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
12420 Parklawn, Drive, Room 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	02/13-20 & 24-25/2020
	FEI NUMBER 3009876430

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Jayant Karajgi, Chief Operating Officer

FIRM NAME	STREET ADDRESS
Shilpa Medicare Limited	S-20 To S-26, Pharm. Formulation Sez, Tsiic, Green Industrial Pa
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Polepally, Jadcherla, Telangana, 509301, India	Sterile/Non-Sterile Drug Product Manufacturer

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

OBSERVATION 1

A. Your Quality Unit failed to ensure that all production and laboratory control operations follow the cGMP requirements. Your Quality Unit has not performed the necessary assessments/reviews to ensure that the objectionable practices observed do not negatively affect the quality attributes of your sterile and non-sterile drug products. Moreover, many of the objectionable conditions noted below suggest that personnel may not have the necessary skill sets/training, experience and/or scientific knowledge with respect to sterile/non-sterile manufacturing processes and related systems in order to adequately assess the CGMPs. For example,

- All the complaints received since 2017 to present for sterile and non-sterile drug products have been classified as "minor";
- No CAPAs have implemented to decrease re-occurrence of complaints related to coring/fragmentation defects observed in vials of (b) (4) (b) (4) mg/vial;
- All the QC Laboratory (Chemical/Micro) Incidents (Un-planned deviations) initiated since 2018 to present have been classified as "minor";
- There is a practice of invalidate failing or OOS results without scientific justification;
- The implemented procedure for in-process sampling is not based on statistical rationale;
- There is no assurance that your process simulation studies (media fills)/smoke studies are representative of the conditions observed and/or that might occur during routine aseptic filling operations of vials.

B. No CAPA has been identified/implemented for the repetitive complaints received due to coring/fragmentation defects observed in vials of (b) (4) (b) (4) mg/vial.

Your firm has failed to thoroughly evaluate in combination with the (b) (4) stopper supplier the multiple complaints received (approximately (12) confirmed complaints) to effectively prevent coring and fragmentation defects in vials of (b) (4) drug product. Up to date, there is no documented evidence or

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empirical data (e.g. penetrability and fragmentation testing) that confirms that your current container closure system is suitable for using with a (b) (4) use to (b) (4) (b) (4)

C. Your firm failed to conduct a thoroughly trend analysis for lots of (b) (4) (b) (4) mg/vial manufactured at Shilpa site.

Specifically, your Quality Control Unit has been releasing lots that showed assay results at the lower or higher side of the specification during in-process and release testing. This discrepancy establishes that the current manufacturing process is not sufficiently robust and reproducible to produce predicted results. The release specification for (b) (4) (b) (4) mg/vial finished product is: (b) (4) and for bulk solution is (b) (4)

For example, the released of finished product during FY2018 and FY2019:

- (b) (4) (b) (4) mg/vial; Batch # (b) (4) Exp. Date: April 2020, Assay result (b) (4) %. The lot was released to USA market
- (b) (4) (b) (4) mg/vial; Batch # (b) (4) Exp. Date: May 2021, Assay result (b) (4) %. The lot was released to USA market
- (b) (4) (b) (4) mg/vial; Batch # (b) (4) Exp. Date: July 2021, Assay result (b) (4) %. The lot was released to USA market

For example, bulk solution (b) (4) and finished product investigated during FY2018 and FY2019. All the following batches were released based on satisfactory re-testing results even though no conclusive root cause was identified for each of the incidents.

- (b) (4) (b) (4) mg/vial; Bulk Solution (b) (4) Batch # (b) (4) Exp. Date: September 2021. Assay result (b) (4) %.
- (b) (4) (b) (4) mg/vial; Batch # (b) (4) Exp. Date: September 2021. Assay result (b) (4) %. The lot was released to USA market.
- (b) (4) (b) (4) mg/vial, Bulk Solution (b) (4) Batch # (b) (4) Exp. Date: July 2021. Assay result (b) (4) %. The lot was released to USA market.
- (b) (4) (b) (4) mg/vial, Batch # (b) (4) Exp. Date: October 2021. Assay result (b) (4) %. The

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lot was released to USA market.

* (b) (4) (b) (4) mg/vial, Batch # (b) (4) Exp. Date: March 2020. Assay result (b) (4) %. The lot was released to USA market.

None of these referenced lots were included into your stability program to ensure that will effectively deliver the drug product until expiry.

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.

A. The list of observations noted below document that your Quality Unit has not performed a thorough systematic assessment and/or implemented the necessary interim controls to ensure the consumer complaints related to defects such as: presence of particles in vials, appearance of (b) (4) drug product, closure integrity and low fill, do not negatively affect the sterile injectable products currently being manufactured and distributed by your firm.

1. Your Quality Unit failed to conduct a thorough assessment and establish adequate corrective and preventive actions (CAPA) in a timely manner to address the systematic trend of complaints related to (b) (4) (b) (4) (b) (4) mg/vial.

For example, from the period between 18 Sep 2017 to 10 Jan 2020, your firm received approximately, 12 complaints regarding particulates (i.e. coring defect) found in (b) (4) lots (i.e. (b) (4) (b) (4) of (b) (4) drug product. For all the cases, your Quality Unit classified the complaints as "minor" and identified the (b) (4) stopper of the vials got ruptured due to the use of a (b) (4)

Your Quality Unit concluded the reported defect was not detected in the control samples and that the penetrability and fragmentation in-coming testing performed to the (b) (4) stopper showed results as expected. Therefore, no

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CAPAs were implemented. However, as part of the complaint investigations, the control samples have never been [(b) (4)] even though your firm acknowledges the [(b) (4)] technique most commonly used by the intended healthcare providers is thru [(b) (4)]. Moreover, the product information leaflet does not specify the [(b) (4)] that should be used to [(b) (4)] neither alert the healthcare providers of not using the [(b) (4)].

