Inspections, Compliance, Enforcement, and Criminal Investigations

Agila Specialties Private Limited 9/9/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-13-26

September 9, 2013

Mr. Venkat Iyer, CEO
Agila Specialties Private Limited
Specialty Formulation Facility, 19A Plot
No. 284-B/1 Boommasandra Jigani Link RD
Bangalore, India

Dear Mr. Iyer:

During our June 17, 2013 through June 27, 2013 inspection of your pharmaceutical manufacturing facility, Agila Specialties Private Limited, Specialty Formulation Facility (SFF), located at Bommasandra Jigani Link Rd, Bangalore, India, investigators from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Part 210 and 211. These violations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's response dated July 18, 2013 and note that it lacks sufficient corrective actions.

Our investigators observed specific violations during the inspection, including, but not limited to, the following:

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

The most significant examples of this violation include:

a. Non-integral and non-sterile gloves are used for aseptic processing.

i. Visible holes and flaking were observed in the **(b)(4)** gloves purporting to be sterile:

- Glove lot # **(b)(4)**

  a. These gloves were used for the processing of **(b)(4)** Injection, **(b)(4)**g/vial batch # **(b)(4)** in Suite **(b)(4)** and batch # **(b)(4)** in Suite **(b)(4)** at the time of the FDA inspection. Flaking and holes were observed in many of the gloves used in Suite **(b)(4)** and **(b)(4)**.

  b. Our investigators examined a sample of the remaining gloves from the same vendor lot in your firm's warehouse. Similar defects were found these gloves. In addition, we found that the primary glove packaging was broken, incomplete, or missing **(b)(4)**. We noted that your QA released these gloves for use in production.

- Glove lot #**(b)(4)**, approved by the QA and stored in the warehouse awaiting use in manufacturing:

  a. In both intact glove packages examined for the integrity of the gloves inside, our investigators found the gloves to have visible holes, flaking, cracking, and/or discoloration.

  b. Damaged or incomplete packages were found in many glove packages examined for package integrity.

  ii. Visible holes and flaking in the gloves, as well as missing **(b)(4)** in the primary packaging, were also found when examining the **(b)(4)** gloves. These gloves, purporting to be sterile, are worn by aseptic manufacturing operators in the **(b)(4)** filling suites at the SFF.

  iii. The cardboard boxes used to ship and store these gloves were also found to be damaged. Crushed insects were found on one of the glove's outer package inside the shipping box.

Both lots of non-integral and non-sterile gloves were used in the manufacturing since 04/29/13. **(b)(4)** batches of injectable drug products were made using these defective glove lots.

These defective gloves are especially concerning in part because they were used to perform manipulations directly over empty vials. During a brief 3-hour observation of your filling operation of **(b)(4)** Injection **(b)(4)** mg batch #**(b)(4)** in Suite **(b)(4)**, our investigators observed at least 20 line interventions using these **(b)(4)** gloves. We are also concerned that the RABS design positions the **(b)(4)** stations over the sterile empty vials on the **(b)(4)**.

Your written response minimizes the importance of ensuring glove integrity and its potential impact on product quality. We disagree with your rationale for the following reasons:

Historical performance data: Your response stated that your firm's examination of incoming glove lots since 2009, using your current sampling procedure, yielded no defects of the samples tested. However, during our inspection, we found that a significant percentage of the gloves already QA-released or being used in production were defective. We are concerned that your vendor qualification program and incoming material release system are deficient. You stated that you will discontinue using the current supplier and qualify new glove suppliers. In your response, please provide the type of tests (methods) and physical examination you conduct to qualify new glove suppliers, the acceptance criteria of the tests/examination of the gloves and primary packaging, criteria for rejection of vendor, and investigation performed, where appropriate.

Procedures to examine gloves prior to use: You responded that you have procedures in place to

verify the integrity of the gloves prior to use. We note that your standard operating procedures (SOPs) lack specific instructions to operators on how to perform examination of glove integrity prior to use. In addition, our investigators interviewed your employees and verified that glove integrity checks had not been performed. Your production records also did not reflect that you had conducted any of the glove verification activities you claimed to have carried out prior to production.

