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WARNING LETTER

# Winder Laboratories, LLC

MARCS-CMS 567869 — 26/03/2019

**Product:** Drugs

**Recipient:**

Steven Pressman

Managing Member, CEO

Winder Laboratories, LLC

716 Patrick Industrial Lane
Winder, GA 30680
United States

**Issuing Office:**

Division of Pharmaceutical Quality Operations II

4040 North Central Expressway, Suite 300
Dallas, TX 75204-3128
United States

**March 26, 2019**

**Case # 567869**

**WARNING LETTER**

**VIA UPS EXPRESS**

Steven Pressman

Managing Member, CEO

Winder Laboratories, LLC

716 Patrick Industrial Lane

Winder, Georgia 30680

Dear Mr. Pressman:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Winder Laboratories, LLC, at 716 Patrick Industrial Lane, Winder, Georgia, from July 9 to 13, 2018, and from July 17 to 18, 2018.

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 August 8, 2018, 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 establish adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).**

You have not validated your cleaning processes used for cleaning non-dedicated manufacturing equipment, such as your fluid bed granulator and V-blender. Our investigator observed a V-blender that was labeled as clean encrusted with off-white powder residue.

Your procedure RMG.111.1 requires "**(b)(4)**" and lacks sufficiently specific instructions. You lacked an adequate scientific approach to evaluate the capability of your current cleaning procedures and did not complete sufficient validation studies.

Your response acknowledged that adequate cleaning validation had not been performed. Your response mentioned that as an interim control, swab and rinse samples have been collected and tested.

In response to this letter, provide:

- A comprehensive plan to evaluate the adequacy of cleaning procedures, practices, and validation studies for each piece of non-dedicated manufacturing equipment.
- Scientific rationale for your cleaning validation strategy to ensure the efficacy of your cleaning procedures.
- A summary of updates to your cleaning validation protocol to incorporate conditions identified as worst case. This should include, but not be limited to, evaluating drugs that have high toxicity, drugs that have lowest solubility in cleaning solvents and solutions, drugs that have characteristics that make them difficult to clean, and swabbing of various equipment locations that are difficult to clean.
- SOP(s) that have been updated to ensure an appropriate program for verification and validation of cleaning procedures for new products, processes, and equipment.
- A summary of all microbial testing performed on equipment and products to demonstrate proper sanitization of equipment.

**2. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards (21 CFR 211.194(a)).**

During the inspection, our investigator identified three drug products in your chromatographic system that included "run single injection," "abort single injection," and "delete result set" messages in their audit trails. This included numerous entries for your Phenohytro Tabletsfinished product. During the inspection, your management acknowledged that these anomalies were not evaluated as part of the batch review.

In your response, you indicated that “trial injections” were performed using diluent, mobile phase, or standard solutions. However, your response lacked evidence to demonstrate that these solutions, and not samples, were injected.

Your analytical method must be properly validated, and successful execution of system suitability should ensure that your equipment is suitable for performing analyses.

Your response also did not address the number of single trial injections that were aborted during your chromatographic runs.

Regarding “delete result set” messages, you noted that an investigation was carried out with the assistance of the software owner. The investigation related to automatic deletions and indicated that empty result sets occurred when no results were produced for the processing job. The audit trail attributes the deletion to the logged-in user. Overall, your response lacked sufficient details on the extent of sample preparation and injection when all three audit trail messages occurred, identification of any circumstances in which a run was stopped or interrupted by the analyst, and explanation of each deviation.

In response to this letter, provide the following:

- An independent and retrospective review of all audit trails since January 1, 2016, including all samples aborted, any deletions, and each sample set aborted or deleted. For each situation:
    - explain the circumstances and reason for the deleted or aborted data;
    - identify the batches impacted; and
    - identify any out-of-specification (OOS) result that was generated. For any such instance, also provide the investigation or confirm that the out-of-specification (OOS) result was not investigated.
- A comprehensive corrective action and preventive action (CAPA) that will ensure that all future aborted or deleted injections will include an explanation of such deviations at the time of performance.
- A thorough, independent assessment of your analytical method validation. For each relevant method, explain why “trial injections” were needed. The assessment also should determine if the trial injection practices before the system suitability testing are due to inadequate methods, and state which analytical methods will be remediated and revalidated.
- If batches are compromised due to trial injections or other data integrity issues, inform this office what action you will take for affected batches on the market.

Also, see requests under the **Data Integrity Remediation** heading.

**3. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).**

a. **Equipment Calibration and Qualification:**

Your firm lacks qualification study records for critical manufacturing equipment. You also lack adequate procedures for calibrating and qualifying the equipment used to manufacture your drug products. Our investigators found that you moved tablet presses, V-shape blenders, fluidized bed granulator, mixers, and packaging line manufacturing equipment between your production rooms and the warehouse (a non-controlled area), depending on the manufacturing schedule. Your firm did not adequately evaluate the impact of relocated equipment would have on the manufacturing process.

