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	DATE(S) OF INSPECTION
CDER/OPQ/OS IAB Attn: Mr. Concepcion Cruz White Oak Building 51, Room 4316 10903 New Hampshire Ave Silver Spring, MD 20993 email: cderosiab@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	09/11-19/2017 FEI NUMBER 3004149463

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Murali K. Divi, Chairman and Managing Director

FIRM NAME	STREET ADDRESS
Divi's Laboratories Ltd. (Unit II)	Chippada Village, Annavaram, Bheemunipatnam Mandal,
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Visakhapatnam District, Andhra Pradesh 531162 India	API manufacturer

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

OBSERVATION 1

Your firm failed to test individual batches of final API for conformity with all appropriate specifications such as purity, strength, and identity prior to (b) (4) Specifically, your firm does not analyze for assay for all final API batches prior to (b) (4) The following final API products were found to not be analyzed for assay:

Active Pharmaceutical Ingredient	Number of final batches not analyzed for Assay prior to (b) (4) in 2016	Number of final batches not analyzed for Assay prior to (b) (4) in 2017
(b) (4) (DMF (b) (4)	(b) (4) batches	(b) (4) batches
(b) (4) DMF# (b) (4)	batches	batches
(b) (4) (DMF# (b) (4)	batches	batches
(b) (4) (DMF# (b) (4)	batches	(b) (4) batches
(b) (4) (DMF# (b) (4)	batches	(b) (4) batches

OBSERVATION 2

Laboratory failures are not thoroughly investigated. Specifically, Out of Specification (OOS) investigations where laboratory error was not clearly identified were invalidated without adequate investigation into manufacturing, process, maintenance, and engineering activities. For example:

a. Investigation No./ 2-PLI/OOS/IP-IM/W/012 for (b) (4) lot number (b) (4) any other individual impurity out of specification ((b) (4)% w/w, Spec of (b) (4)% w/w), preliminary investigation did not identify laboratory error. Your preliminary laboratory investigation on February 20, 2017, interviewed that analyst on sample analysis, preparation of sample, environment and glassware and found no errors.

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

Your March 03. 2017 extended preliminary laboratory investigation report, described data obtained from fresh preparation analysis is not comparable to initial analyzed data as the peak did not elute. Your further investigation report dated March 12, 2017, into the peak identified the peak as being (b) (4) which also manufactured at your site. Your gap analysis report shows your analyst stating he cleaned the balance area and weighting pan before performing weighing activity and taken precautions during sample transfer. However, you concluded that this was a cross contamination in your laboratory. Your investigation also shows that the same impurity has eluted in 17 other previous batches.

Your documented manufacturing investigation only verified that there was no deviation being reported in the batch records and operations were followed. There was no thorough investigation into manufacturing, process, maintenance, and engineering activities and involved the relevant departments that may have attributed to batch contamination. Original results were invalidated without clear identification of laboratory error and adequate investigation into manufacturing, process, maintenance, and engineering. Original results were invalidated and batch was released using retest results. In addition, another OOS investigation (No./ 2-PLI/OOS/IP-IM/W/010) initiated 5 days prior to this OOS for an impurity eluting at the same relative retention time was attributed to another cross contamination during sampling and original results invalidated.

Within specification impurity at the same relative retention time has been quantified (b) (4) times since the above OOS.

b. Investigation No./ 2-PLI/OOS/FP(b) (4) W/001 for (b) (4) lot number (b) (4) any other individual impurity out of specification (b) (4) % w/w, specification (b) (4) % w/w) your preliminary investigation report dated January 9, 2017 , interviewed that analyst on sample analysis, preparation of sample, environment and glassware and found no errors. Reinjection and retest from HPLC bottle and (b) (4) bottle' analysis also showed that same impurity eluted in your sample at out of specification limits. The peak was identified by your laboratory as being (b) (4) that is also manufactured at your site. Your extended investigation dated February 13, 2017, interview of your analyst performing (b) (4) activity as not performing any analysis before performing the (b) (4) You state that he performed secondary verification activities in ROI and LOD analysis and attributed the contamination coming from unhygienic hands due to lack of washing his hands after the secondary verification activity even though the analyst stated he performed the activity in clean and dedicated location, he has wiped his

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hands and did not observe any product on his hands.

