Badrivishal Chemicals & Pharmaceuticals 3/2/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter 320-17-28**
Return Receipt Requested

March 2, 2017

Mr. Deepak Rawat
Chief Executive Officer
Badrivishal Chemicals & Pharmaceuticals
Plot No. 13, Revenue Colony
Talegaon – Chakan Road
Talegaon Dabhade, Dist. Pune 410 507
Maharashtra
India

Dear Mr. Rawat:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Badrivishal Chemicals & Pharmaceuticals at Gat No. 29, Village Jambwade (Induri), Post Sudumbre, Taluka Maval, Dist. Pune, Maharashtra, from August 16 to 19, 2016.

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 September 8, 2016, response in detail.

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

1. Failure to validate and monitor the water purification system to ensure that water is of appropriate quality and suitable for its intended use.

During the inspection, our investigators found that your water purification system was not adequately monitored and controlled. Because you use water as a drug component and for cleaning your facility and equipment, these failures pose significant risk to the safety of your drugs.

Source water
You failed to test the source water for your **(b)(4)** water system. The source water emanates from a nearby river and passes through farmland, where it is subject to agricultural runoff and animal waste, before reaching your facility. Your firm stores the source water in an **(b)(4)** tank that has a large **(b)(4)**-facing hole that is open to the environment. Your storage method does not protect your water from dirt and other contaminants, or from the ingress and proliferation of pests and objectionable organisms.

Sanitization and validation
You did not follow your own sanitization procedures for your **(b)(4)** water system. Your procedures specify **(b)(4)** of sanitization at **(b)(4)**, yet our investigators identified instances where you sanitized for as little as 10 minutes without justification.

During the inspection, you stated that in March 2016 you initiated, but have not yet completed, a performance qualification of the **(b)(4)** water system. Your firm has used this unqualified system routinely since its installation in 2014, despite having no scientific evidence that the system is capable of producing water of adequate quality.

Testing
Our investigators found that you were aware that the total aerobic microbial counts (TAMC) for all in-process water samples **(b)(4)** had exceeded your limit of **(b)(4)** colony forming units (cfu)/mL for multiple months. You failed to investigate these deviations.

Furthermore, your firm did not demonstrate an adequate understanding of the process that your **(b)(4)** water system relies on to kill microorganisms. **(b)(4)** is typically **(b)(4)** sanitization steps. However, you only use **(b)(4)** to reduce TAMC to acceptable levels in the **(b)(4)** water. This suggests that it is a critical step in your process, but you did not consider operating parameters that affect performance, such as water flow rate, **(b)(4)**, water **(b)(4)**, and **(b)(4)** age. Additionally, your interpretation of your results is confounded by the fact that your methods are not verified.

In your response, you committed to testing your source water for microbiological contamination. You indicated that you set microbial limits of **(b)(4)** cfu/mL for the source water, and that you removed the microbial limits for the in-process samples of your **(b)(4)** water system.

Your response is inadequate. You failed to provide sufficient detail about how you will remediate your **(b)(4)** water system. In response to this letter, provide:

- a plan to address the open **(b)(4)** source-water storage tank
- a status update of the performance qualification that you initiated in March 2016
- corrective and preventive actions if source water test results exceed the limits
- scientific rationale for setting microbial limits

Contaminated **(b)(4)** water has been the root cause of multiple recalls by other drug manufacturers of non-sterile **(b)(4)** liquids, including instances of adulteration with *Burkholderia cepacia*, an opportunistic pathogen. Therefore, it is imperative that appropriate action and alert limits be established based on validation data; these limits must be low enough to signal significant changes from normal operating conditions.

2. Failure of your quality unit to prepare, review, and approve documents related to the manufacturing of API.

On August 16, 2016, our investigators found a large number of trash bags behind a building on your property. The trash bags contained torn original laboratory and production records, such as analytical test reports, **(b)(4)** water testing reports, and sample notebooks. The information on these discarded, torn documents did not match the official records. Your quality unit did not investigate these discrepancies. On August 18, 2016, when our investigators revisited the area where the trash bags had been, they found that the documents had been removed from the site. These findings indicate that your quality unit is not exercising its responsibilities.

