DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
United States Food and Drug Administration 12420 Parklawn Drive, Room 2032, Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	07/22/2019 - 07/26/2019
	FEI NUMBER 3007197995

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Vishnukant Bhutada, Managing Director

FIRM NAME	STREET ADDRESS
Shilpa Medicare Limited	33 33a & 40 To 47 Raichur Industrial Growth Centre, Chicksugur
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Raichur, Karnataka, 5841734 India	Active Pharmaceutical Ingredients Manufacturer

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

Quality 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. Specifically,

A. Out of Specification (OOS) Investigation Nos. OOS/004/18/U-2 was initiated on 22 January 2018 for (b) (4) batch no. (b) (4) (manufactured (b) (4) (b) (4) stability batch at the 36-month stability time point (Long Term: 25 ± 2 °C and 60 ± 5 %RH) and OOS/005/18/U-2 was initiated on 22 January 2018 for (b) (4) batch no. (b) (4) (b) (4) stability batch at the 36-month stability time point (Long Term: 30 ± 2 ° C and 60 ± 5 %RH). The OOS failure during Related Substances (Method-II) testing was initially categorized as (b) (4) which exceeded the specification limit of NMT (b) (4) % ((b) (4) %) for long term and (b) (4) % for intermediate condition and any unspecified impurity which exceeded the specification limit of NMT (b) (4) % ((b) (4) % for long-term and intermediate conditions). The product has a five-year retest date/expiry (60 months). No assignable root cause was identified during (b) (4) of the investigation Other deficiencies with the investigation include, but are not limited to:

• Step # (b) (4) Phase-(b) (4) Investigation) of SOP #SOP/QA/GEN/003/12 (Procedure for Handling and Investigating Out of Specification (OOS) states Phase (b) (4) investigation shall be carried out with team members consist of cross functional departments (Production, QC, QA, Research & Development, and Technology Transfer) and the investigation should be focus on review of Batch processing Records, Batch Cleaning Records, and other relevant documents which could be supportive of the investigation. The review of these records shall also be extended to pre and post batches, of manufacturing and distribution records. The firm failed to assemble a cross functional team to review Batch processing Records, Batch Cleaning Records, and other relevant documents records
• Retesting of sample was carried out by (b) (4) to differences between conclusions in

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phase(b)(4) investigation and SOP.
• You invalidated the initial OOS results and accepted the average results by(b)(4) analysts.
• You attributed the root cause identification to probability of contamination of diluent. As per preventive action, the SOP for good chromatographic practices (SOP/U- 2/QC/GEN/O 10) was revised with incorporation of procedure for precaution during diluent preparation (SOP/U-2/QC/GEN/010/10). It was not discussed in the investigation report.

B. During the walkthrough on 24 July 2019, three power failures occurred within the facility during a 15-minute interval and a back-up generator did not resume power. Additionally, while reviewing audit trails for two stability chambers (#SML2/QC/HC/005 and #SML2/QC/HC/001) it was noted that the facility frequently loses power, sometimes for over 8 hours. The firm has not maintained any records for power failures that occurred within the manufacturing areas and the QC lab, and has not conducted any investigation or assessment regarding the impact of the power failures to in-process product, QC Laboratory equipment calibration and on-going testing. In addition, there is no procedure to handle power failures in the laboratories and SOP #SOP/U-2/ENG/GEN/053/02 (Handling of Power Failure, Effective Date 29 May 2019) does not extend to conducting an investigation to demonstrate that an assessment was made to on-going manufacturing operations and laboratory testing operations at the facility to determine if there is any impact.

Facilities & Equipment System

OBSERVATION 2

Equipment used in the manufacture of intermediates and APIs is not present within the facility.

Specifically,

(b) (4) of the(b) (4) pieces of equipment used to manufacture(b) (4) of the submission batches for API (b) (4) (b) (4) used in(b) (4) (b) (4) capsules were not present in the facility. At the time of the inspection the below pieces of equipment were already discarded based on a change control from 02/2019. No documentation or assessment of what replacement equipment will be used to make this API was

performed until the second day (23 July 2019) of the inspection. In addition, no notification of these changes was sent to the agency, the existing process flowchart for the product was not updated, and there is no documentation substantiating the decommission of the equipment.

Equipment Name	Equipment ID #	Capacity	Material of Construction
(b) (4)			

OBSERVATION 3

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 API finished materials. Specifically,

The following pieces of equipment used to manufacture (b) (4) and (b) (4) API were observed unmaintained during facility walkthroughs. All equipment noted below is non-dedicated and was in a clean state during my visual observation.

