WARNING LETTER

Bershtel Enterprises LLC dba WePackItAll

MARCS-CMS 570885 — 02/05/2019

Delivery Method: VIA SIGNATURE CONFIRMED DELIVE

Product: Drugs
Pharmaceutical Quality
Current Good Manufacturing Practices (CGMP)

Recipient:

Mr. Jack S. Bershtel

Managing Partner

Bershtel Enterprises LLC dba WePackItAll

2745 Huntington Drive
Duarte, CA 91010-2302
United States

Issuing Office:

Division of Pharmaceutical Quality Operations IV

19701 Fairchild
Irvine, CA 92612-2506
United States

WARNING LETTER

VIA SIGNATURE CONFIRMED DELIVERY

CMS 570885

May 2, 2019

Mr. Jack S. Bershtel
Managing Partner
Bershtel Enterprises LLC dba WePackItAll
2745 Huntington Drive
Duarte, CA 91010-2302

Dear Mr. Bershtel:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Bershtel Enterprises LLC dba WePackItAll, FEI 3010166980, at 2745 Huntington Dr., Duarte, from October 15 to November 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 November 14, 2018, response in detail.

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

1. 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 and sterilization processes. Your firm also failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas (21 CFR 211.113(b) & 211.42(c)(10)).

You manufacture under contract a multi-dose, preservative-free, homeopathic ophthalmic drug product for **(b)(4)**. via your broker, **(b)(4)** without adequate controls to ensure sterility of containers/closures and finished ophthalmic drug product. If ophthalmic drugs are not sterile, they pose an unacceptable risk to patients including infection and potential for vision loss.

In addition, it is essential that multi-dose ophthalmic drug products contain one or more suitable substances that will preserve a product and minimize the hazard of injury resulting from incidental contamination during use.

Your filling suite is not suitable for filling sterile drugs, whether aseptically filled or terminally sterilized. For example, you lacked the following:

Floors, walls, and ceilings of smooth, hard surfaces that are easily cleaned
An air supply filtered through high-efficiency particulate air filters under positive pressure
An adequate system for monitoring environmental conditions
A system for cleaning and disinfecting the room to produce aseptic conditions
A system for maintaining equipment used to control the aseptic conditions

Significantly, you also failed to establish procedures for the sterilization of a drug product that is required to be sterile.

For example, you used bulk drug product to fill finished ophthalmic drug product without sterilization before or after filling. During the inspection, you told our investigator that you did not have procedures for filling ophthalmic drugs and you confirmed that you were not equipped to perform sterile drug production.

You also shared a copy of a “waiver” document signed by **(b)(4)** and **(b)(4)** indicating that eye drops would be filled by your firm in a non-sterile environment. Even though you manufacture this drug product on a contractual basis, you are still responsible for ensuring compliance with CGMP for the manufacturing activities you perform. You manufactured a drug product required to be sterile under unacceptable conditions. Your disregard for assuring appropriate manufacturing quality standards puts patients at risk.

To help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, see FDA’s guidance document Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice at https://www.fda.gov/media/71026/download (https://www.fda.gov/media/71026/download).

In your response, you stated that **(b)(4)** did not provide you with hold time information and that as the product owner they bore full responsibility for the manufacturing process and product quality. You committed to cease filling ophthalmic drugs or any other drugs that require sterile processes and to ask customers for

more information in your quality agreements moving forward. However, your response was inadequate because you failed to understand that you cannot waive your responsibility to comply with CGMP for any drug manufacturing activities you perform including, but not limited to, filling and primary packaging. In addition, you did not provide information on how you will determine what drugs are required to be sterile. You also failed to provide the process you will use to screen drug products you are requested to manufacture to avoid manufacturing drug products that require controls beyond your capability.

In response to this letter, provide the following:

Detailed supporting documentation of your corrective actions and preventive actions (CAPA), including, but not limited to, hold times and customer screening criteria for drugs that you may manufacture.

Your CAPA to implement routine management oversight of manufacturing to ensure you have appropriate facilities, capable equipment, vigilant performance monitoring, prompt execution of repairs, effective preventive maintenance, timely upgrades to equipment and facilities, and any other needed actions.

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).

You released ophthalmic drug product without an adequate investigation into visible contaminants you found in ophthalmic bulk drug product. For example, you notified **(b)(4)** of "white specs" before manufacturing, and then relied upon email communication from **(b)(4)** claiming **(b)(4)** gave approval to proceed with manufacturing despite the presence of contamination. You did not conduct a thorough investigation into a root cause of the particulates you identified or assess how the particulates may affect product safety, quality, and purity. You cannot ensure the safety, purity, and quality of your drug products when you perform inadequate investigations.

