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	3/12/2018-3/20/2018*
	FEI NUMBER 3004956904

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Ravindra K. Pandey, Head of Formulation Operations

FIRM NAME	STREET ADDRESS
Alembic Pharmaceuticals Limited	Village Panelav, Near Baska
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Tajpura, Gujarat, 389350 India	Oral Solid Dosage 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:
Laboratory Control System

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.

A. Specifically, your firm failed to take appropriate corrective and preventative actions to reduce the high number of invalidations in a timely manner when Out of Specification (OOS) results were observed as evidenced by the following: In 2016, your firm reported 140 OOS results (raw materials, in-process and finished products) for U.S. marketed drug products for Dissolution, Assay, (b) (4) , Content Uniformity and Related Substances. Your Quality Control Unit (QCU) invalidated 131 of the 140 OOS results (94% invalidation rate) due to analyst error (i.e. sample preparation), glass contamination, etc. In 2017, your firm reported 129 OOS results and your QCU invalidated 117 (91% invalidation rate). In 2018 (January-March), your firm reported 30 OOS results and your QCU invalidated 19 (63% invalidation rate).

The following examples include, but are not limited to, OOS results that were invalidated by your firm's QCU without scientific rationale and supporting documentation:

a. OOS #ALP/QA/OOS-8042: Opened on February 2, 2018 for high assay, (b) (4) % (specification: (b) (4) %-(b) (4) %) for (b) (4) Tablets USP (b) (4) mg (stage: (b) (4) tablets) batch # (b) (4) (mfg.: 12/17, exp.: (b) (4)). Your firm attributed the root cause as a sample preparation error which is not supported since the re-injection, re-filled and re-

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diluted sample confirmed the high OOS result for assay. In addition, your firm failed to evaluate the other (b) (4) Tablets USP (b) (4) mg batch # (b) (4) that was prepared by the same analyst that your firm stated conducted the sample preparation inadequately.

b. OOS #ALP/QA/OOS-8027: Opened on January 24, 2018 for an OOS individual impurity result of (b) (4) % (specification: NMT (b) (4) %) for the Related Substances Test for (b) (4) (b) (4) Capsules USP (b) (4) mg (stage: 6 Month CRT Stability) batch # (b) (4) (mfg.: 04/17, exp. (b) (4) . Your firm attributed the root cause as glassware contamination (volumetric flask), stopper, or mortar and pestle which is not supported as glass contamination cannot be considered for the failing results of all samples: T1 ((b) (4) %), T2 ((b) (4) %), re-injection ((b) (4) %), re-filled ((b) (4) %) and re-centrifuged ((b) (4) %). Other root causes such as contamination of the sample during collection or (b) (4) preparation was not investigated.

c. OOS #ALP/QA/OOS-8058: Opened on February 22, 2018 for low assay, (b) (4) % (specification: (b) (4) %- (b) (4) %) for (b) (4) and (b) (4) Tablets USP (b) (4) mg/ (b) (4) mg (stage: (b) (4) batch # (b) (4) mfg.: 01/2018, exp.: (b) (4)). Your firm attributed the root cause as a sample preparation error (weighing of (b) (4) which resulted in lower % assay). During the repeat analysis, your analyst was instructed to (b) (4) and then weigh (this action deviated from the current Method: APL/IT0269-00). In addition, your firm's preventative measure was to train analysts to verify the physical appearance of the sample rather than evaluating the current method to ensure the sample is (b) (4)

d. OOS #ALP/QA/OOS-6491: Opened on December 11, 2016 for high assay, (b) (4) % (specification: (b) (4) %- (b) (4) %) for Validation Batch: (b) (4) Tablets (b) (4) mg (stage: (b) (4) tablets) batch # (b) (4) (mfg.: 11/16, exp.: (b) (4) . Your firm attributed the root cause as a dilution error (analyst wrongly used graduated pipettes). In addition, your firm failed to evaluate the other (b) (4) Tablets USP (b) (4) mg batch # (b) (4) and

batch #(b) (4) that was prepared by the same analyst that your firm stated conducted the sample preparation inadequately.

e. OOS #ALP/QA/OOS-6114: Opened on April 2016 for high assay, (b) (4) % (specification: (b) (4) %- (b) (4) %) for (b) (4) Tablets (b) (4) mg (stage: (b) (4) tablets) batch #(b) (4) (mfg.: 04/16, exp.: (b) (4) . Your firm attributed the root cause as improper standard preparation, unknown error in sample preparation, minor spillage of working standard while transferring it to a volumetric flask or air entrapment in the detector or in mobile phase line at the time of injection. There was no evidence of spillage by the analyst and there was no evidence of air entrapment as the results were higher.