2. Consumer Complaint Investigation MC-INJ-CM023-19-018 was initiated on 02 October 2019 for [(b) (4)] Injection [(b) (4)] mg/[(b) (4)] mL; Lot [(b) (4)] Expiration Date 12/2020. The complainant stated that "Attempting to remove [(b) (4)] from a [(b) (4)] vial resulted in the entire [(b) (4)] enclosure coming free of the glass portion of the vial. This happened to two vials in this lot". The control samples of Lots [(b) (4)] and Lot [(b) (4)] were physically evaluated for similar seal defect and reported that the sealing quality of the vials was found satisfactory. However, during the batch sealing activity of drug product [(b) (4)] njection [(b) (4)] mg/[(b) (4)] mL ([(b) (4)] mg/mL); Lot [(b) (4)] it was observed that filled and full stoppered vials were not sealed properly in sealing machine (Equipment ID SMLJ [(b) (4)] 049). Unplanned deviation UP-PDI-19-001 was initiated and reported that [(b) (4)] were not [(b) (4)] properly and the [(b) (4)] was misaligned. Your Quality Unit concluded that "there might be the probability that few vials with loose sealing might have missed out during visual inspection." Therefore, the observed discrepancy might be an isolated case. However, it was noted the closure integrity of the control sample vials were not subjected to seal tightness test and non-destructive leak test. No additional actions were taken against Lot [(b) (4)].

Similar events were reported in the following complaints investigations:

- MC-INJ-CM023-20-002 – [(b) (4)] [(b) (4)] mg/vial; Lot [(b) (4)] Expiration Date 07/2021. The complainant stated that "when we went to pop the top off the vial entire top came off."
- MC-INJ-CM023-20-001 – [(b) (4)] [(b) (4)] mg/vial; Lot [(b) (4)] Expiration Date 07/2021. The complainant stated that "Tried to use 4 vials. One vial the [(b) (4)] top fell into the vial."

3. Consumer Complaint Investigation MC-INJ-CM017-19-002 was initiated on 30 January 2019 for [(b) (4)] [(b) (4)] [(b) (4)] mg/vial; Lot [(b) (4)] Expiration Date 04/2020. The complainant stated that "I have 2 vials of [(b) (4)] One vial was hazy, and the other vial has particle floating in it". The vial that showed the particles was analyzed by LC-MS/MS at the R&D laboratory, which reported the mass spectra of the [(b) (4)]

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(b) (4) vial shows (b) (4) impurity (b) (4) No other substance was identified in the sample. In addition, the hazy vial complaint sample was subjected to Light Transmission Testing "for information only". The out-of-specification (OOS) result observed was (b) (4) %. The specification limit is Not Less Than (NLT) (b) (4) %. No additional chemical/microbiology testing were carried-out to this complaint sample even though a definitive root cause was not identified. Instead you attributed the appearance failure to "external factors used for (b) (4) practices followed, and handling procedures of the vials may influence/leads to the slight haziness" with no supporting evidence.

REPEAT OBSERVATION

B. Your investigations into unexpected out-of-specifications results (OOS) are found inadequate. Specifically, you invalidate failing or OOS results without scientific justification. Your current practice is to always perform a re-sampling and proceed with a retesting of the product, based on the retest passing results and hypothetical analysis (i.e. experiments of malpractice sample preparation to identify which results correspond to OOS and conclude a root cause), invalidate the unfavorable results and release the batches or report meeting stability interval. Moreover, there are instances in that you failed to implement corrective and preventive actions (CAPA) for avoiding re-occurrence.

For example,

1. Out-of-Specification (OOS) Investigation Report SJ/OOS/18/038 was initiated on 18 May 2018 for (b) (4) (b) (4) (b) (4) mg/vial; Commercial Batches (b) (4) Exp. Date: April 2020; due to particulate matter OOS results obtained for (b) (4) batches. Based on the preliminary investigation, (i.e. check list, form # QAD/GEN/022/F01-04) no obvious error was found. A total of (b) (4) concurrently batches (b) (4) samples per batch) were analyzed, in which the last (b) (4) batches obtained OOS results. No root cause was identified during the investigation. Your QC laboratory re-sampled and re-tested the (b) (4) failing batches in (b) (4) (total of (b) (4) samples per batch) obtaining passing or favorable results. Although you firm had no evidence to support a definitive root cause, OOS report # SJ/OOS/18/038 concluded the initial OOS result was due to analyst's time gap of (b) (4) between the sample preparations of the first (b) (4) batches and the last (b) (4) batches. No CAPA was implemented.

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2. Out-of-Specification (OOS) Investigation report SJ/OOS/18/033 was initiated on 30 April 2018 for (b) (4) (b) (4) (b) (4) mg/vial; Commercial Batch # (b) (4) Exp. Date: March 2020; due to OOS in assay testing for (b) (4) solution and suspension samples. For example, the OOS results observed for solution and suspension are (b) (4) respectively. The specification limits for both testing is (b) (4) Based on the preliminary investigation (i.e. check list, form # QAD/GEN/022/F01-04) no obvious error was found and re-injection, re-filling and re-dilution confirmed the initial OOS results. Your QC laboratory re-sampled and re-tested both batches in triplicate obtaining passing results. The OOS Report SJ/OOS/18/033 concluded the initial OOS results were due to analyst's error (i.e. sample preparation: improper sample (b) (4) or sample spillage) even though there is no scientific evidence or empirical data to support a definitive root cause. Similar inadequate investigation was also observed in investigation OOS Report SJ/OOS/19/145 for (b) (4) (b) (4) (b) (4) mg/vial; Commercial Batch # (b) (4) Exp. Date: October 2021; due to OOS result in assay testing for (b) (4) solution (i.e. (b) (4) %). No CAPA was implemented for either investigations.

3. Out-of-Specification (OOS) Investigation Report SJ/OOS/19/095 was initiated on 04 Aug 2019 for (b) (4) (b) (4) (b) (4) mg/vial; Commercial Batch (b) (4) Exp. Date: July 2021 due to OOS result (b) (4) %) in assay testing for in process bulk sample (after compounding and before (b) (4) . The specification limits is (b) (4) % (b) (4) %. Based on the preliminary investigation, (i.e. check list, form # QAD/GEN/022/F01-04) no obvious error was found. Re-injection and re-filling of the sample confirmed the original OOS results. Your QC laboratory re-sampled and re-tested the referenced batch in (b) (4) obtaining passing results at the upper side of the specifications (i.e. (b) (4) %), similar to initial OOS result. No additional testing was carried-out. Your Quality Unit released Batch # (b) (4) for further processing to (b) (4) Batches (b) (4) Although your firm had no scientific evidence to support a definitive root cause, OOS Report SJ/OOS/19/095 concluded the initial OOS assay result were due to an error in the standard preparation. No CAPA was implemented.

