DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Springs, MD 20993 (301) 796-3334 Fax: (301) 847 8738 Industry Information: www.fda.gov/oc/industry	08/01/2014 08/08/2014 FEI NUMBER 3003813519

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Sridhar S. Rao, Global Head Quality, Injectables

FIRM NAME	STREET ADDRESS
Agila Specialties Private Ltd.	Sterile Product Division, Opp IIM, Bilekahalli, Bannerghatta Road
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Bangalore, Karnataka 560 076, India	Sterile Drug Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other drug products that may have been associated with the specific failure or discrepancy.

Investigations into complaints of discolored (b) (4) found vials that did not meet impurity and assay specifications due to (b) (4) It was hypothesized the (b) (4) was caused by (b) (4) between the (b) (4) of (b) (4) and capping. The investigation was not expanded to evaluate the impact or possibility of whether othe (b) (4) products could have also had vials that were exposed to (b) (4) between (b) (4) and capping. Other (b) (4) products distributed to the US market include:

(b) (4) njection (b) (4) ng
(b) (4) Injection (b) (4) and (b) (4) g
(b) (4) njection (b) (4) ng/(b) (4) nL
(b) (4) Injection USP (b) (4) ng

OBSERVATION 2

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

1. Investigations into the root cause of complaints about discolored (b) (4) with high impurities did not include a through and documented evaluation of the root cause. The investigations identify (b) (4) as the root cause, but do not describe how the (b) (4) was occurring or why it is not uniform within a batch. It was verbally reported that the root cause may have been (b) (4) to the (b) (4) when (b) (4) occurs (b) (4) Actions were taken to adjust the process for the (b) (4) of vials at the (b) (4) of (b) (4) The investigation reports do not contain data to support that this was the root cause.
2. When variance occurs between the number of syringes at the end of filling and the number of syringes visually inspected, there is no investigation into the difference unless the discrepancy equals (b) (4) of the batch size. There is a lack of scientific rationale for this limit. The following discrepancies were observed:
   a. Lot (b) (4) discrepancy of 185 syringes.
   b. Lot discrepancy of 66 syringes.

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c. Lot (b) (4) discrepancy or 58 syringes.
d. Lot discrepancy of 46 syringes.
e. Lot discrepancy of 11 syringes.

3. Environmental Monitoring OOS investigations did not include a thorough evaluation of root causes or verification of preventative actions.
   a. A new environmental isolate was identified (Bacillus spp) in the grade B and later the Grade A area. The corrective action included a disinfectant efficacy study against the new organism, but did not include an investigation into root causes for how the organism was introduced into these areas. Bacillus was also identified later in Grade C and D areas and during monitoring of the purified water system.
   b. The corrective action for the investigations include retraining of all personnel involved. There is no process to ensure effectiveness of the training including monitoring of gowning techniques or documented observation of proper clean room aseptic practices.
4. There is no justification for not considering the number of rejected units during in-process visual inspection when calculating the total number of rejects in the lot. The total number of rejects is used to determine whether acceptance criteria are met.

OBSERVATION 3

Complaint procedures are deficient in that they do not include provisions that allow for the review and determination of an investigation by the quality control unit.

1. Prior to 31 October 2013 there was no requirement for the Pharmacovigilance (PV) Group to share complaint information with the quality unit. As a result, reports received by the pharmacovigilance may not have been investigated with respect to their impact on the quality of product. For example:

   a. 2013SP002695 - for (b) (4) g, reviewed by the PV group as part of a report of nephrotoxicity. Included in the report were details that the product was discolored and took longer than expected to (b) (4) but this was not investigated by the quality unit.

   b. 2013SP002530 - for (b) (4) g, reviewed by the PV group as part of a report of nephrotoxicity. Included in the report were details that the product hardened into a (b) (4) when (b) (4) but this was not investigated by the quality unit.

   c. 2013SP002920 and 2013SP002589- two reports for (b) (4), reviewed by the PV group for a report of ineffective product. The report was never evaluated by quality personnel with respect to ineffective product.

