DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Building 51, Room 4316 Silver Spring, MD 20993-0002, USA (301) 796-3334 Fax: (304) 847-8738 Industry Information: www.fda.gov/oc/industry	04/17/2017 - 04/28/2017*
	FEI NUMBER 3005029956

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Ashish Hajarnis, Vice President (Works)

FIRM NAME	STREET ADDRESS
Torrent Pharmaceuticals Limited	Ahmedabad Mehsana Highway
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Indrad, Taluka-Kadi, Gujarat, India 382721	Drug and API Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Quality System

OBSERVATION 1

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

Specifically,

1. The following deficiencies were noted with the change control program:

   a. Change control records were not closed in a timely manner. Section 4.0 of SOP CQA-055, Version 4.0, Change Control Management Across all the Locations, effective date 1 DEC 16 states that it is the responsibility of the Head of Quality to complete a 'Periodic review of status of Change control forms for its implementation'. However, according to the Review of Change Control Form for the year 2016, Quarter 4 (Document no. CCFS/INF/16/Q4 approved on 7 FEB 17):

Year	Number of Change Control Records that Remain Open
2011	3
2012	65
2013	168
2014	226

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No final action has been taken for the changes that have not been implemented, and a final assessment has not been made for those changes that have been implemented.

b. A Change Control record was not initiated per SOP CQA-055, Version 4.0, Change Control Management Across all the Locations, effective date 1 December, 2016. The Stability Study Data Sheet, RLT/3476/01, effective date 3 June 2016, for the Dissolution Testing of (b) (4) Tablets (b) (4) mg) was updated to include instructions to ensure that the pH meter is calibrated with buffers at pH (b) (4) and (b) (4) immediately before adjusting the pH of the dissolution media.

2. Batch Record Review by Quality Assurance (QA) was deficient:

a. The production batch record for (b) (4) Stage (b) (4) Batch (b) (4) had (b) (4) weights recorded for the standard preparation and (b) (4) weights recorded for the sample preparation. There were (b) (4) printouts for weight, and the two printouts dated 16 OCT 16 were stamped with the word 'DISREGARD'. There was no indication or reference recorded in the batch record stating why these weights were disregarded, why the printouts for the weights dated 18 OCT 16 were accepted, or why the incorrect weights on the previous page were not crossed out. The batch record was reviewed and approved by QA on 20 OCT 16, but this discrepancy was not noted or corrected.

b. The production batch record for (b) (4) Finished API batch (b) (4) was missing a page. This discrepancy was noted during production and a deviation was raised. The operator recorded the results on the back of page 44 of the issued batch record. This page was not signed as reviewed or verified by QA.

3. Validation batches that fail to meet specification are subsequently not considered to be validation batches without a justification. For example, Validation Protocol PV/BTD.77.05-4E/15 stated that three consecutive validation batches of (b) (4) were manufactured. However, Validation Report PVR/BTD.77.05-4E/16 only included data from two batches (b) (4) and (b) (4)) and did not evaluate batch (b) (4) which failed to meet specification.

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4. Poor documentation practices were observed such as the failure to include details such as product name, product strength, nature of the problem, or summary of the conclusion of the investigation in deviation investigation records and change control records such as CCF/INF/16/0352 and CCF/INF/15/0533.

OBSERVATION 2

There is a failure to thoroughly investigate discrepancies whether or not the batch has been distributed.

Specifically,

Investigation OOS/IN/A/FP/15/019 dated 10 OCT 15 reported out-of-specification (OOS) results for description for (b) (4) Stage (b) (4) batches (b) (4) and (b) (4) A (b) (4) color was observed.

Investigation OOS/IN/A/FP/15/023 dated 7 NOV 15 reported OOS results for description for (b) (4) Stage (b) (4) batches (b) (4), (b) (4), and (b) (4) reported as (b) (4), (b) (4), and (b) (4)

The specification for description of (b) (4) Stage (b) (4) was originally (b) (4) to (b) (4)

(b) (4) Stage (b) (4) is an intermediate in the production of (b) (4) finished API (b) (4) (b) (4) Stage (b) (4) material is (b) (4) in nature and is (b) (4) This intermediate product is packaged and sampled (b) (4)

The investigation into the observed color changes concluded that the presumptive root cause was exposure to moisture during handling. However, it has not been determined whether: (i) the color change impacts material on the surface, or if the entire batch is affected, and (ii) whether moisture can cause a color change to (b) (4) (b) (4), or (b) (4) Furthermore, there is no color standard for analysts to use for comparison during analysis. Further, per CCF/TRC/15/1649, dated 20 NOV 15, the specification for description was changed to (b) (4) to (b) (4) color powder'.

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Laboratory Control System

OBSERVATION 3

Laboratory equipment used for analytical testing was used outside of the calibrated range.

Specifically, the HPLCs, GCs and dissolution units located in the API, formulation (finished dosage form) and stability sample quality control testing laboratories were used outside of the calibrated range. For example:

a. SOP No.: IPQC-124-02, Annexure VIII, titled "Wavelength Accuracy Check" states that wavelength accuracy for HPLCs should be calibrated at (b) (4) ±(b) (4) nm. However, according to test method STP No. CTP/1405, Version 00, a wavelength of (b) (4) nm is used to detect degradation products of (b) (4) by HPLC for the (b) (4) and (b) (4) tablets (b) (4) ng/(b) (4) mg - batch (b) (4) using HPLC 1112 located in the Stability Laboratory.

b. An unqualified thermocouple (Identification No. TH/1285, Serial No. 32400093WS) was used for the verification of GC column oven temperature (eg. GC-1050 located in formulation laboratory and GC-1882 located at API laboratory). This thermocouple was certified for measurements between 50°C to 450°C. However, according to SOP IPQC-136-03, titled "Procedure for operation, cleaning and calibration of Gas Chromatograph with head space"; the column oven temperature of the GC should be verified and adjusted with the aid of a calibrated thermocouple at the temperature points of (b) (4) and (b) (4) °C. A temperature of (b) (4) °C is outside of the certified working range of the thermocouple.

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c. According to the SOP: CQA-078, Version 03 titled, "Procedure for analysis, reporting and reviewing of analytical data", a (b) (4) working standard solution should be injected after a set of (b) (4) or (b) (4) dissolution samples for quantitative analyses. No (b) (4) working standard solution was used for dissolution tests conducted at the API, formulation (finished dosage form) and stability sample testing laboratory(eg. Dissolution unit : DI/1265 located in formulation laboratory and DI/456 located in stability laboratory).

OBSERVATION 4

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

Specifically, during the establishment of system suitability for chromatographic analyses, the firm did not prepare or use a second working standard solution (Check Standard Solution) to confirm the potency, accuracy and purity of the working standard solutions (Primary Standard Solution). A single standard preparation was used to determine the potency, accuracy and purity of the active pharmaceutical ingredient in the sample solution.

For example: for the assay, content uniformity, and degradation product tests of (b) (4) & (b) (4) Tablets ((b) (4) mg/(b) (4) mg) recorded in Analytical Report No. 040000203053, a Check Standard was not used.

For the assay, content uniformity, and degradation product tests of (b) (4) & (b) (4) Tablets ((b) (4) mg/(b) (4) mg) recorded in Analytical Report No. 040000203966, a Check Standard was not used.

*DATES OF INSPECTION
4/17/2017(Mon),4/18/2017(Tue),4/19/2017(Wed),4/20/2017(Thu),4/21/2017(Fri),4/24/2017(Mon),4/25/2017 (Tue),4/26/2017(Wed),4/27/2017(Thu),4/28/2017(Fri)

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