4. Out-of-Specification (OOS) Investigation Report SJ/OOS/19/121 was initiated on 16 Oct 2019 for (b) (4) (b) (4) (b) (4) mg/vial; Commercial Batch (b) (4) Exp. Date: September 2021; due to OOS in assay testing for (b) (4) solution of (b) (4) %. The specification limits is (b) (4) Based on the preliminary investigation, (i.e. check list, form # QAD/GEN/022/F01-04) no obvious error was found. Re-injection, re-filling and re-dilution confirmed the initial OOS result. Your QC laboratory re-sampled and re-tested the batch in (b) (4) obtaining passing results (i.e (b) (4) averaging (b) (4) in which (b) (4) of the (b) (4)

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(3) showed a result at the lower side of the specification and similar to the initial OOS result. No conclusive root cause was identified. Your Quality Unit released the Batch (b) (4) based solely on the rationale that the average assay re testing result, the average of the dissolution and the content uniformity for Batch (b) (4) are similar to the results obtained for (b) (4) Batch (b) (4) However, the Investigation Report SJ/OOS/19/121 only considered the averaged results and did not include an assessment of the individual results. For example, Batch (b) (4) (i.e. CU: (b) (4) % MIN & (b) (4) % MAX; Diss. (b) (4) MIN & (b) (4) % MAX) and Batch (b) (4) (i.e. CU: (b) (4) % MIN & (b) (4) % MAX, Diss. (b) (4) % MIN & (b) (4) % MAX). Although you firm had no scientific evidence to support a definitive root cause, OOS Report SJ/OOS/19/121 concluded the initial OOS result for Batch (b) (4) was due to sample preparation (i.e. stock solution). No CAPA was implemented.

5. Out-of-Specification (OOS) Investigation Report SJ/OOS/19/022 was initiated on 13 Mar 2019 for stability sample of (b) (4) Capsules (b) (4) mg, 25°C/60%RH, 3 Month, Batch (b) (4) due to OOS result observed in Related Substance of (b) (4) % for unknown impurity. The specification limit is NMT (b) (4) %. Based on the preliminary investigation, (i.e. check list, form # QAD/GEN/022/F01-04) no obvious error was found. Re-injection and re-filling confirmed the initial OOS result. No obvious error was found during Phase I & II investigations. Manufacturing investigation was also conducted and reported no discrepancies during the manufacturing process of Lot (b) (4) Your QC laboratory re-sampled and re-tested the referenced batch in (b) (4) obtaining favorable results. Your QC laboratory concluded the presence of the OOS unknown impurity was due analytical error (might be associated with contamination). However, a definitive root cause behind this contamination was not identified. No CAPA was implemented.

6. Out of Specification (OOS) Investigation Report SJ/00S/19/076 was initiated on 26 Jun 2019 for finished product (b) (4) Tablets (b) (4) mg Batch (b) (4) Exp Date: February 2021; due to OOS of (b) (4) % in (b) (4) by HPLC. The specification limit is NMT (b) (4) %. Based on the preliminary investigation, (i.e. check list, form # QAD/GEN/022/F01-04) no obvious error was found. Re-injection and re-filling confirmed the initial OOS result. Both results showed OOS about (b) (4) %. No obvious error was found during Phase I & II investigations. Manufacturing investigation was also conducted and reported that no discrepancies were identified during the manufacturing process for Batch # (b) (4) Your QC laboratory re-sampled and re-tested the batch in (b) (4) obtaining favorable results. Although your QC laboratory had no scientific evidence the batch was released. OOS Report SJ/OOS/19/076, concluded as the most probable root cause inconsistency of the HPLC column. However, all the system suitability parameters were within validated method acceptance criterion. In

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addition, the instrument malfunction error was ruled out during Phase-Ib investigation. Moreover, the re-injection of same vial and the re-filling of diluted sample injected of Batch (b) (4) during Phase I investigation showed same initial OOS results; therefore, not supporting rationale.

Similar event was also observed in SJ/OOS/19/035 for stability sample (b) (4) (b) (4) mg & (b) (4) mg, Batches: (b) (4) Acc 40°C/75% RH, 1 Month, Exp Date: October 2020.

7. Unplanned deviation report (also known as Laboratory Incident) UP-QCD-18-037 was initiated on 19 Oct 2018 for raw material (b) (4) Batches (b) (4) due to analyst used a GC instrument Perkin Elmer with Headspace sampler instead of Agilent with headspace sampler. The original results obtained were within specifications. However, they were invalidated and repeated because the analytical test procedure QCD/RMSTP/10000014 (b) (4) requires the use of Agilent instrument. No scientific justification was identified to invalidate the original results, since no changes to the sample preparations, system suitability, and or significant parameters were made.

REPEAT OBSERVATION

C. The control procedures SOP/QAD/GEN/022-05 entitled "Handling of Out of Specification Results" Rev. 05 and SOP/QAD/GEN/086-01 entitled "Reporting, Investigation and Disposition of Unplanned Deviations in Ample Logic Software" Rev. 01 do not require the analyst's participation as part of the OOS investigation reports and/or as part of the Incident Investigation reports (i.e. known as unplanned deviations). Your current practice is to generate a checklist (i.e. form # QAD/GED/022/F01-04) during Phase I investigation. However, there is no documented evidence that the analyst that observed the initial OOS result(s) participates during the Phase I investigation.

OBSERVATION 3

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically, your Quality Unit approved for distribution lots of (b) (4) Injection (b) (4) mg/vial without

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completing the validation process and characterizing the critical in-process controls.

(b) (4) Injection (b) (4) mg/vial release/regulatory specification range is (b) (4)

Out-of-Specification Report SJ/OOS/18/012 was initiated on 16 February 2018 for (b) (4) Injection (b) (4) mg/vial; 1st validation Lot (b) (4) Expiration Date 01/2020. Samples (b) (4) showed OOS results in assay testing by HPLC. For example, the samples (b) (4) showed results of (b) (4) (b) (4) and samples (b) (4) showed results of (b) (4) Your QC laboratory performed re-injections of Sample (b) (4) (b) (4) and reanalysis of the same sample in (b) (4) All the results obtained confirmed the initial OOS results. Manufacturing investigation was also carried out, no discrepancies were observed. Your QC laboratory concluded the OOS results stand valid. Based on the evaluation of the OOS results, it was proposed to revise the process validation protocol (SMLJ/PVP (b) (4) 044-00) to discard the initial (b) (4) mL of sample solution during (b) (4) as well as (b) (4) before sampling for analysis. (b) (4) Injection (b) (4) mg/vial; validation Lot (b) (4) was released for distribution.

