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	6/4/2019-6/11/2019*
	FEI NUMBER 3005669319

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Mehul Shah, Managing Director and Owner

FIRM NAME	STREET ADDRESS
Encube Ethicals Pvt. Ltd.	C1 - C4 and C17 - C20, Madkaim Industrial Estate, Madkaim
CITY, STATE, ZIP CODE, COUNTRY Ponda, Goa, 403404 India	TYPE ESTABLISHMENT INSPECTED Topical Contract 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:

OBSERVATION 1

Established laboratory control mechanisms are not followed and documented at the time of performance.

Specifically, your firm failed to fully document the investigation OOS/18/089 dated 07/06/2018 [dd/mm/yyyy]- where Phase 1 did not rule out laboratory error, but it was determined that laboratory error was the cause of the Out of Specification (OOS). The laboratory checklist shows no error on the part of the analyst. The conclusion states in part, "The analyst had taken the centrifuge tube from the "To be cleaned glassware tray", manually cleaned it and re-used it for this analysis." There is no documentation elsewhere in the OOS report that the analyst provided this information before this determination was made.

B. Your firm failed to store all reference and working standards per their labeled storage conditions to ensure their purity and fitness for use for assay and impurity/related substances analyses. No comparative analysis studies were conducted to show the standards fitness for use prior to their use in batch release testing to show whether the lack of proper storage impacted the quality of the standard.

For example, reference standards, such as, (b) (4) -room temperature, light sensitive, and hygroscopic used to analyze US marketed products, (b) (4) cream (b) (4)%, (b) (4) Cream, and (b) (4) Ointment USP, were stored in refrigerator #A/QC/314 without regard to the labeled storage conditions. The reference and working standards

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refrigerators are only monitored for temperature, not monitored for humidity or any other quality factors. Other examples observed include, but are not limited to the following:

(b) (4)

OBSERVATION 2

Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans and test procedures designed to assure that components, in-process materials and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically, your firm failed to establish and follow laboratory procedures for re-testing original or re-sampled material when no assignable root cause is found during a full scale laboratory investigation. No protocol or approvals are required before retesting or re-sampling material and drug products not conforming to established specifications.

A. OOS/16/F/001 expiry November 2017 dated 01/06/2016 – where no laboratory error or calculation error was identified during Phase 1 of the investigation, and no assignable root cause could be determined during Phase 2 of the investigation. Therefore, the original sample was retested in duplicate. Because of the passing test results the original OOS was invalidated and the batch was released. No test

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plan or protocol was created and approved for the retest and no parameters for the retest were established.

OBSERVATION 3

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

Specifically,

A. Your firm failed to document all test related data for the microbiological analysis of (b) (4) analyses, environmental monitoring, and product testing. I observed the "Bacteriological Colony Counter ID#: EE/QC/403" Logbook shows monitoring records for the plate counting for (b) (4) analysis, environmental monitoring, and product testing are not accurately documented. The date, start, and end time is routinely not documented for plate counting activities conducted, instead the field are lined through with N/A. The data to be entered in those fields is applicable to the test being performed and its documentation.

B. Your firm failed to establish and implement equipment use logs for the incubators. A reconciliation of appropriate samples in the incubators could be performed to verify all required samples for (b) (4) analysis, environmental monitoring, and product testing were present in the incubators.

C. Your firm failed to document the reading of Microbial Limit Tests to ensure the plates read are attributable/specifically identified to the reported results. For example, 2 plates are read, but not identified as Plates 1 or 2 on the plate or the raw data sheet.

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OBSERVATION 4

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, your firm failed to thoroughly investigate and document investigations pertaining to failure investigations including but not limited to the following examples:

A. Customer complaint # PC-E1-17-0216 dated 08 Sep 2017 for (b) (4) Ointment where the expiration date could not be found on the products. Your firm found there had been (b) (4) shipments of batches of this product to the customer. The investigation fails to document the details of the retain (control) sample review and fails to document whether 1 or all (b) (4) batches were reviewed and what the specific findings were of each one.

OBSERVATION 5

Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent malfunctions that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, your firm failed to establish, maintain, and clean refrigerators used in the storage of reference and working standards.

For example, but not limited to:

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A. Your firm failed to establish and implement cleaning procedures and procedures for documenting the cleaning of the freezer portion of Refrigerator ID# EE/QC/164 which is used to store reference and working standards. Further, your firm failed to establish a preventive maintenance plan for this refrigerator, and conduct preventive maintenance on this refrigerator. A layer of ice was coating the freezer and the temperature probe was observed sitting in the ice. Water was observed to be pooled at the bottom of the refrigerator affecting the integrity of the labels of the working and reference standards sitting in the water.

B. Your firm failed to maintain and establish an appropriate preventive maintenance plan for reference and working standards storage of Refrigerator A/QC/313. I observed a water line to be broken with a significant amount of water pooled in the bottom with standards sitting in the water.

C. Your firm failed to maintain incubators in the Microbiology laboratory to prevent malfunctions. The current preventive maintenance checklist does not require the checking of all functional parts of the incubator. I observed the gaskets on all incubators to be in a state of disrepair and not properly sealing the door. At the time of the observation, no work order had been initiated for correction.

OBSERVATION 6

The use of instruments not meeting established specifications was observed.

Specifically, your firm failed to fully qualify and maintenance laboratory equipment used in the storage of reference and working standards and microbiology analyses.

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For example, but not limited to the following:

A. For Refrigerator ID# EE/QC/164, used to store reference and working standards, your firm failed to perform a temperature mapping study of the freezer and qualification under static (empty) and dynamic (loaded) conditions of the refrigerator.

OBSERVATION 7

Written procedures describing the handling of complaints do not include 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, a determination as to the need for an investigation of any unexplained discrepancy and explaining the reasons for the failure of the batch or any of its components to meet specifications.

Specifically, your firm failed to investigate at least 15 complaints received after the expiry of drug products, and further failed to provide written justification for the determination that a complaint investigation was not needed. Section 5.2.10 of complaint procedure, "QA/013, Handling of Market Complaints, Rev. 17, Effective Date: 18/08/2018", states in part, "Complaints received after expiry of product may not be entertained but suitably replied."

For example, Complaint # PC-E1-19-0101 dated 2/04/2019 [dd/mm/yyyy] for (b) (4) Cream (b) (4) G (b) (4) was not investigated where a customer reported that the product was not efficacious. The customer was not able to provide lot number & expiry date of the product, so the complaint was not investigated and no justification was provided.

***DATES OF INSPECTION**

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6/04/2019(Tue), 6/05/2019(Wed), 6/06/2019(Thu), 6/07/2019(Fri), 6/10/2019(Mon), 6/11/2019(Tue)

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Annotations to Observations

Observation 1: Not annotated

Observation 2: Not annotated

Observation 3: Not annotated

Observation 4: Not annotated

Observation 5: Not annotated

Observation 6: Not annotated

Observation 7: Not annotated

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