

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Office of Surveillance, Inspection Assessment Branch Food and Drug Administration-CDER/OC/DMPQ/ICT 10903 New Hampshire Avenue, Bldg 51, Room 4225 Silver Spring, MD 20993 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION November 6 - 17, 2017
Phone: 001-301-796-3334 Fax: 001-301-847-8738	FEI NUMBER 3006076314	

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Dr. Rav Kumar, Managing Director, ARPL

FIRM NAME Apotex Research Private Limited	STREET ADDRESS Plot 1 & 2, Bommasandra Ind. Area, 4th Phase, Jigani Link Road
CITY, STATE AND ZIP CODE Bangalore, Karnataka, 560099 India	TYPE OF ESTABLISHMENT INSPECTED Drug product manufacturer

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

Observation 1

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

- A. The following discrepancies were noted during the review of the cleaning processes. Specifically,
- a. There is no cleaning validation associated with the (b) (4) visual inspection machines located on line (b) (4) through (b) (4) or the (b) (4) located on line (b) (4) through (b) (4) in the large volume manufacturing plant.
 - b. Evidence could not be provided that the product used in the cleaning validation of the (b) (4) (b) (4) located in the large volume manufacturing plant uses the worst case product. These (b) (4) are mobile and can be moved from line to line.
 - c. Equipment assigned to campaign production of successive batches of the product, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants. ARI/06/RPT/87/A Campaign Batches Manufacturing Report (b) (4) Tablets report, dated 25 Jan 2017 states the worst case product was identified based on the evaluation of the potential bioburden risk associated with the length of a campaign that was run on the largest equipment train in the large volume manufacturing plant (LVMP). Upon review of the data to support this report it was noted the worst case product was not used and the type of equipment associated with each equipment train was not evaluated.
 - d. Efficacy testing could not be provided for the (b) (4) (b) (4) is used for the cleaning of (b) (4) Three of these products are manufactured on the same line as (b) (4)

This is a repeat observation.

- B. The following discrepancies were noted during the review of manufacturing controls. Specifically,
- a. There are no (b) (4) hold time studies to support the (b) (4) over the proposed (b) (4) hold times for the following application products:

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(b) (4) tablets, (b) (4) ng (b) (4) ng (b) (4) ng
(b) (4) Capsules, (b) (4) ng and (b) (4) ng
b. The Formulation and Development data for (b) (4) tablets,
(b) (4) ng, (b) (4) ng, (b) (4) ng proposed a control strategy for the compression of the tablets to include a specified dwell time of (b) (4) based on analytical data for tablets produced during these development trials, including (b) (4) and dissolution testing as well as physical tablet attributes such as hardness, thickness, and friability. During execution of the Exhibit batch (b) (4) the dwell time control was marked as "NA" without rationalization. For Exhibit batch (b) (4) the batch instructions note the recommended (b) (4) machine speed with respect to dwell time is (b) (4) rpm to (b) (4) rpm. During execution of this batch, the machine speed was recorded as run at (b) (4) rpm. No further rationalization for the difference was provided in the record.
c. Process validation of the Dispensing, (b) (4) of (b) (4) % for (b) (4) requires the (b) (4) batches in the (b) (4). The (b) (4) batches are only tested for (b) (4) prior to (b) (4). The process validation for (b) (4) also did not test the individual batches for assay prior to (b) (4).

Observation 2
Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed.

Specifically,
A. Deviation 498253 - initiated March 6, 2017 after a Laboratory Investigation (LIR) for a (b) (4) OOS (OOS in the (b) (4) testing) determined there was no identified laboratory error during the (b) (4) (b) (4) analysis of (b) (4) Capsules, (b) (4) ng lot (b) (4). The cause of the (b) (4) failure was also not determined during the manufacturing investigation, and no corrective or preventative actions were proposed under this Deviation. This batch is noted as the Biobatch for this application product.
B. Deviation 584954 - initiated Aug. 9, 2017 when (b) (4) Tablets (b) (4) ng lots (b) (4) failed the AQL inspection of the finished tablets due to capped and edgeworn tablets. The investigation concluded that the most probable root cause for the reported problem included the increasing (b) (4) force experienced during the batches (up to (b) (4)) however in review of historical data from the initial process validation batches, recorded (b) (4) forces ranged from (b) (4) - (b) (4). The impacted lots were

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TYPE OF ESTABLISHMENT INSPECTED

Drug product manufacturer

physically sorted for the capping defects and the investigation was closed without root cause. On 10/23/2017, deviation 626398 was opened for a failure of the AQL inspection for (b) (4) Tablets, (b) (4) ng lot (b) (4) due to capped tablets

C. As a consequence of an investigation into failed environmental monitoring results in the men's (b) (4) and the bin to be washed area, the personnel in the microbiology and production departments were instructed not to move around the environmental monitoring sample point to avoid the failures in the future due to personnel movement.

