Diamond Wipes International, Inc. 3/7/18

Division of Pharmaceutical Quality Operations IV
19701 Fairchild Road
Los Angeles, CA 92612

Warning Letter

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

March 7, 2018

Ms. Eve Yen
President
Diamond Wipes International, Inc.
4651 Schaefer Avenue
Chino, CA 91710

Dear Ms. Yen:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Diamond Wipes International Inc., at 4651 Schaefer Avenue, Chino, California from May 8–17, 2017.

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 June 7, 2017, response in detail.

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

1. 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 demonstrated that your water system is capable of consistently producing water suitable for pharmaceutical dosage form manufacturing, and, at a minimum, meets the USP monograph for purified water and appropriate microbial limits.

You used water for manufacturing operations that exceeded your microbiological total count action limit in eight instances and exceeded your alert limit numerous times during a 14-month period. You failed to adequately investigate the lack of water system control, and implement adequate corrective actions and preventive actions (CAPA). Notably, in addition to high numbers of microbes (in some cases too numerous to count) in your system, your firm isolated *Pseudomonas* spp., *Burkholderia* spp., and other potentially- pathogenic gram-negative bacteria from the system.

You used water from this system to manufacture your topical drug products over an extended period. For example, you released several lots of antibacterial and acne treatment wipes that were formulated with unacceptable quality "**(b)(4)**" water. Water is the **(b)(4)** ingredient in these formulations.

Your response described an effort to retrospectively investigate the water system contamination problems. You stated that you tested finished product retain samples and found no microbiological contamination. In addition, although your investigation determined there were no analytical errors, you disregarded a finding of *Burkholderia* spp. in your water system "…due to no microbial identification report."

Your response failed to adequately address potential risks to your product posed by objectionable microbiological contamination in your water system. In addition, you did not commit to perform a thorough remediation of your purified water system design and to validate the modified system.

Quality control testing is insufficient to address significant water system control problems. Testing of retains does not provide substantial confidence that contaminated product was not distributed. Microbiological contamination is non-uniform, and negative retain sample results are therefore insufficient to establish the acceptability of other units produced in the affected lots.

You also relaxed your microbiological water alert limit to greater than or equal to **(b)(4)**, and your action limit to greater than or equal to **(b)(4)**. You lack a scientific justification for these relaxed limits, as they are not consistent with the intended use of your aqueous-based drug products which are applied topically. It is critical that your firm incorporates an understanding of the intended uses of your products when determining appropriate manufacturing and testing standards. Benzalkonium chloride antiseptic drugs that are similar to your firm's handwipes product have been historically found to harbor objectionable water-borne microorganisms such as *B. cepacia* when good manufacturing practices were not strictly followed.

In response to this letter, provide:

- A comprehensive evaluation of the water system design, including a thorough CAPA plan to install and validate a suitable water system.
- An effective program for ongoing control, maintenance, and monitoring that ensures the remediated system consistently produces water that meets Purified Water, USP monograph specifications and appropriate microbial limits. Regarding the latter, total count limits significantly tighter than your proposed action and alert limits are generally appropriate for topical products.

- 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. Specify actions that you will take in response to the risk assessment, such as customer notifications and product recalls.
- Your scientific rationale for the microbiological test limits (i.e., total counts, objectionable microbes) for each of your finished drug products, based on their intended use.
- A CAPA that ensures routine species identification of microbes in your water system.

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)

The following drug products were found to contain fungal levels significantly beyond your specification of less than **(b)(4)**:

- Acne treatment facial wipes lot C27
- Acne treatment pads lot 17B6160

Both lots were released without investigation.

Your response stated that you retested acne treatment facial wipes lot C27 before distribution, and retesting did not confirm the initial failed result for yeast and mold. You stated that you did not investigate the initial failing result because you did not obtain a second failing test result, and added that this practice is **(b)(4)**.

Any out-of-specification result is considered to represent the quality of a lot unless a thorough investigation conclusively supports invalidation of the result. It is unacceptable to invalidate an OOS result if you lack a documented investigation that scientifically supports such a conclusion. When no laboratory root cause for an OOS result is identified, or the postulated causes are not conclusively demonstrated, it is essential that you conduct a thorough investigation of all potential production causes (e.g., review of lot manufacturing records, adequacy of manufacturing steps, process capability, deviation history, lot testing history).