Disinfection of the gloves: Your response that the sterility assurance concerns for the drug product batches can be mitigated by decontamination or disinfection of the gloves is not well supported. The exposure of the primary packages to **(b)(4)** (**(b)(4)**) only decontaminates the outer surface of the primary packaging and is not intended to permit penetration of the **(b)(4)** to the gloves inside. The disinfection of the "sterile" gloves by **(b)(4)** (**(b)(4)**) has also not been validated to establish that disinfection can be achieved. Use of non-integral and non-sterile gloves poses significant risk to the sterility of the drug product.

Media fills: Your suggestion to justify use of non-integral gloves via media fills would not be acceptable, as fundamentally poor production practices are not appropriate or reproducible.

In summary, we disagree with your response that your firm is "in a state of control" and the use of defective gloves is not a significant problem.

During the inspection, you informed us that "sterile" gloves from the same supplier, **(b)(4)**, are used since 2009 in several other manufacturing facilities, the **(b)(4)** and **(b)(4)**. We are concerned with the lack of sterility assurance of all the aseptically filled drug products you manufactured at these sites. Please provide in your response to this letter the corrective action you intend to implement at all sites that may be affected by similar practices. We acknowledge that you have put all SFF manufactured products on hold. In your response, please provide your plan for the final disposition of drug products that are currently on hold. If you intend to rework these batches, please submit the protocol and final report demonstrating validity of the rework process. If you intend to conduct additional sampling and testing alone or in conjunction with a rework, please submit the protocol describing the statistical basis and scientific validity supporting the sampling and testing approach.

b. Your media fill studies are inadequate.

Our review of the media fill batch record #MVVL-13001, performed on 03/11/13, showed that a significant number of media fill vials were rejected without justification. Of the **(b)(4)** vials filled, **(b)(4)** vials were incubated; 176 vials were rejected for "Other Rejections." You did not document the locations at which these "Other" vials were rejected and the reason for rejection. Further, a properly performed media fill includes simulations of expected operations (e.g., you should include removal and re-assembly of the **(b)(4)** conveyor during the media fill).

Please note that no amount of successful media fills can be used to validate poor aseptic design, operations, controls, and practices. Sterility assurance requires a holistic approach in every aspect of the aseptic operations. Your firm should conduct a careful risk assessment of your aseptic operation with the aim of achieving a high degree of sterility assurance.

We acknowledge your commitment to make corrections to the above observations. In your response, please submit new media fill data incorporating all the appropriate controls and documentation, including relevant corrections cited in this inspection. Our investigators will evaluate the acceptability of these media fills during our next inspection.

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing (21 CFR 211.42(c)(10)(iv)).

a. Your firm did not adequately assess contamination risk to determine the worst-case locations and timing for your active viable air monitoring sites. We noted that you performed a total of **(b)(4)** active air sample collections per **(b)(4)** during idle conditions (**(b)(4)**), each of which are located at the backside of the filling machine and are not representative of the conditions during production. Your sampling was not conducted under dynamic conditions.

b. Your active air sampling is deficient. The microbiologist sprays the "**(b)(4)**" of the air sampler where **(b)(4)** with **(b)(4)**, followed by wiping with a cloth. The media plate is loaded onto the air sampler **(b)(4)** later. There is no assurance that residual **(b)(4)** does not impact the detection of contaminants.

c. Our inspection found that there is no assurance that personnel monitoring (finger dabs), with periodic use of the **(b)(4)** to disinfect the gloves, is conducted at a time that allows accurate recovery and counts of contaminants.

We acknowledge your correction to assure appropriate active air sampler disinfection. In your response, please provide an enlarged diagram of the locations of air sampling (viable and non-viable), your plan to perform active air sampling under dynamic conditions, and the modified SOP on how personnel monitoring is conducted to address our concerns.

3. Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas of such other control systems necessary to prevent contamination or mix -ups (21 CFR 211.42(c)).

a. You do not disinfect the **(b)(4)** conveyor after storage outside the ISO-5 area; this conveyor is used to transport filled and partially stoppered vials to the **(b)(4)**.

b. Our inspection found that the same "mop" is used throughout the production of a batch and is even stored outside the ISO-5 area before re-use. This "mop" is used to disinfect the RABS **(b)(4)** and equipment surfaces inside the RABS during setup and manufacturing activities. The repeated use of the same "mop" poses a significant risk of cross-contamination to the open vials with microbial and/or particulate matter from the cloth mop.

