and equivalent to or better than applicable USP compendial methods. The reproducibility of your

test methods is essential to determine if your drug products meet established specifications for microbial attributes.

You failed to establish the adequacy of release testing procedures, and you released batches of drug products for distribution without conducting adequate testing to confirm critical quality attributes. For example, you did not use USP chemical and microbiological methods to test incoming drug substance or to test and release finished drug product, nor did you show equivalency or superiority for your alternate in-house methods.

Your response is inadequate. You committed to validate your analytical methods and retest affected batches. However, you did not provide sufficient evidence to demonstrate in-house methods are equivalent or superior to the USP methods. Therefore, your commitment to retest affected batches may not yield reliable and valid results.

Test methods must be validated to show they are suitable for their intended use, and equivalent or better than applicable USP compendial methods. The reproducibility of your test methods is essential to determine if your drug products meet established specifications for assay and microbial attributes.

Your firm is a contract testing lab that analyzes drugs for your customers. You did not use a suitable method to test your client's over-the-counter (OTC) drug products. For example, your method was not verified to be equivalent or better than the United States Pharmacopeia (USP) method used to test multiple OTC) drug products for potential microbial contamination. Your method for Plate Count **(b)(4)** growth media is different in composition to the Soybean-Casein Digest Agar required for plate count methods by USP<61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests. You have not demonstrated your method is equivalent or better than the USP<61> compendial method. Additionally, you failed to perform method suitability for the microbial testing of **(b)(4)** and **(b)(4)** OTC drug products. The **(b)(4)** drug product is intended for **(b)(4)** symptoms in children.

Method suitability testing ensures the method can reliably determine the presence of microbial growth in the drug product. Without evaluating the validity of methods, you lack assurance that the data provided to customers was an accurate reflection of pharmaceutical drug product quality and safety.

In your response you state you "have initiated a comprehensive validation of Test Method STP-002 Microbiological Testing of Raw Materials and Products" and "will conduct a suitability test for each product category."

Your response is inadequate. You do not provide sufficient information to demonstrate that your methods are equivalent or better than the applicable USP compendial methods and suitable for their intended use. In addition, you state you will develop methods for each drug

category; however, you do not provide data supporting your method for each product category is suitable for each individual drug product.

You failed to establish the adequacy of release testing procedures, and you released batches of drug products for distribution without conducting adequate testing to confirm critical quality attributes. For example, you did not use USP chemical and microbiological methods to test incoming drug substance or to test and release finished drug product, nor did you show equivalency or superiority for your alternate in-house methods.

Your response is inadequate. You committed to validate your analytical methods and retest affected batches. However, you did not provide sufficient evidence to demonstrate in-house methods are equivalent or superior to the USP methods. Therefore, your commitment to retest affected batches may not yield reliable and valid results.

Test methods must be validated to show they are suitable for their intended use, and equivalent or better than applicable USP compendial methods. The reproducibility of your test methods is essential to determine if your drug products meet established specifications for assay and microbial attributes.

Your response to our request for records under section 704(a)(4) indicated that you failed to adequately validate the test method used to analyze raw materials and finished drug products. Method validation or verification has not been completed for the active ingredient assay testing for **(b)(4)**. Your analytical method does not demonstrate specificity, accuracy, precision, and robustness. Additionally, it appears that your firm is not performing microbiological testing for each batch of your drug products before release. In your response, you state that your drug product has low **(b)(4)** at less than **(b)(4)** and that microbial proliferation is not possible. However, you have not validated your overall manufacturing process or conducted stability studies to determine if microbial contamination proliferates throughout the shelf life of the product. You have not provided a comprehensive microbial risk assessment of your manufacturing steps, such as in-process hold times, storage conditions, and the microbial load of your **(b)(4)** ingredients. The statement in your response that you intend to conduct reduced microbial testing is insufficient, based on the limited information you provided and the lack of documentation to support your approach.

211.166 Stability testing.

Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

Your firm does not have adequate stability testing data to demonstrate that the microbiological properties of your drug products meet established specifications and that they remain acceptable for the duration of their labeled shelf lives of **(b)(4)**. During the inspection

you were unable to provide raw data for any microbiological testing conducted. In addition, your firm lacked adequate stability chambers to ensure appropriate storage conditions (e.g., temperature and humidity) for your stability samples.

In your response you state that you will draft written testing program protocols to identify all marketed products for immediate stability testing, retrieve representative samples for testing initiation, and assign interim expiry dates pending preliminary data generation.

