WARNING LETTER

Indiana Chem-Port

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Delivery Method:

Via Email

Product:

Drugs

Recipient:

Mr. Hitendra Desai

General Manager

Indiana Chem-Port

349 GIDC Industrial Estate
Makarpura, Vadodara Gujarat
India

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-22-11

AMENDED

February 2, 2022

Dear Mr. Desai:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Indiana Chem-Port, FEI 3005564386, at 349 GIDC Industrial Estate, Makarpura, Vadodara, Gujarat, India, from August 2 to 7, 2021.

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 drugs 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 acknowledge receipt of your October 15, 2021, response to our Form FDA 483.

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

1. Failure to ensure that equipment surfaces in contact with API do not alter the quality of the API beyond the official or other established specifications.

You failed to ensure the equipment used in the manufacture of API is suitable for its intended use and is properly maintained. For example:

• Rust-like residues were observed on product contact surfaces of your equipment labeled as clean, including **(b)(4)** vessels and hoses.
• Tape was used on **(b)(4)** paddles to prevent black material from screws from contaminating your API.
• A **(b)(4)** was used to attach a **(b)(4)** to a piece of equipment.
• Several holes were observed in a **(b)(4)**.

Further, you lacked a procedure to qualify your manufacturing and quality control laboratory equipment. You currently manufacture and test **(b)(4)** API in unqualified equipment.

In your response you indicated that the rust-like residue cannot be rust. Your response is inadequate. You failed to identify the source of the brownish residue on the **(b)(4)** vessels and hoses. Your response does not adequately address the poor condition and state of disrepair of your equipment which increases the risk of foreign material contaminating your **(b)(4)** API. Notably, your **(b)(4)** API, is intended for the production of a sterile injectable drug product, **(b)(4)**.

In response to this letter provide:

• 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.
• Provide a plan to ensure that your equipment is of appropriate design, adequate size, and suitably located for its intended use. The plan should include CAPAs that ensure product contact surfaces do not alter the quality of the intermediates and API.

2. Failure to demonstrate that your manufacturing process can reproducibly manufacture an API meeting its predetermined quality attributes.

You failed to validate the manufacturing process for **(b)(4)** API. You stated you have not validated the manufacturing process for **(b)(4)** API because the batches are manufactured by customer orders. You made several changes to your manufacturing process without justification or change control. For example, you changed the amounts of **(b)(4)** water and **(b)(4)** added.

See FDA's guidance document *Process Validation: General Principles and Practices for general principles and approaches that FDA considers to be appropriate elements of process validation* at https://www.fda.gov/media/71021/download (https://www.fda.gov/media/71021/download).

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed and controlled to assure the raw materials, in-process materials, and finished drugs are of the intended quality.

Process qualification studies determine whether an initial state of control has been established. Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of the variables affecting process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

Failure to implement adequate process validation practices can result in insufficient understanding of process variables or failure to detect a drift in capability, which increases the risk of drug quality defects.

In response to this letter provide:

• A remediation plan that better assures ongoing management oversight throughout the manufacturing lifecycle of all drug products. Provide a more data-driven and scientifically sound program that identifies sources of process variability and assures that manufacturing operations meet appropriate parameters and quality standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, determining the capability and reliability of each manufacturing process step and its controls, and vigilant ongoing monitoring of process performance and product quality.

• A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.

• A timeline for performing process performance qualification for each of your marketed drug products.

• Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.

• Provide a detailed program for designing, validating, maintaining, controlling, and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also, include your program for qualification of your equipment and facility.

• A comprehensive, independent assessment of your in-process monitoring and sampling operations, focusing on each upstream process step that can introduce variability. Provide your remediation plan to improve: (1) in-process detection of variation; (2) upstream controls; and (3) sampling plan.

• Provide your updated master batch record for **(b)(4)** API.

• Provide an independent risk assessment for your distributed **(b)(4)** API that may have been impacted by changes made in your manufacturing process without adequate evaluation.

3. Failure to adequately validate written procedures for the cleaning and maintenance of equipment and failure to establish adequate written procedures for cleaning equipment and its release for use in manufacture of API.

You failed to adequately validate your cleaning process for non-dedicated manufacturing equipment as required by your Validation Master Plan. During the inspection, you did not provide written cleaning procedures for non-dedicated equipment, including your **(b)(4)** vessel, **(b)(4)**, and **(b)(4)**. Equipment operators stated they cleaned equipment without following a procedure. You lack assurance that your equipment is adequately cleaned to prevent cross-contamination from other products.

In response to this letter provide:

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

• A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an assessment whether cross-contaminated products may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices and encompass each piece of manufacturing equipment used to manufacture more than one product.

• A CAPA plan, based on the 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.

4. Failure to design a documented, on-going stability testing program to monitor the stability characteristics of API and to use the results to confirm appropriate storage conditions and retest or expiry dates.

You failed to implement an adequate stability program for **(b)(4)** API. For example, you lacked appropriate stability protocols. You established the current, **(b)(4)** retest date for **(b)(4)** API by testing reserve samples from one batch (batch **(b)(4)**). This batch was manufactured in 2016 and stored in the reserve sample room which is not controlled for humidity. Despite basing your retest dating on this batch, you destroyed batch records associated with batch **(b)(4)**.

In addition, this batch record was destroyed while the batch remained in U.S. distribution. You lacked adequate scientific data to assure that your **(b)(4)** API will maintain its quality attributes throughout its purported shelf-life and storage conditions. This could adversely affect the quality of the drugs that your customers manufacture from your API.

In response to this letter provide:

• A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:
  o Stability indicating methods
  o Stability studies for each drug product in its marketed container-closure system before distribution is permitted
  o An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid
  o Detailed definition of the specific attributes to be tested at each station (timepoint)

• All procedures that describe these and other elements of your remediated stability program.

5. Failure to have a quality unit that is independent of production and fulfills quality assurance (QA) and quality control (QC) duties.

Your quality unit (QU) lacked adequate responsibilities and authorities to assure reliable operations. Your QU failed to ensure good documentation practices in your facility as evidenced by:
• A Batch Manufacturing Production logbook was found with pages torn out

• Numerous signed and partially completed batch records which lacked the “Controlled Copy” stamp were found in the unofficial R&D laboratory

• Destruction of **(b)(4)** API batch record for batch **(b)(4)** that contained manufacturing and analysis records, despite this batch remaining in U.S. distribution. You also destroyed the batch retain sample.

You are responsible for establishing and following appropriate record retention procedures for your API that remains within retest period.

In response to this letter provide:

• 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

• How top management supports quality assurance and reliable operations, including, but not limited to, timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.

• 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.

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/media/119267/download (https://www.fda.gov/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 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.

• 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.

• A management strategy for your firm that includes the details of your global CAPA 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.

Drug Registration Violation

Based upon the information obtained from the August 2 to 7, 2021, inspection, and drug application data for the sterile finished drug product **(b)(4)**, Indiana Chem-Port (FEI 3005564386) has been identified as a manufacturer of **(b)(4)** API used to manufacture the finished drug product. Under section 510(i)(1) of the Act (21 U.S.C. § 360(i)(1)), Indiana Chem-Port is required to submit registration information annually by electronic means for each establishment it owns or operates that is engaged in the manufacture, preparation,

propagation, compounding, or processing of a drug that is in commercial distribution in the United States. Indiana Chem-Port has not fulfilled its registration requirement. As a result, all drugs manufactured in this establishment are misbranded under Section 502(o) of the FD&C Act [21 U.S.C. 352(o)].

In addition, according to the records obtained at the time of inspection, Indiana Chem-Port (FEI 3005564386) manufactures drugs for commercial distribution in the United States which have not been properly listed with FDA. The drug includes:

• **(b)(4)** API

There are no drug listing submissions to FDA under the name of or labeler code for Indiana Chem-Port (FEI 3005564386). Under section 510 of the FD&C Act as amended and 21 CFR (21 U.S.C. 360(j)(1), 21 CFR 207.17 and 207.41), all drugs manufactured, prepared, propagated, compounded, or processed for U.S. commercial distribution must be listed with FDA. Failure to properly list drug products is prohibited and will render the drugs misbranded. (21 U.S.C. 331(p) and 352(o))

Additional API CGMP Guidance

FDA considers the expectations outlined in ICH Q7 when determining whether API are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients for guidance regarding CGMP for the manufacture of API* at https://www.fda.gov/media/71518/download (https://www.fda.gov/media/71518/download).

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 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.

FDA placed your firm on Import Alert 66-40 on December 13, 2021.

Correct any deviations promptly. 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 any deviations.

Failure to address any deviations may also result in the FDA continuing to refuse admission of articles manufactured at Indiana Chem-Port, at 349 GIDC Industrial Estate, Gujarat into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority that appear to be

adulterated or misbranded may be detained or refused admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B) and are misbranded under section 502 of the FD&C Act, respectively.

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.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov. Identify your response with FEI 3005564386.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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