B. Your firm's Quality Unit failed to support the root cause through scientific rationale and supporting documentation for Production Deviation # APL/DC17017 during the packaging operations for (b) (4) Tablets USP (b) (4) mg batch # (b) (4) (dated: April 16, 2017). The Deviation was initiated during in-process checks by QA for (b) (4) failures. Your firm determined the root cause as the following: correlation between the speed of the machine and sealing (b) (4) contribute to the quality of sealing, powder accumulation during longer packaging runs and improper (b) (4) quality. Your firm failed to take appropriate corrective and preventative actions such as evaluating the potential requirement to change the speed of the machine and sealing (b) (4) (b) (4) cycles per minute with a (b) (4) range between (b) (4) to (b) (4)) and the quality of (b) (4) received from the supplier.

OBSERVATION 2

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Employees are not given training in the particular operations they perform as part of their function and written procedures required by current good manufacturing practice regulations.

Specifically, your firm's SOP #ALP/QC/SOP032 (dated January 4, 2018) titled, "Qualification of Analyst" is inadequate as Section 5.1.19 states, "re-qualification of an analyst is to be done if (b) (4) consecutive OOS results are observed due to human error"; therefore, your Quality Control Analysts' are not being properly qualified as evidenced by the following example: Analyst (b) (6) was qualified for the Assay Analysis of (b) (4) Capsules (b) (4) mg (batch # (b) (4) in (b) (4) on May 15, 2017. On June 10, 2017, analyst (b) (6) conducted the Assay Analysis of (b) (4) Capsules (b) (4) mg (batch # (b) (4)) intended for the Canadian market which resulted in an Out of Specification (OOS) result for low Assay (invalidated due to analyst error). On November 25, 2017, analyst (b) (6) conducted the Assay Analysis of (b) (4) Tablets (b) (4) mg (batch # (b) (4) intended for the U.S. market which resulted in an OOS result for low Assay (invalidated due to analyst error). On February 2, 2018, analyst (b) (6) conducted the Assay Analysis of (b) (4) Tablets (b) (4) mg (batch # (b) (4) intended for the U.S. market which resulted in an OOS result for high Assay (invalidated due to analyst error).

Analyst (b) (6) was observed conducting the Assay Analysis and Content Uniformity Analysis for multiple U.S. marketed drug products (i.e. (b) (4) Tablets, (b) (4) Tablets, (b) (4) Tablets and (b) (4) Capsules) for which she was not properly trained on the test methods.

In addition, your firm failed to take appropriate corrective and preventative actions to re-qualify the Analyst in a timely manner and instead allowed her to conduct a total of (b) (4) analyses for assay and content uniformity involving (b) (4) batches. She was re-qualified on March 9, 2018.

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Production System

OBSERVATION 3

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically, the (b) (4) Hold Time Studies that your firm has conducted for drug products marketed in the US are deficient. The batch sizes used for the establishment of (b) (4) Hold Times do not represent the commercial batch size of the drug products. To date, your firm has conducted (b) (4) Hold Time Studies utilizing this approach for all (b) (4) representing approximately (b) (4) drug products intended for the US market as evidenced by the following examples:

Drug Product	Batch Size (b) (4) Stage)	Process	Quantity Used for the (b) (4) Hold Time Study	Established Hold Time (b) (4) Stage)
(b) (4) (b) (4) Tablets USP (b) (4) mg	(b) (4)			
(b) (4) Tablets (b) (4) mg				
(b) (4)				

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Capsules (b) (4) mg (b) (4)	(b) (4)			
Tablets (b) (4) mg				
(b) (4) (b) (4) & (b) (4) (b) (4) Tablets mg				
(b) (4) (b) (4) & (b) (4) (b) (4) Tablets mg				

Since March 2016, approximately 113 investigations have been initiated for either (b) (4) or Assay failures at the (b) (4) stage for products marketed in the US.

***DATES OF INSPECTION**
3/12/2018(Mon), 3/13/2018(Tue), 3/14/2018(Wed), 3/15/2018(Thu), 3/16/2018(Fri), 3/19/2018(Mon), 3/20/2018(Tue)

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