2. There is no process to determine which Agila site a complaint is distributed to when a lot number is not identified. For example, multiple reports for an unidentified lot of (b) (4) that caused nephrotoxicity were received, including 2013SP002695. The complaint was forwarded to the quality unit at the SFF manufacturing site, but not the SPD manufacturing site. Both the SFF and SPD site manufactured (b) (4).

3. Trending of complaints does not consider complaints that are initially classified as unsubstantiated. For example, during 2012 there were seven complaints related to discolored (b) (4) upon (b) (4) Since they were all closed as unsubstantiated, it was not evaluated whether this was a trend that required further evaluation.

OBSERVATION 4

An (b) (4) Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.

Commitments for timely reporting in the established quality agreements with customers were not met to ensure filing of a Field Alert Report within three working days. For example:

1. A complaint about discolored (b) (4) lot (b) (4) was received 07 July 2012. The complaint sample was received 25 July 2012. It was confirmed that the sample was integral and discolored. The observations from the complaint sample were not shared with (b) (4) he party responsible for filing field alerts, until 14 August 2012.

2. A complaint about discolored (b) (4) ot (b) (4) was received 11 July 2012. The complaint sample was received 19 July 2012. It was confirmed that the sample was integral and discolored. The observations from the complaint sample were not shared wit (b) (4) the party responsible for filing field alerts, until 14 August 2012.

3. A review of retain samples on 15 August 2012 identified (b) (4) lots (b) (4) that each contained a discolored vial. This additional information was not provided to (b) (4) until 24 August 2012.

4. The review of retain samples on 15 August 2012 also identified discolored vials of unexpired product from lot (b) (4) These lots were distributed by (b) (4) the party responsible for filing field alerts. (b) (4) was not notified until 7 September 2012. The notification did not include relevant information, including that discolored vials had been found that did not meet specifications.

OBSERVATION 5

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

1. The assessment for establishing passive air and surface monitoring locations inside of the filling barrier of the (b) (4) PFS line does not evaluate critical locations.

   a. The assessment for the settle plates does not evaluate the area near the filling zone, the RAB (b) (4) he stopper (b) (4) or the (b) (4) for incoming empty syringes. There i (b) (4) passive plate collected inside the filling barrier, which is located near the (b) (4) of the filling barrier where the filled syringes have already been stoppered.

   b. The assessment for surface monitoring locations inside of the filling barrier does not evaluate surfaces in critical areas. Examples include the (b) (4) the stopper (b) (4) or the (b) (4) Additionally, the

sampling locations for the stopper (b) (4) and (b) (4) were chosen to be monitored with a contact plate. It was observed that these surfaces do not have a large enough flat surface for monitoring with a contact plate.

2. On 6 August 2014 the microbiologist collecting finger dabs of the RAB (b) (4) on the (b) (4) PFS filling line did not ensure each finger contacted the surface of the contact plate.

3. "Environmental Monitoring Program in Production Area", No: MIP/023/R271 states that while performing (b) (4) surface and personnel monitoring that the plates shall be placed on the contact surface with a (b) (6) touch and be closed immediately. This involves a (b) (4) motion ensuring that all plate surfaces contact the surface. During monitoring of the microbiologists it was observed that the (b) (4) plate was swiftly applied in one direction and then quickly removed.

4. Environmental monitoring samples collected inside of the grade A area are not labeled with sample information before exposure and are not always immediately labeled. For example, on 28 July 2014 points 002NUHHP (b) (4) and (b) (4) were sampled at 17:30, but not labeled until 21:39.

