WARNING LETTER

Vitae Enim Vitae Scientific Inc.

MARCS-CMS 620576 — MARCH 17, 2022

Delivery Method:

Via Email

Product:

Drugs

Recipient:

Mr. Charles L. Cavallino

Managing Director

Vitae Enim Vitae Scientific Inc.

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United States

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Issuing Office:

Division of Pharmaceutical Quality Operations IV

United States

WARNING LETTER

March 17, 2022

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Dear Mr. Cavallino:

The U.S. Food and Drug Administration inspected your drug manufacturing facility, Vitae Enim Vitae Scientific Inc., FEI 3014384422, at 3030 Bunker Hill St., Ste 203, San Diego, California, from September 13 to 22, 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 October 11, 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 investigator observed specific violations including, but not limited to, the following.

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Smoke Study Deficiencies

Your procedures did not include a requirement for smoke studies to be performed in ISO 5 classified areas. You also failed to perform smoke studies prior to the inspection. You performed a cursory smoke study during the inspection on September 21, 2021, only after questions from the

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investigator. You have been manufacturing and distributing since January 2020 without assurance your aseptic processing is designed to protect sterile drug product and its containers and closures.

Thorough smoke studies are essential to evaluate the critical ISO 5 aseptic processing areas and the effects of interventions on unidirectional airflow, and to ensure needed design remediations.

We also note that there were multiple design deficiencies in both your ISO 5 cabinet and its aseptic processing line which represent fundamental contamination risks. For example:

• The equipment design, layout, and operating practices of the aseptic processing line, its filling cabinet and the cleanroom pose hazards to sterile products you manufacture.
• The HEPA-filtered airflow is insufficient to ensure robust ISO 5 aseptic conditions throughout the aseptic processing line.
• Your filling machine frequently alarmed during aseptic processing. You explained some of these high priority alarms may be due to air disrupting load balance cells used for weight measurement. You failed to evaluate the impact of the airflow on your aseptic processing line.

In addition, inadequate aseptic processing operator gowning (e.g., some components are not sterile) practices also pose a significant contamination hazard in your aseptic processing operation.

Your response is inadequate. You failed to provide a protocol or a clear description of the extremely limited static smoke study you conducted during the inspection. Your smoke study was not performed under dynamic conditions and did not evaluate personnel interventions. The study also lacked adequate visualization of airflow in the ISO 5 area, including filling, stoppering, and capping areas. Based on our review of your brief recording, we did not observe “unidirectional airflow and sweeping action away from product” as reported in your response to our information request dated February 1, 2022.

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In addition, the revised procedure you submitted does not require smoke studies to be performed under dynamic conditions and only includes **(b)(4)** study as part of the HEPA requalification. In your response to the information request dated February 1, 2022, you stated that smoke studies will not be conducted and that you intend to rely on the **(b)(4)** HEPA filter tests, **(b)(4)** calibration of the magnehelic gauges, and **(b)(4)** verification checks which you believe replace the need to show unidirectional airflow on the aseptic processing line. This conclusion is flawed as these activities do not provide an assessment of unidirectional airflow protection of the aseptic processing line and are not a substitute for smoke studies.

Sterile products are exposed in the ISO 5 area, and therefore vulnerable to contamination. Your aseptic manufacturing process should be designed, qualified, and operations executed, to prevent contamination. Flaws in the design of cleanrooms and aseptic processing lines can lead to an influx of contamination into the critical ISO 5 aseptic processing area and pose a significant hazard to product sterility.

Process Simulation Deficiencies

You failed to establish a procedure which outlines specific training for personnel responsible for the microbiological examination of media fill vials. You also did not require qualified individuals (e.g., microbiologist) to inspect incubated media fill vials for microbial growth.

Your response is inadequate. You committed to revise procedures, train employees, and have appropriate personnel from a microbiology laboratory "inspect the next set of media fills for possible contamination." However, you failed to perform a full assessment of your media fill program and you did not evaluate the impact of untrained personnel on the reliability of past media fill results. You did not provide detailed information regarding the content of your training program and implementation dates for your revised procedures. Furthermore, you failed to indicate if a microbiologist with the appropriate combination of education, training, and experience will provide continuous oversight over media fill vial examinations as a permanent standard operating procedure in the future.

