WARNING LETTER

Vi-Jon, LLC

MARCS-CMS 622087 — MARCH 31, 2022

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Richard Koulouris

Chairman and CEO

Vi-Jon, LLC

8800 Page Avenue
St. Louis, MO 63114
United States

Issuing Office:

Division of Pharmaceutical Quality Operations III

United States

March 31, 2022

WARNING LETTER

Case# 622087

Dear Mr. Koulouris:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Vi-Jon, LLC, FEI 1941150, at 8515 Page Avenue, St. Louis, MO, from October 4 to October 13, 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).

We reviewed your November 3, 2021, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

During our inspection, our investigators 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)).

You manufacture over-the-counter (OTC) drug products including benzalkonium chloride-based hand sanitizer[1]. Water is a component in your OTC hand sanitizer drug product. Your sampling plan for your water system is not representative of the overall system and is not appropriate to provide meaningful results for detecting system variability.

Specifically, you sample from only **(b)(4)** point of use (POU) ports for chemical and microbial attributes on **(b)(4)** of production operations. However, our investigator noted at least **(b)(4)** POU ports where you obtain water for drug product manufacturing.

Additionally, you have detected *Burkholderia cepacia (B. cepacia)* in your finished drug products on numerous occasions. Since *B. cepacia* is a waterborne organism, this recurring product contamination further indicates the impact of insufficient monitoring and control of your water system. You did not have appropriate limits to identify an adverse pattern of *B. cepacia* in your water system, nor did you routinely test your water system for the presence of *B. cepacia* utilizing validated methods.

In your response, you stated that you are updating your water system drawings and have identified at least **(b)(4)** POU ports. You also stated that you will perform a "**(b)(4)**" to determine the appropriate number of additional water ports that you will sample. Further, you stated that you will add a specification for the absence of *B. cepacia* to your water testing. Your response is inadequate. You did not provide sufficient details regarding your **(b)(4)**, including how you will ensure that your water system design is appropriate for its intended use, maintained and sampled appropriately, and subject to closer scrutiny to enable prompt detection when the system may be falling out of a state of control.

Because water is used as a component in your non-sterile drug products, the lack of data regarding the state of control of your water system poses a potential risk of introducing objectionable microbial contamination into your products. Pharmaceutical water must be suitable for its intended use and routinely tested to ensure ongoing conformance with appropriate chemical and microbiological attributes.

In your response to this letter, provide the following:

• The chemical and microbiological quality control specifications you use to test and release each incoming lot of components for use in manufacturing.

• 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 water system. Ensure that the total count limits for your system 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 system consistently produces water that meets Purified Water, USP monograph specifications and appropriate microbial limits.

• A comprehensive, independent assessment of the design and control of your firm's manufacturing operations, with a detailed and thorough review of all microbiological hazards.

• A detailed risk assessment addressing the hazards posed by distributing drug products with potentially objectionable contamination. Specify actions you will take in response to the risk assessment, such as customer notifications and product recalls.

• Complete investigations into all batches with potential objectionable microbial contamination or an out-of-specification (OOS) microbiological result (whether or not later invalidated). The investigations should detail your findings regarding the root causes of the contamination.

• Appropriate microbiological batch release specifications (i.e., total counts, identification of bioburden to detect objectionable microbes) for each of your drug products.

• All chemical and microbial test methods used to analyze each of your drug products.

• 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 and microbiological quality (total counts and identification of bioburden to detect any objectionable microbes) of each batch. If testing yields an OOS result, indicate the corrective actions you will take, including notifying customers and initiating recalls.

2. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

Our investigators documented several deficiencies in your equipment maintenance and cleaning program. For example, a leak was observed from a pump within the water purification system. A work order dated May 7, 2021, documented the leak but as of the date of the inspection, the quality unit (QU) had not been notified of the leak, as required by your procedure. Accordingly, an investigation or deviation had not been initiated. A second leak at the **(b)(4)** was observed with water absorbent pads in place to contain the leak. That leak was also not documented. Your water system operating procedure states that leak checks should be performed **(b)(4)**. You lacked documentation supporting the occurrence of these water leak checks. Water leaks are potential areas of entry for microbial growth, which may contaminate component water and subsequently have an adverse impact on the quality of your drug products manufactured.

