DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, since March 2014, the firm has received approximately 51 consumer complaints, including one MedWatch report, related to potential mold contamination of [redacted] and [redacted] sterile products; an evaluation of six (6) randomly selected complaint investigations revealed 5 which were inadequately investigated. In one example, a complainant identified a tube that had been open for one week which had "a dot of something on the tip" and noted that later a "black thread of substance came out". The investigation included an evaluation of the retain sample, and did not identify black particles. In another example, a complainant indicated that it "looks like black mold/mildew inside the cap, the tube has been opened for one month". The investigation included an evaluation of manufacturing deviations, and a check of retain samples. No corrective or preventive actions were established. Your firm indicated that they believe that the issue is due to "secondary contamination", defined as contamination that is initiated after the product leaves the manufacturing facility. However, one complaint noted that "the new bottle was full of black particles, the solution cannot be squeezed out, the top was full of black gunk and the solution has black particles in it". Investigations into potential contamination failed to include the following: 1) a check for [redacted] content in complaint or retain samples, 2) potential impact of shipping conditions on product quality, 3) a review of other batches produced in the same campaign, 4) an evaluation of primary packaging component sterility, 5) a study to simulate the usage of the product under normal conditions to challenge the time when contamination appears, in an effort to support the proposed root cause. Complaints for potential mold contamination include 11 lots currently within their expiration period, to include:
### OBSERVATION 2
The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

1) Your quality control unit has failed to detect several instances in which the good documentation practices have not been followed. For example:

   Several discrepancies were observed in the QC chemistry laboratory finished product sample log book used to document the storage conditions of samples following receipt in the QC laboratory. For example:

   a) The log book contains spaces to indicate whether an incoming sample is stored at ambient temperature or at 2-8°C. For entries covering 17 February 2016 to 18 May 2016, 24 instances
were observed where samples had been marked as being stored at both ambient and refrigerated temperature, whereas each sample could have only been stored at one temperature prior to analysis in the QC laboratory. Finished product samples with discrepant entries include those taken from Gel, Gel, Gel, Gel, and Gel. As the log book serves as the only record for sample storage temperature following receipt by the QC chemistry laboratory, it is unclear whether these samples were appropriately stored prior to analysis.

b) Write-overs for finished product storage temperature were observed. Specifically, two instances of dashes changed to X’s for storage condition were noted for Gel and Gel.

c) Finished product log book entries had been marked as reviewed by a QC laboratory supervisor, who noted that log book review consists only of checks for empty spaces. As such, these discrepant entries had not been identified or investigated for their impact on stored samples, or their corresponding analytical data.

2) Analytical worksheets used for prepared media, sterility checks are not dated contemporaneously with the specific incubation end date. For example, analytical worksheets were prepared on 12 May 2016 for two bottles of and one bottle of under incubation. However, the analytical sheets were observed on 18 May 2016 with a pre-written incubation end date of 26 May 2016.

3) Your quality control unit has failed to detect deficiencies related to the cleanliness of the in the sterile filling areas. For example:

a) There is no scientific justification provided for cleaning the internal surface of the aseptic processing area on a basis, or for the use of a cleaning agent that has not been demonstrated as suitable and effective to remove spores or mold.
b) A white film/residue was observed on the hanging (b)(4) connecting the laminar air flow to the (b)(4) barriers separating the “Zone A” aseptic filling area from “Zone B”. No investigation was performed to determine the source of this residue, or to assess its potential impact on product quality. Film/residue was present on the (b)(4) hanging above the open product bottles during the aseptic filling of (b)(4) suspension (b)(4) ml, batch (b)(4), on filling line (b)(4).

4) Deficiencies for the configuration and review of analytical instrument audit trails were observed. For example:

a) The procedure for audit trail was made effective in April of 2016, and includes instructions for routine review of audit trails on analytical equipment; however, no retrospective review was performed for available audit trail data covering analytical tests performed prior to April 2016. For example, HPLC instrument PM 460 had available activity logs extending to at least February 2012.

b) The FT-IR instrument is used to perform identity testing of finished goods and raw materials. The audit trail settings are not configured to include record of all tests performed on the instrument. For example, an analysis was performed to obtain the identity of (b)(4) USP-NF on 15 April 2016. Although this test was captured in the instrument log book, the printed audit trail reviewed did not include the test. The review of the instrument audit trail failed to identify this discrepancy.

c) The HPLC instruments are used to perform analytical testing of raw materials, in-process samples, and finished products. The procedure in-place for audit trail review is inadequate in that it specifies the limited review of (b)(4) per instrument. (b)(4) No review is made of the system activity log to ensure a comprehensive audit of system usage.