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In response to this letter, provide:
• A comprehensive, independent risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:
  o All human interactions within the ISO 5 area
  o Equipment placement and ergonomics
  o Air quality in the ISO 5 area and surrounding room
  o Facility layout
  o Personnel flows and material flows (throughout all rooms used to conduct and support sterile operations)
  o Personnel gowning standards
• A detailed remediation plan with timelines to address the findings of the independent contamination hazards risk assessment. Describe how you will remediate the design and control of your aseptic processing operation. In particular, include comprehensive improvements in the design of both your aseptic processing lines and cleanrooms. Also describe your plans for qualification and validation of your extensively remediated operations.
• Your plan to conduct smoke studies after you comprehensively remediate the design flaws in your aseptic operation under static and dynamic conditions. Regarding the latter, include comprehensive evaluations of aseptic interventions, operator positioning, and airflow impact within the aseptic processing area. Commit to provide full records of smoke studies to this office upon completion, including both static and dynamic smoke studies.
• A comprehensive independent review of your media fill program.
• An evaluation of the impact of unqualified personnel performing microbiological examinations of media fill units, including an analysis of how unqualified staff can undermine the ability to detect contaminated units

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

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Your environmental monitoring program is deficient. You did not perform active viable air sampling during aseptic processing. In addition, your environmental monitoring procedures for viable and non-viable sampling lacked adequate information on:

- Alert levels
- Frequency of sampling
- When the samples are taken
- Duration of sampling
- Sample size
- Responding to deviations from alert levels
- Routine review of environmental data
- Evaluation of trends.

Vigilant and responsive environmental and personnel monitoring programs should be designed to provide meaningful information on the state of control of your aseptic processing environment and ancillary classified areas. Adverse trends and potential routes of contamination should be identified promptly, allowing for implementation of appropriate follow-up measures to prevent contamination.

Your response is inadequate because you failed to comprehensively address your environmental monitoring deficiencies and the effect of your deficient practices on the quality of distributed drug products.

In response to this letter, provide:

- A comprehensive independent review of your personnel and environmental monitoring program, including but not limited to:
  - o A plan to fully remediate these programs. For example, describe changes to equipment, procedures and practices that will ensure meaningful ongoing data is collected to promptly detect and respond to emerging microbial trends from your classified areas. Provide an updated timeline for implementation of your program, including procedural changes.
  - o A risk assessment based on a retrospective review of personnel and environmental monitoring data since you initiated sterile manufacturing in November 2019.

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3. You 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).

Inadequate oversight of contract testing laboratory

Your Quality Unit (QU) failed to provide adequate oversight of your contract testing laboratory. For example, you failed to ensure analytical and microbiological test methods used by your contract testing laboratory for sterile drug products were validated (or verified). Your contract testing laboratory performed numerous raw material tests, as well as release and stability tests for your sterile drug products (e.g., assay, particulate matter, endotoxin, and sterility). Furthermore, you failed to evaluate chemical and microbiological method validation and verification as part of the supplier quality audit report of the contract laboratory. In the quality agreement with your contract laboratory, you accepted responsibility for overseeing method validation and verification, but you failed to perform this role.

Your QU is responsible for ensuring the test methods used and data obtained by your contract testing laboratories are accurate and reliable. The release of drug products without assurance they have the identity, strength, quality, and purity they purport or are represented to possess could result in undetected hazards to patients.

Your response is inadequate. You acknowledged you did not have the method verification and validation records, and you requested the documents from your contract testing laboratory. In addition, you stated you would move testing in-house that you "determine to be critical" to your operations. However, you did not provide further details of your laboratory capabilities for testing. Your response stated a change control and risk assessment would be developed for these new activities, but you did not provide timelines for completion.