Batch resampling was authorized by QA on March 18, 2017 and passing resample was reported extended preliminary laboratory investigation report on April 12, 2017. Manufacturing investigation form was filled on June 2, 2017 after passing resample results and did not document adequate investigation into manufacturing, process development, maintenance, and engineering activities that may have attributed to batch contamination. The root cause was attributed to contamination from unhygienic hands during (b) (4) activity and original results were invalidated. Batch was released, (b) (4) and distributed to the US.

OBSERVATION 3

Review of Analytical incident/excursion investigations as per your Atypical or out of trend results procedure (2-RA/OP/03) showed instances in which samples injection sequence was completed but results were not calculated and/or compared to specification to ensure OOS results were not obtained and sample result screening is not occurring prior to invalidating the run for system suitability or chromatograph issues. For instance:

a. On January 12, 2017, Incident 2-AI/FP(b) (4)W/002 was initiated after testing of 6(b) (4) lots for theoretical plate count failure of(b) (4) peak in standard solution. Sample results were invalidated without evaluation of results to ensure OOS results were not obtained.

b. On December 27, 2016, incident 2-AI/FP(b) (4) V/020 was initiated after testing of stability lot(b) (4) ((b) (4) (40C/75 %RH, day 180) for baseline disturbance in sample prep(b) (4) System suitability was met and disturbance was attributed to air bubble in flow cell. Sequence was invalidated without evaluating and comparing of results to ensure OOS results were not obtained.

c. On January 23, 2017, incident 2-AI/FP(b) (4)W/002 was initiated after testing of 6(b) (4) lots for related compound and assay testing due to abnormal peak shape fronting at product peak in peak identification solution, sample solution and sample injections. System suitability was met. Peak was associated to mobile phase contamination or improper pH adjustment. Sequence was invalidated without evaluating and comparing of obtained results to ensure OOS results were not obtained.

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OBSERVATION 4

Your firm has failed to validate the manufacturing (b) (4) cleaning length of time from (b) (4) of the (b) (4) to the (b) (4) of (b) (4) production runs for manufacturing equipment to ensure your cleaning procedures are effective for the removal of the build-up of contaminants, degradants and microbes. The (b) (4) length in the chemical synthesis production area is (b) (4) to include equipment such as; reactors, (b) (4) (b) (4) API (b) (4) length in the Pharma blocks are (b) (4) to (b) (4) of continuous production. Equipment in the pharma blocks include: (b) (4) (b) (4)

There is no documentation to ensure your cleaning procedures are effective to remove microbial contaminants in the worst case locations of the different equipment after the (b) (4) length of (b) (4) or (b) (4) of continuous production. For example, the last continuous production in the (b) (4) Pharma block for (b) (4) was from (b) (4) to (b) (4) (b) (4) batches of (b) (4) were processed through the (b) (4) (b) (4) and (b) (4) before a complete (b) (4) clean was conducted. (b) (4) batches of (b) (4) were processed in the (b) (4) during this (b) (4)

OBSERVATION 5

Your firm does not have adequate (b) (4) cleaning instructions (Issue Control#5) for the major equipment in the (b) (4) Pharma block for (b) (4) Major equipment in the pharma blocks include: (b) (4) (b) (4) (b) (4) The (b) (4) batch cleaning record does not have detailed step by step instructions for how to clean the equipment, what parts to dismantle, supplies needed for cleaning, water temperature or pressure, and the volume of water needed for flushing the equipment.

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OBSERVATION 6

Batch records are not always recorded contemporaneously at the completion of an operation. For example:

On 9/12/2017 during the production of (b) (4) batch (b) (4) the (b) (4) n charge production employee had signed the "CHECKED BY" column at step (b) (4) in the manufacturing record to increase the batch (b) (4) to (b) (4) However the "DONE BY" column was not signed by the chemist and the operation was not completed.

On 9/12/2017 during the production of (b) (4) batch (b) (4) batch record operation step (b) (4) displays the initials of the chemist and (b) (4) in charge manager had signed the "CHECKED BY" and "DONE BY" column as completed. However the operation time "TO' and "DURATION" details are not completed for the operation; as well as the (b) (4) volumes of the (b) (4)

9/19/17

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