Samson Pharmaceuticals, Inc. 12/13/18

WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

December 13, 2018

Mr. Jay G. Kassir
President and CEO
Samson Pharmaceuticals, Inc.
2027 Leo Avenue
Commerce, CA 90040

Dear Mr. Kassir:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Samson Pharmaceuticals, Inc., at 2027 Leo Avenue, Commerce, California from January 24 to February 9, 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 February 20, 2018, 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 perform aseptic processing operations within specifically defined areas that have floors, walls, and ceilings of smooth hard surfaces that are easily cleanable, and failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. (21 CFR 211.42(c)(10)(i) and 21 CFR 211.42(c)(10)(iv)).

Your aseptic processing facility is not appropriately maintained. Your **(b) (4)** floors in the aseptic facility are damaged and walls are cracked, rendering them difficult to clean and disinfect. We also observed peeling paint on cleanroom wall surfaces, which can be a source of foreign matter contamination.

Your firm also failed to establish alert and action levels for monitoring personnel during aseptic operations. Your microbial counts on personnel monitoring samples exceed

appropriate microbial counts for the ISO 5 area. Notably, exceedingly high microbial counts were obtained on gloves and other gowning locations of operators participating in manufacturing operations for Pure Eyes **(b) (4)**. Substantial counts were also observed before the production of other lots. You manufacture eye drops labeled as sterile under conditions that render your product vulnerable to contamination with microorganisms. This creates an unacceptable risk for consumers using your product.

Your response stated that you are repairing your walls and floors while seeking a more sustainable solution to resolve the unacceptable cleanroom conditions. You also said you would establish personnel monitoring alert and action levels.

Your response is inadequate because you did not investigate these facility and environmental monitoring deficiencies and assess their effect on the quality of the distributed drug product. You also lacked interim risk mitigation measures, including implementing enhanced facility and environmental controls before manufacturing any new lots. Furthermore, you did not commit to a thorough assessment of your aseptic processing operations to ensure comprehensive remediation of your facilities, equipment, and processes.

Your also did not commit to the performance of routine monitoring of personnel who have conducted aseptic operations. Notably, our inspection findings indicate that excessive microbial counts are found on operators even before they begin aseptic manufacturing operations.

In response to this letter, provide:
• A comprehensive identification of all contamination hazards with respect to your aseptic processes, equipment, and facilities. Provide an independent risk assessment that covers, among other things, all human interactions with the ISO 5 area, equipment placement and ergonomics, air quality in the ISO 5 area and surrounding room, facility layout, personnel flow, and material flow.
• A detailed corrective action and preventative action (CAPA) plan, with timelines, to address the findings of the contamination hazards risk assessment. Describe how you will significantly improve design and control of the aseptic processing operation. Also include significant enhancements to personnel qualifications, practices, and gowning.
• A comprehensive assessment and CAPA plan for your environmental monitoring program (including personnel monitoring) to ensure it supports robust environmental control in your aseptic processing facility. Your assessment should include justification of sampling locations, frequency of sampling, alert and action limits, the adequacy of your sampling techniques, and trending program.
• An independent and immediate risk assessment of Pure Eyes **(b) (4)** and other lots produced under unacceptable conditions. Specify what actions you will take, such as notifying customers and recalling products, if your risk assessment indicates that your drug products may be adversely impacted by your inadequate aseptic processing operations.

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic processes (21 CFR 211.113(b)).

Your firm failed to conduct media fill simulations at appropriate intervals to test whether your aseptic procedures are adequate to prevent contamination during actual drug production. You manufactured **(b) (4)** batches of sterile eye drops between 2015 and 2017 but performed only one media fill simulation on December 26, 2017. There is no assurance that your firm can

consistently and reliably produce sterile drug products because of your substantial lack of aseptic processing operation validation.

Your response stated that you will perform **(b) (4)** media fill **(b) (4)**. This is inadequate. You should conduct media fill simulations every six months for each shift and each processing line.

Also, you lacked smoke studies under dynamic conditions, and the smoke study you provided under static conditions failed to adequately visualize the air flow pattern.

In your response to this letter, provide:
• An independent assessment of your media fill program and processing line qualification, and a CAPA plan to ensure full remediation.
• Provide smoke studies under dynamic conditions, with thorough and complete evaluations of aseptic interventions. Include a video DVD of your dynamic smoke study.

See FDA's guidance document *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf.

3. Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods (21 CFR 211.165(e)).

Your firm failed to validate your use of **(b) (4)** system to perform sterility testing and did not demonstrate equivalency of the **(b) (4)** method to the USP <71> sterility test method. The threshold bioluminescence signal (in relative light units, RLU) was inappropriate and did not provide adequate sensitivity for detecting a non-sterile batch. Several positive control samples spiked with microorganisms yielded negative test results (due to the inappropriately high RLU specification). Your test method is insufficient to reliably detect non-sterility and support release of batches of drug products into the market. You also invalidated, with little or no investigation, test results that may have indicated non-sterility.