In addition,

Out-of-Specification Report SJ/OOS/18/013 was initiated on 23 February 2018 for (b) (4) Injection (b) (4) mg/vial; 2nd validation Lot (b) (4) Expiration Date 01/2020. Samples (b) (4) showed OOS results in assay testing by HPLC. For example, the samples (b) (4) showed results of (b) (4) (b) (4) and samples (b) (4) showed results of (b) (4) Your QC laboratory performed reanalysis of (b) (4) subjected samples in (b) (4) The retest results of all (b) (4) sample preparations confirmed the initial OOS results. Manufacturing investigation was also carried out, no discrepancies were observed. Your QC laboratory concluded the OOS results stand valid. Although corrective action was taken as by discarding (b) (4) mL sample solution at each (b) (4) OOS results were obtained once again. Based on the evaluation of the OOS results, it was proposed to revise the process validation protocol (SMLJ/PVP/ (b) (4) 044-01) to increase the discarded volume of sample solution during (b) (4) from (b) (4) mL to (b) (4) mL. In addition, it was implemented to discard approximately (b) (4) mL (b) (4) before filling. (b) (4) Injection (b) (4) mg/vial; validation Lot (b) (4) was released for distribution.

In addition,

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12420 Parklawn, Drive, Room 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	02/13-20 & 24-25/2020
	FEI NUMBER 3009876430

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Jayant Karajgi, Chief Operating Officer

FIRM NAME	STREET ADDRESS
Shilpa Medicare Limited	S-20 To S-26, Pharm. Formulation Sez, Tsiic, Green Industrial Pa
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Polepally, Jadcherla, Telangana, 509301, India	Sterile/Non-Sterile Drug Product Manufacturer

Out-of-Specification Report SJ/OOS/18/022 was initiated on 26 March 2018 for (b) (4) Injection (b) (4) mg/vial; 5th validation Lot (b) (4) Expiration Date 02/2020. Sample (b) (4) obtained an OOS result of (b) (4) % in assay testing by HPLC. Your QC laboratory performed reinjections of the original sample solution and reanalysis with fresh sample preparations in (b) (4) The results obtained confirmed the initial OOS results. Manufacturing investigation was also carried out, no discrepancies were observed. Your QC laboratory concluded the OOS results stand valid. No definite root cause was identified. Based on the evaluation of the OOS results, the following CAPAs were proposed: (b) (4)

(b) (4)

(b) (4)

Injection (b) (4) mg/vial; validation Lot (b) (4) was released for distribution.

OBSERVATION 4

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity. Specifically, your Quality Control Unit (QCU) failed to establish scientifically sound and appropriate analytical test procedures designed to assure that representative sample vials of (b) (4) Injection (b) (4) mg/vial (b) (4) product) filling process are taken for analysis and conform to expected quality attributes.

Your firm validated analytical procedure entitled "Assay Validation for (b) (4) njection (b) (4) mg/vial) by HPLC", Report SJ/AMV/(b) (4) FP/AS/026R/R0; effective on 25 Feb 2014, for the determination of (b) (4) content in (b) (4) njection (b) (4) mg/vial drug product. Per test procedure QCD/FPSTP/2000081/R19 (b) (4) Injection (b) (4) mg/vial", the assay solution (b) (4)

(b) (4)

(b) (4) As per procedure SOP/QAD/GEN/031-06 entitled "Sampling of In-Process and Finished Products" Rev 06, Sections 5.11.3.5 states (b) (4)

(b) (4) Nonetheless, your firm only uses (b) (4) drug product vials for the assay testing of the (b) (4) solution. However, there is no documented evidence to show at which (b) (4) of the filling process (b) (4) the vials analyzed.

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On the other hand, the assay for the (b) (4) suspension requires only (b) (4) vial (b) (4) (b) (4) There is no documented evidence to show at which stage of the filling process (b) (4) the vials analyzed. The validated batch size of (b) (4) Injection (b) (4) mg/vial is between (b) (4) vials.

This practice also impacts the analytical testing of the following US intended/approved and marketed products:

- (b) (4) Injection USP, (b) (4) g/vial
- (b) (4) (b) (4) mg (b) (4) injection, (b) (4) mg/vial
- (b) (4) Injection (b) (4) mg/vial (Shilpa)
- (b) (4) Injection USP, (b) (4) mg/vial

In addition, this practice also impacts the analytical testing of the following filed drug product intended for USA market:

- (b) (4) Injection USP (b) (4) mg/vial (b) (4)

OBSERVATION 5

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

There is no assurance that your process simulation studies (media fills) performed in the (b) (4) of the Production Department Injectable (b) (4) filling Line (b) (4) are representative of the conditions observed and/or that might occur during routine aseptic filling operations of vials.

For example, the media fill batch records for (b) (4) filling Line (b) (4) Lot (b) (4) approved on 17 Sep 2019 does not describe in detail how the non-routine intervention "Repairs by maintaining personnel" was performed by engineering personnel during process simulation. This intervention was carried-out (b) (4) times during the media fill process of Lot (b) (4) No scientific rationale was provided to justify the frequency of this non-routine intervention. In each of the instances, the intervention was done by (b) (4) person. However, the media fill BMR does not include a description about the activities that were simulated.

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On 20/Feb/2020, I witnessed the aseptic filling process of (b) (4) Injection (b) (4) mg/vial; Lot (b) (4). This product was filled in the (b) (4) of (b) (4) Line (b) (4). Around (b) (4) I observed two (2) operators (i.e. manufacturing operator and engineer) working simultaneously in the (b) (4) area doing a non-routine intervention (i.e. removal of stoppering (b) (4). This intervention is not included in the lists of the routine/non-routine interventions allowed for (b) (4) Line (b) (4). The same intervention was also performed around (b) (4) but in these two (2) instances three (3) operators were working simultaneously in the Line (b) (4) (b) (4) area. Per your Validation Deputy Manager, this non-routine intervention is identified in the commercial BMR of (b) (4) Injection (b) (4) mg/vial as "Repairs by maintaining personnel". Thus, this incident confirms that there is no assurance that equipment adjustments/mechanical interventions (i.e. non-routine interventions) that occur during commercial filling activities are accurately simulated during the media fill studies of (b) (4) of (b) (4) Line (b) (4). This is evidenced on the current practice of reporting in the commercial BMRs all the interventions related to mechanical interventions as "Repairs by maintaining personnel". In addition, the duration at which this intervention is simulated during the process simulation activities are not accurately established.

