DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	Use this check box to generate the required 483 statement on page 1 for medical device observations. ☐
DISTRICT OFFICE ADDRESS AND PHONE NUMBER 12420 Parklawn, Drive, Room 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 06/03/2024 - 06/12/2024* FEI NUMBER 3005029956
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Dr. Sushil Jaiswal, Executive Director of Quality	
FIRM NAME Torrent Pharmaceuticals Limited	STREET ADDRESS Taluka-Kadi, Ahmadabad Mehsana Highway
CITY, STATE, ZIP CODE, COUNTRY Indrad, Gujarat, 382721 India	TYPE OF ESTABLISHMENT INSPECTED Finished Product and API Manufacturer (Non-sterile)

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 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 AT THE PHONE NUMBER AND ADDRESS ABOVE.

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

FINISHED PRODUCT INSPECTIONAL OBSERVATIONS

QUALITY SYSTEM

OBSERVATION 1

There is no testing program designed to assess the stability characteristic of drug products.

Specifically,

Your Quality Unit failed to ensure the drug products sold into the US market are stable throughout the product shelf life.

A. Your batches of drug products had confirmed/valid out of trend (OOT) results but were released by QA and distributed into the (b) (4) market from October-2022 to May-2024. This was in deviation of your Quality Unit's responsibilities towards batch disposition per procedure CQA-070-06, titled: "Procedure for Investigation of Out of Trend (OOT) Results in Drug Product Manufacturing", effective date: 06-Apr-2023, Attachment-I "Flow Chart For OOT Investigation", which states test results concluded as confirmed/valid OOT upon (b) (4) (b) (4)(b) (4) and manufacturing investigation required "Batch disposition by QA". The evaluation of OOT trend of batches at release for years 2022 and 2023 revealed that total 70 valid OOT batches were distributed into (b) (4) market of which about 34 batches were reported as valid OOT for Assay by HPLC test, 35 batches for Dissolution by HPLC and 1 for Organic Impurities by HPLC and 1 batch for Content Uniformity by HPLC test. None of these valid OOT batches were charged on stability and monitored throughout the (b) (4) shelf life.

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	Upadhyay Steven Brettler	Pratik S. Upadhyay, Investigator – Dedicated Drug Cadre Steven A. Brettler, Investigator – GDUFA	06/12/2024

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Further, many of the annual stability batches were also observed to have valid OOT results on long term stability (25°C/60%RH), but your Quality Unit continued to remain these valid OOT batches into the (b) (4) market. For example, but not limited to:

(b) (4)

[redacted]

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(b) (4) [redacted]

B. The evaluation of historical stability trend of your drug products revealed the potential for the assay of the drug products to decrease during the product shelf life of (b) (4) For example, but not limited to:

(b) (4) [redacted]

As a result of the potential for the product to transition from valid OOT to OOS for assay before expiry, during the inspection on 11-Jun-2024 your firm filed Field Alert Report (FAR) for (b) (4) Tablets USP (b) (4) mg (b) (4) .

Alternatively, stability trends have also shown unexpected increases in Assay by HPLC test results such as:

- (b) (4) mg lot (b) (4) which showed a +4% Assay from (b) (4) % to (b) (4) % at 12 months
- (b) mg lot which showed a +3.2% Assay from (b) (4) % to (b) (4) % at 6 months
- (b) (4) mg lot (b) (4) which showed a +4% Assay from (b) (4) % to (b) (4) % at 22 months
- (b) (4) (b) (4) mg lot (b) (4) , which showed a +4.3% Assay from (b) (4) % to (b) (4) % at 12 months
- (b) (4) mg lot (b) (4) , which showed a +2.6% Assay from (b) (4) % to (b) (4) % at 6 months

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(b) (4) (b) (4) mg lot (b) (4) which showed a +11.4% Assay from (b) (4) % to (b) (4) % at 18 months

Per your Quality Unit, these increases in the Assay test results have remained unknown for (b) (4) Tablets whereas for (b) (4) Tablets it was attributed to issues with the accuracy of your analytical test method (STP No.: (b) (4) Version:10) for which the firm has not initiated and documented any formal quality event. The evaluation of email communications revealed that your Quality Unit identified these issues in year 2022 and per the email dated 17-dec-2022 they initiated a series of testing activities to determine the root cause. However, there has been no progress made for over approximately 18 months (since December 2022) to perform the revalidation of the analytical test method and to evaluate the root cause. Your firm continued to keep manufacturing and releasing (b) (4) Tablets batches into the US. market using an analytical test method that is both not fully understood and potentially giving unreliable Assay test results. The variations in the assay test results are reflective of the potential for the OOT batches to be true OOS and increase the risk for subpotent products within the (b) (4) market.

The evaluation of the Adverse Drug Events (ADEs) log for 01-Jun-2022 to 02-Apr-2024 revealed that your firm received multiple market complaints relating to lack of efficacy for the unknown batches. Many of these complaints were not logged in at your site and investigated as Product Quality Complaints (PQCs).

C. Your OOT investigations are deficiently conducted in that the evaluation of historical trend of OOT results was performed only on the expired batches. There was no monitoring performed for the OOT test results on the ongoing stability batches that were also resulting into the OOT valid test results for the same product.

