WARNING LETTER

Professional Disposables International, Inc.

MARCS-CMS 617201 — JANUARY 07, 2022

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Mr. Zachary Julius

Chief Executive Officer

Professional Disposables International, Inc.

2 Nice-Pak Park
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United States

Issuing Office:

Division of Pharmaceutical Quality Operations I

United States

WARNING LETTER
WL# 617201

January 7, 2022

Dear Mr. Julius:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Professional Disposables International, Inc., FEI 2411192, at 2 Nice-Pak Park, Orangeburg, NY, during the period of May 5-7, 10, 13-14, 18, 21, 24-28, 2021, June 3, 9-10, and 23, 2021.

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, our inspection revealed that you failed to submit NDA Field Alert reports (FARs) to FDA in compliance with 21 C.F.R. § 314.81(b)(1)(i) and (ii) as required by section 505(k) of the Act [21 U.S.C. § 355(k)]. An applicant is required to submit, within three working days of receipt, information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the

distributed drug product, or any failure of one or more distributed batches of drug product to meet the specifications established for it in the application.

We reviewed your July 16, 2021 response to our Form FDA 483 in detail, and acknowledge receipt of your subsequent correspondence.

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

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).

Your investigations into out-of-specification (OOS) test results were inadequate. You failed to investigate the OOS results in a timely manner, appropriately identify root causes, expand investigations to all potentially affected batches, implement corrective action and preventive action (CAPA), and evaluate CAPA effectiveness.

A. Your investigation OOS 20-0032-NY for Prevantics Swabstick (3.15% w/v CHG and 70% v/v IPA) batch 12000124 was initiated on February 6, 2020, for a Chlorhexidine Gluconate (CHG) assay release test result. The percent of CHG reported was 1.57% **(b)(4)**.

Your quality unit (QU) attributed the OOS result to a pipetting error or incorrect dilution without appropriate supporting evidence, as your analyst did not retain any of the glassware used for sample preparation. Additionally, you retested the batch, **(b)(4)** samples, without **(b)(4)** the original sample. Your firm failed to initiate **(b)(4)** investigation to review your manufacturing process and did not initiate a CAPA. Batch 12000124 was released based on the passing retest result.

B. Your investigation OOS 20-0099-NY for Prevantics® Swab (3.15% w/v CHG and 70% v/v IPA) batch 11900228ES was initiated on March 19, 2020, for CHG **(b)(4)**.

On March 25, 2020, you "**(b)(4)**" the **(b)(4)** of the original sample stock solution and reported two additional OOS results of **(b)(4)** and **(b)(4)**. Your laboratory investigation did not document an assignable laboratory root cause for the OOS result. You retested the Prevantics® Swab batch 11900228ES almost **(b)(4)**. These **(b)(4)** results were within specification.

On July 17, 2020, your QU closed this investigation, almost four months after the initial OOS was obtained. You concluded that the initial OOS result was due to variation among analysts and within the HPLC instrument, without supporting evidence. Moreover, you did not perform an assessment of other batches analyzed using the same HPLC instrument. Your firm failed to initiate a **(b)(4)** investigation to review your manufacturing process, did not initiate a CAPA, and did not determine if other batches were affected.

C. Your investigation OOS 20-0210-NY for Prevantics® Swab (3.15% w/v CHG and 70% v/v IPA) batch 11800257JS at **(b)(4)** was initiated **(b)(4)** after the OOS result obtained.

On March 19, 2020, you reported an incorrect passing assay value of **(b)(4)** (spec. **(b)(4)**) for CHG assay. **(b)(4)**, your quality control unit reviewed the test results and determined that the reported result **(b)(4)** was calculated in error and the result should have been **(b)(4)**, which is an OOS result.

On June 19, 2020, an OOS investigation was opened. You attributed the root cause to a calculation error made by an analyst. On June 23, 2020, and August 12, 2020, new samples were tested and passing results were obtained. Your firm invalidated the initial OOS result and closed the investigation on August 19, 2020, two months after the OOS investigation was initiated, with no explanation for the delay. Your firm failed to initiate a **(b)(4)** investigation to review your manufacturing process, did not initiate a CAPA, and did not determine if other batches were affected.

Furthermore, our review of the annual report for NDA 21524 submitted to the agency on July 16, 2021, found

that you incorrectly reported the **(b)(4)** result, a passing result for the **(b)(4)** interval. Neither a FAR nor an amendment to the annual report was submitted to the Agency.

In all three investigations, you concluded, without adequate scientific justification, that analytical error was the most probable root cause for the original OOS results. Your firm also failed to initiate a **(b)(4)** production review or CAPA at the conclusion of the investigations, including a comprehensive evaluation of the product development, manufacturing validation, previous failing results obtained, and analytical test method.

Your response is inadequate. Although you suggested possible root causes, you lacked scientific evidence to support your conclusions that laboratory errors had occurred. Your firm also failed to initiate appropriate CAPAs. The batch with the OOS result for release testing was released based on passing retest results. For the stability timepoint OOS result batches, there was no evaluation to determine if any other marketed batches were associated with the failure. Further, your response did not evaluate whether other OOS results were inappropriately invalidated (approximately 55 of 78 OOS results were invalidated from May 5, 2019, to May 4, 2021).

