DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
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 Phone: 001-301-796-3334 Fax: 001-301-847-8738 Industry Information: www.fda.gov/oc/industry	November 20 - 30, 2017
	FEI NUMBER 3009876430

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Vishnukant Bhutada, Managing Director

FIRM NAME	STREET ADDRESS
Shilpa Medicare Limited	S-20 to S-26 Pharma. Formulations SEZ; TSIIC, Green Ind. Park
CITY, STATE AND ZIP CODE Polepally, Jadcherla, Mahabubnagar, Telangana, INDIA	TYPE OF ESTABLISHMENT INSPECTED Sterile and non-sterile Drug Manufacturer

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 OR ACTION 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 FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

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

Observation 1

(b) (4) (b) (4) Injection (b) (4) mg/vial is labeled with "The (b) (4) product may be kept in the vial or drawn into a (b) (4) **When (b) (4) (b) (4) injection (b) (4) mg/vial is (b) (4) using (b) (4) that has not been (b) (4), the (b) (4) product may be held under (b) (4) conditions** for up to (b) (4). When (b) (4) (b) (4) injection (b) (4) mg/vial is (b) (4) using (b) (4) **(b) (4), the (b) (4) product may be stored under (b) (4) conditions** for up to (b) (4) ." "(b) (4) (b) (4) injection (b) (4) mg/vial (b) (4) with (b) (4) (b) (4) for (b) (4) administration may be stored for up to (b) (4) (b) (4) at (b) (4) °C or for up to (b) (4) between 2°C and 8°C**; when (b) (4) with (b) (4) **(b) (4) (b) (4) it may be stored for (b) (4) between 2°C and 8°C". Review of the data generated from the hold time study shows that the product would fail:

- For (b) (4) impurity when (b) (4) with (b) (4) ml room temp (b) (4) and held for (b) (4)
- For (b) (4) impurity and assay when (b) (4) with (b) (4) ml 2-8°C (b) (4) and stored at 2-8°C for (b) (4)

Observation 2

Scientific rational could not be provided for the following commercial product specifications:

A. Release specification for (b) (4) (b) (4) Injection (b) (4) mg/vial is set at not less than (b) (4) % and not more than (b) (4) % of label claim while the shelf life specifications are set at not less than (b) (4) % and not more than (b) (4) % of label claim.

B. (b) (4) (b) (4) Injection (b) (4) mg/vial can be diluted with (b) (4) ml (b) (4) for (b) (4) injection or (b) (4) ml (b) (4) (b) (4) (b) (4) injection. No impurity specifications are listed for release and shelf life testing specifications for the (b) (4) ml (b) (4) product. Instead the impurity specifications are listed as "For information".

Observation 3

Procedures for the cleaning and maintenance of equipment are deficient regarding sufficient detail of the methods, equipment, and materials used in the cleaning and maintenance operation, and the methods of disassembly and reassembling equipment as necessary to assure proper cleaning and maintenance.

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A. Cleaning validation for each product determined how many times the operators need to repeat the cleaning procedure prior to it removing the residue left from the previous batch. This could range from (b) (4) to (b) (4) times. Operators do not document the number of times cleaning was repeated. The cleaning procedure does not specify whether a (b) (4) should be used and only states "if required, rub with (b) (4)". The operators do not document the use of the (b) (4).

B. There is no cleaning procedure or cleaning validation for the (b) (4)

C. How to collect the rinse sample following manual cleaning is not specified in a procedure.

Observation 4

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. Your firm did not initiate an investigation into repetitive complaints received regarding (b) (4) (b) (4) Injection appearance of (b) (4) product. All investigations concluded the complaint batch/product is acceptable toward product quality perspective.

B. Your firm invalidated initial out-of-specification (OOS) laboratory results in favor of passing results without an adequate investigation.

Observation 5

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.

A. During the watching of (b) (4) (b) (4) injection production on 21 Nov. 2017, I noted the firm was not documenting all interventions. I observed (b) (4) interventions between the weight check ((b) (4) and (b) (4) Only one of these interventions was documented.

