WARNING LETTER

AllerQuest LLC

MARCS-CMS 578557 — JUN 24, 2019

Delivery Method: UPS Overnight
Product: Drugs

Recipient:

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Dear Dr. Mendelson:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, AllerQuest LLC, FEI: 3006900385, at 10 Farmington Valley Drive, Suite 106, Plainville, Connecticut, from January 31 to March 1, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your March 22, 2019, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

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

You manufacture sterile injectable drug products in a facility that is not adequately designed or controlled for sterile drug operations.

For example, your ISO 5 critical area where you aseptically fill ampules directly interfaces with double doors. These double doors have substantial gaps in multiple locations and are immediately adjacent to an unclassified area. This poses a hazard for the influx of unclassified air directly into a critical zone. During the inspection, you applied tape to try to seal the voids.

Aseptic processes should be designed to minimize exposure of sterile articles to potential contamination hazards, including but not limited to variation in environmental conditions. Any area that adjoins and can impact an ISO 5 area should be appropriately designed, maintained, and classified.

Your aseptic processing line design is inadequate. The production line has limited protection and a high degree of exposure to contamination hazards from manual intervention and the surrounding air.

For additional guidance on aseptic processing see FDA's guidance document *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at https://www.fda.gov/media/71026/download (https://www.fda.gov/media/71026/download).

In your response you committed to engaging third-party consultants to assist with the remediation of your facility. However, you failed to provide adequate supportive documentation to evaluate the effectiveness of your corrective actions and preventive actions (CAPA). You also mention that all batches of your drug product have passed sterility testing for release. However, finished product testing alone is limited in its ability to establish sterility of all units because contamination is not normally uniformly distributed.

Many significant elements in aseptic processing can influence the quality and safety of sterile drugs. If each element is not strictly controlled, there is potential for a non-sterile drug product.

It is unclear if you continue to manufacture and distribute sterile drug products using a production process that was not adequately designed and controlled.

In response to this letter, provide the following.

- Your interim plans for the manufacture and distribution of your sterile drug products while you remediate your facility and equipment design, and all other inadequacies.

- Comprehensive identification of all contamination hazards with respect to your aseptic processes, equipment, and facilities. Provide an independent risk assessment that covers, among other things, all human interactions with the ISO 5 area, equipment placement and ergonomics, air quality in the ISO 5 area and surrounding room, facility layout, personnel flow, and material flow.

- A detailed CAPA plan, with timelines, to address the findings of the contamination hazards risk assessment. Describe how you will significantly improve aseptic processing operation design and control and personnel qualification.

- Detailed supportive documentation of your CAPA.
  - Include detailed updates on your plans for facility remediation including how you will assure adequate separation of the ISO 5 critical area from unclassified areas. This plan should include how you will address all filling operations (ampule and vial filling).
  - Include your change-over procedures for your ampule filling and vial filling operations as well as updated smoke studies of ampule filling and vial filling operations after remediation of your facility.

º Provide a detailed description of equipment changeover practices between the ampule filling machine and vial filling machine in the ISO 5 curtained area. Include details such as how equipment is moved around the facility, disassembled, stored, and installed for production.

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

Your firm had various departures from your established actions limits throughout your ISO 5 critical area and clean rooms but failed to adequately address them. Loss of environmental control can significantly increase contamination risk of drugs intended to be sterile.

Cleaning and Disinfection
You failed to ensure sufficient use of a sporicidal agent in your disinfection program. For example, your firm identified *Bacillus, sp*., a spore-forming organism, within the ISO 5 critical area by the ampule feed track on the filling machine. After you found *Bacillus, sp*. in the aseptic core, you cleaned the area with **(b)(4)** and **(b)(4)**, neither of which are sporicidal.

Environmental and Personnel Monitoring
You did not adequately investigate the cause of multiple excursions above your action limit, including a potential adverse pattern of fungal contamination.

Essential to an adequate environmental monitoring (EM) program is a timely and thorough evaluation of action limit excursions, identifying potential routes of contamination, as well as identifying appropriate follow-up measures to prevent contamination risks to the product.

In addition, your personnel monitoring program is inadequate. For example, fingertip monitoring should have an action limit of one colony forming unit (CFU). However, you established operator annual requalification limits as "NMT **(b)(4)**CFU" for fingertip sampling. An ongoing goal for manufacturing personnel in the aseptic processing room is to maintain contamination-free gloves throughout operations. Results that do not meet established limits should trigger appropriate attention.

Temperature, Humidity, and Pressure
Your firm lacks a continuous monitoring system to ensure that the quality of your aseptic processing environment is adequately maintained. You relied on personnel being present at the time of a temperature, humidity, or pressure excursion for it to be manually detected and recorded. Over a period of years, you documented numerous temperature and humidity excursions across your aseptic processing areas. However, you failed to consistently report these excursions appropriately as required by your procedure, and to implement effective CAPAs.

