DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	1/17/2019-1/25/2019*
	FEI NUMBER 3006644152

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Aditi Panandikar, Managing Director	
FIRM NAME Indoco Remedies Limited (Plant I)	STREET ADDRESS L - 14 I D C Verna Industrial Road,
CITY, STATE, ZIP CODE, COUNTRY Vasco Da Gama, Goa, 403722 India	TYPE ESTABLISHMENT INSPECTED Tablet 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 WE OBSERVED:

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

1. Investigation DEV-(b) (4)-18-033 included investigation of compression force values recorded in (b) (4) tablet batches that did not match electronic machine data. The investigation found that production and IPQA personnel purposely recorded values within established limits even though the actual values were not within established limits. The investigation and assessment of (b) (4) tablet batches released to the US market was not thorough:

A. The investigation did not determine what had caused the manufacturing process to have variability in compression force and filling weight depth outside of the ranges established during process validation and subsequent batch manufacturing. During interviews with (b) (4) production and IPQA personnel directly involved with recording inaccurate values, the personnel stated the need to record inaccurate values had not occurred during previously manufactured batches. Established parameters for compression force and fill depth were eliminated without identifying the source of the variability observed in recent batches that was inconsistent with previous batches.

B. There is no assurance the automatic weight controls (AWC) was turned on and set appropriately during the commercially released batches to reject tablets with high or low compression forces.

C. The investigation only identified compression force, which was cited during an (b) (4) inspection, to be recorded inaccurately. However, the fill depth (weight) settings entered by personnel into the

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machine settings captured by the PLC electronic data exceeded the batch record parameters, even though the values recorded in the batch record were always within the established parameters.

D. Additional discrepancies between the PLC or balance printouts and data recorded in batch records were not identified and further investigated. For example:

i. During batch (b) (4) the (b) (4) was turned "off" from (b) (4) and the operator recorded the value as "on" during the (b) (4) check.

ii. During batch (b) (4) the PLC data showed the machine main motor was not on from (b) (4) (b) (4) and there was "disk inching" indicating the machine had not been performing as expected. No stoppage or explanation was recorded in the batch record and in-process checks were still documented while tablets were not being produced.

iii. Changes to the filling machine parameters for filling depth were made without corresponding data or written justification that changes were needed.

iv. During batch (b) (4) the in-process checks done by production personnel were documented at 15:05 and 15:35. These were recorded before the QA check documented at 14:58. During batch (b) (4) the checks for (b) (4) finished at (b) (4) for (b) (6) and was initially recorded in the column before the (b) (4) check.

v. The printouts from (b) (4) in-process tests showed errors recorded in the batch record for (b) (4) at the (b) (4) check and the friability test was not completed until (b) (4) (b) (4) after the time noted in the batch record for the check of (b) (4)

E. Controls have not been established to ensure changes to the automatic weight control during the batch are appropriate and documented.

F. Additional production and IPQA personnel responsible for manufacturing and in-process checks from 2017 (b) (4) batches were not interviewed to evaluate the extent of purposeful recording of inaccurate data.

2. Investigation OOS-(b) (4) 1-18-236 was opened when one sample point of batch (b) (4) (b) (4) was out of specification with an assay value of (b) (4) % compared to a specification of (b) (4) %. The investigation identified a sampling error in that not enough sample was collected. No data was gathered to support the conclusion that sampling a lower amount would cause the OOS result. The product was resampled without an approved "Protocol for Re-Sampling". A (b) (4) preparation of a retest result was used to invalidate the original OOS result.

At the time of the original sampling, the batch records did not contain any instruction for how much sample should have been collected. No action was taken to add sampling instructions in the batch record for this product or any other product.

3. Investigation OOS-(b) (4) -18-108 was opened when (b) (4) tablet stability batch (b) (4) failed the appearance test for color for the 30°C/(b) (4) % RH sample at the 18-month timepoint. The investigation concluded this was expected, but does not include any data to support why this color change would be expected.

