WARNING LETTER

Turbare Manufacturing MARCS-CMS 713516 — SEPTEMBER 16, 2025

- **Warning Letters**
  - About Warning and Close-Out Letters

Delivery Method:

Via Electronic Mail - Delivery and Read Receipt Requested

Product:

Drugs

Recipient:

Laura Martin

CEO

Turbare Manufacturing

925 Jeanette DriveConway, AR 72032-6651United States

Issuing Office:

Center for Drug Evaluation and Research (CDER)

United States

WARNING LETTER

WL # 713516

September 16, 2025

Dear Ms. Martin:

You registered your facility with the U.S. Food and Drug Administration (FDA) as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353b][1] on June 23, 2023, and most recently on January 25, 2025. From January 14, 2025, to January 24, 2025, an FDA investigator inspected your facility, Turbare

Manufacturing, located at 925 Jeanette Drive, Conway, Arkansas 72032. During the inspection, the investigator noted serious deficiencies in your practices for producing drug products intended or expected to be sterile, which put patients at risk.

FDA issued a Form FDA 483 to your facility on January 24, 2025. We reviewed your February 14, 2025, and April 30, 2025, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. FDA also acknowledges that, on February 18, 2025, your firm initiated a voluntary recall of Bevacizumab 1.25mg/0.05mL in 0.25mL Syringe, Lot # 12192024**(b)(4)** and Lot # 12122024**(b)(4)**, due to lack of sterility assurance. Based on this inspection, it appears you produced drugs that violate the FDCA.

A. Compounded Drug Products under the FDCA

Under section 503B(b) of the FDCA, a compounder can register as an outsourcing facility with FDA. Drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility qualify for exemptions from the drug approval requirements in section 505 of the FDCA [21 U.S.C. § 355(a)], the requirement in section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] that labeling bear adequate directions for use and the Drug Supply Chain Security Act requirements in section 582 of the FDCA [21 U.S.C. § 360eee-1] if the conditions in section 503B of the FDCA are met.

An outsourcing facility, which is defined in section 503B(d)(4) of the FDCA [21 U.S.C. § 353b(d)(4)], is a facility at one geographic location or address that — (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. Outsourcing facilities must comply with other applicable provisions of the FDCA, including section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (CGMP), and section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions. Generally, CGMP requirements for the preparation of drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

B. Violations of the FDCA

Adulterated Drug Products

The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator observed that:

1. Your firm failed to conduct process simulation (media fill) studies that closely simulate aseptic production operations under the worst-case, most challenging, and stressful conditions.

The FDA investigator also noted CGMP violations at your facility, that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

2. Your firm failed to establish acceptance criteria for the sampling and testing conducted by the quality control unit that are adequate to assure that batches of drug products meet appropriate statistical quality control criteria as a condition for their approval and release (21 CFR 211.165(d)).

3. 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 processes (21 CFR 211.113(b)).

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

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a revised draft guidance, *Current Good Manufacturing Practice — Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act*. This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.

Under section 301(a) of the FDCA [21 U.S.C. § 331(a)], the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, it is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

C. Corrective Actions

We have reviewed your facility's responses to the Form FDA 483. We also acknowledge your voluntary recall of Bevacizumab 1.25mg/0.05mL in 0.25mL Syringe, Lot # 12192024**(b)(4)** and Lot # 12122024**(b)(4)**, due to lack of sterility assurance.

Some of your corrective actions appear deficient:

1. Regarding your firm's failure to thoroughly investigate any unexplained discrepancy, or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed:

a. We acknowledge the actions taken by your firm in response to your failure to investigate the recovery of 1 cfu mold (i.e., *Curvularia intermedia*) from an operator's **(b)(4)** sample during personnel monitoring, performed in association with (aseptic processing) media fill lot # 11252024**(b)(4)**, including Investigation Record # NCR-25-002 and Document Change Request # DCR-071, as well as updates to/implementation of the following documents: SOP-048 (*Routine Environmental Monitoring*), TEM-034 (*EM Investigation Template*), and

SOP-088 (*Reading of Microbiological Culture Media*). However, while your investigation attempts to identify the source and impact of the contamination, you failed to determine why the excursion itself was not investigated at the time of occurrence. Consequently, there is no assurance of your ability to initiate investigations in a timely manner. Furthermore, your investigation concludes the likely root cause of the excursion was "*ineffective cleaning, due to stressing the environment for Media Fill…*" While process simulation (i.e., media-fill) studies should be conducted under "worst-case" scenarios (e.g., simulating largest batch size, longest processing time, and routine & non-routine interventions), they should also be conducted in accordance with all related approved procedures (e.g., cleaning procedures).

