Quali Controle & Qual-Controle-C.E.Bac 3/5/18

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-38

March 5, 2018

Mr. Emmanuel Souhaut
President
Quali-Controle & Quali-Controle C.E.BAC
29 Rue Paul Vaillant-Couturier
Meru 60110
France

Dear Mr. Souhaut:

The U.S. Food and Drug Administration (FDA) inspected your drug contract testing laboratory, Quali-Controle & Quali-Controle C.E.BAC, at 29 Rue Paul Vaillant-Couturier, Meru, from September 14 to 15, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for testing finished pharmaceuticals, 21 CFR parts 210 and 211.

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 October 6, 2017, response in detail and acknowledge receipt of your subsequent correspondence. We note that your response lacks sufficient corrective actions.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

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

For example, your non-compendial test methods used to analyze your customers' drug products had not been validated.

In your response, you indicated that a comment has been added to your Certificate of Analysis (CoA) to inform your customer that the analyses are conducted using unvalidated test methods. You also committed to inform your customers that all future test methods will need to be properly transferred or validated to legitimize the results obtained in your laboratory.

Your response was inadequate. It is essential for a contract test laboratory to use validated or verified methods to ensure that results of pharmaceutical analyses subject to CGMP are accurate. Accountability in the supply chain is compromised when a 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, although you stated that you would advise your customers about the requirement for validation and/or transfer of test methods for *future* analyses, your response did not address how you will review the results of all analyses you have previously conducted using unvalidated non-compendial methods or how you will communicate with your customers about these non-compliant analyses.

In response to this letter, provide the following:

- Protocol and timelines for the validation or method transfer of all non-compendial methods, and verification of all compendial methods used at your facility to test products for release.
- An assessment of the use of unvalidated and unverified methods on products released to the U.S. market, and your plans to communicate with your customers regarding previously tested drugs for which you used unvalidated or unverified methods.
- Your procedure to assure that all future non-compendial methods used in your facility are properly validated or transferred, and all compendial methods are verified prior to use.

2. 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 original atomic absorption analysis of **(b)(4)** sample 15/0871 was out-of-specification (OOS). A retest of the sample was also OOS. A third sample was retested and found within specifications. You invalidated the OOS results without justification or documented investigation.

In your response, you stated that dirty glassware used in all prior preparations and tests was the root cause for the failures; you claimed that rinsing the glassware before testing resolved the problem.

Your response was inadequate because you have no scientific justification for the assigned root cause, nor have you implemented adequate corrective actions and preventive actions (CAPA).

As a contract laboratory, you must comply with the CGMP regulations that apply to 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..."

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. It is essential that you understand your responsibility to operate in full compliance with CGMP, and to inform all of your customers of significant problems encountered during the testing of these drugs. 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.

In your response to this letter, provide the following:

- Retrospective review of all OOS test results to determine if results were invalidated without scientific justification. Your review should also identify those instances where a documented investigation was not performed, and your plans for communicating these deviations with your clients. Submit a report of your review with the findings, and your CAPA plan to prevent recurrence.
- Your revised written procedure for OOS investigations.

Quality Agreement

You and your customer, **(b)(4)**, have a quality agreement specifying the testing method that must be used for your drug product. Your firm failed to follow the procedure set forth in your quality agreement regarding the use of the United States Pharmacopeia for drug component testing. You also failed to obtain prior approval from your customer before changing the test method, as required in your quality agreement.

For more information on how quality agreements may be helpful for defining, establishing, and documenting responsibilities for CGMP activities, see FDA's guidance document, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, at **http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf)**.

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 all your facilities.

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

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at Quali-Controle & Quali-Controle C.E.BAC at 29 Rue Paul Vaillant-Couturier, Meru, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles 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 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Ms. Chhaya Shetty
Interdisciplinary Scientist, Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4355
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3002807958.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

cc: **(b)(4)**

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