OBSERVATION 6

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

During observation of a recording for (b) (4) PFS set-up and filling for batch (b) (4) on 28 July 2014, the following behavior was observed:

1. Operators did not move with slow and controlled movements. They were observed to bump into and touch each other.
2. Personnel monitoring of the operators hands occurs with the operator's hands inside of the filling barrier. This required a microbiologist to open the barrier (b) (4) and also place their hands inside of the filling barrier.
3. After completing interventions or environmental monitoring inside of the filling barrier, the personnel would not immediately close the barrier (b) (4)

OBSERVATION 7

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

1. During the cleaning of the PFS (b) (4) filling machine on 27-28 July 2014 the following deviations from cleaning procedures PDN/019/R17 and PDN/116/R6 were noted:

   a. The operator did not clean from the (b) (4) areas to (b) (4) areas.
   b. The operator did not wipe unidirectionally.
   c. The operator did not follow procedures for folding of the wipe.

2. The (b) (4) and (b) (4) installed on the (b) (4) PFS filling machine cannot be (b) (4) The cleaning and disinfection process for these pieces of the machine has not been validated.

OBSERVATION 8

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design and of adequate size to facilitate operations for its intended use and cleaning and maintenance.

1. On 6 August 2014, (b) (4) pieces were observed attached to the end of the (b) (4) used on the (b) (4) PFS filling line. It was reported these had been attached by operators to (b) (4) he syringes. The (b) (4) was observed to be left on the (b) (4) after it had been cleaned and stored in the clean (b) (4) storage room.

2. For the purified water system:

   a. There is (b) (4) probe located on (b) (4) loop of the purified water system, located between the (b) (4) and the holding tank. During sanitization, this probe is used to ensure the minimum (b) (4) and (b) (4) are met. However, at this location there is no assurance the purified water holding tank or the distribution points along the loop reach the required (b) (4) and (b) (4)

   b. A leak was observed in the piping between the (b) (4) unit and where the water enters into the storage tank.

   c. A dead leg section of piping of approximately (b) (4) inches in length and (b) (4) inches in diameter was observed on the piping prior to the (b) (4)

   d. The roof in the room where the purified water system is located was leaking. Water was dripping on to the purified water storage tanks.

3. There is insufficient space in the stability chambers to accommodate all products. Eleven pallets, including 18 lots, of product were observed in the finished product warehouse that were labeled as stability samples. It was reported that there was not enough space to place these batches in the stability chamber to begin the stability studies.

OBSERVATION 9

Established test procedures are not followed.

1. During use of the (b) (4) system for identification of environmental isolates, numerous isolates were re-run and resulted in biochemical reactions that differed between each run. This demonstrates the (b) (4) were not prepared properly.

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2. It was observed that 3 of (b) (4) plates associated with the Growth Promotion Testing performed on 7/30/14 had areas in which the growth was "blotchy". This demonstrates the analyst did not properly spread the inoculum to allow for accurate colony counts.

3. Analysts are permitted to make manual changes to the integration parameters of HPLC chromatograms when integration by the software is not "proper". Procedure ACQC003/PF02/W1001/R0 does not define "proper" or when manual changes to the chromatograms are permitted, what the acceptable changes are, or how the manually manipulated chromatograms will be reviewed.

OBSERVATION 10

Changes to written procedures are not reviewed and approved by the quality control unit.

Change control 35550 was issued to change the stoppering process of (b) (4) Vials at the (b) (4) of (b) (4) from stoppering (b) (4) o stoppering (b) (4) The change control documentation does not describe the rationale for making this change.

OBSERVATION 11

Procedures for the preparation of master production and control records are not followed.

The GMP records used to record activities occurring inside of the filling rooms are made on laminated sheets. Original raw data is recorded in marker on the surface of the sheets. The marker can be erased. Examples include: the intervention record, personnel monitoring records, and glove integrity check sheets.

OBSERVATION 12

Procedures describing the warehousing of drug products are not followed.

On 01 August 2014 there were numerous pallets in the finished product warehouse that did not have identification of their status. The warehouse contained a mix of released, quarantined, and returned product. However, the status of all pallets was not identified, including pallets of (b) (4) lot (b) (4) quarantined) and (b) (4) (returned).

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