Your response is inadequate because it fails to include sufficient details on your stability program, including how you will ensure adequate sampling and appropriate specifications. Additionally, it does not include a retrospective risk assessment for your distributed drug products that are currently on the U.S. market and within expiry. Without appropriate stability studies, you do not have scientific evidence to support whether your drug products meet established specifications and retain their quality attributes throughout their assigned shelf life.

Your firm failed to test an adequate number of drug product batches as defined by your written stability procedure. This is a repeat violation noted in previous inspections.

In your response, you state that you will continue placing batches of drug product on stability and commit to updating your stability procedure based on market demands.

Your response is inadequate because you failed to address the lack of appropriate stability data to support the expiry dates of your drug products that are currently on the market. Further, you failed to provide sufficient details on the interim measures you will take to ensure product maintains its critical quality attributes throughout its shelf life.

Without appropriate stability studies, you do not have scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

Your firm failed to establish an adequate stability program, which includes data from long-term or accelerated storage conditions to demonstrate that your product remains acceptable throughout its labeled expiry period. Without appropriate stability studies, there is no scientific evidence to support that your drug product retains its quality attributes throughout the labeled (b)(4) expiry period.

In your response, you state that you will begin stability studies. Your response is inadequate because it lacks sufficient detail describing your stability program procedures and protocols, or equipment for these studies.

For products without appropriate stability studies, there is insufficient scientific evidence to support that drug products will meet established specifications and retain their quality attributes through their labeled expiry.

Based on the stability records and information you provided, you did not demonstrate the quality attributes of your drug products remain acceptable throughout the labeled expiry period. For example, you did not include active ingredient testing as part of your stability program.

Without appropriate stability studies, you do not have scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

Based on the stability records and information you provided, you did not demonstrate the quality attributes of your drug products remain acceptable throughout the labeled expiry period. For example, you did not include active ingredient testing as part of your stability program.

Without appropriate stability studies, you do not have scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

The records and information you provided did not demonstrate that your firm has an adequate stability program for the OTC anti-microbial wipes you manufacture. For example, you conducted stability studies under "accelerated aging experiments" for your anti-microbial wipes without scientific justification. These experiments were conducted over a **(b)(4)** period at **(b)(4)**°C and 75% relative humidity. In addition, you did not perform stability studies under long-term storage conditions to support the **(b)(4)** expiration date on the label.

Without appropriate stability studies, you do not have scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

Your firm does not have adequate stability data to demonstrate that the chemical and microbiological properties of your drug products meet established specifications and remain acceptable throughout their labeled shelf life. For example, you have not established an appropriate stability program (e.g., frequency and methods) to assess stability characteristics, to ensure that your drug products meet their appropriate strength and quality attributes through their **(b)(4)** shelf life.

In your response, you propose to perform tests once a year during the stability test period. However, your response is inadequate because you do not provide scientific rationale or a formal written risk assessment to support this yearly frequency.

Without appropriate stability studies, you lack adequate scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

You failed to demonstrate the quality attributes of your drug products remain acceptable throughout the labeled expiration period. For example, during the inspection, you indicated to the investigator you recorded microbial results on the stability-study data sheet without performing the testing and without any supporting data. You also did not record assay results on your stability-study data sheets for multiple stability time points.

In your response, you explain you have established a compliant stability program, which includes establishing stability SOPs and protocols, implementing accelerated and long-term stability conditions, and submitting initial stability samples to an accredited laboratory. You also state you removed the unsupported **(b)(4)** expiration date while you determine whether the shelf-life is supported by data.

Your response is inadequate. You do not describe in detail your stability plan with defined stability conditions, time points, and testing of the appropriate critical quality attributes for drug stability, including but not limited to microbiological and impurity testing. Also, you do not specify the expiration date that you are currently using for your finished products after you removed the **(b)(4)** expiration date.

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 stability program was not adequate to ensure that the drug products you manufacture, maintain their identity, strength, quality, purity, and safety throughout their shelf lives. For example, your stability study for **(b)(4)** concluded that a **(b)(4)** expiration is supported at a temperature of **(b)(4)** to **(b)(4)** degrees Celsius (**(b)(4)** to **(b)(4)** degrees Fahrenheit). However, your firm labeled much wider storage conditions as **(b)(4)** to **(b)(4)** degrees Fahrenheit at the instruction of your customer, without adequate data to support the wider labeled storage conditions. We note that you reduced the range of the labeled temperature limits, but they were still outside the range of your stability data.