REPEAT OBSERVATION

OBSERVATION 6

Drug product samples are not representative of the entire batch and properly identified

A. Your control procedure SOP/QAD/GEN/031-06 entitled " Sampling of in-process and finished products"; effective date 26 Oct 2018, used for sampling (b) (4) and sealed vials is inadequate in that does not adopt statistical procedures for sampling sterile finished drug products. For example, the procedure SOP/QAD/GEN/031-06 does not require the sampling of vials between (b) (4) that correspond to (b) (4) of the batch to ensure that representative samples for the entire batch are collected. Your current practice is to always collect samples from the same (b) (4) without considering the batch size.

B. Your Quality Unit failed to accurately collect the proper amount of (b) (4) and sealed vials for chemical analyses (e.g. assay, CU and Dissolution, among others). The control procedure SOP QAD/GEN/031-06 entitled "Sampling of In-process and Finished Products"; Rev. 06 and the Quality forms QAD/GEN/031/F04-03 and

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F01-01; Rev. 03 and 01, instruct the QA personnel on how to collect the samples and the required amount for each finished drug product families. However, these control procedures/forms does not consider the (b) (4) of content uniformity (b) (4) and the (b) (4) of the dissolution testing (b) (4) (b) (4) if applicable. Your current practice promote the continuous re-sampling when OOS/OOT results is observed and/or any other type of investigation if required.

Example of discrepancy is illustrated in the table below:

Product	Current Quantity Vials for sent to Laboratory for Release	Quantity of Vials Required	Quantity of Stability Samples vials missing per interval
(b) (4)			

*Addition of the CU and Dissolution samples missing. **Addition of CU missing.
***Not considering the re-test samples.

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Note: The minimum amounts does not consider the extra vials required for re-testing, if required

This inadequate sampling process also impacts the entire stability program, including (b) (4)
For example, if re-test and/or additional (b) (4) of dissolution testing are required, new samples must be pull out from the stability chambers. Therefore, the re-test and the (b) (4) of dissolution testing will not be part of the same original stability samples interval.

REPEAT OBSERVATION

OBSERVATION 7

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

1. The filling/sealing machine (b) (4) (SMLJ (b) (4) /082) is used to aseptically fill liquids and (b) (4) sterile drug vials. The Qualification Report PQR (b) (4) 064-05 R01 entitled "Routine Qualification Report for (b) (4) (b) (4) approved on 26 October 2019 concluded the filling and sealing machine (b) (4) (SMLJ/ (b) (4) 082) "complies" with respect to the observed NVP count (b) (4) mentioned in the Protocol PQ (b) (4) 064-05. Per this protocol, a total of (b) (4) are distributed throughout the filling and sealing (b) (4) SMLJ/ (b) (4) 082). However, there is no scientific justification to demonstrate that the selected distribution of sampling locations (b) (4) produces meaningful result and represents the critical zones. In addition, there is no documented evidence in the protocol/report that describes how the critical operations (e.g. operator's interventions, set-up activities and exposition time of open vials) were evaluated to consider the current locations as sampling critical locations.

A. The routine continuous NVPC monitoring performs during aseptic filling process is carried out in (b) (4) locations of the filling and sealing (b) (4) i.e. filling station, stoppering station, (b) (4) (b) (4) loading and unloading conveyor). Nevertheless, no risk assessment was conducted for evaluating/selecting the existing installed online NVPC locations. Moreover, there is no control

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procedure in place that specifies the rationale/requirements to be considered (e.g. critical operations, distance, height, length) during the selection of the (b) (4) locations. This failure also impacts the filling line (Equipment ID SMLJ(b) (4) 049) located at (b) (4) block.

There is no NVPC online monitoring in Grade A(b) (4) of the(b) (4) (SMLJ/(b) (4) 082)(b) (4) Line (b) (4) between the stoppering station and the(b) (4) although operators' interventions and process activities (e.g. removal of(b) (4) filled containers in(b) (4) area and place the(b) (4) around the vials) are performed between these critical zones. In addition, there is no NVPC online monitoring between the stoppering station to(b) (4) loading/unloading conveyer with(b) (4) (distance(b) (4) (b) (4) loading/unloading conveyor with(b) (4) to (b) (4) distance(b) (4) and the(b) (4) and(b) (4) loading/unloading conveyor with (b) (4) to (b) (4) distance(b) (4)

C. There is no NVPC online monitoring in Grade A(b) (4) in the(b) (4) Some of the interventions carry out in this area are: adjustment of sealing(b) (4) removal of fallen seals from(b) (4) adjustment of(b) (4) and repairs by maintaining personnel, among others.

2. There is no assurance that your dynamic air flow pattern studies (smoke studies) performed inside the(b) (4) SMLJ(b) (4) 082(b) (4) and SMLJ(b) (4) 049(b) (4) are representative of the conditions observed and/or that might occur during routine aseptic filling operations of vials.

Specifically, your air flow pattern studies conducted during filling equipment assembly and process for SMLJ/(b) (4) 082(b) (4) and SMLJ(b) (4) 049(b) (4); Protocols P/MIS/323-1 and P/MIS/272-01; approved on 20 September 2018, and documented in the DVD titled "Air Flow Visualization through Smoke Study in Dynamic Conditions Area", utilized to ensure unidirectional airflow during manufacture of aseptically filled drug products (Liquids and (b) (4) are inadequate.

