Vital Laboratories Pvt Ltd Plant II 10/10/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter** 320-18-01

October 10, 2017

Mr. Rajiv Bajaj
Director
Vital Laboratories Private Limited
Plot 1710 & A1 2208, Phase III GIDC
Vapi, Gujarat 396195
India

Dear Mr. Bajaj:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Vital Laboratories Private Limited Plant-II, at Plot No.1710 & A1-2208, Phase III GIDC Estate, Vapi, Gujarat, from April 3–6, 2017.

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, your API 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 April 27, 2017 response in detail.

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

1. Failure to ensure all production deviations are reported and evaluated, and that critical deviations are investigated and the conclusions are recorded.

Your firm failed to follow your written procedures for production and to report, evaluate, and investigate deviations from production procedures. For example, your **(b)(4)** batch records specify an in-process assay for **(b)(4)**. You did not perform these in-process assay tests for at least five batches in 2016, but had no explanation for the failure to conduct these tests. Additionally, your **(b)(4)** batch records specify a yield reconciliation formula to **(b)(4)**. Without any justification, you failed to use the specified formula for at least three batches in 2016.

In your response, you stated that the "for information only" in-process assay requirement for **(b)(4)** was "occasionally performed, without any rationale" because the **(b)(4)** in-process test provided similar information and was within specifications for those batches. You also stated that you revised your master production records to remove the in-process assay test requirement: you only require it when **(b)(4)** values are out of specification. You also admitted that the **(b)(4)** yield formula in the master production record was incorrect.

Your response is inadequate. You did not review all your production records to determine if other steps were "occasionally performed, without any rationale," or if master batch record formulas for any of your other drugs were incorrect.

In your response to this letter, conduct and provide the results of a review of your firm's production records to identify instances of production deviations for all drugs distributed in the United States within expiry. Conduct a risk analysis to determine the product quality effects of any such identified failures, and indicate the specific steps you will take to investigate and respond to any critical deviations.

2. Failure to adequately document the completion of each significant step in the batch production records with signatures of the persons performing and directly supervising or checking each critical step in the operation.

Your batch production records omitted signature fields to document who performed, directly supervised, and checked each critical step in your manufacturing process. For example, the batch production record for **(b)(4)** batch **(b)(4)**, Section E, *Packing Details*, indicates a gross weight of **(b)(4)**, a tare weight of **(b)(4)**, and a calculated net weight of **(b)(4)** for "Drum No. 4." The correct calculated net weight should be **(b)(4)**. There are no signatures to identify who performed the weighing operation and who subsequently verified it. We also observed that the "done by" and "checked by" fields in many of your other batch production records were completed by the same person. During the inspection, you stated that it was general practice for supervisors to initial or sign for operators.

In your response, you stated that you revised your **(b)(4)** batch records to include space for operators and verifiers to sign. You explained that supervisors were signing for operators because the operators' "hands were dirty" and your corrective action and preventive action (CAPA) was to provide operators with gloves. Additionally, you noted that your batch records were in English but many of your operators only understand Hindi. Thus, you proposed bilingual English and Hindi batch records to improve operator understanding and compliance.

Your response is inadequate. Your revision of the batch record for **(b)(4)** was insufficient because you did not review all batch records for all of your drugs to identify any additional critical steps (besides weighing) that may have been inadequately performed, documented, and reviewed or checked. Your CAPA of providing gloves to operators and proposal to generate bilingual batch records did not directly address the observed deficiency of supervisors signing records on behalf of operators who performed critical steps.-

In your response to this letter, provide the results of a retrospective investigation of batch records for all of your API distributed to the U.S. that are within expiry. Your review should identify any instances in which your batch records indicate inadequate performance, documentation, or review of critical steps in the operation, and should include a risk assessment to determine the impact on the quality of your API for any such identified instances. Also provide the specific actions you have taken to ensure that current and future batch records for all products are adequate and signed correctly, such as establishing a documented system of regular, periodic quality unit audits of your batch records.

3. Failure to adequately investigate and document out-of-specification results and implement appropriate corrective actions.

