WARNING LETTER

Indoco Remedies Limited

MARCS-CMS 575313 — JUL 16, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Suresh G. Kare

Chairman

Indoco Remedies Limited

Indoco House, 166 CST Road
Mumbai 400098
India

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Via UPS

Warning Letter 320-19-29

Return Receipt Requested

July 9, 2019

Mr. Suresh G. Kare
Chairman
Indoco Remedies Limited
Indoco House, 166 CST Road
Santacruz (E), Mumbai 400 098
India

Dear Mr. Kare:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Indoco Remedies Limited (Plant I) at L-14 IDC Verna Industrial Road, Vasco Da Gama, Goa, from January 17 to 25, 2019.

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 February 15, 2019, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. 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).

Compression machine process control values were not adequately reported in your batch production records during the manufacture of **(b)(4)** mg tablets intended for the U.S. market. Your quality unit used these deficient records to release batches of this drug product.

While multiple batch records of **(b)(4)** mg tablet included handwritten values routinely within process parameters, the values recorded by the programmable logic controller (PLC) of your compression machine were frequently outside your established process parameters. For example, **(b)(4)** mg batch **(b)(4)** had compression force values handwritten **(b)(4)** in the batch record ranging from **(b)(4)** (your limit was **(b)(4)**).

However, the PLC data recorded individual values ranging from **(b)(4)** for the same time period. In addition to compression force values, handwritten values for filling depth and automatic weight control (AWC) did not accurately reflect the values within the PLC data.

An inspection conducted by the **(b)(4)** in March 2018 found similar discrepancies between the compression force values in batch records and PLC data.

Your response acknowledged discrepancies including missing data, “mis-matched data,” non-contemporaneous entries, and other inconsistencies in your batch records. It also acknowledged inadequate procedures for compression machine setup and adjustments during operations intended to maintain process control, and a lack of documentation of these critical activities.

Your response is insufficient. The integrity of all data within your manufacturing records is called into question by the actions of your staff involved in compression operations. You did not commit to perform a comprehensive retrospective evaluation of the integrity of data throughout your manufacturing operation. You also did not adequately address how you will ensure that AWC is consistently maintained and documented throughout compression by providing detailed procedures for setup and changing of parameters during a batch, and address how all associated parameters will be controlled.

It is essential that you use appropriate continuous process controls to promptly respond to variation in your process, and prevent sporadic loss of control during processing. Additionally, you did not sufficiently detail your batch record changes for each strength of **(b)(4)** tablets.

In response to this letter, provide:

- Procedures that establish use of appropriate AWC and other control procedures in your compression operation. This includes but is not limited to detailed procedures for batch setup and subsequent adjustments for AWC; identification of all parameters that can impact consistency of compression; and complete documentation of all batch production activities.
- Your updated master production and control batch records for drug products that fully document each manufacturing operation. Also submit your most recent executed batch production and control record with full machine printouts for each strength of your **(b)(4)** tablet drug product.
- An independent review of all your process parameters for the manufacture of your **(b)(4)** dosage form drug products to ensure adequacy of ranges, setup parameters, and in-process monitoring for detecting variation in your process.
- A data-driven and scientifically sound program that identifies and controls variability, to ensure production and packaging processes consistently meet appropriate manufacturing standards and parameters. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, and determining the capability and reliability of each manufacturing process step and control.
- Your corrective action and preventive action (CAPA) plan as requested in the Data Integrity Remediation section of this letter below. As one facet of the comprehensive CAPA plan, an independent reviewer(s) should provide a thorough retrospective assessment of manufacturing data validity since February 1, 2016, and perform thorough interviews of production staff (both operators and supervisors). This assessment should augment the internal investigation that you have performed and include but not be limited to an independent review of the integrity of **(b)(4)** in-process checks **(b)(4)** and disintegration testing, and evaluate any missing compression operation data. The retrospective assessment should fully determine the degree to which this in-process testing data has information gaps (whether due to omissions or lost data), personnel sign-offs occurred at times where staff were not present, and to what extent current data can be relied upon for this product and other products.

2. 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 investigation into discrepancies found within **(b)(4)** mg tablet batch records was inadequate.
Specifically, document DEV-G1-18-033 provided the details of your investigation into multiple batch record discrepancies between compression force values written in **(b)(4)** mg batch records and the data electronically recorded in the PLC of compression equipment. Your investigation was inadequate because it lacked the following:

- A review of the integrity of the data by contrasting handwritten and electronic data for all process control values recorded by your PLC during **(b)(4)** tablets manufacture to determine if other discrepancies had occurred.
- A sufficient extension of your investigation to other strengths of **(b)(4)** batches and other products manufactured at your facility.
- A substantive root cause for the significant variability of compression machine process control values throughout the manufacturing of **(b)(4)** tablets.
- A CAPA plan to resolve the root causes of this variability.

