Indoco Remedies Limited 3/27/17

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-17-31

March 27, 2017

Ms. Aida Dias
Vice President, Corporate Quality Assurance
Indoco Remedies Limited
Plant II & III, L-32, 33, 34
Verna Industrial Estate Area
Verna, Goa, 403722
India

Dear Ms. Dias:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Indoco Remedies Limited, Plants II & III, L-32, 33, 34 Verna Industrial Estate Area, Verna, Goa, from August 31 to September 4, 2016.

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 September 20, 2016, 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 establish and follow adequate written procedures describing the handling of all written and oral complaints regarding a drug product, including provisions for review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with 21 CFR 211.192 (21 CFR 211.198).

From January 2012 to August 2016, your firm received numerous (approximately 1,500) consumer complaints related to leaking, empty, and under-filled sterile **(b)(4)** solution **(b)(4)**% bottles. Your firm's investigation indicates this persistent critical quality defect is due to a filling machine issue in which the **(b)(4)** is improperly placed into the bottle **(b)(4)**. Because of this recurring malfunction, operators frequently perform aseptic interventions at the insertion station when they detect stuck **(b)(4)** defects. These defects are not easily detected, and the line has produced finished, capped units with non-integral container-closures. In addition, in some cases, **(b)(4)** cracks do not immediately occur in finished units, but instead develop days later. Specifically, your investigation states, "…it is evident that a wrong placement of the **(b)(4)** on the bottle on the filling machines must be resulting in a damaged or cracked **(b)(4)** which does not occur immediately and occurs on standing for a few days." Because of the location and delayed timing of these defects, they are not readily detectable by final manual or automated inspections.

This unreliable process compromises the quality, integrity, and sterility of **(b)(4)** solution. Although you implemented various corrective actions and preventive actions (CAPA) since 2013, you have continued to receive a large number of non-integrity complaints. It is unclear whether the latest CAPA sufficiently addresses the root causes of this recurring container-closure integrity defect and will correct the problem.

Your response indicates that process improvements, and particularly the implementation of a new **(b)(4)**% leak test machine, "will ensure that **(b)(4)** vial of a batch is leak tested at site and a 100% assurance level can be achieved…" However, leak testing of finished units at the end of processing will not detect leaks that your firm found emerge after several days of standing or during shipment. Also, you have not evaluated whether primary packaging component deficiencies, including the **(b)(4)** feature on the **(b)(4)** of **(b)(4)** solution **(b)(4)**%, require a reassessment of product design.

In addition, your response includes an action level threshold for initiating investigations that is based on the number of complaints received per batch rather than the criticality of the product complaint. For example, according to your response, receipt of **(b)(4)** to **(b)(4)** complaints per batch yields a low-risk rating with "no immediate action" taken. **(b)(4)** complaints yield a high-risk rating and a field alert report (FAR) filing. You lack scientific justification for your investigation threshold, which is not commensurate with potential patient hazard. Any complaint of lost integrity of your sterile drugs should be considered as a serious problem with marketed product and trigger an appropriate investigation.

We note that your health hazard evaluation 16-08-025, dated September 13, 2016, classified these defects as high severity, including potential for a serious permanent injury. However, you concluded that the need for action is "moderate" because you consider the probability of patient exposure to the non-integral product to be low.

In response to this letter, provide:

- a risk assessment of all lots of **(b)(4)** solution **(b)(4)**% currently in the U.S. market and within expiry;
- an updated investigation into the root cause(s) of **(b)(4)** solution **(b)(4)**% non-integrity defects and an improved CAPA plan;
- assessment of your other **(b)(4)** products to determine if they are experiencing similar non-integrity defects;

- shipping studies, including a detailed description of how product handling and shipping conditions can cause **(b)(4)** solution **(b)(4)**% non-integrity;
- a reassessment of the suitability of your primary packaging components and qualification status of your vendors, with special focus on the **(b)(4)**;
- thorough process capability assessments of the **(b)(4)** placement and capping stations on your **(b)(4)** manufacturing line;
- revised procedures that remove the high tolerance for critical quality complaints, and ensure high vigilance when a defective product appears to be in distribution; and
- specific improvements made to your overall complaint handling and investigations systems to ensure effective CAPAs and timely correction of manufacturing quality problems.

2. Your firm has failed to ensure the responsibilities and procedures applicable to your quality control unit are followed (21 CFR 211.22(d)).

Under your quality agreement with your customer, **(b)(4)**, you must notify them within **(b)(4)** if your firm determines that any batch of distributed drug product should be subject to a field alert report (FAR). However, at the time of the inspection, there was no evidence that you had sent this notification to your customer although numerous complaints had been received for multiple lots regarding leaking, empty, and under-filled bottle defects. Your failure to follow the provisions of your quality agreement and appropriately notify your customer of the quality problems discussed in this letter may have delayed your customer's ability to take important actions to ensure the quality, safety, and efficacy of its products, including notifying FDA via a FAR under 21 CFR 314.81. We note that **(b)(4)** submitted a FAR after the close of our inspection of your facility.

Your firm acts as a contract manufacturer for various drug products. Your failure to comply with CGMP may significantly affect the quality, safety, and efficacy of the drugs you manufacture for your clients. It is essential that you understand your responsibility to operate in full compliance with CGMP, and to immediately inform your customers (e.g., owners, sponsors) of production problems or quality issues that may pose a patient hazard. Your customer also remains responsible for oversight of contract manufacturers to ensure its products are being made in compliance with CGMP.

In response to this letter, provide your standard operating procedures for:

- identifying manufacturing and quality issues (including but not limited to events requiring a FAR) that need to be promptly reported to your customers; and
- notifying customers of potential FAR issues, your related training program, and identification of all appropriate staff who must take the training.

Repeat observations

In a previous inspection, conducted from February 18 to 23, 2011, FDA cited a similar CGMP observation concerning 17 complaints for leakage or crusty residue observed with **(b)(4)** solution USP and **(b)(4)** solution **(b)(4)**%. Our current inspection also documented leakage complaints in multiple drug products including **(b)(4)** solution USP and **(b)(4)** solution **(b)(4)**%. These repeated failures demonstrate that your facility’s oversight and control over the manufacture of drugs are inadequate.

You should immediately and comprehensively assess your company’s global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements.

CGMP 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. 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.

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 in all your facilities.

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 Indoco Remedies Limited, Plants II & III, L-32, 33, 34 Verna Industrial Estate Area, Verna, 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:

Loan Chin
Pharmacist
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 3005124189.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director
Office of Manufacturing Quality