DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave,Bldg 51,Rm 4225 Silver Springs, MD 20993 (301)796-3334 Fax:(301)847-8738	8/31/2016-9/4/2016
	FEI NUMBER 3005124189

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Aida Dias , Vice President, Corporate Quality Assurance

FIRM NAME	STREET ADDRESS
Indoco Remedies Limited	Plant II & III, L-32, 33, 34, Verna Industrial Estate Area
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Verna, Goa, 403722India	Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

Quality System

OBSERVATION 1

Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

Specifically, between January and August 2016, approximately 459 complaints describing leaking or empty bottles for sterile (b) (4) products have been received. Although a failure-mode-evaluation-analysis has resulted in procedural revisions and other corrections, complaints continue for batches made subsequent to those corrections, with trends as high as 24 complaints for one batch (b) (4) Solution, lot (b) (4); along with 13 complaints for lot (b) (4) and 9 complaints for lot (b) (4). The investigation has failed to expand to consider all batches of this product, as well as others, which may be impacted.

Although equipment to perform 100% (b) (4) leak testing on all units produced is planned for qualification, production continues, and there are approximately (b) (4) lots of (b) (4) Solution on the market potentially impacted by this defect. Complaints of this nature have been seen at lower rates for the following products as well:

- (b) (4) Solution
- (b) (4) and (b) (4) Solution
- (b) (4) Solution
- (b) (4) Solution

OBSERVATION 2

The quality control unit lacks the responsibility and authority to approve and reject all drug products.

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	Nicholas A Violand, Investigator 9/4/2016 X Nicholas A Violand Nicholas A Violand Investigator Signed by: Nicholas A. Violand -S	9/4/2016

Specifically, two contaminants have been identified in several stability batches of (b) (4) Solution, (b) (4) (b) (4), at the 9-month, 12-month, and 18-month stability stations, with values as high as (b) (4)% for an individual unknown impurity (specification limit (b) (4)%). Although these contaminants have been identified as leachables from the product label, and the product label has since been changed from a semi-migrant to a non-migrant label found to not leach the contaminants, there are approximately 71 batches on the market within expiry that are known to contain these leachables. There are no filed limits for these contaminants, and their toxicity is unknown; however, the firm has estimated that a (b) (4) dose of (b) (4) pm, which is equivalent to approximately (b) (4)%, is acceptable in marketed finished product.

OBSERVATION 3

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically, there have been multiple OOS investigations for assay of bulk sample in (b) (4) Solution, all of which have been identified as due to sampling technique. Although three specific procedural corrections were discussed as being necessary ((b) (4) of sampling valve, waiting (b) (4) after (b) (4) completion, and verifying settling of (b) (4) prior to sampling), these corrections were not clearly made in the sampling procedure or batch record. At least one operator has been retrained on the procedure twice, and this discrepancy has occurred at least ten times. The procedure for Corrective and Preventive Action, SOP QS/023, section 5.3.1.3.2, requires preventive action to be taken to prevent reoccurrence of an incident.

Production System

OBSERVATION 4

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.

Specifically,

a. Validation of the limits of usage, washing, and sterilization cycles for gowning used in production of sterile (b) (4) and injectable products has not been adequately performed. This encompasses the hood, goggles, boiler suit (one piece suit), and booties worn by operators. The supplier of the gowning has performed a study

demonstrating that (b) (4) washing and sterilization cycles does not generate holes or unacceptable levels of particulates, but this s not represent conditions at the site, in which gowning is worn for up to (b) (4) while working in aseptic processing between washing and sterilization cycles. The firm has set their usage limit to (b) (4) cycles, based on the supplier's study, which does not support the firm's usage conditions.

b. The defect library used for qualification of personnel that will be performing visual inspection of sterile injectable products does not specifically include units containing small particles, which may be difficult to detect. It contains defects for glass particles, (b) (4) particles, and (b) (4) particles. Pending application products (b) (4) (b) (4) (b) (4) Injection, and (b) (4) (b) (4) Injection, will be inspected by personnel that have been insufficiently qualified to detect smaller particles at an acceptable level of reliability.

Facilities and Equipment System

OBSERVATION 5

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design and suitably located to facilitate operations for its intended use and cleaning and maintenance.

Specifically,

a. The vial washer that will be used for injectable products filled on Line (b) has surrounding (b) (4) that keep the outfeed for washed vials under Grade A laminar air flow, and is surrounded by a Grade D area. The space is insufficiently designed, in that personnel moving vials into washed (b) (4) for depyrogenation are standing in Grade D zone, which is also where the (b) (4) and lids are held until they are loaded. There is no continuous non-viable particle monitoring in the Grade A zone where operators use gloved hands to load the vial (b) (4), and there is no assurance that vials will not become contaminated with particulates during this operation.

b. Sterilized components such as (b) (4) bottle (b) (4) and caps, and stoppers for injectable products, are held outside the enclosed filling zone on top of a (b) (4) on Line (b) The storage area is not enclosed or held under laminar air flow, to ensure that personnel working in the Grade B area do not contaminate the exterior of the component bags with particulates before they are wiped with (b) (4) and moved into the aseptic filling line for transfer to their respective (b) (4).

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c. Sterilized tools used in the Grade A filling area of Line (b)(4) for (b) (4) and injectable products are held inside (b) (4) mugs, the design of which does not permit laminar air flow to pass through them, and inside which turbulence may be created. There is no assurance that these tools, which include forceps for removing fallen vials and scissors for opening component bags, do not collect particulates that may contaminate product on the filling line.

Postmarket Reporting

OBSERVATION 6

An (b) (4)-Field Alert Report was not submitted within three working days of receipt of information concerning bacteriological contamination and significant chemical, physical, or other change or deterioration in a distributed drug product.

Specifically, between January and August 2016, approximately 459 complaints of leaking or empty bottles of various (b) (4) products have been received, which span multiple lots. There have been no (b) (4) Field Alert Reports filed that describe the failure of the sterile barrier in these complaints, which encompass:

- (b) (4) Solution, (b) (4) (b) (4)
- (b) (4) Solution, (b) (4) (b) (4)
- (b) (4) and (b) (4) Solution, (b) (4) (b) (4)
- (b) (4) Solution, (b) (4 (b) (4)
- (b) (4) Solution, (b) (4 (b) (4)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."