B. Media fills are performed following SOP/QAD/GEN/043-06 Procedure for Aseptic Process Simulation, dated 20 May 2017. This procedure requires all personnel authorized to enter in the aseptic processing and filling area to participate in a media fill run at least (b) (4) in (b) (4) The firm does not track personnel activities in media fill. Production operators, Quality Assurance personnel, microbiologists and engineers were listed as being qualified during media fills without performing any interventions.

In addition, the firm reports the media fill duration by tracking the start and end time of filling. This does not take into account the extended breaks and the intermittent breaks taken by the operators. For example,

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media fill (b) (4) specifies the total duration of the fill time as (b) (4) and (b) (4) Actual fill time was approximately (b) (4) and (b) (4). During these breaks operators stated they ensure open vials are removed from the line.

C. The firm does not track the (b) (4) (b) (4) used on the closed (b) (4) used to manufacture sterile drug product. The (b) (4) (b) (4) are given a (b) (4) expiry day by the manufacturer. The (b) (4) that have been replaced on the line are documented as not having an expiry date.

D. For each pair of sterile (b) (4) tested, the firm only requires a minimum of (b) (4). The firm does not ensure that the whole (b) (4) is sterile. These applies to both the (b) (4) (b) (4) b) (4) b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) sterile.

E. Microbial testing on swab samples is performed using a pour plate method. The (b) (4) (b) (4) media should be '(b) (4)' prior to pouring the (b) (4) into the plate containing the sample. This equipment used along with the temperature of the media is not documented. Management confirmed the temperature of the media at this step is critical.

F. The monitoring program does not cover all critical surfaces that come in contact with the product. The firm does not monitor the filling (b) (4) at the conclusion of sterile filling to support sterile conditions were maintained throughout the filling process.

G. During the validation of the microbial method used during the analysis of environmental monitoring plates, the actual conditions of use are not validated. The firm does not demonstrate that the microbial growth media provides conditions such that compromised and/or stress organisms are able to propagate within a varied microbial population. In addition, the media used for the (b) (4) plate method does not undergo growth promotion for how it is used. Growth promotion is performed (b) (4) (b) (4) (b) (4). The media is used for (b) (4) at (b) (4) then moved into the (b) (4) ncubator.

H. The procedure used for (b) (4) SOP/PDI/GEN/050-05 Procedure to Start Activity in New Facility/ After Major (b) (4) & (b) (4) Activity is not being followed. (b) (4) is performed (b) (4) Operators are not performing the (b) (4), the (b) (4) (b) (4) activity or the (b) (4) (b) (4) hold time as specified in the procedure.

Observation 6

The written stability program for drug products does not include reliable, meaningful, and specific test methods. The methods used during the stability program for (b) (4) Tablets (b) (4) mg & (b) (4) mg, (b) (4) (b) (4) Injection, (b) (4) Injection, (b) (4) mg/ml and (b) (4) (b) (4) Injection, (b) (4) mg/vial have not been proven to be

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stability indicating.

A. (b) (4) Tablets (b) (4) mg & (b) (4) mg: The stress studies performed during the validation of (b) (4) tablets resulted in a mass balance of (b) (4) % when exposed to (b) (4) . This discrepancy was not investigated. Needing to detect all impurities generated from the degradation of (b) (4) tablets was not an acceptance criterion.

B. (b) (4) (b) (4) Injection: Mass balance was not performed during the stress studies performed on (b) (4) Three impurity methods are needed to determine impurities in (b) (4) (b) (4) Injection.

C. (b) (4) njection, (b) (4) mg/ml: The acceptance criteria for the stress studies performed during the validation did not require all impurities to be detected. The acceptance criteria are listed as all degradation products if any should be well separated from (b) (4) peak and each other, the peak purity angle should be less than purity threshold as per waters empower – 2 software and calculate the mass balance of stress degradation samples (for information only). The following results were noted during the stress studies:

	Initial testing			Repeat testing		
Degradation condition	Control	(b) (4)	(b) (4)	Control	(b) (4)	(b) (4)
Assay	(b) (4) %	(b) (4) %	(b) (4) %	(b) (4) %	(b) (4) %	(b) (4) %
Mass Balance	(b) (4) %	(b) (4) %	(b) (4) %	(b) (4) %	(b) (4) %	(b) (4) %

Due to the (b) (4) mass balance, the stress studies for acid and basic conditions were repeated. During the retesting, the sample was not degraded and therefore it still cannot be determined if the method can detect the impurities generated by acid and basic exposure.