Investigators also observed raw material leaking from a valve in the material transfer manifold located above tank #422. A **(b)(4)** bucket underneath the leak was nearly half full of what appeared to be a green-blue gelatinous material, and the outside of the bucket appeared to be encrusted with white and brown filth. This material was identified as "the surfactant **(b)(4)**." Your procedure for the storage of raw materials did not adequately assure the proper cleaning and maintenance of equipment.

We also observed rust in the laboratory's laminar air flow hood. The state of maintenance of your laboratory is important to ensure its reliability.

In your response, you stated that new personnel were not assigned or trained on the **(b)(4)** check as specified in your procedure. Additionally, you stated that your procedure lacked sufficient details regarding responsibilities of your quality monitoring program. You also stated that the leaking **(b)(4)** and pump were placed out of service and a change control order was submitted for their repairs. Additionally, your water system drawings are being updated and reviewed by your QU and Engineering to prepare for your water system "capital project." Regarding the leaking of "the surfactant **(b)(4)**", you stated that a work order was submitted to replace the valve and that you will be replacing the piping.

Your response is inadequate. Your response lacked sufficient details to ensure that you have fully remediated your water system and that the various leaks did not impact product quality. You also failed to discuss how you will ensure similar issues in the maintenance of your facility and equipment will not recur.

It is important that you demonstrate that your cleaning and maintenance procedures are adequate and that they are followed to prevent contamination of your drug products.

In your response to this letter, provide the following:

• A comprehensive, independent review and extensive remediation plan for the design, control, and maintenance of the water system.

• A purified water system validation report. Also include the summary of all improvements made to system design and to the program for ongoing control and maintenance.

• A detailed risk assessment addressing the potential effects of the observed water system failures on the quality of all lots of drug products currently in the U.S. market.

• A detailed description of the water system components, include a piping and instrumentation diagram (P&ID), that your firm used to manufacture drug products. Describe the **(b)(4)** and state if it was in series or parallel. In addition, include the updated information on P&ID for your remediated water system and an assessment that verifies the P&ID matches the actual water system design.

• Your corrective action and preventive action (CAPA) plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

3. 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 failed to adequately investigate OOS results and complaints. For example:

• *B. cepacia* was found in your Topical Fungicide Formula lot **(b)(4)**. You destroyed this lot, but you did not adequately investigate the root cause of the microbial contamination. During the investigation, you found *B. cepacia* in a transfer hose, and *Vibrio cholerae* in the "**(b)(4)**" Production Line Bottle Hopper. You ultimately determined that the root cause was a failed sanitization cycle of the water system where it alarmed multiple times during the cycle.

However, you did not determine whether your water system was contaminated with *B. cepacia* or why your water system sanitization cycle alarmed multiple times. You also did not determine the source of the contamination in your transfer hose and bottle hopper. Your CAPA consisted of retraining employees to only clear alarms **(b)(4)** during water system sanitization cycles.

• You initiated an investigation of a complaint regarding missing lot codes on **(b)(4)** FOAM Hand Sanitizer lot 0480285. The root cause was determined to be the overfilling of bottles which resulted in the lot codes being wiped off. However, the root cause for the overfilling of the bottles was not adequately investigated, despite production logs showing that there were approximately nine other stoppage events related to overfilling which resulted in missing lot codes. The QU was unaware of these nine additional stoppage events.

• You did not implement an appropriate CAPA during the investigation into a complaint regarding illegible lot codes for Germ-X 1000ML 70% ALC FOAM SANI INS lot 0520546. You concluded that the "most probable cause" for the smeared lot codes was an isolated event due to overfilled units. However, our investigator noted multiple complaints regarding missing or illegible lot codes that were not investigated adequately.