Your smoke studies do not demonstrate how the air flow pattern of the(b) (4) area of the(b) (4) and(b) (4) (b) (4) vial filling lines is affected by the following corrective interventions: repairs by maintaining personnel, (b) (4) (b) (4) In addition, your smoke studies do not demonstrate the air flow pattern of the(b) (4) and(b) (4) (b) (4) is or not affected, when two (2)

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or three (3) operators are doing interventions simultaneously in the (b) (4) area. On 20 Feb 2020, I witnessed the filling process of (b) (4) Injection (b) (4) mg/vial; Lot (b) (4) in (b) (4) filling line. I observed at least three times 2 and 3 operators doing interventions simultaneously on the (b) (4) filling line. However, these interventions have never been simulated/evaluated in your dynamic air flow pattern studies.

OBSERVATION 8

An (b) (4) Field Alert Report was not submitted within three working days of receipt of information concerning significant chemical, physical, or other change or deterioration in a distributed drug product.

Your Quality Unit failed to submit Field Alert Reports (FARs) within required timeframe. Specifically, from the period between 18 Sep 2017 to 05 Dec 2018, your firm received approximately, eight (8) complaints reporting particulates (i.e. coring defect) in vials of (b) (4) Injection drug product. Your Quality Unit classified these complaints as "minor". Further evaluations of the returned complaint samples identified the (b) (4) stopper of the vials got ruptured due to the use of a (b) (4) that is for (b) (4) (b) (4) the drug product from the vial. Nonetheless, your evaluations did not include a verification of the (b) (4) Injection control samples under the same puncturing technique use by the complainants. Moreover, your firm has failed to thoroughly evaluate in combination with the (b) (4) stopper supplier the multiple complaints received to effectively prevent coring and fragmentation defects in vials of (b) (4) Injection drug product.

OBSERVATION 9

Testing and release of drug products for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specification prior to release.

Specifically, your Quality Assurance and/or Quality Control department failed to ensure that the analytical testing which involves chromatographic data (i.e. HPLC, GC, IC and others) for the raw materials, in-process testing, finished product and stability studies meet the proper accuracy and reliability. This is evidenced in the following:
1. The reproducibility tests (i.e. relative standard deviation percent, RSD %), as part of the system suitability and/ or specifications is not always established and/or properly executed to ensure the instrument performance

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throughout a chromatographic run. Your current practice is to calculate % RSD individually for each standard bracket against the system suitability (b) (4) However, does not calculate the % RSD for the entire run as part of the system suitability. This practice is allowed under procedure SOP/QCD/GEN/024-17 entitled "Chromeleon Chromatographic Data Station" Rev 17.

2. The control procedure SOP/QCD/GEN/024-17 entitled "Chromeleon Chromatographic Data Station" Rev. 17; Section 5.13 allows to use different processing methods (i.e. integration parameters) during the evaluation of a sequence chromatographic data run. For example, the blanks and samples injections are being (b) (4) under (b) (4) Method # (b) (4) the system suitability standard injections (i.e. resolution solutions) are being (b) (4) under (b) (4) Method # (b) (4) and the control standard injections (i.e. standard (b) (4)) are being (b) (4) under (b) (4) Method # (b) (4) This practice conforms the chromatographic run and the end batch results are performed with (b) (4) or more (b) (4) methods (as needed), which that makes the manipulation of data and/or results feasible. Examples of this inadequate practice were found in the analytical batch records for (b) (4) (b) (4) injection (b) (4) mg/vial, Batch # (b) (4) Exp. Date: December 2021 and for (b) (4) (b) (4) Injection (b) (4) g/vial), Batch # (b) (4) Exp. Date: January 2021. In addition, the procedure SOP/QCD/GEN/024-17 instructs the analysts to perform manual integrations under supervision along with QA authorization in those cases in which the peak(s) in the chromatogram couldn't be integrated using the automatic integration parameters or single (b) (4)

3. Your QC laboratory failed to follow the control procedure SOP/QCD/GEN/024-17 entitled "Chromeleon Chromatographic Data Station"; Rev 17 in that, it specifies that if the system is interrupted for any reason and affects the detector not being "ON", it is necessary to perform a new system suitability as per standard procedure. For example, Unplanned Deviation # UP-QCD-18-033 (Laboratory Incident) open on 24 Aug 2018 reported that in-process (b) (4) Injection for (b) (4) mg/vial, Batch # (b) (4) Exp. Date: 07/2020; assay chromatogram sequence IP-1800113_AB_001 being run in HPLC System (Equipment ID # SMLJ /QCD/062), was interrupted during sample injection # (b) (4) (i.e. Blank, time of interruption approx. 4:19:45 pm), affecting the last (b) (4) Per UP-QCD-18-033, the sequence was interrupted due to (b) (4) Your QC unit continued with the chromatographic run expecting UPS battery back-up to take effect until the site power generator. However, the UPS battery failed and the HPLC system (Equipment ID # SMLJ /QCD/062) was shutdown. The sequence run was re-initialized after a delay of approximately (b) (4) Only re-injections of Sample # (b) (4) Blank) and Sample # (b) (4) Standard) were performed. The sequence chromatographic run was reprocessed as normal (as if

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no interruption was made). However, your QC unit failed to perform a new system suitability, re-injecting the affected standard bracket, including the sample affected by the power interruption.

OBSERVATION 10

Control procedures are not established which monitor the output and 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.

The control procedure SOP/PDI/GEN/083-06, entitled, "Procedure for Preparation of Visual Inspection Standard Rejection Kit and Visual Inspector Qualification", effective date 21 September 2018, was found inadequate. The personnel performing the final visual inspection of finished sterile injectable vials ((b) (4) product) are not challenged on the identification and detection of intrinsic/extrinsic particles that potentially could be found as part of the filling process (e.g. (b) (4) particles). In addition, the visual inspectors are not trained to identify defects in (b) (4) vials such as, cracks vial, (b) (4) product between vial and stopper and (b) (4) appearance.

