# Accupack Midwest, Inc. MARCS-CMS 680228 — AUGUST 15, 2024

August 15, 2024

WARNING LETTER

Delivery Method:
VIA UPS
Product:
Drugs

August 15, 2024

**WARNING LETTER**

CASE #680228

Dear Mr. Proctor:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Accupack Midwest, Inc., FEI 1000122754, at 1060 Meta Drive, Cincinnati, Ohio 45237, from February 22 to 27, 2024.

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).

We reviewed your March 18, 2024, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. In addition, on June 17, 2024, FDA held a teleconference with you to discuss additional information concerning your CGMP operations, including test methods for your **(b)(4)** water system, process validation, and finished product testing.

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

**1. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials,**

**labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).**

Your firm contract manufactures over-the-counter (OTC) drug products, including sunscreens, anti-itch creams, and analgesics. Your firm uses water as a component in your drug products. However, you failed to establish adequate specifications for your component water. For example, you lacked adequate limits and testing for objectionable microorganisms. You also lacked total organic carbon or conductivity limits and testing to ensure that your water met Purified Water USP monograph specifications. You also failed to adequately monitor your water system to ensure that the system is operating properly and continuously producing water suitable for its intended use. Several failures were noted during your firm's **(b)(4)** testing on your water samples where your firm resampled and retested the water without an appropriate investigation (see 21 CFR 211.192).

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 your drug products.

In response to this letter, provide:

- A comprehensive remediation plan for the design,

control, and maintenance of the water system.

- A purified water system validation report. Also include the summary of any improvements made to system design and to the program for ongoing control and maintenance.
- 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.
- The current action/alert limits for total counts and objectionable organisms used for your Purified Water system. Ensure that the total count limits for your purified water are appropriately stringent in view of the intended use of each of the products produced by your firm.
- A procedure governing your program for ongoing control, maintenance, and monitoring that ensures the remediated system consistently produce water that meets Purified Water, USP monograph specifications and appropriate microbial limits.
- 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 comprehensive, independent assessment of your

overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, corrective action and preventive action (CAPA) effectiveness, quality assurance oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

**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 has not established that your processes used to manufacture OTC drug products were validated. Equipment qualification had not been performed on drug product manufacturing equipment, and you lack appropriate qualification of your water system.

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 and assure the quality of raw material inputs, in-process materials, and finished drugs.

Process qualification studies includes intensive monitoring and testing of throughout each significant process stage to characterize intra-batch variation and evaluates batches to 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 is necessary to ensure 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 detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification (PPQ), and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
- A timeline for performing PPQ for each of your

marketed drug products.
- 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.

**CGMP Consultant Recommended**

We acknowledge your commitment to temporarily cease the production of drugs at this facility while you implement corrective actions.

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 audit1 of your entire operation for CGMP compliance and evaluate the completion and efficacy of your CAPAs before you pursue resolution of your firm's compliance status with the 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.

Your response should refer to Case # 680228. Please address your reply via email to: ORAPHARM3_RESPONSES@fda.hhs.gov

Attention: Sneha Patel, Compliance Officer
U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

If you have questions regarding the contents of this letter, please contact Compliance Officer, Sneha Patel at (313) 393-8254.

Sincerely,
/S/

Rebecca E. Dowd
Program Division Director
Division of Pharmaceutical Quality Operation III

Office of Regulatory Affairs

---

***1*** i.e. Quality System, Facilities & Equipment System, Materials System, Production System, Packaging & Labeling System, and Laboratory Control System per FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations at https://www.fda.gov/media/71023/download.