WARNING LETTER

Stason Pharmaceuticals, Inc.

MARCS-CMS 604889 — JULY 08, 2020

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Mr. Harry T. Fan

Chief Executive Officer

Stason Pharmaceuticals, Inc.

11 Morgan
Irvine, CA 92618
United States

Issuing Office:

Division of Pharmaceutical Quality Operations IV

United States

WARNING LETTER

July 8, 2020

Dear Mr. Fan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Stason Pharmaceuticals, Inc., FEI 1000160561, at 11 Morgan, Irvine, from October 3 to 25, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (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 November 18, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondences.

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

1. 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 was not able to assure that your temozolomide capsules met dissolution attributes throughout its shelf life. You obtained out-of-specification (OOS) results for dissolution testing for multiple lots during stability studies and during testing of retain samples. Investigations were conducted for some OOS results and a relaxed specification was ultimately approved. However, you did not determine a root cause for dissolution variability, nor implement adequate corrective action and preventive action (CAPA) to prevent future dissolution failures using the new specification.

For example, temozolomide capsules, lot 18J043B, failed dissolution testing at the **(b)(4)** stability timepoint with a Stage 3 testing average result of **(b)(4)**% at **(b)(4)**. This lot failed the new, expanded specification of not less than **(b)(4)**% at **(b)(4)**. We acknowledge that the lot was recalled. However, your investigation into the failure was inadequate because it lacked determination of root cause(s) and a CAPA to prevent recurrence. You initially suspected overdrying of the product due to the combined effects of a strong desiccant and sealing improvements, and you conducted studies with alternate desiccants. However, stability data obtained from these studies suggested that decreasing absorption capacity of the desiccant did not improve the dissolution profile.

We acknowledge that FDA approved your expanded dissolution specification. However, your response was inadequate because you did not determine a clear root cause of the dissolution failure found in a lot after the specification was revised. We also acknowledge that your firm continues to perform studies to identify an alternate desiccant. However, your firm was unable to demonstrate that dissolution failures were indeed occurring due to overdrying of the capsules. Your response was inadequate because you failed to provide adequate details regarding the new desiccant study that you were initiating or the formulation modification that you were evaluating. You also did not provide the study protocol or the new CAPA (19-020) that you opened.

In addition, your firm lacked adequate interim measures to address cleaning issues, including a verification failure, following the manufacture of methotrexate tablets.

In response to this letter, provide the following:

- A comprehensive assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure that all phases of investigations are conducted appropriately.
- Your completed root cause investigation and CAPA for dissolution failures observed during release, stability, or any other testing. This should include, but not be limited to, desiccant and formulation

studies, and also address whether additional lots have been placed on the annual stability program to monitor for diminished dissolution performance over the temozolomide capsules shelf life.

- A comprehensive table of all dissolution testing performed on all lots of temozolomide capsules from 2017 to present. This table should include the following parameters:

o Results for all dissolution testing conducted for this product, with designation whether tests were performed as part of batch release, stability studies, complaint sample testing, retain evaluation, or any other testing.
o Lot number.
o Product strength.
o Date(s) of manufacture.
o Date(s) of testing, including dates for tests that were repeated.
o All individual and average results from each stage of dissolution testing (i.e., Stage 1, Stage 2, Stage 3).
o Any failure to meet specification, unexplained discrepancy, unexpected result, out-of-trend result, or invalidated result.
o The specification in place at the time of each test.
o All investigations that were initiated as a result of testing.
o All lots that were placed into your stability program. Also provide the number of lots shipped each year.

- Dissolution testing of retain samples for all lots of temozolomide capsules within expiry.
- A comprehensive assessment of your manufacturing process for temozolomide capsules, including, but not limited to, an evaluation of active ingredients, excipients, raw materials, containers/closures, suppliers, equipment suitability (e.g., mixing, drying, compression), and process variables. Include any supplier or other manufacturing changes that may be the cause of the dissolution issues, and place special emphasis on the potential influence of formulation ingredient variability (both physical and chemical characteristics) on dissolution behavior.
- A summary of current standard operating procedures (SOP) that ensure an appropriate program is in place for verification and validation of cleaning procedures for new products, processes, and equipment. Describe in detail how your firm responds to deviations from limits during cleaning verification studies for a new product that is being concurrently added to shared-use commercial production equipment. Also provide an update on the latest methotrexate cleaning verification and validation outcomes, and note any modifications made to cleaning procedures and practices.