We acknowledge your effort in revising the standard operation procedure (SOP) associated with investigating OOS laboratory test results (**(b)(4)**). However, the revised SOP **(b)(4)** version 9 remains deficient. The procedure is not clear on how or when an OOS **(b)(4)** investigation should be initiated and does not ensure that an invalidation of OOS results due to a laboratory error is only based on clear evidence.

Also, your response does not include a comprehensive assessment of your quality system to ensure that OOS investigations are identified and handled in a timely manner.

For more information about handling failing, OOS, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document *Investigating Out-of- Specification (OOS) Test Results for Pharmaceutical Production* at: https://www.fda.gov/media/71001/download (https://www.fda.gov/media/71001/download).

We acknowledge that you plan to implement a CAPA for each OOS investigation cited on the Form FDA-483. However, your CAPA plan does not include any proposed action for the above referenced batches released for distribution and the testing of retain samples to ensure that batches currently on the U.S. market are not compromised.

Furthermore, we acknowledge your decision to initiate a voluntary recall of multiple batches of Povidone-Iodine that failed to meet assay specification. However, Professional Disposables International (PDI), Inc. did not extend the recall to the other products, Prevantics (chlorhexidine gluconate 3.15% (w/v) and isopropyl alcohol 70% (v/v)) Swabstick, Maxi Swabstick and Swab, which also failed to meet assay specifications.

In your response, provide:

• 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, CAPA effectiveness, QU oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

• Provide a revised procedure describing when an OOS laboratory investigation would trigger a **(b)(4)** investigation (e.g., review of production and sampling procedures, additional laboratory testing, interpretation of investigation results, and initiation of CAPAs).

• A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for U.S. products currently in the U.S. market and within expiry as of the date of this letter for the last three years from the initial date of inspection and a report summarizing the findings of the analysis, including the following for each OOS:

o Determine whether the scientific justification and evidence related to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
o For investigations that conclusively establish laboratory root cause, provide rationale, and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
o For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history). Provide a summary of potential manufacturing root causes for each investigation, and any manufacturing operation improvements.

• A summary of results from testing retain samples of all drug product batches within expiry. You should test all appropriate quality attributes including, but not limited to, identity and strength of active ingredients of each batch. If testing yields an OOS result, indicate the corrective actions you will take, including notifying customers and initiating voluntary recalls.

Field Alert Reporting Violations

The inspection revealed that you failed to submit NDA FARs to FDA in compliance with 21 CFR § 314.81(b)(1)(i) and (ii) as required by section 505(k) of the Act [21 U.S.C. § 355(k)] for failing assay results for distributed batches 12000124, 11900228ES, and 11800257JS under NDA 21524. An applicant is required to submit, within three working days of receipt, information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of drug product to meet the specifications established for it in the application.

The intent of the 21 CFR § 314.81(b)(1) regulation is to establish an early warning system so that significant problems are brought to the Agency's attention by applicant holders to prevent potential safety hazards from drug products already in distribution.

We request that PDI, Inc. conducts a retrospective review of all identified OOS events for Prevantics products and perform an assessment of batches that have been distributed, and for which FARs should have been filed in accordance with 21 CFR § 314.81(b)(1) regulation but were not submitted to the Agency.

PDI, Inc. must develop and implement an SOP and appropriate training of all relevant employees detailing the process and responsibilities for handling FARs. PDI, Inc. must send email correspondence to the ORA Division I Recall Coordinator (ORAPharm1Recalls@fda.hhs.gov) if voluntary recalls of the affected batches are deemed necessary. We will verify the implementation and effectiveness of this corrective action during a future inspection of your facility.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, including those you failed to correct, we strongly recommend engaging a qualified consultant, 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.

Firm’s Recall of Drug Product

On July 18, 2021, **(b)(4)** who is the distributor of the Betadine Swab Sticks (Povidone-Iodine Solution 10%) drug product, submitted a FAR to the agency due to the OOS test results in assay reported by PDI, Inc. **(b)(4)** initiated a voluntary recall of Betadine Swab Sticks (Povidone-Iodine Solution 10%) drug product associated with the OOS result.

Povidone-Iodine Production Suspended

We acknowledge your commitment to suspend production of Povidone-Iodine drug products at this facility. In response to this letter, clarify whether you intend to resume manufacturing Povidone-Iodine drug product for the U.S. market at this facility in the future.

If you plan to resume manufacturing Povidone-Iodine drug product for the U.S. market, notify Division of Pharmaceutical Quality Operations I via before resuming your operations at email: ORAPHARM1_RESPONSES@fda.hhs.gov.

Conclusion

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility/in connection with your product(s). You are responsible for investigating and determining the causes of any violations and for preventing their recurrence or the occurrence of other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

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.

If you believe that your products are not in violation of the FD&C Act (or you have complied with FDA regulations), include your reasoning and any supporting information for our consideration.

Send your electronic reply to ORAPHARM1_RESPONSES@fda.hhs.gov. Your written notification should refer to Warning Letter CMS #617201 and include FEI: 2411192.

If you have questions regarding the content of this letter, please contact Jose Hernandez-Guzman, Compliance Officer at jose.hernandez-guzman@fda.hhs.gov or 631-787-3002 x1017 and Liatte Closs, Compliance Officer at liatte.closs@fda.hhs.gov.

Sincerely,
/S/

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