U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Sri Krishna Pharmaceuticals Ltd. - Unit II 4/1/16

Department of Health and Human Services

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

Warning Letter

Via UPS

WL: 320-16-09

April 1, 2016

Dr. V.V. Subba Reddy
Chairman
Sri Krishna Pharmaceuticals Ltd. - Unit II
A-35, IDA, Nacharam
Hyderabad, Andhra Pradesh
India

Dear Dr. Reddy:

The U.S. Food and Drug Administration (FDA) inspected your pharmaceutical manufacturing facility, Sri Krishna Pharmaceuticals Ltd. - Unit II, located at A-35, IDA, Nacharam, Hyderabad, Andhra Pradesh, India, from December 1- 4, 2014. Our investigator identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211.

These violations cause your drug products to be 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), in that 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 December 24, 2014, in detail and note that it lacks sufficient corrective actions. We also acknowledge receiving additional

correspondence from your firm.

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

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

Your laboratory records did not contain all raw data generated during each test for finished drug products manufactured at your firm. Your quality unit relied on incomplete records to make batch release decisions in support of regulatory submissions to the Agency.

During the inspection, your management acknowledged that employees in your QC laboratories conduct trial HPLC injections prior to the injections submitted as the reported test results. These trial injection data files were stored on separate drives from the reported test result data. In some cases original data files were deleted. The results from these trial injections and other original data were not reported. Our investigator found the following examples:

a. A QC analyst injected eleven identically or similarly named samples for impurity and assay analysis approximately one to fifteen seconds apart from one another, according to the HPLC audit trail for **(b)(4)** DMF submission batches **(b)(4)** and **(b)(4)**. A second analyst injected eight similarly named impurity and assay samples approximately twelve to sixteen seconds apart, according to the HPLC audit trail for the analysis of **(b)(4)** batches **(b)(4)** and **(b)(4)**. Neither analyst reported all results obtained during testing. The laboratory incident reports concluded the first analyst deleted 28 original files due to pressure fluctuations and ghost peaks, while the second analyst deleted original trial injections of working standard and sample testing data due to a problem associated with peak shape. However, your laboratory incident reports provide no evidence to support these conclusions. Both analysts also changed the clock prior to reanalyzing the samples.

b. A QC analyst injected sample P140818008.lcd for the assay analysis of **(b)(4)** (batch **(b)(4)**) prior to the reported sample injections. The “trails” [*sic*] folder where the original sample injection file was saved had been deleted. Your response acknowledges that an analyst deleted eight injections, including the blank, six standards, and a sample.

c. A QC analyst deleted original test method validation data and admitted plans to fabricate sample preparation data. According to the HPLC audit trail, on October 7 and 8, the QC analyst injected two sets of similarly named samples of **(b)(4)** (#1:P141007001.lcd and #1:P 141007001.lcd) for an impurity analysis method validation study. Your analyst deleted data from the first set of injections and submitted only the second set in the validation documentation. The analyst stated that he planned to back-date the preparation data within the worksheets once all testing was complete. However, aside from balance scale tickets, your firm was unable to provide sample preparation data for either sample. Your response states that you

abandoned the method validation study, but you continue to use that method for routine testing. In response to this letter, provide the method validation study that supports your current method for analyzing impurities in **(b)(4)**.

d. You did not include metadata with audit trails in your **(b)(4)** data back-up. In November 2014 the system for HPLC #025 crashed and lost all data collected on the instrument, including audit trail information. We acknowledge that you have implemented **(b)(4)** and **(b)(4)** system back-ups. In your response to this letter, provide a copy of the associated procedures and details on how the back-ups are performed.

e. Prior to October 2014, your gas chromatography instrument sent injection data to PCs without audit trails. The instrument logbook documented analyses that did not appear in the audit trail after your firm said it turned on the audit trail function. Your response does not explain the missing injection data. In response to this letter, compare the logbook and the audit trail and provide an explanation for the discrepancies identified during the inspection.

f. A QC analyst injected sample **(b)(4)**141119009 for the assay analysis of **(b)(4)** batch **(b)(4)**, prior to the reported sample injection. The trial injection was stored in the "trails" [*sic*] folder located on a personal computer. The release chromatogram identified injection **(b)(4)**141119009 as the sample. The trial and release chromatograms for **(b)(4)**141119009 do not match, and they identify different peaks. Your response concluded trial injection **(b)(4)**141119009 was a blank. However, the chromatogram for **(b)(4)**141119009, collected during the inspection, shows **(b)(4)** peaks. You do not explain or provide evidence for how you concluded that this injection was a blank. Furthermore, your response includes a chromatogram for trial injection **(b)(4)**141119009 that differs from the chromatogram our investigator collected. It appears to have been reintegrated; the y-axis scale was changed, and only two of the original **(b)(4)** peaks can be seen.

When analysts delete nonconforming test results, the quality unit is presented with incomplete and inaccurate information about the quality of the products. None of your explanations justify your failure to maintain complete records, nor do they support your practice of repeating tests or deleting test results.

2. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

During the inspection, our investigator reviewed data from your high performance liquid chromatography (HPLC) analysis for release testing, including assay and impurity testing. Your quality control analysts used administrator privileges to change the controls for the time and date settings and manipulate file names to overwrite injections and delete original HPLC test data. Analysts also routinely turned HPLC audit trails on and off. Your response acknowledges these practices.

