WARNING LETTER

Pharmasol Corporation

MARCS-CMS 570727 — 14/03/2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Marc L. Badia

President

Pharmasol Corporation

One Norfolk Avenue
South Easton, MA 02375
United States

Issuing Office:

Division of Pharmaceutical Quality Operations I

10 Waterview Blvd, 3rd Floor
Parsippany, NJ 07054
United States

WARNING LETTER
CMS #566286

03/14/2019

VIA UPS OVERNIGHT
Marc L. Badia, President
Pharmasol Corporation
One Norfolk Avenue
South Easton, MA 02375

Dear Mr. Badia:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facilities, Pharmasol Corporation, FEI 1250001, at One Norfolk Avenue, South Easton, Massachusetts, from July 23 to August 20, 2018, and Pharmasol Corporation, FEI 3014685473, at 146 Campanelli Parkway, Stoughton, Massachusetts, from August 2 to August 20, 2018.

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 September 12, 2018, responses in detail and acknowledge receipt of your subsequent correspondence.

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

South Easton Facility

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).

You failed to conduct thorough investigations into out-of-specification (OOS) stability testing results, including for drug products that required immediate action due to quality defects.

Your client reported leaking in stability units for three validation lots **(b)(4)** The lots were later rejected. You changed the container-closure system but failed to make sure the leakage was corrected before the initial drug product release in December 2017. During the inspection, FDA found that stability samples manufactured with your new container-closure system were still leaking. Your firm received four complaints of leakage in this drug product in 2018 that you classified as “unconfirmed.” Notably, your firm had other recurring losses of container-closure integrity with at least one other drug product (following product development). These losses were only revealed once you conducted stability studies.

In your response, you suggested that the leaking did not compromise the quality of the drug product. You proposed to stop placing stability samples in a horizontal position, adding “upward arrows” to the shipping cartons, evaluating shipping containers for the necessity of additional dividers, and providing shipper instructions to “keep product upright.” Your response was inadequate in that you did not identify a root cause or suggest a corrective action for the leakage.

Drug products lacking an integral container-closure system may lose efficacy due to loss of solvent, degrade due to exposure to oxygen, fail to meet potency specifications, or suffer from microbial contamination. Furthermore, patients may not receive the required number of doses for their treatment.

In response to this letter, provide the following.

 Your comprehensive investigations into the root causes of leaking containers. Include evaluations of the adequacy of your specifications and tolerances, control of incoming components, the manufacturing process, in-process checks, and final inspections.

 Your corrective action and preventive action (CAPA) plan for all root causes of nonintegral container/closure systems.

 An improved process for risk assessment and an updated assessment of patient hazards associated with loss of package integrity.

 A comprehensive, independent assessment of your overall system for investigating deviations, atypical events, complaints, out-of-specification results, and failures. Your CAPA plan should include but not be limited to improvements in investigations, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA effectiveness.

2. Your firm failed to establish an adequate quality control unit, and procedures applicable to the 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) and (d)).

You lack adequate quality oversight. Your quality unit (QU) failed to review, approve, and close investigations (e.g., laboratory, complaint, and deviations) and CAPA within reasonable time limits. For example, at the time of our inspection, more than 40 deviations were open after your specified due dates. One was open for more than a year.

These open investigations included significant drug product quality issues, such as leaking containers, deviations from key production parameters (e.g., mixing speeds), and OOS solvent assay results in finished drug product release testing. During our inspection, you explained that you believed that lapses in quality system performance were due to the strained quality system, your firm's cumbersome procedures, and inefficient management of resources.

Additionally, your QU did not follow your own procedure for out-of-limit results in your environmental monitoring for viable organisms, which requires investigation and room disinfection. You also did not test for yeasts and molds for two months: you claimed the culture media, **(b)(4)**, were unavailable.

In your response you committed to restructuring your QU and adding chemists, a new stability supervisor, and a director of quality assurance. You wrote that all microbiologically "sensitive" drug products manufactured met all release criteria. You also wrote that you would use a contract microbiology laboratory if you were unable to procure **(b)(4)** in the future.

Your response was inadequate. Regarding your firm's response on environmental monitoring, you did not explain why your QU failed to investigate the cause of out-of-limit results or why your QU did not disinfect the room as required by your procedures. Additionally, you failed to provide a CAPA to ensure that alternate qualified suppliers of microbial test media are available for environmental testing to ensure that sampling is performed as required to verify that your facility is maintained in a clean and sanitary condition.