OBSERVATION 11

Laboratory records do not include complete records of the periodic calibration of laboratory instruments. Specifically, your QC laboratory failed to qualify/calibrate the laboratory analytical instruments to ensure that they are suitable for intended use. For example,

1. The Operation Qualification (OQ) of the Perkin Elmer FT-IR Spectra-Two Spectrophotometer ID # SMLJ/QCD/078, used for the identification tests (ID) of the drug substances and the finished products, is performed every (b) (4) by QC personnel. This OQ activity failed to include the IR-UATR (i.e. IR assembly unit intended for routine analysis). In addition, there is no Performance Qualification (i.e. system suitability) required before use of the IR and/or IR-UATR to ensure instrument performance. Furthermore, the laboratory does not have available a certified (b) (4) filter reference standard, required for the OQ and PQ of the IR-UATR. Example of this deficiency was observed in the review of the OQ for Perkin Elmer FT-IR Spectra-Two Spectrophotometer ID # SMLJ/QCD/078, dated 30 Jan 2020. Example of instrument use and lack of a PQ is

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evidenced in the released of the API (b) (4) Batch # (b) (4) (i.e. release date: 18 Nov 2019) tested under the IR. In addition, to the instrument logbook # R-QCD/GEN/007/F01/20-058, which is evidenced its used for various materials and products testing. The procedure # SOP/QCD/OPC/033-04, entitled "Operation, Cleaning and Calibration of FT-IR Spectrophotometer"; Rev 04, does not include and/or require the OQ for the use of the IR-UATR and/or PQ before use.

2. The OQ of the Perkin Elmer UV/VIS Spectrophotometer Lambda 35 ID # SMLJ/QCD/059, used for ID and quantification testing (e.g. assay and dissolution) of drug substances and finished products, is performed (b) (4) (b) (4) This OQ activity failed to include a linearity test and acetone stray light (i.e. required by USP) tests to ensure the instrument performance. In addition, the control procedure SOP/QCD/OPC/036-06 entitled "Operation, Cleaning and Calibration of UV-Visible Spectrophotometer"; Rev. 6, does not require subjected testing. Example of this deficiency was observed in the review of the OQ of the Perkin Elmer UV/VIS Spectrophotometer Lambda 35 ID # SMLJ/QCD/059, dated on 11 Feb 2020. Example of instrument used is evidenced in the released of the finished products (b) (4) Injection (b) (4) mg, Batch # (b) (4) i.e. release date: 19 Jul 2019) and (b) (4) (b) (4) g/vial), Batch # (b) (4) (i.e. released date: 26 Mar 2019). In addition, to the instrument logbook # R-QCD/GEN/007/F01/20-059, which evidence its used for various materials and products testing.

3. The Gas Chromatography (GC) OQ performed (b) (4) failed to include all necessary tests to ensure the instrument performance in a consistent manner. Example of discrepancy is evidenced in the OQ of the Agilent Gas Chromatography ID # SMLJ/QCD/175, dated on 22 Aug 2019, where a reproducibility, linearity and carry over tests of the liquid sample were performed to the back injector, but not to the front injector. The linearity test was included for the TCD detector (i.e. back) and not the FID detector (i.e. front), and noise and drift tests were not performed for both detectors. In addition, no qualification was performed for the headspace oven. The procedure SOP/QCD/OPC/100-02 entitled "Operation, Cleaning and Calibration of Agilent Gas Chromatograph with Chromeleon Software"; Rev 02, does not require the noise and drift test for the GC detectors, and headspace oven qualification. Furthermore, the internal specifications for the reproducibility test (i.e. % RSD NMT (b) (4) %) and the retention time (i.e. NMT (b) (4) %) does not represent the historical performance of the GC. Example of instrument used is evidenced in the released API (b) (4) Batch # (b) (4) (i.e. released date: 18 Nov 2019). In addition, to the instrument logbook # R-QCD/GEN/007/F01/20-048, which evidence its used for various materials and products testing.

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	FEI NUMBER 3009876430

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. Jayant Karajgi, Chief Operating Officer

FIRM NAME	STREET ADDRESS
Shilpa Medicare Limited	S-20 To S-26, Pharm. Formulation Sez, Tsiic, Green Industrial Pa
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4. The OQ performed for the dissolution bath ElectroLab Dissolution Tester with ElectroLab Syringe Pump Sample Collector ID # SMLJ/QCD/355, dated on 7 Nov 2019; and qualified under procedure SOP/QCD/OPC/089-05 entitled "Operation, Cleaning and Calibration of ElectroLab Dissolution Tester with Auto Sampler"; Rev 05, disclosed the following discrepancies:

a. The shafts (i.e. for apparatus 1 and 2), vessels and baskets unique numbers are not included in the dissolution mechanical calibration (MC) report to ensure the position in which they were evaluated and for future positioning during routine testing. In addition, the dissolution baskets are not identified with a unique number. Therefore, there is no assurance, which baskets were evaluated during qualification and to which of the dissolution baths it belongs. The identification and the fixed positioning is not required by control procedure SOP/QCD/OPC/089-05. In addition, it was observed that the shaft paddle ID # E18405-7 (In-house ID # 355-7) is broken. The paddle blade is displaced and can be removed. The instrument was placed out-of-service after this issue was brought to QC laboratory manager attention.

b. The vessels/shafts centering (i.e. eccentricity test) test is inadequate in that no numerical value or measurement determination at top/bottom of the vessel as required by USP<711> and/or ATSM (E2503-7) standards.

c. The qualification of the dissolution sampler unit ElectroLab Syringe Pump Model: ESC-12DX attached to the dissolution bath failed to include a volume linearity and carryover testing to ensure that each tubing lines and syringes are clean after each run. This is not required by the procedure SOP/QCD/OPC/089-05.

Similar deficiencies were also observed for the OQ of the dissolution bath Sotax CP7 Smart Dissolution Tester (i. e. USP Type IV) with Auto-Sampler ID # SMLJ/QCD/257, dated on 7 Jan 2020. Example of instrument used is evidenced in the released of the finished product (b) (4) Injection (b) (4) mg/vial, Batch # (b) (4) i.e. release date: 14 FEB 2020). In addition, to the instrument logbook # R-QCD/GEN/007/F01/20-046 which evidenced its used in various batches of (b) (4) product testing.

d. There is no documentation about the certified devices (i.e. wobble dial gauges, thermometer, tachometer, timers, protractor, etc.) used during the OQ (i.e. mechanical calibration and/or the Performance Verification Test (PVT)) of the dissolution bath reported under the form QCD/GEN/007/F10-00.

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e. The OQ for all the dissolution baths does not include a vibration test. This is not required by the procedure SOP/QCD/OPC/089-05.

f. The (b) (4) used for monitoring the critical dissolution parameter (i.e. (b) (4) in each vessel and the bath are not qualified for the intended (b) (4) ranged being used. This is not required by the procedure SOP/QCD/OPC/089-05.

g. The (b) (4) RPM test limit (i.e. (b) (4) is inadequate and does not comply with the requirements of USP<711> and/or ATSM (E2503-7) standards.

h. The display time (i.e. example: (b) (4)) of the certified timer is not documented to compare and evaluate with the dissolution build in timer.