Your firm ignored aberrant analytical test results rather than investigating them, determining the root cause, and implementing appropriate corrective actions. You relied on these out-of-specification (OOS) results to assign “expiration dates” to your API. For example, our investigator reviewed your 48-month stability gas chromatography (GC) test results for **(b)(4)** content in **(b)(4)** validation batches **(b)(4)**, **(b)(4)**, and **(b)(4)**.

Our investigator observed that all three chromatograms for these batches displayed an unknown peak at an earlier retention time than the internal standard peak. The unknown peak did not appear in the internal standard blank run. Prior to our inspection, you did not initiate an investigation into this OOS result, nor did your firm determine the root cause or assess the effects of the unknown peak on the quality of your drugs. Instead, you reviewed, approved, and used the stability data for these batches to determine the “expiration date” for your commercial **(b)(4)** API batches.

In your response, you stated that you performed a retrospective investigation, and determined that the unknown peak was due to “injector contamination” of **(b)(4)** precipitation in the needle of the GC injector. You concluded that the unknown peaks were isolated, and did not reflect systemic product quality deviations or affect the reported values of **(b)(4)** or labeled expiration dates. You revised your procedures to require chemists to document and investigate OOS results, and stated that you would purchase new GC equipment.

Your response is inadequate. You did not expand the scope of your investigation to determine if other drugs tested on the same GC equipment were affected by similar “injector contamination” events. You also failed to explain why you neglected to investigate these aberrant test results in the first instance, or relied on OOS results to assign “expiration dates” to your API.

In your response to this letter, provide your investigation report and risk analysis for all drugs tested on the affected GC equipment since 2015. Indicate the steps you will take for any analytical test results you identify as having been affected by needle contamination or carryover. Also provide your revised stability program to indicate how you will ensure that your "expiration dates" are based only on analytical data that meets scientifically valid and appropriate specifications.

4. Failure of your quality unit to adequately perform annual product reviews.

We reviewed your annual product reviews (APR) for multiple products and observed a variety of deficiencies. For example, the stability data from your 2016 **(b)(4)** APR was identical to the data included in your 2015 APR for the same API. Your 2016 **(b)(4)** APR also included stability data that could not have been generated at the time points provided in the APR. Your 2016 APR for **(b)(4)** also included multiple errors. For example, the mean values for product quality attributes such as water content, impurities, and optical rotation exceed the maximum values. Product quality tables of numerical minimum values also reported maximum values as "not detected." In another instance, mean values were reported for a single batch.

Such reporting errors are repeat deviations from FDA's 2013 inspection of this site.

In your response, you attributed these APR errors to personnel using the previous year's APR as a template. You revised your procedures to include a blank template. You also stated that "all the error was transcription error and review error by all managers of concerned departments." You indicated that you would avoid such errors in the future by using enterprise resource planning to compile QMS data online.

Your response is inadequate. You did not explain how your use of an enterprise resource planning system will prevent APR errors in the future. Further, you did not perform a retrospective review of all APR to ensure that there were no errors that may have compromised or obscured indicia of drug quality.

In your response to this letter, conduct a retrospective review of all APR for the past three years, and provide a tabular summary of your review. Also provide annotated copies of your revised 2015 and 2016 **(b)(4)** and **(b)(4)** APR, referencing the underlying data along with copies of the records containing the underlying data.

Repeat deviations at multiple sites

FDA cited similar CGMP deviations at other facilities in your firm's network. Specifically, when FDA inspected Vital Laboratories Private Limited Plant-I (formerly known as Vital Healthcare Private Limited) in Vapi, Gujarat, in 2015, it was classified as unacceptable for drug manufacturing as a result of observations that were similar to those observed during Plant-II's inspection. These repeated failures at multiple sites demonstrate that your company's oversight and control over the manufacture of drugs is inadequate.

Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure

that systems, processes, and ultimately, manufactured products, conform to FDA requirements.

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 and 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 fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Conclusion
Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you correct all deviations 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 deviations may also result in FDA refusing admission of articles manufactured at Vital Laboratories Private Limited Plant-II, at Plot No.1710 & A1-2208, Phase III GIDC Estate, Vapi, Gujarat 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 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:

William Yang, PhD
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue

Silver Spring, MD 20993
USA

Please identify your response with FEI 3007474872.

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