Consequently, the intentional lack of cleaning may confound the results of the media fill study. Your response suggests your process simulation procedures should be reassessed and modified, as necessary.

b. We acknowledge actions taken by your firm in response to your failure to investigate the recovery of 1 cfu from an operator's **(b)(4)** fingertip sample, performed in association with the production of Bevacizumab 1.25mg/0.05mL in 0.25mL syringes, Lot # 11132024**(b)(4)** in BSC 0003, including the closure of DCR-071, updates to SOP-048, and the implementation of TEM-034, etc. However, we note that while section 6.10.1 of SOP-048 (*Routine Environmental Monitoring*) reads in part "…investigations are targeted for closure within **(b)(4)** from initiation," it does not appear to specify a time frame within which such investigations must be initiated. Consequently, there's no procedural safeguard to prevent delays in initiating investigations into environmental monitoring excursions.

c. We acknowledge actions taken by your firm in response to your failure to identify and investigate the failure of two batches of drug product (i.e., Bevacizumab, Lot # 12122024**(b)(4)** and Lot # 12192024**(b)(4)**) to comply with appropriate Acceptable Quality Limits (AQL) for visible particulates. We acknowledged the voluntary recall of the two aforementioned lots of drug product, as well as revisions to SOP-075 (*Acceptable Quality Limit (AQL)*), which align with the generally acceptable standards established in **(b)(4)**. However, we remain concerned with conclusions derived from Incident ID # INC-25-002, specifically your contention the batches in question were acceptable based on an examination of an additional **(b)(4)** units from retain samples of each of the lots. For example, per document number FRM-071 (Version 02, 12 DEC2024), your "AQL" at the time the batches were produced was **(b)(4)**%. Your defect rates for those categorized as "Major" were erroneously calculated as 0.3% and 0.1% for Lot # 12192024**(b)(4)** and Lot # 12122024**(b)(4)**, respectively. However, the rate should be calculated based on the actual sample size (i.e., **(b)(4)** units), which results in a 13.3% and 6.7% "Major" defect rate for Lot # 12192024**(b)(4)** and Lot # 12122024**(b)(4)**, respectively, which should have triggered a non-conformance investigation. Your retrospective investigation fails to address this deficiency.

2. Regarding your firm's failure to establish acceptance criteria for the sampling and testing conducted by the quality control unit that are adequate to assure that batches of drug products meet appropriate statistical quality control criteria as a condition for their approval and release:

a. We acknowledge actions taken by your firm in response to your failure to establish statistically valid sampling plans as part of your visual inspection program. Specifically, we acknowledge updates to SOP-075 (*Acceptable Quality Limit (AQL)*), including the

implementation of AQL sampling plans consistent with generally accepted standards for acceptance sampling by attribute (e.g., **(b)(4)**) for your visual inspection processes. We also note you established process flow charts to guide the decision matrix when either the 100% visual inspection or an AQL inspection fail. According to your process (i.e., per SOP-075), the failure of the initial 100% visual inspection for critical defects triggers a non-conformance investigation. However, you failed to provide a rationale for allowing a second 100% visual inspection, without an investigation in cases where the initial 100% visual inspection fails for minor and/or major defects.