In your response, you stated that you have updated your user access in your production so that only supervisors have access to "acknowledge the alarms." Additionally, you stated that you will review your complaint practices, add trend analysis, and will conduct a retrospective review of "critical" complaints covering all products that are within expiration. You will also perform a gap analysis of the current risk assessment process and ensure documentation of the risk. You also stated, that once completed, all procedures will be updated, and your team will be trained on these changes. Your response is inadequate. You did not discuss reviewing the QU roles and responsibilities or notifying your customers of any outcomes of your investigations. Additionally, you should review all complaints, not just "critical" ones, to determine their impact on product quality.

Inadequate investigations may result in not identifying or mitigating the root causes of non-conformances and does not ensure consistent production of safe and effective products.

In your response to this letter, provide the following:

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

• A comprehensive, independent assessment of your change management system. This assessment should include, but not be limited to, your procedure(s) to ensure changes are justified, reviewed, and approved by your QU. Your change management program should also include provisions for determining change effectiveness.

• 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

4. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in the master production and control records, or other records (21 CFR 211.68(b)).

Your firm failed to implement adequate controls to support the integrity of your electronic data and to ensure that only appropriate individuals had administrative rights. For example, your **(b)(4)** microbiological testing instrument used for drug product release testing is controlled by a stand-alone computer which does not have appropriate controls in place to prevent deletion of raw laboratory data. All QU users utilized a shared generic account to access the computer which had administrative privileges capable of changing and deleting files. During the inspection, one of your employees opened the computer's recycle bin and noted that approximately **(b)(4)** files and folders were deleted. Further, these deleted items included at least **(b)(4)** files of the "**(b)(4)**" format which your personnel stated were most likely **(b)(4)** data files. The names of **(b)(4)** of those deleted files were similar to drug product formulas produced since 2017.

Additionally, for your **(b)(4)** analytical software, the QU management did not review high-performance liquid chromatography (HPLC) audit trails for drug product testing before release of a batch. The QU reviewed the audit trails only on an **(b)(4)** basis. This is a repeat violation from the 2017 inspection.

In your response, you stated that the common user login was discontinued and administrative rights were assigned to Information Technology personnel outside of the QU. Additionally, you stated that your software is being updated and you will create a new procedure governing user access. Additionally, your response stated that your **(b)(4)** software is being upgraded to a new version and the audit trail for each sample will be printed and added to the data packet for peer and quality assurance (QA) review.

Your response is inadequate because it did not provide sufficient corrective actions to secure the **(b)(4)** software and associated stand-alone computer. You did not describe the user access levels, access privileges, and authorized users for the **(b)(4)** system to collect data, review data, or perform other functions. Your plan to maintain data integrity by allowing only one microbiologist access to the system is not a robust strategy because you have not created a system of access levels and privileges to secure

integrity of your data. You also did not describe where data will be stored to prevent inappropriate access or deletion. Additionally, your response lacked a retrospective assessment of drug product release data collected on the **(b)(4)** instrument or a broader evaluation of how system security vulnerabilities may have impacted data integrity.

Lastly, we recognize the **(b)(4)** software upgrade described. However, your proposed data review procedure is inadequate. The use of static copies of laboratory records (of raw chromatograms, processed chromatograms, and audit trails) are inadequate as they do not preserve the dynamic record format of the full analytical test result which should be a part of the QA review process for release. You must ensure that original laboratory records, including paper and electronic records, are subject to QA review to ensure that all test results and associated information are appropriately reported.

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document *Data Integrity and Compliance With Drug CGMP* for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers-guidance-industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers-guidance-industry).

In your response to this letter, provide the following:

A comprehensive, independent assessment and CAPA plan for computer system security and integrity. Include a report that identifies design and control vulnerabilities, and appropriate remediations for each of your laboratory computer systems. This should include but not be limited to:

• A list of all hardware that includes all equipment, both standalone and network, in your laboratory.

• Identification of vulnerabilities in hardware and software, encompassing both networked and non-networked systems.

• A list of all software configurations (both equipment software and laboratory information management system (**(b)(4)**)) and versions, details of all user privileges, and oversight responsibilities for each of your laboratory systems. Regarding user privileges, specify user roles and associated user privileges (including the specific permissions allowed for anyone who has administrative rights) for all staff who have access to the laboratory computer systems, and their organizational affiliation and title. Also describe how you will ensure laboratory staff are not given administrative rights, or other permissions that compromise data retention or reliability.

