WARNING LETTER

Jost Chemical Co.

MARCS-CMS 626894 — JULY 18, 2022

Delivery Method:

UPS

Product:

Drugs

Recipient:

Mr. Jerry L. Jost

President and CEO

Jost Chemical Co.

8150 Lackland Rd
Saint Louis, MO 63114
United States

Issuing Office:

Division of Pharmaceutical Quality Operations III

United States

July 18, 2022

WARNING LETTER

WL # 626894

Dear Mr. Jost:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Jost Chemical Co., FEI 3001239108, at 8150 Lackland Rd., Saint Louis, Missouri, from January 10 to 21, 2022.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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 February 10, 2022, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. During our inspection, our investigators observed specific deviations including, but not limited to, the following.

1. Failure of your quality unit to ensure that quality-related complaints are investigated and resolved, and failure to extend investigations to other batches that may have been associated with a specific failure or deviation.

Your investigation into a quality-related complaint and out of specification (OOS) results was inadequate. For example, in August 2018, you received a complaint for Potassium Sulfate, USP lot 36830004 due to mold contamination. Retain testing showed a "gross mold failure" that failed to meet your specification of no more than (NMT) **(b)(4)** in lot 36830004. You also identified levels of mold in two additional lots that also failed to meet the specification. You did not initiate a formal recall with FDA notification but instead informed your clients the lots failed to meet specifications and instructed them to return or destroy the failing lots. In addition, your retests showed pervasive mold in three lots, but you did not expand your investigation sufficiently to include other potentially impacted lots to fully address the scope of the problem. Further, your investigation did not adequately document:

• The drug product lots produced and campaign length
• The historical review of the type of failure, product, or equipment
• Actions taken to remediate your assigned root cause

Your response is inadequate. You propose to improve your investigation procedures. However, you do not commit to evaluate the impact on products manufactured from the date of the failure in March 2018 through September 2018, the date of implementation of corrective actions and preventive actions (CAPA). In addition, your OOS investigation procedure does not include sufficient detail to ensure your quality unit (QU) conducted a thorough investigation to evaluate all lots potentially affected by an unexplained discrepancy, or to evaluate the effectiveness of implemented CAPA.

In response to this letter, provide:

• A retrospective review of OOS investigations you have initiated for the past three years to identify investigations that were not expanded to include all potentially impacted lots. The review should include, but not be limited to, identifying gaps in scope determination, root cause determination, CAPA implementation and effectiveness. Provide your revised OOS investigations procedure.

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

• 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. Failure to establish adequate written procedures for cleaning equipment and its release for use in manufacture of API.

Your cleaning validation for your non-dedicated manufacturing equipment is inadequate.

A. Your quality assurance personnel stated that equipment cleaning is performed between manufacturing campaigns which can vary in length between **(b)(4)** and **(b)(4)** and between **(b)(4)** lots. However, your cleaning validation (18PRO054) did not document or detail the campaign length evaluated for all equipment. Further, your cleaning procedure did not define the campaign length before cleaning. The cleaning validation also failed to include testing for microbial contamination.

B. You performed cleaning validation on one manufacturing equipment train using a product you identified as worst-case. However, your cleaning validation program did not adequately evaluate the remaining equipment used to manufacture API at your firm.

Your response is inadequate. Although you state you are currently performing cleaning validation for a **(b)(4)** lot campaign, your cleaning validation lacks the following:

• Adequate evaluation of remaining equipment used in API manufacture

• Testing for microbial contamination

• An evaluation of the bioburden that may be present during a prolonged manufacturing run

Notably, your cleaning procedures allow for other cleaning agents to be used, for which no cleaning validation was provided.

In response to this letter, provide:

• A CAPA plan, based on an independent, retrospective assessment of your cleaning program, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning execution for all products and equipment; and all other needed remediations.

• Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst-case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:

o Drugs with higher toxicities

o Drugs with higher drug potencies

o Drugs of lower solubility in their cleaning solvents

o Drugs with characteristics that make them difficult to clean

o Swabbing locations for areas that are most difficult to clean

o Maximum hold times before cleaning

In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

• A summary of updated procedures that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.

• Provide all cleaning validation reports for your manufacturing equipment trains used to manufacture API. Clearly identify the cleaning agents used, equipment trains, and API(s) selected. Provide your scientific rationale for the cleaning agents and API selections.

3. Failure to ensure that all test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and purity, and failure to ensure laboratory data is complete and attributable.

Your microbial test procedure is inadequate. Your procedure did not include growth promotion studies to verify the adequacy of the media for its intended use. You used microbial growth media prepared in-house and relied only on the original media vendor certificate of analysis (CoA) test results.

In addition, the records reviewed did not include the identity of the analysts who inoculated the plates for microbial testing.

Your response is inadequate. You state you will **(b)(4)**. However, you do not commit to review historical microbiological data to evaluate the impact of inadequate microbiological laboratory practices on the reliability of test results.

In response to this letter, provide:

• A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

• 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 API 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 OOS microbiological result (whether or not later invalidated). The investigations should detail your findings regarding the root causes of the contamination.

4. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to establish and follow written procedures for the operation and maintenance of your computerized systems.

You have insufficient controls over CGMP data. For example:

• You lacked unique passwords for laboratory instruments used to generate analytical data for finished API products.

• Your analytical systems lacked controls to prevent users from deleting electronic data.

• You lacked procedures governing the review of audit trails of both production and laboratory equipment by your QU.

• You lacked procedures or controls for critical alarms for your production process.

Your response is inadequate. You propose to issue unique passwords and establish an audit trail and review procedure. Your response does not include interim control measures and procedural changes for the control and review of analytical data. You also have not specified the frequency of audit trail reviews of your analytical instrument systems. In addition, you do not provide details for evaluating criteria for the selection of critical process steps for alarms.

Lastly, you do not commit to perform a retrospective review of laboratory and production data to evaluate the impact of inadequate controls over CGMP data on the reliability of your results.

In response to this letter, provide:

• A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate,

contemporaneous records throughout your operation.

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

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

o Identification of vulnerabilities in hardware and software, encompassing both networked and non-networked systems (e.g., PLC)

o A list of all software configurations (both equipment software and LIMS) 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.

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

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

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

o 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 LIMS network

Data Integrity Remediation

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*: Questions and Answers for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/119267/download (/media/119267/download).

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

Water systems

Your firm manufactures API that are used by your customers to produce sterile drug products. You have not demonstrated that the **(b)(4)** used to clean your manufacturing equipment is suitable for its intended use. The 2021 **(b)(4)** report as provided in your response showed mold counts varied significantly between April and October. Notably, you reported that approximately 83 percent of your microbial product failures were mold-related failures. Your current frequency of testing and water quality standards are inadequate to ensure control over your manufacturing processes. You are responsible for ensuring the water for equipment cleaning and manufacturing is of suitable quality and does not potentially contribute to contamination of microbes or microbial byproducts to API processes.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations 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 deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of any deviations and for preventing their recurrence or the occurrence of other violations and deviations.

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 deviations 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 deviations may also prevent other Federal agencies from awarding contracts.

Failure to address deviations 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 deviations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to address deviations.

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 deviations 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.

Please address your reply via email to: ORAPHARM3_RESPONSES@fda.hhs.gov

Attention: Nicholas F. Lyons, Director of Compliance
U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Your written notification should refer to the Warning Letter Case Number above (#626894). If you have questions regarding the contents of this letter, please contact Nicholas Lyons at (312) 596-4220.

Sincerely,
/S/

CDR Jeffrey D. Meng
Program Division Director
Division of Pharmaceutical Quality Operations III

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