OBSERVATION 3
Written records are not always made of investigations into unexplained discrepancies.
Specifically, discrepancies for microbiological tests, such as apparent contamination or dried, cracked, and shriveled are not always documented and investigated. For example:

1) A plate for growth promotion testing using Micrococcus luteus contained 2 colonies of different color, pale white, as compared to the yellow colors of M. luteus. No investigation into the cause or source of this apparent contamination was initiated. The firm’s QC Microbiological Manager noted that the observation of contamination of growth media should be considered a laboratory deviation. There was no documentation made on the analytical worksheet to capture the observed apparent contamination.

2) Used for verification of spore strip counts were observed to be desiccated, shriveled, and cracked. On 16 May 2016, a laboratory technician recorded the data from plates used to verify the spore count of commercial spore strips. The same plates were observed on 17 May 2016 to be cracked, severely dehydrated, and shriveled. No investigation into the effect of desiccated, shriveled, and cracked media was performed, and no laboratory deviation was initiated following the observation. There was no documentation made on the analytical worksheet to capture the observed condition of the growth media.

OBSERVATION 4
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed.

Specifically, your firm has validated loading patterns that are not followed, failed to demonstrate suitability of disinfectant.

1) Validated loading patterns for the are not always utilized. Production sheets were observed to document loads containing goggles, mops, and sponges in excess of the validated loading quantities. A load was observed to contain 14 goggles, whereas the validated load contained only. Another load was observed to contain 15 mops and 15 sponges, a total of...
30, whereas the validated load contained only 1 total. Goggles, mops, and sponges are all utilized for during normal operation in the aseptic processing areas.

2) Deficiencies were observed related to cleaning and the disinfecants used for cleaning of areas used for the aseptic filling of [redacted] drug products. For example, the qualification of your clean room disinfectant [redacted] failed to demonstrate that it is suitable and effective to remove microorganisms from different surfaces. This disinfectant failed to meet qualification criteria when challenged with the mold Aspergillus brasiliensis. After exposure disinfection, you recovered A. brasiliensis on [redacted] and [redacted]. However, your procedures for routine cleaning of the aseptic manufacturing area, below [redacted] continue to require the use of the unqualified disinfectant during [redacted] with a qualified disinfectant used on [redacted].

This is a recurrent observation.

OBSERVATION 5
Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

Specifically, the data documented to report laboratory results is not precise, or is not complete. For example:

1) Recorded colony counts from incubated [redacted] plates do not always include the total count for colonies present. For example:

   a) A growth promotion testing [redacted] plate for [redacted] was read by a laboratory technician, and a recorded result of 7 CFU for Candida albicans was made on 13 May 2016. On 17 May 2016, the same plate was observed to contain 8 CFU.
b) A growth promotion testing plate for Staphylococcus epidermidis was read by a laboratory technician, and a recorded result of 47 CFU for Staphylococcus epidermidis was made on 13 May 2016. On 17 May 2016, the same plate was observed to contain 48 CFU.

2) A growth promotion test using Staphylococcus aureus and Enterococcus faecalis for a lot of was reported as passing the growth promotion test, despite no colonies counts being recorded on the analytical worksheet for the test media. The space to document CFU counts was filled in with a dash for both strains. The firm’s specification for was listed as growth with less than CFU. As no colony counts were recorded, it is unclear whether the test was successful, as was documented on the worksheet.

3) A bio-indicator analytical data sheet for equipment sterilization verification failed to include complete information regarding the type of bio-indicator utilized, such as spore strips or spore containing ampoules. No check was included for the types of bio-indicators used; the data sheet was signed as verified by a quality control supervisor.

*DATES OF INSPECTION*
5/17/2016(Tue), 5/18/2016(Wed), 5/19/2016(Thu), 5/20/2016(Fri), 5/23/2016(Mon), 5/24/2016(Tue), 5/25/2016(Wed)