In your response, you committed to revising the stability protocol for this product and placing future lots on stability. You also state that you "can no longer rely on written justifications from product owners to deviate from the general [C]GMP requirements." Your response is inadequate in that you do not include a comprehensive review of your stability program, nor do you provide your revised stability protocol. Additionally, your response does not describe a retrospective review of batches which lack adequate stability data to support labeled expiration dates and storage conditions.

Without the appropriate stability studies, you do not have adequate scientific evidence to support that your drug product retains its quality attributes throughout the labeled **(b)(4)** expiry period.

Your firm failed to establish an adequate stability program with data demonstrating that the drug products remain acceptable throughout the labeled expiry date. For example, you

assigned **(b)(4)** expiration dates to **(b)(4)** batch **(b)(4)**, **(b)(4)** batch **(b)(4)**, and **(b)(4)** batch **(b)(4)** without initiating stability testing.

Without appropriate stability studies, you lack sufficient scientific evidence to support that your drug products retain their quality attributes throughout the labeled expiry period or determine appropriate storage conditions for your drug products.

In your response, you state that you will begin stability studies. Your response is inadequate because it lacks sufficient detail describing your stability program procedures and protocols, or equipment for these studies.

Your response to our request for records under section 704(a)(4) indicated that you have not performed stability studies for the OTC drug products you manufacture, despite your drug product's displaying an expiration date on the label.

Without the appropriate stability studies, you do not have scientific evidence to support whether your drug product's active ingredient maintains its strength, purity, and quality throughout the shelf life of the product.

Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products (21 CFR 211.166(a)).

Your firm does not have an adequate stability testing program to demonstrate that the chemical and microbiological properties of your drug products meet established specifications, and that they remain acceptable for the duration of their labeled shelf lives **(b)(4)**. For example, you failed to revise the SOP for your stability program, issued March 23, 2020, as you previously committed to do, and the procedure does not address ongoing stability testing to monitor your drug's quality attributes throughout its shelf life.

Without an appropriate stability program, you lack adequate scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through your labeled expiry.

In your response, you stated that you will segregate and identify stability samples from retain samples for each manufactured batch, and that you will conduct a thorough inventory and assessment of all existing retain samples to identify batches requiring immediate stability evaluation.

Your response is inadequate because you did not provide suitable justification that the selection of retain samples is adequate to support all existing distributed batches through labeled expiry.

You lacked an adequate stability testing program for your drug products. For example, you lacked sufficient data to support the labeled expiry. You also lacked stability chambers to

adequately store your stability samples. Further, the stability samples are not stored in the same container closure system in which your drug product is marketed.

In your response, you state that you updated your stability program SOP to include requirements for finished packaged drug product stability data and that you anticipate commencing your stability program by **(b)(4)**.

Your response is inadequate because it lacks sufficient detail and does not provide a retrospective risk assessment for your drug products released without adequate stability testing.

Without appropriate stability studies, you do not have scientific evidence to support whether your drug products meet established specifications and retain their quality attributes throughout their assigned shelf life.

Your firm failed to establish an adequate stability program with data from long-term or accelerated storage conditions, demonstrating that the drug products remain acceptable throughout the labeled expiry period. The stability protocol provided was an incomplete 24-month stability report for **(b)(4)** that lacked recorded results and the appropriate signatures. Without the appropriate stability studies, you do not have adequate scientific evidence to support that your drug product retains its quality attributes throughout the labeled **(b)(4)** expiry period.

Your firm does not have adequate stability data to demonstrate that the chemical and microbiological properties of your drug products meet established specifications and remain acceptable throughout their labeled shelf life. For example, you have not established an appropriate stability program (e.g., frequency and methods) to assess stability characteristics, to ensure that your drug products meet their appropriate strength and quality attributes through their **(b)(4)** shelf life.

In your response, you propose to perform tests once a year during the stability test period. However, your response is inadequate because you do not provide scientific rationale or a formal written risk assessment to support this yearly frequency.

Without appropriate stability studies, you lack adequate scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

The records and information you provided did not demonstrate that the chemical and microbiological properties of your drug products remain acceptable throughout the labeled expiry period. For example, your February 26, 2025, response states that there was no stability data to support the **(b)(4)** shelf life for **(b)(4)** shipped to the United States.

Without stability studies, you do not have scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

You failed to follow your written stability procedure for your finished drug products. For example, you did not complete timely stability testing for approximately **(b)(4)** stability samples for U.S. commercial drug products within the stipulated timeline (**(b)(4)** after sample pull). Stability testing was overdue by 3 months or longer for a large proportion of your samples.