D. Your procedure for OOT investigations (SOP No.: CQA-070-06) is deficient. Per this procedure, there are no requirements to take any market action if a valid OOT is observed at a long-term stability condition on an annual stability batch that is commercialized into the US market and evaluate the impact of the valid OOT on all the other batches manufactured in that year.

OBSERVATION 2 (Repeat Observation from September 2022)

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.

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Specifically,

A. OOS Number: OOS/B/ST/22/084, Date of Event: 09-Dec-2022, Product: (b) (4) Tablets (b) (4) mg (b) (4) count bottles), Batch Type: (b) (4) batch of Process Validation, Batch Number: (b) (4) Stability time point: 3 Month, 25°C/60%RH, Issue: OOS found for Dissolution by HPLC test in the (b) (4) (b) (4) sample (b) (4) result documented as (b) (4) % against a specification of NMT (b) (4) %. This OOS was final classified as valid on 28-Jan-2023, the batch had an expiry of (b) (4) . No market action was taken based on the rational that the valid OOS was found for (b) (4) count bottles whereas the (b) (4) and (b) (4) count bottles met specification at the same stability timepoint. The (b) (4) count bottle is marketed in the US. However, the same bulk batch number (b) (4) of (b) (4) tablets was used to package the different finished bottles of the same packaging components. In addition, this Process Validation represented (b) (4) commercial batches of (b) (4) Tablets (b) (4) mg drug product manufactured until (b) (4) that are sold into the US market.

B. Your OOS Investigation procedure CQA-057-06, Titled: Procedure for Investigation of Out-of-Specification Results (OOS), Effective date: 06-Apr-2024 is deficient to define handling of confirmed/valid stability related OOS investigation along with responsibilities of QA head/designee for filing field alert(s) and initiating batch recall(s).

FACILITY AND EQUIPMENT SYSTEM

OBSERVATION 3 (Repeat Observation from September 2022)

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

Specifically,

A. Your (b) (4) cleaning procedure for non-dedicated manufacturing equipment cleaning is inadequate in that it does not ensure the removal of (b) (4) materials of the previously manufactured drug products to avoid potential cross-contamination.

For example,

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On 03-Jun-2024, I observed large deposition of (b) (4) colored (b) (4) materials inside the (b) (4) product non-contact areas) of your (b) (4) ID: GR-122, located in manufacturing (b) (4) (b) (4) This (b) (4) equipment is used to manufacture (b) (4) dosage drug products for the (b) (4) and ROW markets. This equipment was cleaned through (b) (4) system at the time of this observation. Per our request, your firm conducted a protocol (GS/IN/TAB/QMS/2024/016, dated: 07-Jun-2024) based evaluation by collecting (b) (4) materials on (b) (4) and tested sample by HPLC. The evaluation revealed presence of (b) (4) (previous product) in the (b) (4) in the ratio of about (b) (4) %.

B. Your Quality Unit lacked adequate oversight on the review and evaluation of Equipment Cleaning Records (ECRs). For example,

1. The column pertaining to "Issue Quality" for (b) (4) remained blank(undocumented equipment cleaning records pertaining to (b) (4) ID: GR-124 was signed under received by, issued by, verified by, and checked by sections on 23-Feb-2024. This document was finally signed your Quality Unit on 13-Mar-2024. Your firm uses (b) (4) % w/w of (b) (4) as a cleaning agent for (b) (4) system.

2. The review of "PREPARATION, USAGE AND DISCARD OF (b) (4) % (b) (4) (b) (4) revealed the (b) (4) for the (b) (4) preparation (Kg) left blank (undocumented) while the (b) (4) preparation detail was signed under prepared by and checked by sections dated 14-Apr-2024.

API INSPECTIONAL OBSERVATIONS

LABORATORY CONTROL SYSTEM

OBSERVATION 4

Your firm failed to establish written procedures for the testing of materials as well as recording or storage of laboratory data.

Specifically, there is no written standard test procedure (STP) for Quality Control (QC) Analysts to perform (b) (4) for IR spectra identification analysis as referenced in United States Pharmacopeia (USP) <197>

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Spectroscopic Identification Tests when there appears to be spectral differences between the IR sample and reference standard. Each time the QC Analysts are to perform a (b) (4) the test and standard solution are not prepared consistently nor the preparation is documented in the laboratory worksheet for review from the Quality Unit.

FACILITY AND EQUIPMENT SYSTEM

OBSERVATION 5

Your firm failed to maintain an adequate clean washing facility for personnel.

Specifically, the men's washroom within (b) (4) API Plant failed to provide hot water (only warm water) after running water from the sink for over sixty (60) seconds. Additionally, the hand drier within the Men's Cleanroom was broken, and there were no single-use towels available to dry personnel hands.

*06/03/2024 (Mon), 06/04/2024 (Tue), 06/05/2024 (Wed), 06/06/2024 (Thur), 06/07/2024 (Fri), 06/10/2024 (Mon), 06/11/2024 (Tue), and 06/12/2024 (Wed).

NIA PSV 06/12/2024

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