Aerosol and Liquid Packaging, Inc. MARCS-CMS 676746 — JULY 24, 2024

July 24, 2024

WARNING LETTER

Delivery Method:
VIA Electronic Mail
Product:
Drugs

Warning Letter
CMS # 676746

7/24/2024

Dear Mr. Jay:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Aerosol and Liquid Packaging, Inc., FEI 1120890, at 3701-A Southwestern Blvd. Ste. 100, Baltimore, MD, from December 4 to 18, 2023.

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).

In addition, your **(b)(4)** drug product is an unapproved new drug introduced or delivered for introduction into interstate commerce in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a), and is misbranded under section 502(ee) of the FD&C Act, 21 U.S.C. 352(ee). Introduction or delivery for introduction of such a product into interstate commerce is prohibited under sections 301(d) and (a) of the FD&C Act, 21 U.S.C. 331(d) and (a). These violations are described in more detail below.

We reviewed your January 5, 2024 response to our Form FDA 483 in detail.

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

1. Your firm failed to conduct at least one test to verify

the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and 211.84(d)(2)).

Your firm contract manufactures over-the-counter (OTC) drug products, including skin and wound cleanser drug product **(b)(4)** Topical Antiseptic Spray. You failed to test incoming active pharmaceutical ingredients (e.g., **(b)(4)**) and other components (e.g., **(b)(4)** water) used to manufacture this drug product to determine their identity, purity, strength, and other appropriate quality attributes. Additionally, your firm relied on the certificates of analysis (COA) from suppliers of your components, including the active ingredient **(b)(4)**, without establishing the reliability of your component suppliers' test analyses at appropriate intervals.

CGMP requires identity testing for each component lot used in drug product manufacturing, and you can only rely on the COA for other component attributes by appropriately validating the suppliers' test results at appropriate intervals.

Further, your firm has not shown that your **(b)(4)** water, which is also used as a component in the drug products, is suitable for aqueous-based dosage form drug product manufacturing, and, at a minimum, meets the **(b)(4)** Water, USP monograph and appropriate microbials limits. For

example, you failed to appropriately test for conductivity, total organic carbon, and microbial organisms.

Without routine water monitoring of an appropriately designed system, you cannot ensure that your water meets minimum microbiological and chemical standards suitable for the manufacture of drug products.

In your response, you state that you will continue to rely on a COA upon receipt of raw materials and a quality signature for their respective release. Further, you state that you will consult with your water system supplier for their recommendations for sanitizing and testing the system. Your response is inadequate. You failed to describe how you will ensure each component lot received will be tested for identity or how you will appropriately validate the COAs you receive from your suppliers. You also did not provide adequate details of how you will test, monitor, and maintain your water system to ensure that it produces water suitable for pharmaceutical manufacturing. Additionally, you did not consider a retrospective evaluation of potential impact to the products currently on the U.S. market, including any plans to test retain samples.

In response to this letter, provide:

- A comprehensive, independent review of your material system to determine whether all suppliers of

components, containers, and closures, are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.

- The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing.
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your standard operating procedure (SOP) that describes this COA validation program.
- A summary of your program for qualifying and overseeing contract facilities that test the drug products you manufacture.

- A comprehensive, independent assessment of your water system design, control, and maintenance.
- A thorough remediation plan to install and operate a suitable water system. Include a robust ongoing control, maintenance, and monitoring program to ensure the remediated system design consistently produces water adhering to **(b)(4)** Water, USP monograph specifications and appropriate microbial limits.
- Regarding the latter, ensure that your total microbial count limit for water is appropriate in view of the intended use of the products produced by your firm.
- A detailed risk assessment addressing the potential effects of the observed water system failures on the quality of all drug product lots currently in U.S. distribution or within expiry. Specify actions that you will take in response to the risk assessment, such as customer notifications and product recalls.
- A procedure for your water system monitoring that specifies routine microbial testing of water to ensure its acceptability for use in each batch of drug products produced by your firm.
- A procedure governing your program for ongoing control, maintenance, and monitoring that ensures the remediated system consistently produces water that meets **(b)(4)** Water, USP monograph specifications and appropriate microbial limits.

2. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

Your firm failed to adequately qualify the equipment and validate the processes used to manufacture the **(b)(4)** Topical Antiseptic Spray drug product. You have not performed process performance qualification (PPQ) studies, nor did you have a meaningful ongoing program for monitoring process control, to ensure stable manufacturing operations and consistent drug quality. This is a repeat observation from the previous April 2014 and September 2016 FDA inspections.

In your response, you state that you will validate the processes used to manufacture all future drug products. Further, you discuss revisions to the calibration and preventative maintenance practices for your drug manufacturing equipment. Your response is inadequate. You failed to provide adequate details of how you will ensure your drug manufacturing processes will consistently meet appropriate specifications and manufacturing standards. You also did not provide adequate details showing how you will ensure all drug manufacturing equipment will be appropriately qualified prior to use. Additionally, you did not

consider a retrospective evaluation of potential impact to the products currently on the U.S. market.

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately to ensure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established.

Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality are necessary to ensure that you maintain a stable manufacturing operation throughout the product lifecycle.

See FDA's guidance document *Process Validation: General Principles and Practices* for general principles and approaches that FDA considers appropriate elements of process validation, at https://www.fda.gov/media/71021/download.

In response to this letter, provide:

- A remediation plan that better assures ongoing management oversight throughout the manufacturing lifecycle of all drug products. Provide a more data-

driven and scientifically sound program that identifies sources of process variability and assures that manufacturing (including both production and packaging) operations meet appropriate parameters and quality standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, determining the capability and reliability of each manufacturing process step and its controls, and vigilant ongoing monitoring of process performance and product quality.

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for PPQ, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
- A timeline for performing appropriate PPQ for each of your marketed drug products.
- Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.
- Provide a detailed program for designing, validating, maintaining, controlling, and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also, include your program for qualification of your equipment and facility.

3. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

Your firm manufactures OTC drug products and industrial-grade products (e.g., laundry detergents) on non-dedicated manufacturing equipment. You failed to conduct cleaning validation studies to demonstrate that your cleaning and disinfection practices are adequate to remove contaminants and other residues from your shared drug product manufacturing equipment.

In your response, you state that you will perform cleaning validations. Your response is inadequate. You failed to provide sufficient details of corrective action such as your plans to perform cleaning validation for your drug manufacturing operations. You also failed to retrospectively assess the finished drug products that are currently on the market and within expiry for potential risk of cross-contamination with other drug products and/or industrial-grade products.

Inadequate removal of active ingredients and residues from manufacturing equipment during cleaning can result in

cross-contamination of the drug products.

In response to this letter, provide the following:

- Confirmation of whether you will discontinue manufacturing drugs on non-dedicated equipment in your facility and implement appropriate controls to prevent cross-contamination.
- If you intended to continue manufacturing both pharmaceutical and non-pharmaceutical products at your facility, provide a plan to show how you will maintain appropriate separation with dedicated manufacturing equipment for your pharmaceutical manufacturing and industrial product manufacturing operations.
- Provide a risk assessment for all drugs you have previously produced on equipment shared with industrial products. For each product, assess the risk of potential contamination due to the shared equipment, and provide your plans for addressing the product quality and patient safety risks for any product still in distribution, including potential recalls or market withdrawals.
- A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment

that may have been improperly cleaned, and an assessment whether cross-contaminated products may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices and encompass each piece of manufacturing equipment used to manufacture more than one product.

- A corrective action and preventive action (CAPA) plan, based on the retrospective assessment of your cleaning and disinfection program, that includes appropriate remediations to your cleaning and disinfection processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning and disinfection. Describe improvements to your cleaning and disinfection program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning and disinfection execution for all products and equipment; and all other needed remediations.
- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include, but not be limited to, identification and evaluation of all worst-case:

o Drugs with higher toxicities
o Drugs with higher drug potencies
o Drugs of lower solubility in their cleaning solvents
o Drugs with characteristics that make them difficult to clean
o Swabbing locations for areas that are most difficult to clean
o Maximum hold times before cleaning

In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

- A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.

4. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

Your firm failed to establish an adequate quality unit (QU) with the responsibilities and authority to oversee the manufacturing of drug products. For example, you failed to ensure:

- Laboratory records include complete data derived from all tests to assure compliance (21 CFR 211.194(a)).
- Consistent and complete batch records (21 CFR 211.188).
- Appropriate written records of major equipment cleaning, maintenance, and use (21 CFR 211.182).
- Performance of periodic (i.e., at least annual) product reviews (21 CFR 211.180(e)).