You were cited for similar QU failures in the 2015 FDA inspection. In your response to the 2015 inspection, you promised to enhance oversight of investigations, allocate new resources, and hire a new stability coordinator. However, significant related problems persisted.

In response to this letter, provide the following.

 A retrospective, independent review of all invalidated OOS (in-process and finished testing) results obtained for drug products currently on the U.S. market within expiry. Assess whether the scientific justification and evidence for each invalidated OOS result was conclusive. For investigations that conclusively established laboratory root cause, determine effectiveness of the CAPA and identify other laboratory methods vulnerable to the same root cause for remediation. For any OOS results with inconclusive or no root cause identified in the laboratory, include a thorough review of production, such as batch manufacturing records, adequacy of the manufacturing steps, raw materials, process capability, deviation history, batch failure history. Provide a CAPA plan that identifies manufacturing root causes and specifies meaningful improvements.

 A review and remediation of your system for investigating OOS results. Provide a CAPA plan to improve OOS handling. Your CAPA plan should ensure that your revised OOS investigations procedure includes:
o Enhanced quality unit oversight of laboratory investigations
o Identification of adverse laboratory control trends
o Resolution of causes of laboratory variation
o Investigations of potential manufacturing causes when a laboratory cause cannot be conclusively identified

 A comprehensive assessment with CAPA to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
o A determination of whether procedures used by your firm are robust and appropriate
o Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
o A complete and final review of each batch and its related information before the QU disposition decision
o Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all drug products

3. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products (21 CFR 211.166(a)).

You did not test stability samples pulled from stability chambers within the **(b)(4)** time frame required by your procedure. In one instance, an 18-month stability sample **(b)(4)** was not tested until 254 days after the sample was received in the laboratory. Your firm's management could not explain this discrepancy at the time of the inspection.

In your response, you committed to hiring additional personnel and allocating additional resources to your firm's stability testing program.

Deficiencies in your stability program are repeat findings from FDA's 2014 and 2015 inspections.

Provide a comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your CAPA plan should include, but not be limited to:
 A remediated SOP describing your stability program
 Stability indicating methods
 Stability studies for each drug product in its container-closure system before you permit distribution
 An ongoing program in which representative batches of each drug product are added each year to the program to determine if shelf-life claims remains valid
 Specific attributes to be tested at each station
 A plan on how you will monitor and ensure that your corrective actions are effective

Stoughton Facility

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).

Our FDA investigator found improperly discarded worksheets in a recycling bin. These worksheets indicated OOS results for measurements of incoming containers and caps for your **(b)(4)** drug product. The final worksheet in your files only reported passing results and there was no reference to OOS measurements.

In your response, you stated that the employee who created these records is no longer with the firm, and these components passed upon reexamination. You also reported that you updated your "good documentation practices" procedure and your procedure for sampling and releasing components.

Your response was inadequate, because it did not provide the re-examination results (including raw data and worksheets) for the bottles and caps to show they met your acceptance criteria.

In response to this letter, provide the following.

 Copies of the original raw data and worksheets documenting your re-examination and measurements of these lots of components.
 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 documentation practices and ensures that you retain complete and accurate records.
 A comprehensive, independent review of your material system to determine whether all containers, closures, and ingredients from each supplier are qualified and assigned appropriate expiration or retest dates. Also determine whether incoming material controls are adequate to prevent your use of unsuitable containers, closures, and components.
 A summary of all OOS results, rejections, and returns for incoming lots of container-closures since January 1, 2016. Include detailed descriptions of each instance and the relevant investigation.

Quality Unit Authority

Your inspectional history indicates that your quality unit is not able to fully exercise its authority and/or responsibilities. Your firm must provide the quality unit with the appropriate authority and sufficient resources to carry out its responsibilities and consistently ensure drug quality.

Repeat Observations at Facility

FDA cited similar CGMP observations in previous inspections of your South Easton facility: September 20 to October 20, 2013; September 16 to October 30, 2014; and July 7 to 16, 2015. You proposed specific remediation for these violations and observations in your responses to our previous communications.

These repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

CGMP Consultant Recommended

Because you failed to correct repeat violations, 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

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.

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 (mailto: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.

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.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

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 orapharm1_responses@fda.hhs.gov (mailto:orapharm1_responses@fda.hhs.gov). Your written notification should refer to the Warning Letter Number above (566286).

If you have any questions, contact Compliance Officer James Mason at james.mason@fda.hhs.gov (mailto:james.mason@fda.hhs.gov) or 570-262-0519.

Sincerely,
/S/

Diana Amador-Toro
Program Division Director/District Director
U.S. Food and Drug Administration
OPQO Division I/New Jersey District

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)