Surmasis Pharmaceutical 11/6/18

Division of Pharmaceutical Quality Operations III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
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November 6, 2018

WARNNG LETTER

Case# 553686

UPS NEXT DAY
SIGNATURE REQUIRED

Mr. Lorne C. Scharnberg
CEO
Surmasis Pharmaceutical
4020 Gannett Avenue
Des Moines, Iowa 50321

Dear Mr. Scharnberg:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Surmasis Pharmaceutical at 4020 Gannett Avenue, Des Moines, Iowa, from February 12 to March 1, 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 March 22, 2018, response in detail.

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

1. Your firm's quality control unit failed to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed (21 CFR 211.192).

Your quality unit procedure, *Out of Specification Investigations* (QCU-007), allowed you to invalidate out-of-specification (OOS) results that you consider to be "outliers" when investigations are inconclusive and fail to show that laboratory error is root cause.

It is inappropriate to use an "outlier test" to invalidate a suspect chemistry result. Such statistical treatments do not identify the cause of an extreme observation, and are only of informational use in an investigation of chemical testing.

When an initial investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing causes must be performed. It is essential for the investigation to fully evaluate the possible sources of manufacturing variation, and further laboratory analyses may also be needed.

If the investigation cannot determine a clear and scientifically sound root cause for the OOS result, you must report the OOS result, along with all other test results, on the certificate of analysis provided to your customer.

Also, your QCU-007 procedure allowed your firm to average the results from any test method following an "outlier" determination. Averaging data is appropriate only for certain methods, samples, and situations (e.g., replicate injections). Your procedure did not restrict data averaging to appropriate situations only.

In your response, you explained that you revised your QCU-007 procedure so that your quality unit reviews all test results, and that your firm will report all "outliers." Your response is inadequate because your revised procedure is still based on the use of "outlier" testing to invalidate an OOS result. It lacks provisions for proper handling of OOS results and thorough investigations.

An OOS test result can occur when a thorough investigation clearly demonstrates that the OOS result does not reflect the quality of the batch. It is also essential for the investigation to include appropriate follow-up and scrutiny to prevent recurrence of deviations or excessive variations, whether in manufacturing or in the laboratory, that may have led to the OOS result.

In response to this letter:

- Provide a retrospective review of all invalidated OOS results obtained for products on the U.S. market. Assess whether the scientific justification and evidence were conclusive. For investigations that established the laboratory root cause conclusively, determine the adequacy of the corrective action and preventive action (CAPA) plan, and ensure that the other laboratory methods vulnerable to the same root cause have been identified for remediation. For any OOS results that had an inconclusive root cause or no root cause identified in the laboratory, include a thorough review of production, such as batch manufacturing records, adequacy of manufacturing steps, raw materials, process capability, deviation history, and batch failure history. Provide a

CAPA plan that identifies the potential manufacturing root causes for all such investigations. Include appropriate process improvements.

- Evaluate all instances in which a statistical "outlier" test was used to invalidate OOS results. Assess batch quality in each instance and take appropriate action on any batch for which quality is not assured.
- Assess your overall system for investigating OOS results. Provide a CAPA plan to improve the quality of OOS investigations. Your CAPA plan should ensure that your revised OOS investigations procedure includes enhanced quality unit oversight of laboratory investigations, identification of adverse laboratory control trends, and investigation of potential manufacturing causes when a laboratory cause cannot be conclusively identified.
- Provide a comprehensive, independent assessment of your overall system for investigations of deviations, atypical events, complaints, OOS results, and failures. Your CAPA plan should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA effectiveness.

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, at **https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf)**.

2. Your firm failed to prepare batch production and control records with complete information relating to the production and control of each batch of drug product produced (21 CFR 211.188).

Your electronic data logs did not retain alarm messages indicating when certain manufacturing parameters exceed their limits during production operations. Specifically, you did not maintain electronic log records of the in-process control alarms for your **(b)(4)** hydrogel coating machine, your **(b)(4)** checkweigher, and your **(b)(4)** packager.

Failure to record excursions of in-process limits for critical manufacturing unit operations, such as applying medicated gels to a fabric liner, rejecting over/underweight patches, and sealing packages, can pose an unacceptable risk to product quality. There is no evidence that you investigated all deviations for their effects on product quality. Specifically, any alarms that may affect manufacturing should be investigated as deviations, and appropriate action should be taken to address variability potentially introduced by the testing equipment or machine fault.

In your response, you provided a list of equipment you will review for electronic data controls, but your response did not address the need to maintain a record of all deviations in the batch record in accordance with 21 CFR Part 211.188, and it lacked a global remediation to ensure electronic record retention.

In response to this letter:

- Provide 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 documentation practices and ensures that you retain complete and accurate records. This review should afford special focus to your electronic record retention and should ensure that electronic data are retained and deviations relevant to manufacturing are captured in your batch records for all manufacturing equipment with automated alarm functions.
- Provide a retrospective review to determine whether potential breaches of your manufacturing parameters had any effect on the quality of products released to the market.

3. 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)).

You used a texture analyzer to measure in-process gelatin bloom, to test elongation, and to test tensile strength of your **(b)(4)** patch. Your audit trails on the texture analyzer showed multiple occasions of additional testing that were not reported for your **(b)(4)** patch, your **(b)(4)** patch, and your **(b)(4)** patch. In addition, you performed instances of additional testing that were not reported on a number of products that could not be identified because your electronic data systems were inadequately controlled. Your systems allowed analysts to assign sample names such as “test1” and “test2,” which do not identify or describe analytical samples. You should maintain data throughout all batch record retention periods with all associated metadata required to reconstruct the CGMP activity.

In your response, you stated that you opened deviations and retrained employees on CGMPs and data integrity. Your response is inadequate. We are unable to fully evaluate your response because you did not provide details on how you would correct your data management and oversight practices, including, but not limited to, audit trails and frequent performance of extra testing. See the Data Integrity Remediation heading immediately below.

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

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, 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 fifteen (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: ORAPHARM3_RESPONSES@fda.hhs.gov.

Attn: Tina Pawlowski
Compliance Officer
U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Please refer to Unique Identification Number (Case# 553686) when replying. If you have questions regarding the contents of this letter, please contact Ms. Pawlowski by phone at (313) 393-8217.

Sincerely,
/S/
Art O. Czabaniuk
Program Division Director
Division of Pharmaceutical Quality Operations III

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)