There was a fundamental failure of production management to effectively oversee the procedures, practices, and suitability of manufacturing operations. In addition, even when a QU consists of one or only a few, those persons are still accountable for overseeing ongoing effectiveness of all systems and procedures, and review of the results of manufacture to ensure state of control and adherence to all quality standards. This is a repeat observation from the previous April 2014 and September 2016 FDA inspections.

In your response, you state that you will only accept official testing results by contract laboratories in the future; equipment cleaning and maintenance logs will be utilized moving forward; and a review of all products will be conducted to ensure that each production packet includes an itemized list of equipment and container cleaning records. Your response is inadequate as you failed to provide adequate details of your corrective actions.

Your firm's quality systems are inadequate. See FDA's guidance document *Quality Systems Approach to Pharmaceutical CGMP Regulations* for help in implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR parts 210 and 211, at https://www.fda.gov/media/71023/download.

In your response to this letter, provide the following:

- 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.
- A comprehensive assessment and remediation plan 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 products.

Unapproved New Drug and Misbranding Violations

(b)(4) is a "drug" as defined by section 201(g)(1)(B) of the FD&C Act, 21 U.S.C. 321(g)(1)(B), because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and/or under section 201(g)(1)(C) of the FD&C Act, 21 U.S.C. 321(g)(1)(C), because it is intended to affect the structure or any function of the body. Specifically, **(b)(4)** is intended for use as a first aid antiseptic.

Examples of claims observed on **(b)(4)** product label, and product website https://www.**(b)(4)**.com/, that provide evidence of the intended uses (as defined in 21 CFR 201.128) of the product as a drug include, but may not be limited to, the following:

"**Drug Facts** . . . **Uses** . . . Antimicrobial skin cleanser helps reduce bacteria that potentially cause infection" [from your product's label]
"**(b)(4)** is a **(b)(4)** topical antiseptic wound spray...helping to reduce inflammation and drainage to promote wound healing." [from your product website, https://www.**(b)(4)**.com/]

“Patient with for wound **(b)(4)** before **(b)(4)** No painful debridement performed.” [from your product website, https://www.**(b)(4)**.com/]

“**(b)(4)**...over-the-counter topical antiseptic that helps **(b)(4)**.” [from your product website, https://www.**(b)(4)**.com/]

“Managed with **(b)(4)** and **(b)(4)** for **(b)(4)**” [from your product website, https://www.**(b)(4)**.com/]

Unapproved New Drug Violations

Based on the above labeling claims, **(b)(4)** is intended for use as a first aid antiseptic. As described below, this drug product is an unapproved new drug marketed in violation of sections 505(a) and 301(d) of the FD&C Act, 21 U.S.C 355(a) and 331(d).

In general, a drug product is a “new drug” within the meaning of section 201(p) of the FD&C Act,21 U.S.C. 321(p), if it is not generally recognized as safe and effective (GRASE) for use under the conditions prescribed, recommended, or suggested in its labeling; and with certain exceptions not applicable here, a new drug may not be introduced or delivered for introduction into interstate commerce without an approved application from FDA in effect, as described in section 505(a) of the FD&C Act, 21 U.S.C. 355(a). No FDA-approved application pursuant to

section 505 of the FD&C Act, 21 U.S.C. 355, is in effect for your drug product identified above.

Your drug product is marketed as a first aid antiseptic drug product and is subject to section 505G of the FD&C Act, 21 U.S.C. 355h, which governs nonprescription drugs marketed without an approved application. Under section 505G of the FD&C Act, certain nonprescription drugs marketed without an approved application — commonly referred to as "OTC monograph drugs"— may be legally marketed if they meet applicable requirements. With respect to OTC first aid antiseptic drug products, such products are deemed to be generally recognized as safe and effective (GRASE) and not a new drug if, among other things, they conform to the conditions of use set forth in Over-the-Counter Monograph M003: First Aid Antiseptic Drug Products for Over-the-Counter Human Use (henceforth "M003" or the "first aid antiseptic monograph").[1] However, **(b)(4)** does not conform to the conditions of use specified in M003 for the reasons described below.

