Sipra Labs Limited 7/23/15

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

Warning Letter

WL: 320-15-13

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

July 23, 2015

Dr. Satya Vemulapalli
Managing Director
Sipra Labs Limited
7-2-1813/5/A, Adjacent to Post Office
Industrial Estate, Sanathnagar
Hyderabad
India

Dear Dr. Vemulapalli:

We inspected your drug contract testing laboratory, Sipra Labs Limited, Hyderabad, India, from February 24, 2014, through March 1, 2014. Our U.S. Food and Drug Administration (FDA) investigator identified significant violations of current good manufacturing practice (CGMP) regulations for testing finished pharmaceuticals and active pharmaceutical ingredients (APIs).

These violations cause the drug products or APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 351(a)(2)(B). The methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We reviewed your firm's response dated March 14, 2014, in detail. We acknowledge receipt of your other responses dated March 30, 2015, June 23, 2015 and July 1, 2015. We note that they lack sufficient corrective actions.

Our investigator observed specific violations during the inspection, including, but not limited to, the following.

1. Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of test methods (21 CFR §211.165(e)).

Our previous inspections of April, 2009 and September, 2011, found that many methods used by your firm to test products had not been verified or validated. Our current inspection found that methods continued to be validated inadequately, and that some methods cited in the last inspection were still not validated. More specifically:

a. Our inspection documented that only four of the fourteen analytical methods identified in the 2011 inspection have since been validated. Ten methods remain unvalidated.

b. The FDA investigator found that you did not follow your established standard operating procedure (SOP) for validation activities.

For example, your "Validation of Analytical Methods" SOP dated Feb. 18, 2013, is applicable to "…all the departments at Sipra labs Limited, Hyderabad." Section 5.1.2.8 of this SOP requires robustness testing. However, you failed to conduct robustness testing as part of your validation package for protocol FRD/PT/13/052-00 "Analytical Method Validation for the Determination of **(b)(4)** Content in **(b)(4)** by ICPMS (Inductively Coupled Plasma Mass Spectrometry)." Further, the validation protocol did not list any variables or show repeatability. A **(b)(4)** were used as the basis for acceptance. Therefore, you approved the validation package based upon a **(b)(4)** analysis without investigating the method's precision, which would require method variations.

In your response, you stated that you perform the testing "…as per the terms of operation mentioned in the quality agreements between the clients and Sipra." Your corrective action was to include a disclaimer statement in your validation protocol that

"the selected parameters do not fulfill the requirements for complete validation package as per Sipra's SOP and ICH guidelines…" As a further proposed corrective action, in your test report, you planned to note that the method has not been validated or verified.

Your response is inadequate. It is essential for a contract test laboratory to use validated methods to ensure that results of pharmaceutical analyses subject to CGMP are accurate. Accountability in the supply chain is compromised when a Certificate of Analysis (COA) reports that results conform to specification without assurance that the test methods used were reliable. Including a disclaimer does not release you from the CGMP requirement to ensure that your test methods are validated and suitable for their intended use. Further, you did not indicate in your response whether you plan to inform your clients that you have not been following your own SOPs on method validation, or that validation packages failed to meet ICH guidelines.

2. Your firm failed to thoroughly investigate unexplained discrepancies or failures of a batch or its components to meet its specification, whether or not the batch has already been distributed (21 CFR §211.192).

As a contract laboratory, you must comply with the CGMP regulations that apply to the operations you perform, including but not limited to, those that address the operations of your quality control unit, laboratory, investigation systems, documentation systems, and other facets of your operation. As set forth in FDA's guidance for industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf), following an OOS result, the laboratory should conduct an initial assessment to determine whether there was a meaningful error in the analytical method. Following such assessment, "[f]or contract laboratories, the laboratory should convey its data, findings, and supporting documentation to the manufacturing firm's quality control unit . . . ." *id* at 3.

The FDA investigator observed that your written procedures do not adequately address the need to investigate anomalies, unexpected events, or out-of-trend results. For example, on February 3, 2014, an analyst noticed an anomaly with the CHNOS analysis of sample **(b)(4)**. The analyst repeated the analysis for sample **(b)(4)** as well as for samples **(b)(4)** and **(b)(4)**.

There was no documentation that the event was reviewed by your laboratory or reported to your client manufacturing firm.

In your response, you stated you had prepared an SOP addressing non-conforming analytical runs/sequence and investigated this specific event. However, you did not

expand the investigation to other drug products that may have been associated with this event or similar anomalies.

In addition, you did not have a validated practice for reusing HPLC/GC vials and stoppers. According to your response, you discontinued reusing HPLC/GC vials or stoppers. However, since this practice was identified as the root cause of at least one Out-of-Specification assay (OOS/AND/13/220), you should perform a risk assessment to evaluate the impact of reusing HPLC/GC vials and stoppers on all previous injections.

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 products you test for your clients. Your clients (e.g., drug manufacturers, application sponsors), in turn, must provide you with all of the scientific data and information needed to support reliable method implementation.

Your procedures must include use of validated methods for each analysis subject to CGMP. It is critical that you provide all test results for evaluation and consideration in final product disposition decisions. When your investigation of out-of-specification results does not determine an assignable cause, all test results should be reported to the customer on the certificate of analysis. We also recommend providing your OOS reports to your customers, and including steps in your procedures to obtain critical information from your customers about the products you test that could affect the suitability of the methods you use.

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

Within 15 working days of receipt of this letter, notify this office, in writing, of the specific steps that you have taken to correct and prevent the recurrence of violations. Provide copies of supporting documentation. Also include an example of a drug manufacturing quality agreement.

If you cannot complete corrective actions within 15 working days, state the reason for the delay and the date by which you will have completed the corrections. Send your reply to:

Xiaohui Shen, Consumer Safety Officer
On behalf of
Global Compliance Branch II
Division of Drug Quality I
Office of Manufacturing Quality
Office of Compliance

CDER
White Oak, Building 51, RM 4223
10903 New Hampshire Ave
Silver Spring, MD 20993

Please identify your response with FEI # 3004544153.

Sincerely,
/S/
Thomas Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research