In your response, you stated the deviation was a result of your staff's belief that it was acceptable to proceed with compression operations and overlook aberrant equipment control values (e.g., compression force, fill depth, AWC) if all key tablet attributes were within specification.

Your response acknowledged that your original investigation was limited and not holistic, and as a result it did not sufficiently determine the scope of the data integrity issues and the causes. Your response is inadequate because you did not provide an adequate root cause of the high variability of process parameters such as fill depth and compression force, and why these values contrasted with the far tighter control demonstrated throughout compression of your validation batches. You did not adequately address the impact of the atypical values on batch quality.

In response to this letter, provide:

- A retrospective, independent evaluation comparing process control values manually recorded within the batch records and the values recorded electronically within the PLC for all strengths of **(b)(4)** batches manufactured for the U.S. market. For example, this evaluation should identify any time periods of tablet compression in which the AWC was set to the "off" position and address the quality of those tablets manufactured during those periods.
- A detailed risk assessment for drug products within expiry in the U.S. market that were compressed under these poorly documented production conditions. Take appropriate corrective actions based on the risk assessment.
- A comprehensive, independent assessment of your overall system for investigations of deviations, atypical events, complaints, out-of-specification (OOS) results, and failures. Your CAPA should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA effectiveness.

3. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards (21 CFR 211.194(a)).

On several occasions, you conducted a new analysis after obtaining an initial OOS test result. These analyses included water content tests on a Karl Fischer instrument and an assay test on an auto titrator instrument. We reviewed the electronic data on these instruments and found OOS testing results which were not reported in the analytical records. Only passing results were ultimately included in the data presented for batch review and disposition decisions. Additionally, your laboratory failed to maintain basic raw laboratory data (e.g., original raw data sheets, original chromatograms, instrument usage logs, original weight printouts) in many instances.

For example, the initial assay tested using the auto titrator instrument for the active pharmaceutical ingredient **(b)(4)**, batch **(b)(4)**, was conducted on December 29, 2018, at 13:50. The initial result was OOS at **(b)(4)**% (specification **(b)(4)**%). The official release data for the assay testing was reported as within specification at **(b)(4)**% on December 29, 2018, at 15:00. The official release package did not include the initial OOS result of **(b)(4)**%. No investigation was performed.

In your response, you indicated that 10 additional cases of unreported OOS results were found, in addition to the nine observed during the inspection. You also discovered 23 instances where the initial results were not OOS but you had repeated testing without justification for the additional analysis.

Your response is inadequate because it did not address the disposition of lots affected by these OOS results discovered during the inspection.

In response to this letter, provide:

- A retrospective, independent review of all invalidated OOS (in-process and finished testing) results for all products since June 1, 2016. Assess whether the scientific justification and evidence for each invalidated OOS result was conclusive. For investigations that establish laboratory root cause, ensure that you identify other laboratory methods vulnerable to the same root cause for remediation.

- A thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, raw materials, process capability, deviation history, batch failure history) for any OOS results with inconclusive or no

root cause identified. A CAPA plan should identify manufacturing root causes and specify meaningful improvements.

- A risk assessment for any drug products in the U.S. market within expiration date for which an OOS result was obtained. Take appropriate actions, including customer notifications or recalls, if drug quality may be impacted.
- A review and remediation of your system for investigating OOS results. Provide a CAPA plan to improve OOS handling. Your CAPA plan should ensure that your revised OOS investigations procedure includes:
    - Enhanced quality unit oversight of laboratory investigations
    - Identification of adverse laboratory control trends
    - Resolution of causes of laboratory variation
    - Investigations of potential manufacturing causes when a laboratory cause cannot be conclusively identified
- A comprehensive, independent review of your laboratory practices, procedures, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to remedy your laboratory system. Your plan should include the process you will use to evaluate the effectiveness of the implemented CAPA plan.

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* for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf).

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. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all 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. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

Process Controls

Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. See FDA's guidance document *Process Validation: General Principles and Practices* for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download (https://www.fda.gov/media/71021/download).

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant highly qualified in data integrity 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.

Quality Systems

Your firm's quality systems are inadequate. See FDA's guidance document *Quality Systems Approach to Pharmaceutical CGMP Regulations* for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download (https://www.fda.gov/media/71023/download).

Conclusion

Violations cited 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 (mailto: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 Indoco Remedies Limited (Plant I) at L-14 IDC Verna Industrial Road, Vasco Da Gama, Goa, 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:

Joseph Lambert, Pharm.D.

Compliance Officer

U.S. Food and Drug Administration

White Oak Building 51, Room 4359

10903 New Hampshire Avenue

Silver Spring, MD 20993

USA

Please identify your response with FEI 3006644152.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

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