• System security provisions, including but not limited to whether unique user names/passwords are always used and their confidentiality safeguarded.

• Detailed procedures for robust use and review of audit trail data, and current status of audit trail implementation for each of your systems.

• Interim control measures and procedural changes for the control, review, and full retention of laboratory data.

• Technological improvements to increase the integration of data generated through electronic systems from standalone equipment (e.g., balances, pH meters, water content testing) into the **(b)(4)** network.

• A detailed summary of your procedural updates and associated training, including but not limited to system security control to prevent unauthorized access, appropriate user role assignments, secondary review of all analyses, and other system controls.

• Your remediated program for ensuring strict ongoing control over electronic and paper-based data to ensure that all additions, deletions, or modifications of information in your records are authorized, and all data is retained. Provide your full CAPA plan and any improvements made to date.

Adulterated Cosmetics: Insanitary Conditions

The cosmetic products (body wash, lotions, and bubble bath) that you manufacture are adulterated within the meaning of section 601(c) of the Act, 21 U.S.C. 361(c), in that they have been prepared, packed, or held under insanitary conditions whereby they may have become contaminated with filth, or whereby they may have been rendered injurious to health. Specifically, during the inspection of your facility, our investigator noted that the **(b)(4)** water system used in the manufacture of cosmetics products may be a potential source of Gram-negative bacterial contamination. Stagnant water and leaking processing lines were observed in the production area. Your firm has a history of investigations that do not appear to adequately determine the root cause of the microbial contamination nor implement effective CAPA (e.g., including routine testing for the absence of potentially pathogenic organisms). Further, there is inadequate cleaning and/or sanitization of equipment used in the manufacturing of cosmetics.

Objectionable Organisms

For further information regarding the significance of *Burkholderia cepacia* complex and other objectionable contamination of non-sterile, water-based drug products, see FDA's advisory notice posted on July 7, 2021, at https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-drug-manufacturers-burkholderia-cepacia-complex-poses-contamination-risk-non-sterile (https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-drug-manufacturers-burkholderia-cepacia-complex-poses-contamination-risk-non-sterile)

Ineffective Quality System

These violations demonstrate a failure of your executive management to exercise proper oversight and control over the manufacture of drugs. You should immediately and comprehensively assess your company's manufacturing operations to ensure that systems, processes, and ultimately, products conform to FDA requirements.

In your response, describe how top management will support QA and reliable operations, including but not limited to, timely provision of resources to proactively address emerging manufacturing and quality issues and to assure a continuing state of control.

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. 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 written notification should refer to the Warning Letter Number above (622087). Please address your reply via email to: ORAPHARM3_RESPONSES@fda.hhs.gov

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

If you have questions regarding the contents of this letter, please contact Eric Mueller, Compliance Officer at (402) 331-8536, ext. 101.

Sincerely,
/S/

Nicholas F. Lyons
Acting Program Division Director
Division of Pharmaceutical Quality Operations III

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1 Due to an increased demand for alcohol-based hand sanitizers during the COVID-19 pandemic, FDA published the Guidance for Industry: *Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)* on March 19, 2020, and subsequently updated the guidance several times. The guidance was withdrawn

effective December 31, 2021 (*86 Fed Reg at 56960*). This guidance communicated the Agency's temporary policy that we did not intend to take action against firms for CGMP violations under section 501(a)(2)(B) of the FD&C Act if such firms prepared alcohol-based hand sanitizers for consumer use (or for use as a health care personnel hand rub) during the public health emergency, provided certain circumstances described in the guidance are present. These circumstances included preparation of hand sanitizer products using only the ingredients and formulas set forth in the guidance. A review of the formulations of the drug products indicates that such products are not prepared consistent with FDA's temporary policy set forth in the guidance. Because Vi-Jon LLC's hand sanitizer products are not consistent with the formulations described in these guidances, they do not fall within any temporary Agency policy not to take action against firms manufacturing hand sanitizer products for violations of section 505 of the FD&C Act.

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