In your response, you indicated that your fluid bed granulator, tablet press, and large V-shape blender usually remained in place. You indicated that before every start of a manufacturing process, a "mini-calibration" is performed, although the data provided seems to be consistent with routine machine set-up activities. You added that the certain equipment was qualified by the firm's previous owner in 2010, but you were unable to provide qualification documents to our inspection team. Your response was inadequate. You did not provide evidence of "mini-calibration" of equipment after it was moved to demonstrate that it continues to be calibrated and qualified before use.

In response to this letter, include:

- A product impact analysis for drug products manufactured on equipment that was moved to production areas from your warehouse.
- An updated calibration and qualification program for all your manufacturing equipment.
- A revised procedure for the relocation, movement, and calibration of manufacturing equipment. Provide details of appropriate calibration and qualification activities that will be needed and describe which equipment operating parameters are to be evaluated before release of equipment for commercial production.
- A data-driven, scientifically sound qualification and validation program that identifies and controls variability, such that your production and packaging processes meet appropriate manufacturing standards and parameters. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, and determining the capability and reliability of each manufacturing process step and control.

b. **Water System:**

Our inspection documented that when the water system was not in use, it was shut down with no recirculation. This practice poses a risk for contamination caused by a "dead leg" in your system that could promote formation of biofilm in the water system.

In your response, you discussed controls in place for your water system. Your response was inadequate because you did not provide information regarding the operational status of the current water system and a comprehensive remediation plan to improve design. It is also deficient in that only monthly monitoring of your water system was provided. You lacked routine (e.g., daily) monitoring to ensure an ongoing state of control.

In response to this letter, provide:

- A comprehensive, independent assessment of your water system design, control, and maintenance.
- A comprehensive CAPA plan for remediating design, control, and maintenance of the water system.
- A copy of your validation and qualification report for your water purification system, storage, and distribution operations. Provide procedures associated with the sampling scheme (i.e., sampling port locations and frequency) and the test results (e.g., chemical and microbial) performed in the last three years. Also include the summary of improvements made to your system design, as well as to the program for ongoing control and maintenance.
- Your plan to routinely collect samples from your water system for microbiological counts and microbial identification.

For general principles and approaches that FDA considers appropriate elements of process validation, see FDA's guidance document *Process Validation: General Principles and Practices*, at: https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf)

**Additional Concerns Related to Out-of-Specification Investigations**

Our investigators found additional CGMP deficiencies related to your handling of out-of- specification investigations evaluated as part of our Pre-Approval coverage. A **(b)(4)** batch failed to meet the assay specification. Your firm changed the HPLC equipment columns, collected a new sample, and initiated retesting without adequately completing a Phase I investigation into the OOS results. You lacked a scientific justification regarding the potential root cause of the failures.

In your response, you referenced assay investigation **(b)(4)** initiated on December 2, 2017, for several batches of **(b)(4)** that were on stability. The investigation attributed the OOS to a laboratory error (i.e., improper sample mixing after preparation by the analyst), although the investigation did not provide a clear indication of laboratory error. Because the root cause was inconclusive, you should have expanded the investigation into possible manufacturing causes.

The inspection also documented failure to follow your OOS SOP regarding **(b)(4)** testing of samples. You also failed to initiate an investigation into leaking bottles of **(b)(4)** observed during your stability long-term, intermediate, and accelerated condition studies.

In your response, you referenced an Attachment 1, which indicated that no corrective and preventive action (CAPA) was required for the OOS incident because the analyst was experienced in the test procedure. Instead, your analyst was instructed to follow the procedure. Additional batches tested by this or other analysts were not evaluated.

**CGMP Consultant Recommended**

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant 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.

**Data Integrity Remediation**

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document "*Data Integrity and Compliance with Drug CGMP"* for guidance on establishing and following CGMP compliant data integrity practices at: https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf)

We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

**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 in your facility.

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.

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.

Your written notification should refer to the Warning Letter Number above (**Case # 567869**). Please electronically submit your signed reply on your firm's letterhead to CDR John W. Diehl, M.S., Director, Compliance Branch, at john.diehl@fda.hhs.gov (mailto:john.diehl@fda.hhs.gov) and orapharm2_responses@fda.hhs.gov (mailto:orapharm2_responses@fda.hhs.gov).

If you have questions regarding the contents of this letter, you may contact Mr. Thao Ta, Compliance Officer, via phone at 214-253-5217 or e-mail at thao.ta@fda.hhs.gov (mailto:thao.ta@fda.hhs.gov).

Sincerely,

/S/

Monica R. Maxwell

Program Division Director

Office of Pharmaceutical Quality Operations,

Division 2

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