The FDA cited a similar observation in your February 2019 inspection. Your March 2019 response committed to ensure that future contract testing laboratories would have verified USP procedures or appropriate method

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validation.

Without appropriate validated (or, as appropriate, verified) methods, you cannot make appropriate batch release decisions, stability decisions, and other decisions that are fundamental to an ongoing assurance of quality.

In response to this letter, provide:
• An independent, comprehensive assessment of all contract laboratory methods, equipment, documentation, and analyst competencies. The assessment should include an evaluation of the reliability of the data generated by your contract testing laboratories. Based on this review:
  o Provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  o An assessment of the impact of these findings on your drug products.
• A list of chemical and microbial specifications for both release and stability test, including test methods, used to analyze each batch of your drug products before a batch disposition decision. In addition, for each provide the following:
  o Your assessment for each method used to test a compendial article or substance to determine if it follows the compendial test procedures.
  o For each method found to differ from the compendial method, provide your detailed plan to determine whether the method is equivalent or better than the compendial method and the date by which this activity will be completed.
  o A list of method verification and validation studies with report approval dates for each sterile and non-sterile drug product.
• A summary of your program for qualifying and overseeing contract facilities that test or perform other CGMP functions on your behalf. Provide documentation of roles and responsibilities for each supplier, including packagers, labelers, distributors, contract manufacturers, contract testing laboratories, or other activities related to your drug product. Include names, addresses, FDA registration information, and a description of services provided.

Inadequate qualification of suppliers

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Your QU failed to adequately evaluate the potential quality impact of a new sterile **(b)(4)** supplier on your sterile drug products. For example, you failed to adequately qualify your new supplier and your change control form does not indicate that you performed water testing prior to accepting the supplier for this drug component. Furthermore, you did not adequately evaluate the removal of pH from your **(b)(4)** specification and its impact on your drug products.

Without appropriate change management, you lack assurance that product quality is not adversely affected.

Your response is inadequate. You committed to revise your change management procedures and perform a retrospective assessment of the sterile **(b)(4)** supplied by your vendor. However, you failed to perform a retrospective assessment of other supplied materials that may impact product quality.

In response to this letter, provide:
• A comprehensive, independent assessment of your change management system. This assessment should include, but not be limited to, your procedures to ensure changes (including supplier changes) are justified, reviewed, and approved by your quality assurance unit. Your change management program should also include provisions for determining change effectiveness (e.g., placing lots on stability when there are significant changes to the operations).
• A retrospective assessment of your change in supplier for sterile **(b)(4)**. This should include, but not be limited to the removal of pH from your sterile **(b)(4)** specification.
• 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.

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4. 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 lacked adequate investigations, including insufficient root cause determination and failure to expand investigations to all potentially affected batches.

For example, your deviation report stated, "when transferring **(b)(4)** from formulation vessel to the ISO 5 filling space… the ink from the tubing started leeching into the solution." It also stated, "It seems the ink, or the process by which the ink is applied to tubing changed." Although you rejected the sub-batch, the investigation lacked a determination of the root cause. Your investigation also lacked a well justified scope, including a review of other batches of **(b)(4)** and other drug products manufactured using the same tubing that may have been adversely affected by this chemical contamination. The investigation also lacked information relating to the toxicity of this foreign contaminant in parenteral products.

Your response is inadequate because you failed to evaluate the potential of ink leaching into previously manufactured batches of drug products. You committed to perform a risk assessment to evaluate the change in transfer tubing. However, you failed to provide your risk assessment in your subsequent responses.

In response to this letter, provide:
• A thorough and complete risk assessment that evaluates how leaching ink may have affected the quality of your drug products. Include the following:
  o A list of products, including batch numbers and dates manufactured which used the tubing
  o The chemical name, composition, and toxicity of the contaminant that leached into the product
• A detailed description of your drug product transfer process prior to implementation of the CAPA. Explain how ink from the outside of the transfer tubing came in contact with the drug product solution and allowed ink to leach into that solution.