A suitable facility monitoring system is crucial for detecting changes that can compromise the environmental control of cleanrooms and ultimately the drug product. Notably, your aseptic operations are particularly vulnerable to loss of control, especially because you periodically cease and restart operations at your facility throughout the year with limited monitoring of the facility during these periods.

In your response, you committed to enhancing your EM program, remediating your HVAC system, and using automated systems to continuously monitor environmental conditions. You also discussed historical EM sampling results and sterility testing. However, you failed to provide adequate supportive documentation to evaluate the adequacy of your CAPA.

In response to this letter, provide the following.
- Detailed supportive documentation of your CAPA, including but not limited to:
  º Historical environmental monitoring data you referenced in your response as well as historical environmental monitoring data from all of your cleanrooms, with designation whether the result was obtained within the ISO 5, ISO 6, and ISO 7 zone (also include exact location of the sample). Also, provide a detailed summary of all environmental monitoring data that exceeded alert and action limits for the past two years.

º A detailed plan to ensure routine monitoring and recording of temperature, pressure, and humidity. Include your provisions to ensure deviations from established limits will generate alarms and be fully documented and adequately investigated.

• Your detailed procedure for routine shutdown and startup of aseptic production operations to significantly improve assurance that the environment is in a robust state of control before production may recommence.

• Comprehensive independent review of your disinfection program and a CAPA plan. The latter should include but not be limited to enhanced use (e.g., increased frequency) of sporicidal agents in your disinfectant program.

• A plan to improve your personnel monitoring program to maintain contamination-free gloves throughout operations.

3. 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).

You found recurrent contamination of your sterile injectable drug products with foreign particulate matter, but you failed to adequately investigate and identify the root causes of the recurrent contamination.

Thousands of drug-filled glass ampules repeatedly failed to meet your release acceptance criteria of "[c]lear, colorless solution, free from particulate matter." You refer to such contamination as a "critical defect" and hypothesized during the inspection that the cause may be glass or aluminum from the manufacturing process. However, you have not identified a root cause of the particulate contamination or implemented effective CAPA.

There is a lack of assurance of the quality of your drug products. For example, during one of your quality assurance audits following 100% visual inspection, additional particulate contamination was found that was not identified during a previous 100% visual inspection conducted for lot release. In addition, you repeatedly discarded contaminated ampules identified from visual inspection, sometimes exceeding 10% of a batch, and then distributed the remainder of the batch. The high percentage of rejected ampules and particulates found in cleared ampules after 100% visual inspection indicate that you may have released drug product that contains particulates.

Your drug product is used for intradermal injection to potentially elicit an allergic reaction in a medical setting. Foreign particulate matter in the ampules could lead to a local nonspecific inflammatory response and could lead to a false positive interpretation of the skin test, continued avoidance of penicillin antibiotics, and all of the risks associated with alternative use of broad-spectrum antibiotics.

In your response, you committed to revising your visual inspection SOP, establishing action and alert limits, and performing a risk assessment of drug products on the market. However, you failed to determine the root cause of the particulate contamination. Product quality cannot be inspected into your drug product: it must be assured by an adequate production process. You also failed to provide adequate supportive documentation to evaluate the adequacy of your CAPA.

In response to this letter, provide the following.

• Detailed supportive documentation of your CAPA including, but not limited to, your risk assessment.

º Your assessment should include an adequate root cause analysis for the recurring particulates, thorough identification of the particulates, and their corresponding origin (intrinsic or extrinsic).

º You should also address any drug product quality or patient safety risks and assess the adequacy of investigations into any deviations, out-of-specification results, or other manufacturing quality issues. Include a full CAPA (e.g., notification to customers, recall, etc.) for any drug products that may have quality or safety risks.

• An improved visual inspection program. Your program should include acceptance and rejection limits for each batch of drug product. The limits should be based on sound statistical principles for the evaluation of particulates in sterile injectable drugs.

• A comprehensive, independent assessment of your system for investigating deviations, atypical events, complaints, OOS results, and failures. Your CAPA plan should include, but not be limited to, improvements in investigations, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA plan effectiveness.

CGMP Consultant

Your consultant should be qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov (mailto:drugshortages@fda.hhs.gov), so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Please send your electronic reply to ORAPHARM1_RESPONSES@fda.hhs.gov (mailto:ORAPHARM1_RESPONSES@fda.hhs.gov). If you have any questions regarding the content of this letter, please reach out to Compliance Officer, James Mason, at james.mason@fda.hhs.gov (mailto:james.mason@fda.hhs.gov). Please identify your response with FEI 3006900385.

/S/
Craig Swanson
Acting Program Division Director/District Director
Office of Pharmaceutical Quality Operations - Division I
New Jersey District

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