The labeling for **(b)(4)** includes claims that provide evidence of intended uses that are not consistent with the permitted indications in M003. For example, the website labeling for your drug product states that **(b)(4)** is, "...helping to reduce inflammation and drainage to promote wound healing," and your drug product "...**(b)(4)**." Furthermore, your website

includes case study pictorials and claims that suggest your drug product resulted in "No painful debridement performed" for a patient that had a wound for **(b)(4)**, and that your drug product is an effective treatment "...for **(b)(4)**." Such indications are not permitted under M003.50(b)[2].

Therefore, **(b)(4)** does not comply with the first aid antiseptic monograph described above or any other final order.[3] Moreover, there is no evident basis under the FD&C Act under which this product would be legally marketed without an approved application. Thus, this product is a new drug within the meaning of section 201(p) of the FD&C Act, 21 U.S.C. 321(p). Accordingly, this product is an unapproved new drug marketed in violation of section 505(a) of the FD&C Act, 21 U.S.C 355(a).

Introduction or delivery for introduction of such a product into interstate commerce is prohibited under section 301(d) of the FD&C Act, 21 U.S.C. 331(d).

Misbranded Drug Violations

Additionally, **(b)(4)** is misbranded under section 502(ee) of the FD&C Act, 21 U.S.C. 352(ee), because this product is a nonprescription drug subject to section 505G of the FD&C Act, 21 U.S.C. 355h, but does not comply with the requirements for marketing under that section and is not the subject of an application approved under section 505 of the

FD&C Act, 21 U.S.C. 355.

The introduction or delivery for introduction of a misbranded drug into interstate commerce violates section 301(a) of the FD&C Act, 21 U.S.C. 331(a).

Repeat Observations at Facility

In previous inspections, dated April 23, 2014, and September 13, 2016, FDA cited similar CGMP observations. You proposed specific remediation for these observations in your response. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

Responsibilities as a Contractor

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

Batch Records in Production

Complete and accurate batch production and control records are necessary to ensure that manufacturing processes are consistently followed and reproducible. Additionally, incomplete manufacturing records deprive you

of the ability to adequately investigate deviations and batch failures, and to perform process validation.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, you should engage a consultant qualified as set forth in 21 CFR 211.34 to evaluate your operations and to assist your firm in meeting CGMP requirements. The qualified consultant should also perform a comprehensive six-system audit of your entire operation for CGMP compliance and evaluate the completion and efficacy of your CAPA before you pursue resolution of your firm's compliance status with FDA.

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

Correct any violations promptly. Failure to promptly and adequately address this matter may result in regulatory or legal action without further notice including, without limitation, seizure and injunction. Unresolved violations may also prevent other Federal agencies from awarding contracts.

Failure to address violations may also cause FDA to withhold issuance of Export Certificates. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any violations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to address any violations.

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done to address any violations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices.

If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic response to orapharm1_responses@fda.hhs.gov. Your written notification should refer to Warning Letter CMS # 676746 and include FEI: 1120890.

If you have any questions, contact Compliance Officer Barbara Wilimczyk-Macri at barbara.wilimczyk@fda.hhs.gov.

Sincerely,
/S/

Lisa Harlan
Program Division Director
OPQO Division I
U.S. Food and Drug Administration

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1 Section 505G(a)(1) of the FD&C Act specifies criteria under which certain nonprescription drugs without an approved application are deemed GRASE and not "new drugs," notably, conformance with conditions detailed in applicable OTC monograph documents issued by FDA under 21 CFR 330 prior to enactment of the CARES Act. In the case of OTC first aid antiseptic drug products, relevant documents were deemed under section 505G to be a final administrative order, Over-the-Counter Monograph M003: First Aid Antiseptic Drug Products for Over-the-Counter

Human Use. (See Order ID OTC000030, available at FDA's website OTC Monographs@FDA, https://www.accessdata.fda.gov/scripts/cder/omuf/.)

2 M003 states that allowed intended use claims include, "'First aid to help' (select one of the following: 'prevent,' ('decrease' ('the risk of' or 'the chance of')), ('reduce' ('the risk of' or 'the chance of')), 'guard against,' or 'protect against') (select one of the following: 'infection,' 'bacterial contamination,' or 'skin infection') 'in minor cuts, scrapes, and burns.'"

3 FDA is not aware of any adequate and well-controlled clinical trials in the published literature that support a determination that **(b)(4)** is GRASE for use under the conditions prescribed, recommended, or suggested in its labeling.