WARNING LETTER

Shriram Institute for Industrial Research

MARCS-CMS 597629 — APRIL 15, 2020

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Dr. Karampendethu Mathai Chacko

Director

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Center for Drug Evaluation and Research | CDER

10903 New Hampshire Avenue
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Warning Letter 320-20-33

April 15, 2020

Dear Dr. Chacko:

The U.S. Food and Drug Administration (FDA) inspected your contract testing laboratory, Shriram Institute for Industrial Research, FEI 3002808145, at 19 University Road, University Campus, Delhi, from October 15 to 22, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, 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 November 7, 2019, 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 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(a)).

Your firm serves as a contract testing laboratory analyzing both API and drug products. Your firm had not enabled the audit trail function on high-performance liquid chromatography (HPLC) units until on or about October 11, 2019, when this FDA inspection was announced.Your analyst acknowledged during the inspection that the audit trail function on the HPLCs units was not enabled until October 2019. This was a repeat observation of your August 2016 FDA inspection.

Despite written commitments after that inspection to install audit trails, you failed to enable audit trail functions on multiple analytical instruments, including your HPLC units.

Customers rely on the integrity of the laboratory data that you generate to make decisions regarding drug quality. It is important to maintain strict control over CGMP electronic data to ensure that all additions, deletions, or modifications of information in your electronic records are authorized and appropriately documented.

In your response, your only corrective action was to designate an instrument engineer "to perform the routine inspection to proper performance of the equipment." Your response is inadequate because it failed to describe specific controls you will implement to ensure audit trails remain enabled and the integrity of your data is not compromised.

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.

2. Your firm failed to establish adequate written responsibilities and procedures applicable to the quality control unit and to follow such written procedures (21 CFR 211.22(d)).

Your Quality Unit (QU) failed to ensure that your laboratory personnel follow written procedures. For example, our investigators observed at least **(b)(4)** samples tested between March 2019 and September 2019 in which out-of-specification (OOS) results were not investigated as required in your procedures. Your head of Quality Assurance informed our investigator during the inspection that failures are investigated only upon customer request. Additionally, our investigators observed procedures not followed for review of analytical logbooks and results.

These observations included:

• Documentation errors covered by adhering new paper over the original value.
• Tests not recorded contemporaneously.
• Sample identification not entered into your "Sample Record Register."
• Electronic data supporting analytical laboratory packets were not reviewed before you released final laboratory results.

In your response, you stated that the procedure for OOS was not followed, but going forward all OOS results will be investigated to identify root causes. Additionally, you committed to conduct further CGMP documentation practice training for your analysts. Your response is inadequate because you failed to perform a risk assessment of your lack of following OOS procedures and poor documentation practices on products you tested for commercial release.

In response to this letter, provide:

• A retrospective, independent risk assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective action and preventive action (CAPA) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, and contemporaneous records throughout your operation. Specify actions you will take in response to the risk assessment, such as customer notifications.

• A retrospective, independent review of all OOS results for all tests. Identify any products which may be intended for the United States for the last three years from the initial date of inspection and a report summarizing the findings of the analysis, including the following for each OOS:
o For all OOS results found by the retrospective review, identify any potential root cause and indicate if your customer was notified of the failure. Include the original test, date of test, testing result, customer, and reason for initiating an investigation.

• The written response from your customers when notified of the testing failure(s).

• A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:

o A determination of whether procedures used by your firm are robust and appropriate
o Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
o A complete and final review of each batch and its related information before the QU disposition decision
o Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products

Test Results Out-of-Specification

For more information about handling failing, out-of-specification, 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* at https://www.fda.gov/media/71001/download (https://www.fda.gov/media/71001/download).

Quality Systems

Your firm's quality systems are inadequate. See FDA's guidance document *Quality Systems Approach to Pharmaceutical CGMP Regulations* for help in implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download (https://www.fda.gov/media/71023/download).

API Deviations

3. Failure to ensure that all test procedures are scientifically sound and appropriate to ensure that your raw materials and API conform to established standards of quality and/or purity.

Our investigators observed many examples of United States Pharmacopeia (USP) labeled material which were tested on your analytical instruments without the completion of system suitability testing prior to analysis. For example, a sample of **(b)(4)** USP, batch **(b)(4)**, was tested using an atomic absorption spectrometer on January 15, 2019, without confirming system suitability testing. This was a repeat observation from the August 2016 FDA inspection.

After the previous inspection, your firm committed to performing system suitability testing on all analytical instruments "wherever required, prior to analysis" of USP tests. Additionally, your firm failed to document the testing method within laboratory records before issuing a certificate of analysis. You lacked adequate documentation to support that the USP labeled drug products were tested with USP methods.

System suitability testing determines whether requirements for precision are satisfied and ensures that the analytical instrument is fit for the intended testing before analyzing samples. It is critical that your system be demonstrated as suitable for use to avoid the possibility of samples erroneously passing when an instrument is not working properly.

Customers rely on your laboratory data for critical information about the quality of drugs and their components. Thus, it is important that your analytical instruments are suitable for their intended use, and that you use appropriate test methods to enable your customers to make proper decisions (e.g., batch disposition).

In your response, you committed to perform system suitability testing on your laboratory equipment prior to analysis. Additionally, you committed to inform your clients of the need to perform method verification before conducting analysis. Your response lacked sufficient interim measures to ensure equipment is suitable and methods are robust while you continue to test drug products. Additionally, you did not conduct a risk assessment for USP tests performed without system suitability testing.

In response to this letter, provide:

• A retrospective, independent risk assessment addressing the hazards posed by providing USP test results of active pharmaceutical ingredients and drug products to clients without documenting the test method or performing system suitability testing on analytical instruments prior to testing. Specify actions you will take in response to the risk assessment, such as customer notifications.

• 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. This assessment should include, but not be limited to:

o Your procedure for carrying out system suitability testing prior to analysis on your laboratory equipment
o Your procedure for method verification for current and new methods performed within your laboratory
o Your procedure for establishing responsibility for performing method verification between you and your clients

Repeat Observations at Facility

In a previous inspection, dated August 2-5, 2016, FDA cited similar CGMP observations. You proposed specific remediation for these observations in your response.

Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

CGMP Consultant Recommended

Based upon the nature of the violations and deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations 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/media/119267/download (https://www.fda.gov/media/119267/download).

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. Your investigation should include:
• A detailed investigation protocol and methodology; a summary of all laboratories and 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 drugs you tested for commercial release. 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 data at your firm.
• Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of drugs, such as notifying your customers and conducting additional testing.
• 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.

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 these violations and deviations and for preventing their recurrence or the occurrence of other violations and deviations.

Until you correct all violations and deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a contract testing laboratory.

Failure to correct these violations and deviations may also result in the FDA refusing admission of articles manufactured by your clients and tested at Shriram Institute for Industrial Research, 19 University Road, University Campus, Delhi into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

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 deviations 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.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Joseph Lambert, Pharm.D.
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3002808145.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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