OBSERVATION 12

Records of the calibration checks and inspections of automatic, mechanical or electronic equipment, including computers or related systems are not maintained.

A. There is a failure to establish adequate controls over QC Laboratory computerized system.

Specifically, Your firm failed to qualify (i.e. IQ, OQ and PQ) the networked systems and databases used for all the analytical testing (i.e. HPLC, GC and IC, among others), which involves all type of chromatographic data such as raw materials, in-process testing, finished product and stability studies. In addition, all the electronic chromatographic data handling and storage is in the MS SQL Server 2008 (b) (4) system. However, there is no a formal mechanism that requires periodic monitoring of server and network.

B. The IT unit failed to design/approve wiring/network diagrams (i.e. from server room, hubs, etc.) and to identify all hubs, interfaces, probes, computers and analytical equipment connected to the network system. In addition, the IT unit failed to establish control procedures for the periodical monitoring of the system and conduct risk assessment to prevent information loss events.

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OBSERVATION 13

The reserve sample of active ingredient does not consist of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications.

1. Your quality unit failed to accurately collect the proper amount of retained samples. The control procedure SOP/QCD/GEN/019-05 entitled "Management of Reserve Samples", Rev. 05, does not consider the second stage of content uniformity (i.e. (b) (4) samples) and the (b) (4) of the dissolution testing (i.e. (b) (4) (b) (4) samples), if applicable.

Example of discrepancy is illustrated in the table below:

Product	Current Quantity Vials Retained	Minimum Quantity of Vials Required (b) (4) test)
(b) (4)		

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*Addition of the CU and Dissolution samples missing. **Addition of CU missing.

2. Your Quality Unit failed to ensure that all finished product with a unique batch number have an adequate amount of retain samples. The control procedure SOP/QCD/GEN/019-05 entitled "Management of Reserve Samples", Rev. 05, indicate in Sections 5.15.3 (b) (4) (b) (4) (b) (4) (b) (4) However, the (b) (4) batch, not necessarily packed concomitantly. The (b) (4) batch consists of only (b) (4) (b) (4) bottle that may not be enough for performing (b) (4) full testing. Your current practice is to use the (b) (4) batch for compliant/stability investigations related to the (b) (4) batches. The following examples were observed:

- (b) (4) Tablets, USP (b) (4) mg, (b) (4) Tab./Bottle
  Batch # (b) (4) (b) (4) batch), Packaged date: 11/8/2018 – (b) (4) Bottles
  Batch # (b) (4) batch), Packaged date: 6/12/2019 – (b) (4) Bottle
- (b) (4) Tablets, USP (b) (4) mg, (b) (4) Tab./Bottle
  Batch # (b) (4) (b) (4) batch), Packaged date: 8/13/2018 - (b) (4) Bottles
  Batch # (b) (4) (b) (4) batch), Packaged date: 3/8/2019 – (b) (4) Bottle
- (b) (4) Tablets, USP (b) (4) mg, (b) (4) Tab./Bottle
  Batch # (b) (4) (b) (4) batch), Packaged date: 8/14/2018 – (b) (4) Bottles
  Batch # (b) (4) (b) (4) batch), Packaged date: 3/9/2019 – (b) (4) Bottle
- (b) (4) Tablets, USP (b) (4) mg, (b) (4) Tab./Bottle
  Batch # (b) (4) (b) (4) batch), Packaged date: 8/21/2018 – (b) (4) Bottles
  Batch # (b) (4) (b) (4) batch), Packaged date: 3/7/2019 – (b) (4) Bottle
- (b) (4) Tablets (b) (4) mg, (b) (4) Tab./Bottle
  Batch # (b) (4) (b) (4) batch), Packaged date: 7/13/2019 – (b) (4) Bottles
  Batch # (b) (4) batch), Packaged date: 7/18/2019 (b) (4) Bottle

OBSERVATION 14

An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling.

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Specifically,

1. The retained samples (at least (b) (4) batches) were found in many instances placed in a (b) (4) bags. However, this additional protecting components added to the product and/or container does not represent the unexposed products and containers in the market and/or obtained by consumers. This practice was inconsistent to products or containers and is not required and/or indicated in firms' procedure SOP/QCD/GEN/019-06 entitled "Management of Reserve Samples", Rev. 06. Your current practice of placing an extra protection to your product/component will delay any deterioration if any and will not be detected during (b) (4) visual inspection. Examples of this discrepancies were observed for the following products:

- (b) (4) Tablets USP, (b) (4) mg – Batches # (b) (4) (b) (4)
- (b) (4) Tablets USP, (b) (4) mg – Batch # (b) (4)
- (b) (4) Capsules, (b) (4) mg – Batch # (b) (4)
- (b) (4) Capsules, (b) (4) mg – Batch # (b) (4)
- (b) (4) Tablets, (b) (4) mg – Batch # (b) (4)

2. Your Quality unit failed to prevent potential cross-contamination and to ensure the quality attributes of your retained samples (i.e. tablets and capsules finished drug products). The control procedure SOP/QCD/GEN/019-05 entitled "Management of Reserve Samples", Rev. 05, does not address or define the retrieval process and the handling of the retained samples. As part of the complaint/stability investigations, the retained samples are transferred to the QC Laboratory for removing the required number of tables/capsules for analysis. However, this action is performed in an open stage area and not in a dispensing room or designated area to avoid the product being overexposed and contaminated.

OBSERVATION 15

Reserve samples are not always handled appropriately and/or provide assurance that proper annual visual inspection is performed.

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There is no assurance that representative samples of (b) (4) lots of (b) (4) drug products are thoroughly examined at least (b) (4) for evidence of deterioration. Specifically, there is no documented evidence that demonstrates in detail the number of sample containers/bottles that were selected to be visually inspected for physical attributes of the finished products/components (e.g. package integrity, label deterioration, drug product appearance and lot number/expiration among others. In addition, the control procedure SOP/QCD/GEN/019-05 entitled "Management of Reserve Samples" Rev 05 does not provide instructions or steps on how to conduct this visual examination.

JEM 02/25/2020

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