Observation 3

For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product.

A. The following Lab Investigation Reports (LIRS) were attributed to analyst error ("Root Cause Chemist") without sufficient justification. This is a repeat observation.

Specifically,

a. LIR16-417-OOT was initiated on 11/04/2016 for the OOT assay noted during the T=3M analysis for (b) (4) Submission batch (b) (4). Specifically, T=3M assay value of (b) (4) % was observed to be more than (b) (4) % different from the initial time point for the same study (b) (4) %. The investigation resulted in replacement of the original initial time point (T=0) sample result greater than 2 months after the original analysis. This new value (b) (4) % was reported in the submission for this product. The rationale for the replacement of the original initial time point was noted as "Assignable Cause: CHEMIST" without sufficient justification.

b. LIR-16-0416 was initiated on 11/04/2016 for (b) (4) batches of (b) (4) Capsules (b) (4) mg (b) (4) batches) and (b) (4) mg (b) (4) batches) due to OOS results obtained during the initial stability assay analysis. Out of these (b) (4) batches, (b) (4) batches of the (b) (4) mg samples were observed to be OOS. The original T=0 analysis for assay results ranged from (b) (4) % to (b) (4) % (mean value of two preps) for all the (b) (4) batches. The samples were re-prepared and tested and replacement values met specifications. This LIR was determined to be due to analyst error without sufficient justification.

c. LIR 17-47 was initiated on 05/17/17 for (b) (4) tablets exhibit batch stability sample T=3 month assay analysis (b) (4) (25C/60% RH) and (b) (4) (40C/75%RH-(b) (4)) due to an OOS and OOT result obtained during this analysis (b) (4) % and (b) (4) % respectively). The assignable root cause was

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Aditi Thakur
Rebecca E. Dombrowski

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Sandra A. Hughes, Investigator
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determined to be analyst error without scientific justification. It was noted that the LIR was extended to the SRIC under the Critical Incident Management and the most contributing factor was determined to be Sample stock preparation error by analyst with a recommendation to extend to manufacturing for investigation. However, no further investigation was extended to manufacturing.

d. LIR# 365008 initiated on 06/08/2016 for the Assay (b) (4) test for (b) (4) %, batch (b) (4). The (b) (4) result was observed to be OOS for the (b) (4) sample ((b) (4) %). The root cause of the investigation was determined to be sampling bias in the laboratory by analyst. The investigation did not extend to manufacturing.

B. Variation investigations are written for poor chromatography during the sequence or invalid data due to chemist error. What constitutes poor chromatography or chemist error is not defined. These reports are not tracked or trended. This results in data being discarded without initiating an LIR. Specifically,

a. VIR- 170541-was initiated 06/02/2016 for (b) (4) tablets batch (b) (4) and (b) (4) was analyzed for assay per (b) (4)

FCTB-10-IN for photo stability. Per the laboratory notebook and variation incident report (VIR-170541) the sample set was observed to have the poor chromatography for the (b) (4) peak. During the investigation, it was observed that no evidence of poor chromatography could be established

b. VIR- 160920-was initiated 10/15/16 for (b) (4) Tablets Batch (b) (4) was analyzed for Assay for (b) C/65%RH HD (b) 1 M time point, sample set 329_S667534_AS_1. One of the sample injections had no API peak (none observed). The VIR noted that an incorrect placebo injection was performed in the sequence instead of a sample without scientifically justifying other options.

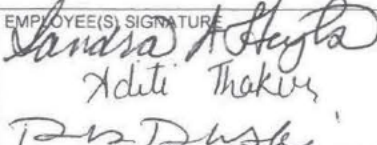
c. VIR- 17- 00312 was initiated on after t = 7 day data was obtained to investigate the initial "low" (b) (4) % results obtained at the time 0 analysis. This resulted in the replacement of the t=0 data without scientific justification (to (b) (4) %). The rationale provided by the Supervisory Analyst was not scientifically justified.

C. ARI/06/SOP/GEN/89/D Handling of File Note/Memorandum allows for the writing of memos. Memos reviewed included additional sample requests, modification of a method, and justification to release a batch.

Observation 4

Production equipment is not maintained at an appropriate interval to prevent malfunctions that could alter the quality of the drug product. Specifically,

A. Equipment maintenance activities are not documented with complete details of actions performed to enable

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assessment of product impact. For example:

Two sequential and unplanned maintenance activities were carried out on (b) (4) machine 21/E/131 from 10/14-16/2017. Neither event was entered into the equipment usage log (categorized as M1 events), and neither event resulted in subsequent cleaning activities.

