WARNING LETTER

Missouri Analytical Laboratories Inc

MARCS-CMS 615319 — SEPTEMBER 30, 2021

Delivery Method:

UPS Next Day

Product:

Drugs

Recipient:

Mr. Richard A. Gilbert

President

Missouri Analytical Laboratories Inc

1820 Delmar Boulevard
Saint Louis, MO 63103
United States

Issuing Office:

Division of Pharmaceutical Quality Operations III

United States

September 30, 2021

WARNING LETTER
WL #615319

Dear Mr. Gilbert:

The U.S. Food and Drug Administration (FDA) inspected your contract testing laboratory, Missouri Analytical Laboratories, Inc., FEI 1946524, located at 1820 Delmar Boulevard, Saint Louis, Missouri, 63103, from May 3 to May 19, 2021.

This warning letter summarizes significant violations of Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals, Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211), and significant deviations from CGMP for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs 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 June 7, 2021, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations and deviations including, but not limited to, the following:

Finished Drug Violations

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).

Your firm failed to thoroughly investigate unexplained discrepancies and out-of-specification (OOS) results. In addition, investigations were closed without adequate scientific justification. For example,

• **(b)(4)**, lot **(b)(4)**, failed assay testing at the **(b)(4)**. Your retest of the original preparation samples also produced failing results. Based on advice from your customer, you retested the lot using freshly prepared samples and obtained passing results. Your laboratory investigation did not determine a root cause for the failure. You relied on resampling and retesting to invalidate the original OOS results without identifying a scientifically justified root cause.

• Your firm failed to detect and thoroughly investigate falsification of **(b)(4)** records. For a period of approximately **(b)(4)** were intentionally documented in the logbook for **(b)(4)** preparation, when the actual cycle was for only **(b)(4)**.

In your response, you provided updated OOS investigation reports, and stated that the OOS failures were caused by known laboratory errors such as inappropriate sample preparations, which were contradictory to your initial investigation conclusions. Your response is inadequate. You lacked evidence to support your revised conclusion of laboratory errors as root causes of the OOS results.

In addition, you stated that you recently initiated a deviation to review the **(b)(4)** records generated during that period. Your response is inadequate. Your investigation lacked a comprehensive assessment into the extent of the falsification of autoclave records and other breaches of data integrity occurring in the laboratory.

In response to this letter, provide:

• A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for the products currently in the U.S. market and within expiry as of the date of this letter and a report summarizing the findings of the analysis, including the following for each OOS:
  o Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
  o For investigations that conclusively establish laboratory root cause, provide rationale, and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for

remediation.
  o For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include notifications sent to clients.

• A retrospective, independent review of all **(b)(4)** records and microbiology testing records for the products currently in the U.S. market and within expiry as of the date of this letter. Provide a report summarizing the findings and applicable remediation plan.

2. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Your firm did not have adequate system security and access control for the **(b)(4)** system. For example, unique user accounts and privilege levels were not assigned to individual users for **(b)(4)** software, and the Windows operating system. The analysts had access to delete and overwrite data. Our investigators found approximately 36 deleted data files or folders in the recycle bin.

In addition, your analysts used individualized non-validated **(b)(4)** spreadsheets to calculate assay, impurity, content uniformity, and dissolution test results for a variety of drug products.

In your response, you stated that you planned to upgrade the **(b)(4)** system. However, you did not provide a CAPA plan for interim controls to prevent the occurrence or recurrence of data and file deletion or modification. Also, you stated that "The deleted files on the desktop were working copies of the original data files. The original data files were still in the database." Your response is inadequate. You did not perform a retrospective review to assess potential impact and ensure data integrity.

In response to this letter, provide:

• A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

• Your action plan with timelines describing your interim controls to prevent the occurrence or recurrence of data and file deletion or modification for all applicable electronic laboratory data systems.

API Deviations

3. Failure to document and explain any deviation and investigate all critical deviations.

You obtained initial OOS **(b)(4)** result for **(b)(4)**, which you attributed to an unknown laboratory error. You repeated the analysis with **(b)(4)** new sample preparations and found that four samples were again OOS. Later you followed your client's protocol to repeat the analysis by **(b)(4)** analysts with **(b)(4)** new sample preparations, which were within specification. You relied on resampling and retesting to invalidate the original OOS results without identifying a scientifically justified root cause.

In your response, you provided an updated OOS investigation report, and stated that the OOS failures were caused by known laboratory errors such as inappropriate sample preparations, which was contradictory to your initial investigation conclusions. Your response is inadequate. You lacked evidence to support your revised conclusion of laboratory errors as root causes of the OOS results.

In response to this letter, provide:

• A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for the products currently in the U.S. market and within expiry as of the date of this letter and a report summarizing the findings of the analysis, including the following for each OOS:
  o Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
  o For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
  o For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include notifications sent to clients.

Test Results Out-of-Specification

For more information about handling failing, OOS, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* for appropriately handling OOS and performing investigations at https://www.fda.gov/media/71001/download (https://www.fda.gov/media/71001/download).

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 test. 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/media/119267/download (https://www.fda.gov/media/119267/download).

We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

• A detailed investigation protocol and methodology; a summary of all systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
• Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
• An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.

• A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of the drugs you tested. 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. Your strategy should include:

• A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate including analytical data, and all data submitted to FDA.
• A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
• Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of the drugs you tested, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
• Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
• A status report for any of the above activities already underway or completed.

Quality Unit Authority

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

Responsibilities of a Contract Testing Lab

FDA considers contractors as extensions of the manufacturer's own facility. Your failure to comply with CGMP may affect the quality, safety, and efficacy of the drugs you test for your clients. It is essential that you understand your responsibility to operate in full compliance with CGMP, and that you inform all your customers of any OOS results or significant problems encountered during the testing of these drugs. See FDA's guidance document *Contract Manufacturing Arrangements for Drugs: Quality Agreements* at https://www.fda.gov/media/86193/download (https://www.fda.gov/media/86193/download).

Conclusion

The violations and deviations cited in this letter are not intended to be an all-inclusive list of violations and deviations that exist at your facility. You are responsible for investigating and determining the causes of any violations and deviations and for preventing their recurrence or the occurrence of other violations and deviations.

Correct any violations and deviations promptly. Failure to promptly and adequately address this matter may result in regulatory or legal action without further notice including, without limitation, seizure and injunction. Unresolved violations and deviations may also prevent other Federal agencies from awarding contracts.

Failure to address violations and deviations may also cause FDA to withhold issuance of Export Certificates. FDA may withhold approval of new applications or supplements listing your facility as a drug manufacturer until any violations and deviations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to address any violations and deviations.

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done to correct your violations and deviations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Please address your reply via email to: ORAPHARM3_RESPONSES@fda.hhs.gov

Attention: Tina M. Pawlowski, Compliance Officer
U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Your written notification should refer to the Warning Letter above (WL #615319). If you have questions regarding the contents of this letter, please contact Tina M. Pawlowski at (313) 393-8217.

Sincerely,
/S/

Nicholas F. Lyons
Acting Program Division Director
Division of Pharmaceutical Quality Operations III

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-act