Your response stated that disinfection of the **(b)(4)** conveyor will be performed. In your response to this letter, please provide corrections for disinfection of the RABS **(b)(4)**, and surfaces inside the RABS, and a new approach that addresses these significant contamination risks.

We also note that your firm allows **(b)(4)** of the RABS to be opened during processing. Please note that opening of the RABS **(b)(4)** during processing should be a rare event and used only for narrowly defined situations, not for routine interventions.

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 has already been distributed (21 CFR 211.192).

You failed to initiate investigations following the identification of discrepancies potentially affecting the safety of sterile finished drug products. You have failed to conduct an investigation of the non-integral gloves found during FDA inspection and continued to manufacture **(b)(4)** batches of drug product using the same lot of defective gloves.

It is noteworthy that the failure to conduct investigation is a repeat observation from 02/2011.

We acknowledge your commitment to undertake a comprehensive review of the existing deviation management system and identify where improvements can be made. Our investigators will evaluate your corrections during our next inspection.

5. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

Our inspection revealed many examples where you failed to exercise proper controls in evaluating the stability of your drug products. For example:

a. Our review of **(b)(4)** Injection, **(b)(4)** mg batch #**(b)(4)** three month stability samples currently under analysis, revealed an inconsistency in the number of vials removed from the stability chamber: 32 vials had been removed but only a total of 2 vials for room temperature and accelerated conditions were tested. You have not accounted for the disposition of the remaining 30 vials. Additionally, our examination of **(b)(4)** Injection **(b)(4)** mg batch #**(b)(4)** three-month stability samples currently under analysis found that one vial from the **(b)(4)**°C/**(b)(4)**% relative humidity (RH) condition had been substituted and tested in place of the **(b)(4)**°C/**(b)(4)**% RH condition.

b. Similar inconsistencies in stability sample reconciliation were found in **(b)(4)** Injection **(b)(4)** mg batch #**(b)(4)**, **(b)(4)** Injection **(b)(4)** mg batch #**(b)(4)**, and **(b)(4)** Injection batch #**(b)(4)**. No explanation was provided regarding the missing vials in all cases.

We acknowledge your corrective actions that will enhance your sample custody and storage and have a stricter accountability of the stability samples. However, your response is inadequate because it did not include a retrospective evaluation of all potentially affected products on stability. Our investigators will evaluate these corrections during our next inspection.

6. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Your firm's **(b)(4)** "Jasco LC-Net II" HPLC instruments do not have restrictions in place to prevent any change or deletion of analytical raw data. Additionally, there is no audit trail in place to determine any previous deletion of raw data.

We acknowledge that you have discontinued usage of all Jasco systems in SFF and other sites effective June 26, 2013, and will assess previous use of the Jasco systems. In your response, please submit an assessment of the integrity of the data from the Jasco systems only for lots of finished product still within expiry as of the date of this letter.

7. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).

Our inspection of your finished drug product cold storage (2- 8°C) room found water damage and the presence of mold growth on finished product shipping containers, and observed pools of water on the floor.

We acknowledge your corrective actions to clean and control the temperature and humidity of the cold room. In your response, please address the presence of mold spores in the cold room. Our investigators will evaluate these corrections during our next inspection.

The items listed above, as well as other deficiencies our investigators found, lead us to question your understanding of basic microbiology and microbial controls that are critical for the manufacture of sterile products. The deficiencies uncovered in this inspection are extensive and indicate that you lack an effective quality management operation.

Until you have completed and FDA has confirmed the corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA continuing to refuse admission of articles manufactured at Agila Specialties Private Limited, Specialty Formulation Facility located at Bommasandra Jigani Link Rd, Bangalore, India, into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles are subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

Please notify this office in writing of any additional specific steps that you have taken to correct the deviations observed on this inspection and at related facilities. Include an explanation of each step being taken to prevent the recurrence of deviations and copies of supporting documentation. Please identify your response with FEI # 3007648351.

If you have questions or concerns regarding this letter, contact Brenda Uratani, Ph.D., Compliance Officer/Associate Director, Regulatory Sciences, at the below address and telephone number:

U.S. Food and Drug Administration
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Office of Manufacturing and Product Quality, Division of International Drug Quality
White Oak, Building 51, Room 4370
10903 New Hampshire Ave
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Sincerely,
/S/
Michael Smedley
Director (Acting)
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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