The first event was initiated 10/14/2017 for air leakage observed on the (b) (4) for the machine (for gasket sealing and machine operation), and was repaired and corrected on 10/16/2017.

The second event was initiated on 10/16/2017 for (b) (4) position showing unknown on HMI' (b) (4) and was repaired as (b) (4) position out of limit alarm. So checked and proper setting done with production support" on 10/16/2017.

Additionally, these same events did not result in a formal deviation investigation and no SIS PQ impact was assessed for previous batches produced on this same equipment. This machine was used in production of (b) (4) Tablets, (b) (4) ng lot (b) (4)

B. The (b) (4) equipment re-evaluation plan for production equipment is not justified in that selected equipment were noted with numerous maintenance activities since the last recorded re-evaluation cycle for the equipment (when equipment maintenance trending is recorded). For example:

a. (b) (4) machine 21/E/019 was noted with 21 unplanned maintenance activities from 10/31/2016 – 10/31/2017. This system is listed as one of the (b) (4) machines proposed for use in the production of (b) (4) Tablets (b) (4) ng (b) (4) ng (b) (4) ng. The most recent re-evaluation of this equipment was compiled 11/24/2015.

b. Encapsulation machine 21/E/293 was noted with 12 unplanned maintenance activities from 10/31/2016-10/31/2017. This system is listed as one of the encapsulation systems proposed for use in the production of (b) (4) Capsules, (b) (4) ng and (b) (4) ng. The most recent re-evaluation of this equipment was compiled 6/15/2016.

c. (b) (4) machine 21/E/131, was noted with 5 unplanned maintenance activities from 10/31/2016 – 10/31/2017. This system is used in the routine (b) (4) of (b) (4) tablets, (b) (4) ng including lot (b) (4) and is listed as a (b) (4) system for intended use for US (b) (4)

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Tablets. The most recent re-evaluation of this equipment was compiled 11/27/2015.

Observation 5

Written procedures for the manufacture of drug products are not established as appropriate. Specifically, The set-up instructions for the assembly of the (b) (4) System (Equipment 21/E/470) located in LVMP for use in production of (b) (4) % per formula (b) (4) reference the incorrect procedure. Specifically, and as it pertains to (b) (4) % lot (b) (4) the instructions for the set-up of this machine referenced written procedure ARI/21/SOP/OPR/85 (for the (b) (4) instead of written procedure ARI/21/SOP/OPR/120 (for the (b) (4)

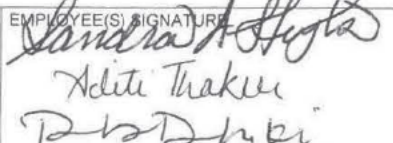
Differences in set up instructions between the two SOPs included HMI screen display/inputs among others. The first version of this formula and Batch Record Instruction is dated 7/22/2016 and also references the incorrect assembly procedure. Over (b) (4) batches have been produced since 7/22/2016 including (b) (4) % lot (b) (4)

Observations 6

Written procedures applicable to the Quality Unit are not always written or followed. Specifically,

The following discrepancies were noted during the review of the following Quality procedures:

- A. Procedures for the control of samples are not established and/or followed. Samples are not adequately tracked within your facility. Specifically,
 - a. Samples from completed stability studies were found 'pending for destruction' for greater than 1 year. For example, (b) (4) Tablets (b) (4) mg Batch (b) (4) and (b) (4) QA completed review on 22 May 2017. These same batches were found in an unmarked, (b) (4) bag at the back of Stability storage room # 1 in the AO laboratory. Each of these batches had reached the final (b) (4) time point and were on a list for destruction.
 - b. A (b) (4) mg API working standard of (b) (4) that accompanied the shipment of (b) (4) API lot (batch) (b) (4) under purchase order (b) (4) was reportedly destroyed with no record to support this destruction. This sample was noted on the exterior of one of the API drums from this shipment, and

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was noted as having been removed from the physical shipment on 11/29/2016. No further record of this sample was presented.

c. The request for samples from inventory is obtained using a Requisition Goods Issue to Cost Center form. This form was not used during the request of additional samples request for stability studies and instead informal communication was utilized.

B. ARI/06/SOP/GEN/149/B Ship Under Quarantine procedure states the responsible QA Head from the receiving site shall confirm agreement with the justification for the shipment under quarantine and complete the acknowledgement letter. Two shipments of quarantine product were shipped to (b) (4) on (b) (4) and (b) (4). Both of these forms were acknowledged by the site head in (b) (4) and not by the site head in (b) (4).

