WARNING LETTER

International Trading Pharm Lab Inc

MARCS-CMS 598537 — APRIL 24, 2020

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Mr. Ismail Elchagea

President and Owner

International Trading Pharm Lab Inc

470 Chamberlain Ave., Suite 12
Paterson, NJ 07522-1000
United States

Issuing Office:

Division of Pharmaceutical Quality Operations I

United States

Warning Letter

CMS # 598537

April 24, 2020

Dear Mr. Elchagea:

The U.S. Food and Drug Administration (FDA) inspected your contract testing laboratory, International Trading Pharmaceuticals Laboratories, Inc. (ITPL), FEI 1000208853, at 470 Chamberlain Avenue, Suite 12, Paterson, New Jersey, from October 15 to 29, 2019.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, the API you tested 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 acknowledge receipt of your December 3, 2019, response to our Form FDA 483 and receipt of your subsequent correspondence. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

During our inspection, our investigator observed specific deviations including, but not limited to, the

following.

1. Failure of your quality unit to ensure that drugs are appropriately tested and the results are reported.

Your quality unit did not provide appropriate oversight to laboratory operations. Several chromatographic injections of samples and standards associated with an out-of-specification (OOS) investigation were not included in your investigation, reviewed by your quality unit, and communicated to your client.

For example, four **(b)(4)** samples tested OOS for assay on October 24, 2017. As part of the OOS investigation, they were all retested on November 11, 2017. One of the four samples you retested as part of your OOS investigation, **(b)(4)** sample ID **(b)(4)**, was re-injected in duplicate under a separate series for assay approximately 14 hours later that same day. The second data set was not captured in the analyst's notebook, it was not included as part of your documented OOS investigation, and your quality unit (QU) was unaware of the sample re-injection.

In addition, **(b)(4)** sample ID **(b)(4)** was tested a second time with injections labeled in part "Experimental" with unknown results obtained, and also was not included as part of your official OOS investigation.

All data—including hypothesis testing, obvious errors and failing, passing, and suspect data—must be in the CGMP records that are retained, subject to review, and provided to your clients for oversight.

In your response, you indicate that auditors will check that no re-testing or trial injections of sample solutions have been performed. However, your response is inadequate because you did not conduct a review of electronic chromatographic data to determine the extent and impact of this practice. Furthermore, the updated procedure included in your response did not state that sample injections cannot be used to verify the system equilibrium. It is unacceptable to use an actual sample of the batch being tested in test, prep, or equilibration runs because this practice can be used to disguise testing into compliance. Only a properly qualified reference standard can be used.

In response to this letter:

• Provide an updated procedure for chromatography analysis that specifies you will not conduct trial injections, and only qualified reference standards will be used to verify suitability of chromatographic test equipment.
• If any results due to "Experimental" or similar injections are found to compromise the results reported to clients, inform this office of any actions or client notifications that are made.

• Provide 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

2. Failure to establish and follow written procedures for investigating critical deviations or the failure of API batches to meet specifications.

Your firm's investigation of OOS results was closed without adequate scientific justification. For example, OOS results were obtained during testing of four **(b)(4)**, United States Pharmacopeia (USP) samples starting on October 24, 2017. Your investigation determined there was an unknown peak co-eluting with the **(b)(4)** peak. However, this determination was not scientifically justified: the sample solution determined to have a co-eluting peak was approximately 15 days old when it was tested. You lack data on solution stability to show that the co-eluting peak was not caused by the age of the sample solution.

During the inspection and in your response, you noted your client refused to authorize solution stability studies, although you informed them that the **(b)(4)** peak may have been breaking down into two peaks because the sample was not fresh. You also stated that, without the permission and authorization of the client, your firm is limited to what can be tested on the sample in case of failure.

Your response was not adequate. Contract analytical testing laboratories are responsible for operating in compliance with CGMP for the operations they conduct, regardless of discussions they may have with clients. Such labs must employ adequate controls to ensure that data, equipment, and test results are reliable and maintained in accordance with CGMP requirements.

(b)(4).

In response to this letter, provide:

• A retrospective, independent review of all invalidated OOS results for drug product and API testing conducted for the last three years, and a report summarizing the findings of the analysis. Include the following for each OOS:
  o Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrate 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 comprehensive review and remediation plan for your OOS result investigation systems. The corrective action and preventive action (CAPA) plan should include but not be limited to the following:
  o Quality unit oversight of laboratory investigations
  o Identification of adverse laboratory control trends
  o Resolution of causes of laboratory variation
  o Adequately scoping each investigation and its CAPA
  o Revised OOS investigation procedures with these and other remediations

3. Failure to verify the suitability of analytical methods.

Your firm failed to ensure that methods used for analyzing drug samples had been verified as suitable for their intended use. For example, your firm conducted **(b)(4)** assay, **(b)(4)** assay, and identity A testing on multiple **(b)(4)** API samples following USP methods without verifying their suitability under actual conditions of use.

In your response, you stated that all testing methods are verified under actual conditions by meeting the system suitability requirements mentioned in the method. Your response is inadequate. System suitability is not a substitute for method verification. For example, your firm had to change the flow rate to achieve proper peak separation for **(b)(4)**, USP samples as part of an OOS investigation, despite passing system suitability results.

In response to this letter, provide:

• The results of a comprehensive independent assessment of all drug test methods to determine the suitability of the method (i.e., method verification, or method validation when using a client-provided method). If verification or validation is needed, provide a plan and timeline for completion of the appropriate activity.
• Updated procedures documenting how the suitability of all testing methods will be determined, when method verification and validation occur, and corresponding training records.

4. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to have adequate controls to prevent omission of data.

Your firm lacks controls to assure the integrity of electronic test data generated by high performance liquid chromatography (HPLC) and gas chromatography (GC) systems. For example, during the inspection our investigator observed that stand-alone computers used to run an HPLC and a GC allowed analysts who test drug samples the ability to delete raw data files and alter date and time stamps. In addition, audit trails were not enabled, so there would be no way to determine whether analysts manipulated data.

Customers rely on the integrity of the laboratory data that you generate. You also need traceability of actions for investigational purposes. 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, you indicated that you created different accounts with controls for your analysts. However, your response was inadequate because you did not appropriately address the lack of audit trails. An audit trail is a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record. You also included a corrective action to print all chromatograms for each analysis. Electronic records are dynamic, and a printout or a static record does not preserve the dynamic record format that is part of the complete original record.

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 to enable audit trails for all applicable electronic laboratory data systems. Also describe your interim controls and specify when procedures will be implemented for the review of all audit trails.

• Updated procedures to ensure all HPLC and GC injection sequences are included in any data packet that undergoes quality unit review.

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 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 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 your test results. Your assessment should include analyses of the risks to patients caused by testing 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 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 your drug testing, such as notifying your customers, conducting additional testing, and drug application actions.
• 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.

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. 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).

It is essential that you understand your responsibility to operate in full compliance with CGMP, and that you inform all your customers of any out-of-specification results or significant problems encountered during drug testing.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations 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

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

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

FDA may also withhold approval of pending new drug applications or supplements listing your facility as a supplier or manufacturer until the above deviations are corrected. We may re-inspect to verify that you have completed your corrective actions.

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

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 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 orapharm1_responses@fda.hhs.gov. Your notification should refer to Warning Letter CMS # 598537 and reference FEI 1000208853.

If you have questions, please contact Compliance Officer CDR Liatte Closs at Liatte.Closs@fda.hhs.gov.

Sincerely,
/S/

Diana Amador-Toro
Program Division Director/District Director
OPQO Division I/New Jersey District

CC:
(b)(4)

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