In your response, you admitted that a "gap exist[ed] in the Quality Assurance department" concerning document control. You stated that you implemented enhanced document controls and trained employees to complete records contemporaneously.

However, your response is inadequate because you did not provide any details of your corrective and preventive actions. You also did not address any changes made to ensure that discrepancies are properly investigated. Furthermore, removal of the trash bags containing additional torn documents prevented our investigators from examining these documents. It also prevented your firm from performing a global reconciliation of all torn documents with their official versions.

In response to this letter, provide:

- details and a summary of the system that you established for reviewing CGMP documents to ensure documents are tracked and disposed of properly
- your procedure for handling discrepancies and ensuring ongoing quality unit oversight

3. Failure to verify the suitability of analytical methods.

You failed to ensure that the methods used by your contract testing laboratory, **(b)(4)**, have been verified as suitable for their intended use. It is your responsibility to use a qualified contract testing laboratory that produces accurate and reliable results.

Your firm contracts with **(b)(4)** for release testing. Your quality assurance agreement with **(b)(4)** does not specify method validation responsibilities. During the inspection, our investigators requested the method verifications for the residual solvent, impurity, and microbiological tests performed by **(b)(4)**. You stated that the requested documents were located at **(b)(4)** and that you would retrieve them within 15 days.

In your response, you did not provide the requested documents from **(b)(4)**, but instead provided draft protocols for the residual solvent, impurity, and microbiological testing. You stated that these protocols would be verified by December 15, 2016, but it is unclear which company would perform the verification experiments.

Your response is inadequate. In response to this letter, clarify which company performed the verification. Also, provide the results of an internal review of all the other test methods for your drugs to determine the need for method verification or method validation, as appropriate. If verification or validation is needed, provide a timeline for completion and the company that will perform the verification or validation.

4. Failure to adequately investigate critical deviations.

(b)(4) sent you impurity testing chromatograms that contained unexplained discrepancies in run times as well as aborted runs and reprocessing of data for at least six batches over at least three months. You did not document or investigate these discrepancies.

In your response, you stated that your firm "did not have expertise to interpret, review the outcome of the HPLC chromatograms as to the standards of regulatory agencies." You proposed having **(b)(4)** retest the six batches in the presence of an "expert representative" from Badrivishal to ensure "good chromatographic practices." Moreover, your quality assurance agreement with **(b)(4)** does not specify communication of out-of-specification results or discrepancies.

Your response is inadequate because it lacks details. In response to this letter, describe the corrective and preventive actions you have taken, such as on-site audits and method validations or verifications, that show **(b)(4)** is now qualified to test your drugs. Also, provide proof that your "expert representative" has sufficient education, training, and experience to perform the indicated function. In addition, provide details about your proposed "outside laboratory data review unit" and laboratory review training content to show they can achieve their intended quality control unit oversight purpose.

For further reference regarding OOS test results, see the FDA guidance for industry, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf.

CGMP consultant recommended

Based upon the nature and pervasiveness 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 fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Quality agreement revisions recommended

Firms using contract testing laboratories must comply with CGMP. FDA is aware that many pharmaceutical product manufacturers use independent contractors, such as production facilities, testing laboratories, packagers, and labelers. FDA regards these contractors as extensions of the manufacturer.

You and **(b)(4)** have a quality assurance agreement regarding the testing of your products. You are responsible for the quality of drugs you produce, regardless of agreements in place with your contract testing laboratory. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength, quality, and purity. See FDA's guidance document, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf.

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. 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, manufacturing operations, 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 and manufacturing 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 drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and 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 of the data you generate, including analytical data, manufacturing records, 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 drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- 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

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 at all Badrivishal 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(a) 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.

FDA placed your firm on Import Alert 66-40 on December 19, 2016.

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 continuing to refuse admission of articles manufactured at Badrivishal Chemicals and Pharmaceuticals located at Gat No. 29, Village Jambwade (Induri) and Plot No. 13, Revenue Colony, Talegaon Dabhade, 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, Ph.D., 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 3004058356.

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

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