Observation 7

Procedures for the control of raw materials and in process material tracking and usage are not followed for the control over these materials as follows:

- A. The inward/outward log to track in process material movement was not filled out to reflect the movement of (b) (4) of (b) (4) lot (b) (4) out of the in process storage room on 11/03/2017.
- B. (b) (4) batch (b) (4) container number (b) (4) was observed in the warehouse on November 6, 2017 at location DB01B1 without a partial pack label on the vendor's container as required according to SOP ARI/21/SOP/GEN/5/J.
- C. Warehouse procedures are deficient in that they do not quarantine products which have yet to be approved for sale. For example, (b) (4) batches of product were released in SAP which should have been quarantined as the applications have yet to be approved.
 - a. Inventory does not accurately reflect product currently in the warehouse and instead reflects product associated with cost. Product is removed from SAP inventory when the decision to destroy product is made and not when the destruction of the material is actually performed.
 - b. During international shipping, product is not labeled/designated as released/quarantine/rejected. Released finished product is indistinguishable from product which is shipped under quarantine or rejected. Product was reviewed being shipping under quarantine to the United States and (b) (4). Rejected product was shipped to (b) (4) for destruction.

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Observation 8

The written stability testing program is not established and/or followed. Specifically,

- A. The following stability program protocols were not completed per written procedures and within the required testing time frame for the respective test point interval. Each was documented under opened deviations as follows:
 - a. PR 581439 initiated on Aug.2, 2017 and applicable to 5 samples and 3 stability protocols
 - b. PR 584320 initiated on Aug 8, 2017 and applicable to 161 samples and 25 stability protocols
 - c. PR 612038 initiated on Sept. 22, 2017 and applicable to 8 samples and 5 stability protocols
 - d. PR 612976 initiated on Sept. 28, 2017 and applicable to 174 samples and 66 stability protocols

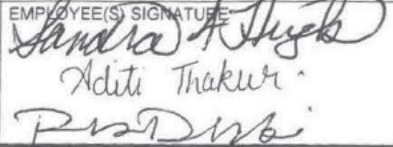
For example, (b) (4) Tablets, (b) (4) ng under protocol ST (b) (4) 075-2016 was due for the 9 month stability analysis on 29-Jul-2017, but was not completed until 28-Aug-2017.
 This is a repeat observation.
- B. The written stability program is not designed to assess the stability characteristics of drug products as appropriate.

The test methods used during stability studies of (b) (4) tablets have not been proven to be reliable, meaningful, and specific. ARI/02/SOP/GEN/25/J Validation of Analytical methods procedure only requires degradation of (b) (4) to (b) (4) % in at least (b) (4) stress conditions. Thus impurities from the stress conditions which are not degraded are not evaluated. This procedure requires mass balance should be between (b) (4) - (b) (4) %. Scientific justification was not provided for failing mass balance in the stress studies performed for the (b) (4) impurity method and the (b) (4) impurity method.

Observation 9

The following issues were noted during the review of the analytical methods used in the finished product release of product for the U.S. market. Specifically,

- A. The software used to conduct high performance liquid chromatography (HPLC) analysis of finished product for unknown impurities is configured to permit extensive use of multiple processing methods without scientific justification. For example, during the analysis of impurities and assay, an analyst can change the integration parameters for each sample run including peak width, detection threshold, minimum area, set

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Dr. Rav Kumar, Managing Director, ARPL

FIRM NAME Apotex Research Private Limited	STREET ADDRESS Plot 1 & 2, Bommasandra Ind. Area, 4th Phase, Jigani Link Road
CITY, STATE AND ZIP CODE Bangalore, Karnataka, 560099 India	TYPE OF ESTABLISHMENT INSPECTED Drug product manufacturer

liftoff %, set touchdown %, valley to valley, integration start, integration stop and tangent skim.
B. Reprocessing is performed on a single injection and does not apply to the entire sequence.

Observation 10

Each batch of non-sterile drug product required to be free of objectionable microorganisms is not tested as necessary. Specifically,

There is no scientific justification for not testing (b) (4) mg and (b) (4) mg per USP. USP <1111> Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use recommends testing (b) (4) for Total Aerobic Microbial Count, Total Combined Yeasts/Molds Count and Absence of (b) (4). Justification for not performing these tests could not be provided.

SA 11/17/17

[A large diagonal line is drawn across the page, crossing out the observation text.]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>Sandra A. Hughes</i> Aditi Thakur <i>Rebecca E. Dombrowski</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Sandra A. Hughes, Investigator Aditi S. Thakur, Chemist Rebecca E. Dombrowski, CSO	DATE ISSUED Nov. 17, 2017
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