A. Your performed clean hold time study in 2016 for the equipment used for the manufacturing of APIs in different production blocks is deficient and you did not follow the established protocols. (b) (4) was being manufactured in production (b) (4) and was moved to (b) (4) in June 2019 due to increase batch size. Clean Holding Time Study Protocol #PC/QA/CHS/001 states in Step (b) (4) "MB Department personnel shall collect the cleaning holding time study samples on the (b) (4) (b) (4) " In addition, it states in Step (b) (4) "If any deviations are noticed while conducting the validation, all those deviations, investigation details and corrective actions taken shall be documented in clean holding time study summary report." You reported in the Summary report (#RPT/QA/CHS/001) that the cleaning holding time study was stopped after (b) (4) analysis due to exceeded results are

observed in TAMC analysis and you did not initiate a deviation for not continuing the study to (b) (4) You added new products to the facility (b) (4) since the last cleaning hold time study and you have not performed another cleaning hold time and/or assessment to ensure the equipment can remain clean for (b) (4).

B. Your performed dirty hold time study in 2016 for some of the production equipment in Block (b) (4) is deficient and you did not follow the established protocols. Some of the equipment listed in the study was used for manufacturing (b) (4) submission batches prior to being removed and replaced by new equipment. Dirty Holding Time Study Protocol #PC/QA/DHS (b) (4) '001 (b) (4) states in Step (b) (4) (b) (4) is sparingly soluble in (b) (4) as per solubility criteria and this product was considered for dirty hold time study as worst case among the below mentioned products." However, there are three other products that are sparingly soluble in (b) (4) and you did not explain how you chose (b) (4) as the worst case scenario. You (b) (4) new products (refer below*) to the facility (b) (4) since the last dirty hold time study and you have not performed another dirty hold time and/ or assessment of how these products compare to (b) (4)

(b) (4)

C. Peeling paint was observed above the (b) (4) opening of (b) (4) (b) (4) 18 during the walkthrough on 22 July 2019, which was used for the submission batches (b) (4) and is projected to be used for commercial operations or the manufacturing of (b) (4) batches.

D. Presence of holes and heavy marks were observed inside (b) (4) -02 located in Block (b) (4) which was used for the submission batches (b) (4) and is projected to be used for commercial operations or the manufacturing of (b) (4) batches. In addition, the ceiling area above the (b) (4) is not finished.

E. Presence of cracks were observed on the walls above the opening of (b) (4) (b) (4) located in Room # (b) (4) Room- (b) (4) on 22 July 2019, which was used for the submission batches (b) (4) and is projected to be used for commercial operations or the manufacturing of (b) (4) batches.

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F. A bolt was observed underneath [(b) (4)] (#AM/[(b) (4)] 01) during the walkthrough of Block-[(b) (4)] on 22 July 2019, which is used for the manufacturing of [(b) (4)] The firm was unable to identify where this came from.

Laboratory Control System

OBSERVATION 4

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically,

A. The data acquisition software (Newtronic ICDAS version 1.2), which is used for monitoring the storage conditions (temperature and relative humidity) for the stability chambers has not been validated and has been in use since 2009. The stability chambers are used to store [(b) (4)] (submission stability batches) and [(b) (4)] commercial) finished API materials for on-going stability studies for U.S marketed products.

a. A change control was not processed for the installation of the software and the equipment was released for use.
b. Validation Master Plan # VMP/SML-2/001 Rev.00 did not address computerized systems and software used by the facility.

B. The audit trail for the Newtronic ICDAS version 1.2 system used for Stability Chamber #SML2/QC/HC/005 (used for storing stability samples for [(b) (4)] and Chamber #SML2/QC/HC/001 (used for storing stability samples for [(b) (4)] recorded several encountered power failures from 01/01/2016 to date which has not been investigated by the Quality Control Unit to determine the impact on the samples. In some instances, the power failures have lasted 9 hours. In addition, there is no SOP for the review of these audit trails. The stability chambers are used to store [(b) (4)] and/or [(b) (4)] finished API materials for on-going stability studies for U. S marketed products.

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OBSERVATION 5

The calibration of instruments is not done at suitable intervals [in accordance with an established written program] [with provisions for remedial action in the event accuracy and/or precision limits are not met]. Specifically,

A. You have not performed a verification of the FT-IR (ID #SML2/QC/IR/00) prior to each use per Step #(b) (4) of SOP # SOP/U-2/QC/OPR/002/06 (Operation and Calibration Procedure for FT-IR, Effective Date 24 November 2017) where it states, "Instrument verification is the procedure of demonstrating that spectrum 100 Instrument is functioning correctly." In addition, you do not maintain a logbook for the verification of the equipment prior to use. The equipment was utilized for testing API(b) (4) Batch #(b) (4) IV-006/18 which was manufactured in July 2018 with August 2019 retest date(b) (4) used in(b) (4) (b) (4) capsules.

B. Step #(b) (4) and (b) (4) of SOP #SOP/ARD/OPR/006/06 (Operation and Calibration Procedure for X-Ray Diffractometer, Effective Date 14 March 2019 allow the analyst to turn off and turn on the equipment. In addition, when the equipment is turned on and off, it is not documented in a document and no system suitability is performed to assure that the equipment is working as intended based on its qualification parameters. This equipment is used for testing (b) (4) finished API materials for release testing and was used for testing (b) (4) Batch #(b) (4) IV/006/18.

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