In your response, you provide details for the backlog of pending stability sample testing, root causes for the delays in stability testing, and state all delayed stability sample testing for U.S. commercial products was completed by December 2024, prior to the inspection. You also implemented quality and executive management oversight for reviewing progress of stability testing, metrics, and upcoming stability testing for resource availability. You developed plans to increase quality control (QC) resources to reduce delayed stability sample testing by increasing QC laboratory capacity, purchasing and qualifying additional equipment, and hiring additional personnel. You plan to perform a stability load assessment for stability samples pulled from March 2025 to December 2025 to evaluate the adequacy of resources in your QC laboratory.

Your response is inadequate. You do not include the test results from the delayed stability analyses or a copy of the investigation report with your written response to demonstrate whether backlogged stability testing was completed and adequately investigated for root cause. Also, you do not provide adequate information on your stability load assessment, with pre-defined criteria, to evaluate adequacy of resources for your stability testing program.

Additionally, your impact assessment for the delayed stability analyses does not adequately address the risk to patient safety. Your firm's failure to perform stability dissolution testing for potassium chloride ER capsules and **(b)(4)** capsules within the specified testing period led to delays in detecting product quality failures, issuing field alert reports**1** and conducting recalls in a timely manner. For example, in multiple instances, potassium chloride ER capsules dissolution failures were not observed for approximately 100 days after stability samples were pulled.

Without an appropriate ongoing stability program, you lack adequate scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

Your firm did not have adequate stability data to demonstrate that the chemical and microbiological properties of your drug products met established specifications and remain acceptable throughout their labeled shelf-life. For example, you distributed drug products intended for wound treatment in children without conducting accelerated or long-term stability studies.

Without appropriate stability studies, you lack adequate scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

Your firm did not establish an adequate ongoing stability testing program to demonstrate that your OTC drug products met established specifications for identity, strength, quality, and purity for the duration of their labeled **(b)(4)** shelf lives.

In your response, you state that you will create a stability protocol outlining the stability, testing, objectives, methodologies, and responsibilities. You also state that you will train your employees accordingly.

Your response is inadequate. You did not provide data to demonstrate that the chemical and microbiological properties of your drug products will remain within specification throughout their expiry period. You also failed to provide interim measures to address whether your drug products that remain on the market are supported by adequate stability data.

Without appropriate stability studies, you do not have scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

Your stability program was not adequate to ensure that the OTC drug products you manufacture maintain their identity, strength, quality, purity, and safety throughout their shelf lives. For example, full shelf-life studies were not conducted for the entire stated expiry period. Additionally, the studies performed lacked adequate identity, microbiological, and impurities testing.

Your response is inadequate because it fails to include sufficient details on your stability program, including how you will ensure adequate ongoing stability testing with scientific justification. Additionally, it does not include a retrospective risk assessment or information on how you will ensure marketed drug products meet stability specifications throughout shelf life.

The records and information you provided did not demonstrate that the chemical and microbiological properties of your drug products remain acceptable throughout the labeled expiry period. For example, your February 26, 2025, response states that there was no stability data to support the **(b)(4)** shelf life for **(b)(4)** shipped to the United States.

Without stability studies, you do not have scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability

testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

Your firm did not have adequate stability data to demonstrate that the quality attributes of your drug products remain acceptable throughout the labeled expiry period. Assay testing for each active ingredient in your drug products was not being performed at each of your pre-determined timepoint intervals. Furthermore, your firm did not establish appropriate limits for impurities or evaluate your drug products for the presence of impurities.

Your firm's response is inadequate. You provided accelerated stability data for your drug products, but you did not include testing for all active ingredients and impurities. For example, the stability data for your (b)(4) lacked testing for one of the active ingredients, (b)(4), and impurities.

Furthermore, in a November 12, 2024 communication your firm committed to updating your stability testing procedures to require active ingredient testing. This communication was a response to a request for records and other information pursuant to section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 374(a)(4).

Your firm does not have an adequate stability testing program to demonstrate that the chemical and microbiological properties of your drug products meet established specifications, and that they remain acceptable for the duration of their labeled shelf lives (b)(4). For example, you failed to revise the SOP for your stability program, issued March 23, 2020, as you previously committed to do, and the procedure does not address ongoing stability testing to monitor your drug's quality attributes throughout its shelf life.

Without an appropriate stability program, you lack adequate scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through your labeled expiry.

In your response, you stated that you will segregate and identify stability samples from retain samples for each manufactured batch, and that you will conduct a thorough inventory and assessment of all existing retain samples to identify batches requiring immediate stability evaluation.