OBSERVATION 2

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

1. Out of Specification (OOS) results from the QC lab on the Karl Fischer instrument QE/291 and the Autotitrator instrument QE/317 were not investigated or documented. The analysis was repeated without reporting the original OOS result and initiating investigation. The following electronic analytical records contained unreported OOS results without investigations:

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Analytical Record	Material	Analysis and Equipment	Time of unreported OOS	Time of reported analysis
IG-0097	(b) (4)	Water Content by KF on QE/291	02 Feb 2018 at 09:14	07 Feb 2018 at 10:02
IG-0460		Water Content by KF on QE/291	15 May 2018 at 10:39	17 May 2018 at 14:30
IG-1049		Assay by Autotitrator on QE/317	29 Dec 2018 at 13:50	29 Dec 2018 at 15:00
IG-0145		Assay by Autotitrator on QE/317	07 Feb 2018 at 12:46	08 Feb 2018 at 12:38
IG-0161		Assay by Autotitrator on QE/317	21 Feb 2018 at (b) (4)	22 Feb 2018 at 10:27
IG-0358		Water Content by KF on QE/291	29 Mar 2018 at 16:21	31 Mar 2018 at 15:38
IG-0688		Assay by Autotitrator on QE/317	19 Sep 2018 at 10:33	19 Sep 2018 at 12:07
IG-0929		Water Content by KF on QE/291	25 Nov 2018 at 14:35	25 Nov 2018 at 15:08
IG-1102		Assay by Autotitrator on QE/317	04 Oct 2017 at 09:29 and 10:02	04 Oct 2017 at 10:31

*Raw materials as part of the manufacturing process for (b) (4) products for the U.S.
**Raw material as part of the manufacturing process for products with pending applications for the U.S.

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The original weight printouts were not available and analytical records did not include any documentation of the original analysis. The instrument usage log books did not contain the record of the original analysis being conducted. Analytical records document electronic audit review of the Karl Fischer systems, but these did not detect the unreported OOS's.

2. Original sample weight data is not available. Weight printouts on December 9, 2017 for the first determination of RL4-0284/17 for Karl Fischer Factor Determination had a time stamp of 9:39, which is after the determination had started at 9:35.

3. Electronic versions of the originally integrated chromatogram are not maintained when chromatograms need to be reprocessed with changes to integration parameters. For example, the following chromatograms were reprocessed and the original electronic chromatogram is not available:

- (b) (4) 3-month stability dissolution testing
- 3-month stability related substances testing
- 6-month stability related substances testing
- Finished Product (b) (4) Assay testing

4. Production personnel stated weight checks are performed after adjusting fill depth (weight) parameters during the ongoing tablet compression process. Records of these checks between the batch record required in-process checks are not maintained.

OBSERVATION 3

Batch production and control records do not include complete information relating to the production and control of each batch.

The person listed in the batch record in the "Done By" column for in-process checks does not perform all tests, does not record any of the data, is not always present when the data is acquired, and their name is added to the "Done By" column by the person signing the "Checked By" column.

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OBSERVATION 4

Procedures for the preparation of master production and control records are not described in a written procedure.

There is no document reconciliation by the Quality Unit. The firm's procedure SOP QA/006 Version 13 Effective May 16, 2017 indicates how to issue documents but not how to reconcile the documents. The firm does not verify the logbook on a (b) (4) basis as stated in the procedure. Form F/QC/235/02/03 on the Precision Balance Calibration Record was issued two copies on December 5, 2018 and two copies again on January 9, 2019 without reconciliation of copies. "Format Issual Register" for Quality Control for 2018 and 2019 log book ID number RG/QD/239 lack reconciliation of issued forms.

OBSERVATION 5

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

1. Procedures for reviewing electronic data and audit trail lack detail necessary to ensure comprehensive review of all data generated. Reviews of Chromeleon (b) (4) audit trails are not documented.

2. Specifications for in-process (b) (4) are not supported with data.

OBSERVATION 6

Written procedures for cleaning and maintenance fail to include description in sufficient detail of methods, equipment and materials used.

There is no requirement to clean or evaluate the air inlet ducts of the (b) (4) in procedure TB2/004 "Operation and Cleaning of (b) (4) ". On January 17, 2018 unidentified material was observed in the air inlet duct of the "clean" (b) (4) T2/105.

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***DATES OF INSPECTION**

1/17/2019(Thu), 1/18/2019(Fri), 1/21/2019(Mon), 1/22/2019(Tue), 1/23/2019(Wed), 1/24/2019(Thu), 1/25/2019(Fri)

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