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• A comprehensive assessment of the overall system for investigating deviations and discrepancies. Provide a detailed action plan to remediate this system to include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, corrective action and preventive action (CAPA) effectiveness, quality oversight, and written procedures. Address how your firm will ensure that all phases of investigations are appropriately conducted.
• Your 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, timely upgrades to equipment and facilities, adherence to appropriate preventive maintenance schedules, effective execution of repairs, and improved systems for ongoing management review.

5. Your firm failed to establish and follow adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product (21 CFR 211.110(a)).

You failed to adequately inspect your sterile drug products for visible defects and contamination.

Your limited post-fill visual inspection of aseptically filled drug products was insufficient to identify defects which may be present. For example, only a small number of vials were inspected, and they were not inspected against solid color backgrounds (i.e., white and black) to identify visible defects such as particulates and cloudiness. You also lacked procedures for this visual inspection activity.

Your response is inadequate. Although you committed to create a visual inspection procedure, you did not provide details or interim controls until your remediated program is in place. You also did not perform a risk assessment for products already released. Furthermore, you did not provide details as to how your program would ensure personnel are able to reliably identify visible defects.

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In response to this letter, provide:
• A formalized 100% visual inspection program designed to detect particulate contamination and other visible defects. Your program should detail the inspection process, identify categories of defects and their associated acceptance and rejection limits for each batch, and include inspector training and qualification.
• A retrospective review of drug product batches released without having undergone a complete and appropriate visual inspection by qualified inspectors.
• Perform a visual inspection of retain samples for all batches already in distribution and provide the results.

Product Recall and Future Manufacturing

We acknowledge you initiated a recall of all products intended to be sterile that are within expiry after discussions with the FDA.

Notify this office if you plan to resume production and distribution of sterile products, so that the FDA may conduct a follow-up inspection. This notification should occur only after the violations at your firm have been fully remediated and verified by an independent third party (see CGMP consultant paragraph below). It is essential that this remediation be supported by well-designed equipment and facilities, robust processes, and satisfactory qualification and validation studies.

We note your recent proposal dated **(b)(4)**, regarding **(b)(4)** of previously manufactured products in your control; however, additional information is required to establish the scientific basis of your approach. This information should include details such as, and not limited to, stability (including integrity) of container-closure systems and formulations for each product, as well as qualification and validation studies.

After receipt of this letter contact this office to schedule a meeting.

Additional Guidance on Aseptic Processing

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See the FDA's guidance document *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at https://www.fda.gov/media/71026/download (https://www.fda.gov/media/71026/download).

Additional Guidance on Process Validation

See the FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that the FDA considers appropriate elements of process validation at Process Validation: General Principles and Practices | FDA

Responsibilities as a Contractor

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

You are responsible for the quality of drugs you produce as a contract facility regardless of agreements in place with application sponsors and product owners. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength, quality, and purity. See the FDA's guidance document *Contract Manufacturing Arrangements for Drugs: Quality Agreements* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/contract-manufacturing-arrangements-drugs-quality-agreements-guidance-industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/contract-manufacturing-arrangements-drugs-quality-agreements-guidance-industry)

Repeat Observations at Facility

In a previous inspection, dated February 2 to 27, 2019, the FDA cited similar CGMP observations. You proposed specific remediation for these observations in your response.

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Repeated failures to address deficient operations demonstrate that executive management oversight and control is inadequate.

CGMP Consultant

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.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, the FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that the 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 the 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.

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Failure to address violations may also cause the FDA to withhold issuance of Export Certificates. The 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 reply to ORAPHARM4_Responses@FDA.HHS.GOV or mail your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
U.S. Food & Drug Administration
19701 Fairchild Road
Irvine, California 92612-2506

Please identify your response with unique identifier 620576.

If you have any further questions, please contact Nayan Patel, Compliance Officer, by email at Nayan.Patel1@fda.hhs.gov or by phone at (303) 236-3010.

Sincerely,
/S/

CDR Steven E. Porter, Jr.
Program Division Director
Division of Pharmaceutical Quality Operations IV

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