D. (b) (4) (b) (4) Injection (b) (4) mg/vial: Not all impurities are integrated during the stress studies and stability testing of (b) (4)

Observation 7

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, 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, an analyst can change the integration parameters for each sample run including inhibit integration, peak slice minimum area, sensitivity, baseline point, peak group start, peak group end.

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Observation 8

Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release. Specifically there is no evidence that each vial produced meets specification.

A. One vial of (b) (4) mg/vial (b) (4) (b) (4) Injection contains (b) (4) ppm. The assay method, degradation products method, and (b) (4) method requires (b) (4) ppm for analysis. The method requires (b) (4) vials of (b) (4) vials to be (b) (4) prior to testing. The impurity (b) (4) method requires an (b) (4) ppm sample to be tested. This analysis also specifies (b) (4) vials to be (b) (4) prior to testing.

B. The particle size distribution method used in the analysis of (b) (4) (b) (4) Injection (b) (4) mg/vial stated "(b) (4) (b) (4) ". Management stated (b) (4) vials would fail the particle size test so a different vial would need to be tested. When vials are discarded is not documented.

C. The methods for (b) (4) Injection USP require the combining of vials prior to preparation of the (b) (4) mg sample for assay and related substances analysis ((b) (4) mg/(b) (4) ml - (b) (4) vials, (b) (4) mg/(b) (4) ml - (b) (4) vial) for (b) (4) mg/ml specifies to (b) (4) (b) (4) vials prior to preparing a (b) (4) mg sample solution. The combining of vials is not specified in the (b) (4) Injection official monograph listed in USP.

Observation 9

Scientific justification could not be provided for the following sample sizes:

A. The filling of the validation of (b) (4) njection USP (b) (4) mg/(b) (4) ml, takes approximately (b) (4) and fills approximately (b) (4) vials. During the validation the firm sampled (b) (4) vials at the (b) (4) of the filling process. These (b) (4) vials are combined prior to testing to obtain (b) (4) result from the (b) (4) (b) (4) of the filling process. The vials were tested for description, pH, and assay. This number of vials sampled was not based on statistical rational and the times when these samples are taken is not documented. In addition to these samples, the firm samples (b) (4) vials total from the (b) (4) (b) (4) after the (b) (4) for finished product testing. These vials are compiled prior to being sent to Quality for testing. Of these (b) (4) vials, (b) (4) sample is tested for assay and impurities.

B. The sampling and testing of sterile (b) (4) is not based on a statistical evaluation. Instead the firm samples (b) (4) pairs of (b) (4) regardless of the amount received. Receiving lots can range from (b) (4) pairs of (b) (4) to

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(b) (4) pairs.

C. The sample size for the testing of (b) (4) is not appropriate for the expected microbial count of the (b) (4) in order to derive statistically valid colony counts. The firm did not obtain any CFUs for the 12 month period reviewed.

D. The process validation for (b) (4) (b) (4) Injection (b) (4) mg/vial only requires (b) (4) sample analysis during filling from the (b) (4) of the filling to ensure product uniformity.

Observation 10

The following defects are not reflected in the visual inspection kits used to train the visual inspectors;

(b) (4) vial/liquid, (b) (4) vials: Sealing (non-integral), broken/cracks, changes in liquid color, absence of stopper/seal, less volume, more volume, color particle, coding, empty vial, molding defects, scratches, spot on (b) (4) spot on (b) (4) seal.

(b) (4) vial/liquid, (b) (4) vials: Broken/cracks, less volume, more volume, empty, appearance, sealing (non-integral).

(b) (4) vial/ (b) (4) (b) (4) vials: Broken/cracks, (b) (4) (b) (4) black particle, glass particle.

(b) (4) vial/ (b) (4) (b) (4) vials: Sealing (non-integral), broken/cracks, glass particle, change in (b) (4) color, absence of stopper/seal, (b) (4) (b) (4) colored particle, coding, empty vial, molding defects, spot on (b) (4) spot on (b) (4) seal.

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