Your response indicated that you are now using the USP <71> sterility test method for releasing your products. Your response is inadequate because you did not demonstrate that the previously released drug product batches passed a reliable sterility test.

In your response to this letter, provide:
• Your **(b) (4)** method validation study protocol and planned dates of completion, if you intend to use the **(b) (4)** method in the future. Any such studies should thoroughly evaluate comparability of the **(b) (4)** and USP <71> methods.
• An independent risk assessment for all drug products tested and released using your **(b) (4)** method. Special attention should be paid to all tests that were invalidated (due to reasons such as failed background, failed positive or negative result, failed reading intervened by light, etc.). USP<71> testing of every batch within expiry should be completed within 6 weeks of receiving this letter. Take appropriate market action if the risk assessment determines that any question remains whether a batch within expiry meets the USP <71> sterility test.

4. Your firm failed to ensure the identity of components, including your active ingredients and excipients from various suppliers (21 CFR 211.84(d)(1) and (2)).

Your firm failed to perform identity testing on your incoming drug manufacturing components. You rely on your suppliers' certificates of analysis (COA) in lieu of performing identity testing. For example, you did not test each lot of glycerin for diethylene glycol (DEG) and ethylene glycol (EG), two hazardous impurities that would be detected with the USP identity test method.

In your response you said that you would implement identity testing on all components within three months and qualify your vendors. Your response is inadequate because you did not address whether you will conduct retrospective DEG and EG testing for your drug products.

In your response to this letter, provide:
• A detailed plan to test each incoming component lot for conformity with all appropriate written specifications for identity, purity, strength, and quality. If you accept your suppliers' COA in lieu of testing each component lot for purity, strength, and quality, describe how you plan to establish the reliability of your suppliers' test results for these attributes at regular intervals and include a commitment to test, at minimum, every incoming component lot (both active and inactive ingredients) for USP identity requirements. Also provide your revised standard operating procedure remediating these deficiencies.
• A comprehensive, independent review of your material system to determine whether all containers, closures, and ingredients from each supplier are adequately qualified and assigned appropriate expiration or retest dates and to determine whether incoming material controls are adequate to prevent use of unsuitable containers, closures, and components.
• Your revised standard operating procedure for testing all incoming lots of glycerin to ensure that they are not contaminated with DEG and EG.
• A detailed risk assessment for drug products that contain glycerin and are within expiry in the U.S. market. As part of your risk assessment, immediately test retain samples of all lots for DEG and EG and take appropriate market action if the testing yields any aberrant results.

See FDA's guidance document, *Testing of Glycerin for Diethylene Glycol*, to help you meet the CGMP requirements when manufacturing drugs containing glycerin, at https://www.fda.gov/downloads/Drugs/Guidances/ucm070347.pdf.

5. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

Your firm failed to conduct a long-term room temperature stability study to support the expiration dates of your over-the-counter drug products. For example, the **(b) (4)** expiration date assigned to Pure Eyes sterile eye drops is based only on an accelerated stability study for a different ophthalmic product. This is contrary to the requirements of your firm's stability and expiration dating procedure, which requires performance of long-term room temperature studies for marketed drug products. You have not demonstrated that your products conform to their quality attributes over their labeled shelf lives.

In your response you said that you would review your procedure and add long-term stability studies **(b) (4)** Your response is inadequate because you did not commit to performing long-term room temperature stability studies. CGMP requires ongoing stability shelf life studies for an adequate number of batches of each marketed drug product.

In your response to this letter, provide:
• A full summary of stability data results for all batches tested, with each time interval,

attributes tested, the testing methods used, and the written stability protocol that was followed. Include testing of all microbiological and chemical attributes, and any updated test data to determine whether the integrity of your container-closure systems (i.e., sterility testing, container-closure integrity analysis) is maintained throughout the entire shelf life.
• A comprehensive assessment and CAPA to ensure the adequacy of your stability program. Your CAPA should include, but should not be limited to, a remediated standard operating procedure describing your stability program, stability-indicating methods, stability studies to support each drug product in its container-closure system before distribution is permitted, an ongoing program in which representative batches of each product are added each year to the program to determine if the shelf life claim remains valid, and specific attributes to be tested at each station.

CGMP consultant recommended

Based upon the nature of the violations 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

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.

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 written response to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
1970 Fairchild Road
Irvine, CA 92612

If you have questions regarding any issues in this letter, please contact Mr. William Millar, Compliance Officer at (510) 337-6896, or william.millar@fda.hhs.gov. Please identify your response with unique identifier CMS 554307.

Sincerely,
/S/
CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV