WARNING LETTER

Claris Injectables Limited

MARCS-CMS 543187 — JUL 05, 2018

Recipient:

Amish Vyas

Claris Injectables Limited

Nr. Parimal Railway Crossing Ellisbridge
Ahmedabad, Gujarat 380006
India

Issuing Office:

Center for Drug Evaluation and Research

United States

U.S. FOOD & DRUG ADMINISTRATION

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Via UPS
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Warning Letter 320-18-62

July 5, 2018

Amish Vyas
Managing Director
Baxter (Claris Injectables Ltd.)
Nr. Parimal Railway Crossing Ellisbridge
Ahmedabad- 380006 Gujarat
India

Dear Mr. Vyas:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Claris Injectables Ltd. at Ahmedabad, from July 27, 2017 to August 4, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 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 August 25, 2017 response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your firm invalidated out-of-specification (OOS) results without adequate investigation and scientific justification. Examples include:

a. In January, 2017, you obtained OOS results for the **(b)(4)** impurity during stability testing of **(b)(4)** injection batches **(b)(4)**. Your OOS investigation reports stated that the postulated cause was "poor column efficiency," although no chromatographic abnormalities were noted and system suitability criteria were met. During the inspection, your lab management indicated that retention times, theoretical plates, and tailing factor appeared appropriate and no specific root cause had been demonstrated. You repeated the analyses, obtained passing results, and invalidated the OOS results.

In March, 2017, you obtained OOS results for the **(b)(4)** impurity during stability testing of **(b)(4)** injection batches **(b)(4)**. You suspected the analyst may have incorrectly rinsed the HPLC vials. New samples prepared and tested by a second analyst using both the original column and a new column, as well as old and new vials, also yielded OOS results. Although you lacked sufficient evidence, your investigation concluded that the OOS results were due to sample vial contamination. You invalidated the OOS results after obtaining passing results from testing retain samples.

After the conclusion of the inspection you initiated a voluntary recall of five batches of **(b)(4)** drug product due to failing **(b)(4)** levels, superpotent assays, and **(b)(4)**, all obtained during stability testing and including batches **(b)(4)**.

Notably, you informed FDA that the apparent root cause of the **(b)(4)** assay failures was excessive **(b)(4)** from your **(b)(4)**. However, the investigation lacked an adequate assessment of all other batches distributed to the U.S. and within expiry that may be potentially affected by **(b)(4)**.

b. Your OOS investigation of the failure of **(b)(4)** batches **(b)(4)** to meet the **(b)(4)** specifications under accelerated stability conditions was also inadequate. You obtained OOS results of **(b)(4)**% and **(b)(4)**%, respectively (specification Not More Than **(b)(4)**%). While the investigation lacked a demonstrated assignable root cause in the laboratory, you obtained passing results during repeat analysis and invalidated the OOS without a Phase II production investigation.

After the inspection, you recalled eight batches of **(b)(4)** due to superpotent assay and **(b)(4)** results obtained during stability testing. While use of substandard **(b)(4)** that allow excessive **(b)(4)** again appears to have caused the specification failures, your response lacked sufficient relevant information on the root cause and scope of this major problem.

In both of the above instances, you failed to expand your OOS investigations in a timely fashion to address potential manufacturing causes. When an investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing causes must be performed. Your acceptance of the passing results from testing a new set of samples based on an unproven hypothesis was insufficient to conclude the investigations.
Your response stated that you will revise your *OOS Management* procedure and perform a retrospective review of your OOS investigations. Your response was inadequate because it lacked identification of root causes and implementation of effective corrective actions and preventive actions (CAPA). It also failed to address inadequacies in the **(b)(4)** you received from your supplier(s), and whether they are still considered qualified for use by your firm.

Notably, your firm has had a worrisome history of recalls due to substandard **(b)(4)**. In 2017, you recalled **(b)(4)** parenteral drug products due to recurring **(b)(4)** complaints. In 2010, your firm conducted a Class I recall of all lots of four parenteral products due to loss of **(b)(4)** integrity and non-sterility.

Also, while your firm has discussed adding a **(b)(4)** as a corrective action for **(b)(4)**, it would not resolve ongoing issues relating to quality of container-closure raw materials or **(b)(4)** fabrication. Durability and quality of your large volume parenteral container-closure systems is critical to ensure their robustness until administration at a clinical facility, who will remove **(b)(4)**, and can temporarily store and then transfer the **(b)(4)** within the facility before use. Your response lacks a commitment to thoroughly review your **(b)(4)** dependability with respect to both container-closure raw material quality and **(b)(4)** fabrication process weaknesses.

In response to this letter, provide:

- A retrospective, independent review of all invalidated OOS (in-process and finished testing) results obtained for products on the U.S. market. Assess whether the scientific justification and evidence was conclusive. For investigations that conclusively establish laboratory root cause, determine adequacy of the CAPA, and ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS results with inconclusive or no root cause identified in the laboratory, include

a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, raw materials, process capability, deviation history, batch failure history).

- Provide a summary report of the retrospective review of all OOS investigations for product that remain within expiry. Include a CAPA plan that identifies manufacturing root causes and specifies meaningful improvements. Include the product name, date of the original result, initial and retest OOS results, detailed rationale for invalidating the OOS result, and the outcome of your thorough reassessment. Also, include any additional market actions you intend to initiate because of the retrospective review.
- A fully remediated OOS investigation procedure, including but not limited to modifications to ensure investigations expand to manufacturing operations when a root cause is not conclusively identified in the laboratory.
- Updated investigation into the root cause of container-closure system failures leading to increased **(b)(4)**.
- Testing of retain samples of batches of all drug products within expiry in the U.S. market that used the **(b)(4)** suppliers (i.e., raw materials, fabricators) associated with excessive **(b)(4)**.
- A comprehensive, independent assessment of the quality of all **(b)(4)** container-closure raw materials (parts such as **(b)(4)**, etc.) and adequacy of all sites who perform **(b)(4)** fabrication processes. This thorough assessment should also include an evaluation of the adequacy of your qualification program for suppliers of container-closure raw materials (**(b)(4)** part suppliers) and manufacturers of both **(b)(4)** and **(b)(4)**.
- A full description of your **(b)(4)** material sourcing process and **(b)(4)** manufacturing process for both **(b)(4)** and **(b)(4)**. Include the roles and responsibilities of all parties involved in the **(b)(4)** supply chain and production. Specifically, for all lot of **(b)(4)** produced since July 1, 2015, provide a detailed summary of all suppliers and manufacturers that you used for your **(b)(4)** materials, and vendor lot numbers. In each case describe who performed the **(b)(4)** formation, fabrication, and final assembly (including the specific nature of any in-house operations, such as use of **(b)(4)** operations). Include any subcontractors or other parties involved with material supply or fabrication.
- Vendor-generated Certificates of Analysis (COA) for **(b)(4)** part manufacturers and suppliers, as well as **(b)(4)** fabricators and assemblers.
- An assessment of your overall system for investigations into deviations, discrepancies, complaints, OOS results, and failures. Your CAPA plan should include, but not be limited to, improved rigor in reviewing the sources of variation in your operation that may cause deviations, failures, or defects, as well as an extensive remediation of your capabilities to ensure CAPA effectiveness.

2. Your firm failed to prepare batch production and control records with complete information relating to the production and control of each batch of drug product produced (21 CFR 211.188).

Our investigator observed an operator recording unreliable data. Specifically, on July 27, 2017, our investigator observed your operator entering datain your *Visual Inspection Test (VIT) For* **(b)(4)** *Line* document for **(b)(4)** injection, USP, batch **(b)(4)** a day after the operation was completed. The document stated that the visual inspections were performed on July 26, 2017. In response to our question regarding how portions of the documentation had been completed without corresponding data, a senior manager at your site could not provide an explanation.

We acknowledge your efforts to update SOPs and retrain personnel. However, your response is inadequate because you did not perform a retrospective assessment into other possible events in which data were not reported accurately or contemporaneously.

In response to this letter, provide:

- A comprehensive, independent risk assessment of production records including but not limited to your visual inspection documentation to determine the completeness, consistency, and accuracy of reported data. Indicate how you determined that the data you used to release product was attributable, legible, contemporaneously recorded, original or a true copy, and accurate. Include a re-examination of retain samples.

- 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 documentation practices, and ensures you retain complete, contemporaneously prepared, and accurate records.

3. Your firm failed to maintain buildings used in the manufacture, processing, packing or holding of drug products in a good state of repair (21 CFR 211.58).

Our investigators observed significant evidence of water damage in your facility, including warped ceiling panels, puddles of water, and water stains. For example, water damage was evident over the **(b)(4)**, and in sky lights, vents, and ceilings above the finished drug product packaging area and in the personnel corridor outside the Quality Control laboratory.

In addition, our investigators observed ceiling panels over the personnel corridor and **(b)(4)** that were not sealed, allowing ingress of air from the building's plenum into post-sterilization areas.

It is essential that your plant management maintains the facility in a good state of repair to ensure ongoing suitability for drug manufacturing.

In your response, you attribute the water damage to monsoon rains that fell in the days prior to the inspection. However, the observed staining, rusting pipes, and warping of walls and ceiling panels appeared to indicate the presence of longer-term water and humidity problems in some cases.Your response focuses on water leak repairs and some enhanced preventive measures. However, it does not adequately address production management's daily responsibilities to promptly address facility damage and the potential for fungal contamination to persist in the facility due to moisture problems.

In response to this letter, provide:

- A comprehensive, independent review of your preventive maintenance program(s) for both facilities and equipment, and a CAPA plan to ensure its effectiveness. Your plan should include but not be limited to contingencies for expected seasonal fluctuations in rainfall.
- A CAPA plan that formalizes routine, vigilant production management oversight of facility conditions to assure prompt detection of issues, execution of repairs, and other appropriate actions.
- Your plan to monitor and control humidity levels in the facility to prevent major environmental control issues due to fungi and other microbial contaminants, which were associated with past product recalls by your firm. Also, explain how your will ensure prompt detection of fungi in the facility.
- Your plan to requalify the facility after remediating the water damage, including your environmental qualification strategy.

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. 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 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.

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. We also recommend that the qualified third party perform a comprehensive audit of your entire operation for CGMP compliance, and evaluate the completion and effectiveness of any corrective actions and preventive actions.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Repeat Violations at Facility and Meeting With FDA

FDA cited similar CGMP violations in a previous warning letter (WL 320-11-003) of November 1, 2010. You proposed specific remediation for these violations in your response. The repeated serious violations at your facility demonstrate that your facility's oversight and control over the manufacture of drugs is inadequate.

In particular, our warning letters discuss the history of recurring serious defects in your marketed **(b)(4)** products, including but not limited to non-sterile **(b)(4)** with visible contamination, **(b)(4)**, and other evidence of lost integrity, and most recently quality issues relating to assay, impurities, and **(b)(4)**. These issues have been exacerbated by the lack of prompt identification and appropriate remediation, and FDA intervention has generally been necessary for your firm to adequately investigate and remove the defective products from distribution

FDA is aware that Baxter acquired this facility the same day the inspection started. We request that you contact Tramara Dam, by e-mail at Tramara.Dam@fda.hhs.gov, within five days of receipt of this letter to schedule a regulatory meeting. Please come prepared to discuss Baxter's comprehensive remediation plans for this facility.

Conclusion

Violations in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

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

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at Claris Injectables Ltd. at Ahmedabad, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of 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).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Carlos M. González, PhD
Compliance Officer
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USA

Please identify your response with FEI 3004610460.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

CC:
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