During the inspection the investigator also noted the following examples of uncontrolled access to electronic systems used to generate data:

a. None of the **(b)(4)** HPLC instruments in your QC laboratory required user-specific log-in names and passwords. Analysts routinely logged in as “Admin” without a password. Your response failed to provide a detailed description of the user roles and responsibilities associated with each instrument in your QC laboratory. In your response to this letter, provide procedures that address user roles and associated privileges for your laboratory instruments.

b. Laboratory data generated by the Karl Fischer autotitrator was not restricted. The program used to run your autotitrator, Tiamo™ 2.3 Light, is unable to record audit trails and cannot support accounts with unique user names and passwords for individual users. We acknowledge your commitment to upgrade to a compliant software package. However, your response is inadequate because you failed to provide an interim solution prior to its installation. In your response to this letter, provide a copy of the performance qualification and training activities associated with the newly purchased software.

c. Your analysts created separate folders on personal computers to store data from trial HPLC injections. For example, during the inspection, our investigator found a data folder labeled “trails” [*sic*]. In response to this letter, provide an assessment of the content of these folders and an evaluation of results that may not have been investigated.

We acknowledge your commitment to set up user access restrictions, discontinue the practice of trial injections, and to institute audit trails for computerized systems. Simply activating audit trail functions and instituting user controls are insufficient to correct the broad data manipulation and deletion problems observed at your facility and to prevent their recurrence. Your response is inadequate because the functions and administrative privileges of the IT Head, QC Head, and other personnel remain unclear. In your response, clarify the specific user roles and associated privileges for each laboratory system, and provide an assessment of the effectiveness of these newly implemented system controls. Also provide a comprehensive assessment of other updates made to your computerized systems.

3. Your firm failed to follow written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and to document same at the time of performance (21 CFR 211.100(b)).

Our investigator discovered that your firm was destroying original batch records and backdating revised replacement pages. For example, our investigator found original pages from five **(b)(4)** batch records (batches **(b)(4)** to **(b)(4)**) discarded outside your facility. Your quality control unit approved revised and backdated master batch record pages that your firm created to replace the discarded pages. The original data were subsequently transcribed and backdated to the time of production. Quality and production managers allowed this practice.

Your response indicated that your firm would not permit backdating in the future and that you would revise procedures to ensure reissued batch record pages are

documented in the incident report register and a change control would be initiated for any minor editorial changes. In response to this letter, provide copies of the revised procedures and an assessment of how widespread the practice of revising and backdating batch records is.

4. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

Your firm said that it initiated a “prospective” process performance qualification protocol to establish the suitability of alternate manufacturing equipment for the manufacture of **(b)(4)**. However, the process qualification protocol was not approved or implemented, and the samples needed to demonstrate batch uniformity were never collected and tested. As a result, you shipped to the United States **(b)(4)** batches (**(b)(4)** to **(b)(4)**) that were manufactured using the unvalidated process with new equipment.

Your firm responded that it will perform a “retrospective” validation using process step-monitoring data and finished product results for **(b)(4)** batches. Your response is inadequate. Process validation, including process qualification, is necessary *before* commercial distribution. You have not explained why manufacturing steps and critical process parameters listed in the validation report do not always match those in your protocol. Your firm failed to plan, design, and execute adequate process validation, and was not in accord with sound pharmaceutical development or quality risk management principles. In response to this letter, provide the prospective process performance qualification protocol and report, if completed.

FDA’s guidance document on *Process Validation: General Principles and Practices* may help you understand our current thinking on approaches to process validation. The guidance is available at **http://www.fda.gov/downloads/Drugs/Guidances/UCM070336.pdf (http://www.fda.gov/downloads/Drugs/Guidances/UCM070336.pdf)**.

Your firm acts as a contract manufacturer for various drug products. 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 manufacture for your clients. There was no evidence that you notified your customers of the manufacturing changes discussed above so that your clients could respond accordingly by, for example, assessing the need to perform stability studies or submit regulatory filings. It is important that you notify your customers of significant problems or discrepancies you encounter during the testing and/or manufacturing of their products. This includes, for example, promptly notifying customers of a significant production problem that could interrupt supply or potentially pose a hazard to the consumer.

Conclusion

The examples above are serious CGMP violations demonstrating that your quality

system does not adequately ensure the accuracy and integrity of the data generated at your facility to support the safety, effectiveness, and quality of the drug products you manufacture. We observed similar issues at your facility in 2007. At that time we found you had improperly integrated HPLC peaks and had not identified and investigated out-of-specification test results.

We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.However, it is your responsibility to ensure that any third-party audit appropriately evaluates the vulnerability of your sophisticated electronic systems to data manipulation. It is also your responsibility to ensure that follow-up actions fully resolve all of your violations. In response to this letter, provide the following.

1. 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 you engage a qualified third-party consultant with specific expertise in the areas where potential breaches were identified to evaluate all data integrity lapses.

2. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

3. 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 that are already underway or completed.

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

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately at drugshortages@fda.hhs.gov so that we 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 in the manufacture of your drug under 21 U.S.C. 356C(a)(1), 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. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA continuing to refuse admission of articles (excluding sodium phenylbutyrate granules) manufactured at Sri Krishna Pharmaceuticals Ltd. - Unit II, located at A-35, IDA, Nacharam, Hyderabad, Andhra Pradesh, into the United States under Section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). The articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3), 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).

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. In addition, if you no longer manufacture or distribute the drug products at issue, provide the dates and reasons you ceased production. Please identify your response with FEI #3005280525**.**

Please send your reply to:

Brooke K. Higgins
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51 Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993

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

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