Your response is inadequate because you did not provide suitable justification that the selection of retain samples is adequate to support all existing distributed batches through labeled expiry.

Your firm failed to establish an adequate stability program, which includes data from long-term or accelerated storage conditions to demonstrate that your product remains acceptable throughout its labeled expiry period. Without appropriate stability studies, there is no scientific evidence to support that your drug product retains its quality attributes throughout the labeled **(b)(4)** expiry period.

In your response, you state that you will begin stability studies. Your response is inadequate because it lacks sufficient detail describing your stability program procedures and protocols, or equipment for these studies.

For products without appropriate stability studies, there is insufficient scientific evidence to support that drug products will meet established specifications and retain their quality attributes through their labeled expiry.

You failed to follow your written stability procedure for your finished drug products. For example, you did not complete timely stability testing for approximately **(b)(4)** stability samples for U.S. commercial drug products within the stipulated timeline (**(b)(4)** after sample pull). Stability testing was overdue by 3 months or longer for a large proportion of your samples.

In your response, you provide details for the backlog of pending stability sample testing, root causes for the delays in stability testing, and state all delayed stability sample testing for U.S. commercial products was completed by December 2024, prior to the inspection. You also implemented quality and executive management oversight for reviewing progress of stability testing, metrics, and upcoming stability testing for resource availability. You developed plans to increase quality control (QC) resources to reduce delayed stability sample testing by increasing QC laboratory capacity, purchasing and qualifying additional equipment, and hiring additional personnel. You plan to perform a stability load assessment for stability samples pulled from March 2025 to December 2025 to evaluate the adequacy of resources in your QC laboratory.

Your response is inadequate. You do not include the test results from the delayed stability analyses or a copy of the investigation report with your written response to demonstrate whether backlogged stability testing was completed and adequately investigated for root cause. Also, you do not provide adequate information on your stability load assessment, with pre-defined criteria, to evaluate adequacy of resources for your stability testing program.

Additionally, your impact assessment for the delayed stability analyses does not adequately address the risk to patient safety. Your firm's failure to perform stability dissolution testing for potassium chloride ER capsules and **(b)(4)** capsules within the specified testing period led to delays in detecting product quality failures, issuing field alert reports**1** and conducting recalls in a timely manner. For example, in multiple instances, potassium chloride ER capsules dissolution failures were not observed for approximately 100 days after stability samples were pulled.

Without an appropriate ongoing stability program, you lack adequate scientific evidence to support whether your drug products meet established specifications and retain their quality attributes through their labeled expiry.

Your firm failed to conduct appropriate laboratory testing to determine whether each batch of drug product purporting to be sterile conforms to such requirements (21 CFR 211.167(a)).

Your firm released your finished OTC drug products to the U.S. market without testing each batch for all appropriate quality attributes. For example, your firm distributed multiple batches of purportedly sterile finished drug products without conducting sterility testing. Without testing all appropriate physical and microbiological quality attributes of your drug products, your quality unit lacks essential safety information required to make suitable batch release decisions.

In your response, you acknowledge that you did not begin sterility testing on your drug products until the end of 2024. You indicate that you will test the retains, per USP <71> Sterility Tests, of lots for which you have retains.

Your response is inadequate because you have not provided proof of method suitability of the sterility test performed by your contract laboratory to ensure its capability to detect microbes in your finished drug product. Additionally, you have failed to indicate if there are batches for which you lack retains and are therefore unable to test for sterility.

Your firm failed to have, for each batch of controlled-release dosage form, appropriate laboratory determination of satisfactory conformance to the specifications for the rate of release of each active ingredient (21 CFR 211.167(c)).

You failed to provide adequate data demonstrating your drug products, **(b)(4)**, have a **(b)(4)** of the active ingredient. For example, you claim your **(b)(4)** lasts for up to **(b)(4)** and that your **(b)(4)** products have **(b)(4)** effect for **(b)(4)**. Your release and stability data for dissolution does not provide data that drug **(b)(4)**. Drug products should not be released without appropriate determination of conformance to final specifications and intended use. There is a lack of assurance of appropriate quality and that your drug will have the intended effect it purports to possess.

In your response, you state that you estimated the therapeutic duration and that you will remove **(b)(4)** claims until you perform adequate studies. Your response is inadequate because you did not provide a retrospective assessment of your drug products on the U.S. market within expiry to identify and take appropriate action on any product quality or patient safety risks.

product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle. See FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download.

This is a repeat violation from your 2019 and 2021 inspections.