In addition, it is important to note that finished product microbiological testing is only the last in a series of controls that are used to evaluate and assure lot quality and consistency. It is essential that robust equipment design and upstream process controls are employed to assure the quality of each lot throughout processing to prevent contamination.

In response to this letter, provide:

- A thorough assessment of your overall systems for investigating deviations, atypical events, out-of-specification results, complaints, and failures. For example, your comprehensive CAPA to these systems should include but not be limited to remediation of your handling of out-of-limit microbiological test results.
- Improved procedures that assure that you promptly review the sources of variation in your operations that may cause errors, deviations, or failures, to detect emerging problems in your operations before they have adverse effects on product quality.
- A detailed investigation and root cause analysis of the source(s) of microbiological contamination for all test results that exceeded your acceptance criteria, and an associated CAPA plan.
- A retrospective review of all lots within expiration date to determine if your firm released other lots not conforming to established specifications or appropriate manufacturing standards.

3. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

You distributed drug product lots prior to conducting all analytical tests, and before your quality control unit (QCU) approved the batch records.

For example, you distributed acne treatment pads lot 17B6160 on April 3, 2017, although assay testing for the active ingredient, salicylic acid, was not completed until four days later, on April 7, 2017.

You also distributed **(b)(4)** acne treatment facial wipe lots on February 15, 2017. However, the QCU did not approve the batch records until 25 days later, on March 10, 2017.

This is a repeat observation from FDA's 2015 inspection at your facility. In 2016, you committed to review all batch records prior to shipment. However, our current inspection found that you did not implement effective corrective actions.

In your response, you stated that you revised your procedures to require the person performing the lot disposition decision to systematically verify that batch records were reviewed.

Your response was inadequate. You did not address why lots were released before your QCU determined that your drug products conformed to all manufacturing standards and quality specifications. In addition, you did not sufficiently address improvements in your quality system to ensure that flaws in lot disposition decisions and all other quality functions will be fully remediated.

In response to this letter, provide:

- A comprehensive assessment of the adequacy of your firm's manufacturing operations.
- A retrospective risk assessment of all unexpired lots of drug products to assess whether any were distributed without prior QCU approval and determine whether each lot met all manufacturing standards and product quality specifications.
- A detailed CAPA plan to ensure full review and final approval of all batch records by the QCU prior to distribution of any lot of drug products.
- A comprehensive assessment and CAPA for your QCU to ensure it is adequately resourced and given the needed authority to effectively discharge its function. The assessment should also include, but not be limited to, determining if procedures used by your firm are robust and appropriate, conducting oversight of manufacturing operations to ensure procedures are followed, approving all investigations, and discharging all other QCU duties.

Responsibilities as a contractor

Your firm acts as a contract manufacturer for drug products. Your failure to comply with CGMP may significantly affect the quality, safety, and efficacy of the drugs you manufacture for your clients. It is essential that you understand your responsibility to operate in full compliance with CGMP, and to immediately inform your customers (e.g., owners, sponsors) of production problems or quality issues that may pose a patient hazard. Your customer also remains responsible for oversight of contract manufacturers to ensure its products are being made in compliance with CGMP.

CGMP consultant recommended

We strongly recommend engaging a consultant, qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. This audit should include a comprehensive evaluation of your operations, including but not limited to: remediation of your water system, sufficiency of the quality unit responsibilities and resources, investigations, CAPA effectiveness, and adequacy of manufacturing processes.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. When significant variability is observed in one or more stages of pharmaceutical production, it is essential that your executive management supports and implements effective actions to address the source of variations and provides for a continued state of control.

Recalls

We contacted your firm to discuss a voluntary recall of lots in distribution that were manufactured with poor-quality water. At the time of this letter, you have not yet initiated a recall, We continue to have concerns regarding the quality of your drug products made with poor-quality water.

Contact us within five days of receipt of this letter to provide an update on your action plan regarding these problematic lots.

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 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 response to:

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

Reference unique identifier CMS 534290 on all correspondence.

If you have any questions about the content of this letter, please contact Jessica Mu, Compliance Officer, at 949-608-4477.

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

Cc:
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