July 01, 2019 **WARNING LETTER**

Mr. Arun Kumar

Chief Executive Officer/Managing Director

Strides Pharma Science Limited

Strides House, Bilekahalli

Bannerghatta Road

Bangalore 560076

India

Dear Mr. Kumar:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Strides Pharma Science Limited at Unit-II, R. S. No.: 32, 33 & 34 PIMS Road Periyakalapet, Puducherry, from January 28 to February 5, 2019.

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

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products 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 February 26, 2019, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

Your quality unit (QU) lacks appropriate responsibility and control over your drug manufacturing operations.

During the inspection, our investigator observed discarded CGMP documents and evidence of uncontrolled shredding of documents. For example, multiple bags of uncontrolled CGMP documents with color coding indicating they were from drug production, quality, and laboratory operations were awaiting shredding. Our investigator also found a blue binder containing CGMP records, including batch records for U.S. drug products, discarded with other records in a 55-gallon drum in your scrap yard. CGMP documents in the binder were dated as recently as January 21, 2019: seven days before our inspection. Your QU did not review or check these documents prior to disposal.

Your QU is responsible for the oversight of your drug manufacturing operations, including the review and approval of documents and document controls, to ensure a complete contemporaneous record of each batch of drug product manufactured. That record is retained for CGMP purposes including annual review. In addition, your QU is responsible for ensuring your production areas are adequately monitored and that employees understand your firm's procedures and their assigned tasks.

The uncontrolled destruction of CGMP records, and your lack of adequate documentation practices, raise questions about the effectiveness of your QU and the integrity and accuracy of your CGMP records.

In your response you state the binder of CGMP documents in your scrap yard was "inadvertently come [sic] to scrap yard" and that you were investigating the issue. You also committed to using bound log books and restricting printing to reduce uncontrolled documents. In addition, you committed to strengthen your training program to include instructor-led classes geared towards good documentation practices.

Your response is inadequate because, while you acknowledge the binder of CGMP records in your scrap yard, you did not assess other documents found in the scrapyard, nor did you assess how poor documentation practices affected distributed drug product or how you would strengthen your QU oversight.

Your firm's quality systems are inadequate. See FDA's guidance document *Quality Systems Approach to Pharmaceutical CGMP Regulations* for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download

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 firm's investigations of out-of-specification (OOS) results were closed without adequate scientific justification.

For example, you opened an OOS investigation for **(b)(4)** USP active pharmaceutical ingredient (API) for an unknown impurity which exceeded your specification. Your investigation identified an "old reagent" as a root cause, despite your inability to reproduce the unknown impurity. You subsequently retested a new sample with fresh reagents and used the passing results to release the API for use in producing your **(b)(4)** USP drug product. You did not evaluate the original failing API sample. Your root cause determination and investigation were not scientifically justified.

In your response you acknowledged that the original sample should have been tested as part of your investigation to determine a root cause and that the final root cause was not definitively concluded. You analyzed reserve samples for the lots of drug product manufactured with the API and found them to meet specifications. You also provided a retrospective review for all of your previous "invalidated" OOS results for products manufactured between January 2017 and March 2019.

Your response is inadequate. You failed to include the data that supports your reserve sample testing for batches manufactured containing the lot of API identified in your OOS investigation. In addition, you identified nine additional OOS investigations in which your root cause determination and investigation were not scientifically justified. You did not extend your investigation to include any associated reserve samples of batches that may have been manufactured using OOS materials.

In response to this letter:

- For any OOS results with inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, raw materials, process capability, deviation history, batch failure history). Provide a corrective action and preventive action (CAPA) plan that identifies root causes and specifies meaningful improvements.
- Provide all reserve sample testing results. Include all analytical data for the API and drug product batches, including any batches manufactured using API with associated OOS results with inconclusive or no root cause.

For more information about proper handling of OOS results and documenting your investigations, refer to the FDA guidance for industry *Investigating OOS Test Results for Pharmaceutical Production* at

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070287.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. See FDA's guidance document *Data Integrity and Compliance With Drug CGMP* for guidance on establishing and following CGMP-compliant data integrity practices
at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf

We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following:

A. 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.

B. 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 analyses of the 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. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

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.

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 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 Strides Pharma Science Limited, FEI 3012448465, at Unit-II, R. S. No.: 32, 33 & 34 PIMS Road Periyakalapet, Puducherry 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 or mail your reply to:

Carla Norris

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 3012448465.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

cc:

Mr. Umesh Kale
President & Chief Quality Officer

Strides Pharma Science Limited

Strides House, Bilekahalli

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