In your response, you said that you resumed production only after getting approval from **(b)(4)** to "reblend" the particles back into solution. You also said, "it was safe to assume this was precipitated powder particulates and not micro contamination" because testing indicated there was no microbiological contamination.

Your response was inadequate because you failed to provide an investigation into the visible particle contamination and you chose to rely on the assumption that limited testing could provide assurance that the rest of the batch is safe for use. Because microbiological contamination is non-uniformly distributed and difficult to detect during testing, it is essential that stringent upstream controls be employed to assure the quality of a batch.

You also failed to evaluate whether your firm initiated and conducted adequate investigations for all drug products you manufacture that have experienced deviations, out-of-specification results, or other manufacturing quality issues.

In addition, the microbiological test methods that you use have not been shown to be adequate for their intended use.

Lastly, your response indicates that you lack a fundamental understanding of CGMP. Your response states, "we do not manufacture drug products we only repack." However, filling, packaging, and reprocessing bulk drug product are all manufacturing operations and are subject to CGMP requirements.

Although you committed to cease manufacture of sterile drugs, in response to this letter, provide the following with respect to other drugs:

A comprehensive, independent, assessment of your overall system for investigations of deviations, atypical events, complaints, out-of-specification results, and failures. Your CAPA should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and Quality Unit (QU) oversight. Also include your process for evaluating CAPA effectiveness.

A retrospective evaluation of all batches of your drug products that remain in the U.S. market to assess the

adequacy of investigations into any deviations, out-of-specification results, or other manufacturing quality issues. Include a full CAPA (e.g., notification to customers; recall) for any drug products that may have a quality or safety risk.

A plan to establish adequate written quality agreements with each of your customers for all CGMP manufacturing activities performed.

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 hroughout 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 products

3. Your firm failed to maintain written records so that the quality standards of each drug product can be evaluated at least annually to determine the need for changes in drug product specifications, manufacturing or control procedures (21 CFR 211.180(e)).

You failed to conduct annual product reviews of drug products and you have no established procedures for conducting these reviews. When our investigator asked about annual product reviews during inspection, you were not aware that it was a requirement and confirmed you have not conducted them.

Manufacturers are required to conduct periodic evaluation of the quality standards for each drug product. Failure to perform product reviews, at least annually, of each of your drug products compromises your ability to evaluate the adequacy of controls over manufacturing and
adherence to appropriate quality standards for each of your drug products.

In your response, you committed to establishing annual drug product review procedures. However, your response was inadequate because you failed to provide supporting documentation to show that you have drafted and implemented such procedures. In addition, you failed to address the potential effects of your lack of control on the quality of drugs that you manufactured that remain within expiry.

In response to this letter, provide the following:

Your plan to ensure that you will complete product quality reviews at least annually for all drug products that you manufacture and distribute within the United States.

Your procedures for investigating, responding to, and correcting any deviations from product quality and safety standards identified as a part of your product quality review findings and risk assessments.

FDA Sample Results & Drug Recall

Finished drug product samples manufactured at your facility were collected for FDA laboratory analysis.

FDA laboratory analysis of multiple lots of collected ophthalmic drug product confirmed they were contaminated with Bacillus spp., high levels of particulate matter, or both.

The product owner **(b)(4)** recalled all lots of **(b)(4)** after being contacted by the FDA regarding contaminated ophthalmic drug product.

Responsibilities of a Contractor

You produce drugs under contract for customers. You are responsible for the quality of drugs you produce as a contract facility regardless of agreements in place with product owners. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the

FD&C Act for safety, identity, strength, quality, and purity. See FDA's guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements at https://www.fda.gov/media/86193/download (https://www.fda.gov/media/86193/download).

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. We recommend you engage a consultant to help you identify drugs that
are required to be sterile, so you can meet your commitment to cease filling ophthalmic drugs or other sterile drugs.

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.

If you are considering the possibility of manufacturing sterile drugs in the future, notify the FDA of your plans in writing in advance. A meeting can then be scheduled between you and the FDA to discuss the CGMP requirements for the manufacture of sterile drugs.

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.

Your written response should refer to the Warning Letter number above (CMS 570885). Please address your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
United States Food and Drug Administration
19701 Fairchild
Irvine, CA 92612

If you have any questions about the content of this letter, please contact Jessica Mu, Compliance Officer, at 949-608-4477 and reference unique identifier CMS 570885 on all correspondence.

Sincerely,
/S/

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

CC: **(b)(4)**
CC: **(b)(4)**

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