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)).

Your firm lacked controls necessary to assure the integrity of electronic test data. Specifically, you failed to implement sufficient controls to support the integrity of your data and to ensure that only appropriate individuals had administrative rights.

Notably, a demonstration performed during the inspection revealed that the computer operating the **(b)(4)** spectrophotometer (ID: L-563) was not secured such that data files could be deleted without the knowledge of your quality unit. This instrument was used for finished product release and stability testing for several drug products.

Your response was inadequate because it failed to include a comprehensive review of all laboratory instruments to determine whether all user roles are appropriate. You acknowledged that your software was not working as intended and you lacked the necessary knowledge or experience to troubleshoot the issue. You noted that you are pursuing remediation for the **(b)(4)** spectrophotometer. Your response was insufficient because it lacked a retrospective assessment into how system vulnerabilities may have impacted data integrity.

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/media/97005/download (https://www.fda.gov/media/97005/download).

In response to this letter, provide the following:

- A comprehensive, independent assessment and CAPA plan for computer system security and integrity. Include a report that identifies vulnerabilities in design and controls, and appropriate remediations for each of your laboratory computer systems. This should include but not be limited to:

o A list of all hardware that includes all equipment, both standalone and network, in your laboratory.
o Identification of vulnerabilities in hardware and software, encompassing both networked and non-networked systems (e.g., PLC).
o A list of all software configurations (both equipment software and LIMS) and versions, details of all user privileges, and oversight responsibilities for each of your laboratory systems. Regarding user privileges, specify user roles and associated user privileges (including the specific permissions allowed for anyone who has administrative rights) for all staff who have access to the laboratory computer systems, and their organizational affiliation and title.
o System security provisions, including but not limited to whether unique user names/ passwords are always used and their confidentiality safeguarded.
o Detailed procedures for robust use and review of audit trails, and current status of audit trail implementation for each of your systems.
o Interim control measures and procedural changes for the control, review, and full retention of laboratory data.
o Technological improvements to increase the integration of data generated through electronic systems from standalone equipment (e.g., balances, pH meters, water content testing) into the LIMS network.
o A detailed summary of your procedural updates and associated training, including but not limited to system security control to prevent unauthorized access, appropriate user role assignments, and other system controls.
o Provisions for oversight by QA managers, executives, and internal auditors with appropriate IT expertise (e.g., to evaluate infrastructure, configuration, network requirements, data management practices, and segregation of duties including administrator rights).
o A remediated program for ensuring strict ongoing control over electronic and paper-based data to ensure that all additions, deletions, or modifications of information in your records are authorized, and all data is retained. Include a full CAPA plan and any improvements made to date.
o An independent, thorough retrospective assessment into the impact of laboratory system design, control, and staff practices on your data accuracy, completeness, and retention since January 1, 2017.

- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 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 resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Conclusion

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 these violations and for preventing their recurrence or the occurrence of other violations.

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 (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). This also 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.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

FDA may also withhold approval of requests for export certificates and approval of pending new drug applications or supplements listing your facility as a supplier or manufacturer until the above violations are corrected. We may re-inspect to verify that you have completed your corrective actions.

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 ORAPHARM4_Responses@FDA.HHS.GOV or mail your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
U.S. Food & Drug Administration
19701 Fairchild Road
Irvine, California 92612-2506

Please identify your response with unique identifier **604889**.

If you have any further questions, please contact Mariza Jafary, Compliance Officer, by email at Mariza.Jafary@fda.hhs.gov or by phone at (949) 608-2977.

Sincerely,
/S/

Steven E. Porter, Jr.
Program Division Director
Division of Pharmaceutical Quality Operations IV

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