3. Regarding your firm's failure 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 processes:

a. We acknowledge your firm's actions, taken in response to your failure to conduct media fills that closely simulate aseptic production operations under the worst-case, most challenging, and stressful conditions, pursuant to an approved written study protocol. We recognize the distinction between aseptic personnel qualification procedures and aseptic process simulation (i.e., media fills). Our review of the document titled *Summary Report for Syringe Repackaging Media Fill – 0.25 ml* **(b)(4)** indicates a single batch (Lot # 01312025**(b)(4)**) was produced on 01/31/2025 yielding a total of **(b)(4)** units (i.e., syringes). The summary report and associated batch records indicate that 25 "Major" defects were identified during the initial 100% visual inspection process, all for "fill volume" defects. This equates to a **(b)(4)**% Major defect rate, under the **(b)(4)**% Defect Alert Limit established by SOP-061 *100% Visual Inspection of Injectable Product*. The report further indicates "… *no variances observed during the execution of the MFP-025-001*." Review of the batch records associated with the media fill indicate that routine and non-routine interventions (e.g., goggle adjustment, spill clean-up, simulated break/shift-change; as well as excessive filling time, batch size, and vial punctures), were employed. However, it is also observed that in accordance with SOP-074, you omitted routine cleaning of the ISO**(b)(4)** room and ISO**(b)(4)** hood prior to production. While it is important to simulate the aseptic process under worst-case, most stressful conditions, it is not appropriate to omit routine pre-production cleaning as this may skew the results. For example, if a microbial excursion is encountered, either in environmental monitoring results or sterility testing results, the root cause may be falsely attributed to the lack of routine, pre-production cleaning, instead of a potential breach in, for example, aseptic technique (e.g., failure to disinfect gloved hands), etc. Furthermore, it is noted this was considered a "requalification" activity. As such, only one full-scale batch was produced. However, since the media fill batches, produced in May 2024, were not considered adequate due to the failure to include routine/non-routine interventions, this protocol should have been treated as an initial media-fill qualification activity consisting of three successful, consecutive full-scale batches.

4. Regarding your firm's failure to establish an adequate system for monitoring environmental conditions in aseptic processing areas:

a. We acknowledge your firm's actions, taken in response to your failure to implement written procedures which adequately describe the process for investigating environmental monitoring excursions. We recognize enhancements made to SOP-048 (*Environmental Monitoring Program*), including section 6.10.1 which describes the processes for conducting EM Investigations. It is noted the procedure requires an evaluation of related documents, including cleaning records, equipment records, batch production records, operator

qualification, etc. The procedure also requires that a root cause analysis and impact assessment be performed, concluding with a recommendation regarding batch disposition, where applicable. We further note the procedure reads, in part "…*actionable environmental or personnel monitoring recoveries require a documented investigation into the potential root cause and subsequent impact… investigations are targeted for closure within* **(b)(4)** *from initiation*." However, as noted in item 1(b), above, it does not appear to specify a time frame within which such investigations must be initiated. Consequently, there is no procedural safeguard to prevent delays in initiating investigations into environmental and personnel monitoring excursions.

Furthermore, according to section 6.4 of SOP-048, active viable air monitoring of the ISO**(b)(4)** area is conducted "*At least* **(b)(4)** *per Production Batch*." However, review of the media fill batch production records for Lot # 01312025**(b)(4)** indicates it can take over **(b)(4)** to complete the syringe repackaging process alone. Consequently, your active air sampling process does not adequately reflect environmental conditions throughout the aseptic production process.

In addition to the issues discussed above, you should note that CGMP requires the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. See section 501 of the FDCA. If you choose to contract with a laboratory to perform some functions required by CGMP, it is essential that you select a qualified contractor and that you maintain sufficient oversight of the contractor's operations to ensure that it is fully CGMP compliant. Regardless of whether you rely on a contract facility, you are responsible for assuring that drugs you produce are neither adulterated nor misbranded. [See 21 CFR 210.1(b), 21 CFR 200.10(b).]

FDA strongly recommends that your management undertake a comprehensive assessment of operations, including facility design, procedures, personnel, processes, maintenance, materials, and systems. In particular, this review should assess your aseptic processing operations. A third-party consultant with relevant sterile drug manufacturing expertise should assist you in conducting this comprehensive evaluation.

D. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility. You are responsible for investigating and determining the causes of any violations and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law, including FDA regulations.

You should take prompt action to address any violations. Failure to adequately address any violations may result in legal action without further notice, including, without limitation, seizure and injunction.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to address any violations. Please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. This letter notifies you of our concerns and provides you an opportunity to address them. If you believe your products are not in violation of the FDCA,

include your reasoning and any supporting information for our consideration. If you cannot completely address this matter within fifteen (15) working days, state the reason for the delay and the time within which you will do so.

All correspondence should refer to the Warning Letter Number above (# 713516) and include a subject line that clearly identifies the submission as a Response to Warning Letter. If you have questions regarding the contents of this letter, please contact compoundinginspections@fda.hhs.gov.

Sincerely,
/S/

F. Gail Bormel, JD, RPh
Director
Office of Compounding Quality and Compliance
Office of Compliance
Center for Drug Evaluation and Research

---

1 See Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).