U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Emcure Pharmaceuticals Limited 3/3/16

Department of Health and Human Services

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

Warning Letter

VIA UPS

WL: 320-16-08

March 3, 2016

Mr. Satish Mehta
Chief Executive Officer
Emcure Pharmaceuticals Ltd.,
Plot No. P-1, IT BT Park Phase II, MIDC, Hinjwadi
Pune 411 057, Maharashtra
India

Dear Mr. Mehta:

From January 27 to February 4, 2015, the U.S. Food and Drug Administration (FDA) inspected your pharmaceutical manufacturing facility, Emcure Pharmaceuticals Limited, located at Plot No. P-1, IT BT Park Phase II, MIDC, Hinjwadi, Pune 411 057, Maharashtra, India.

We identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 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 FD&C 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 reviewed your February 25, 2015, response in detail. We acknowledge receipt of subsequent responses.

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)).

Poor Aseptic Processing Techniques
Our investigators observed poor aseptic processing techniques during the manufacture of **(b)(4)** injection USP (aseptically filled for U.S. market) batch **(b)(4)**, and **(b)(4)** injection (aseptically filled for U.S. market) batch **(b)(4)**. These poor

techniques, which may compromise the sterility of injectable products, included the following.

a. Your operator placed a **(b)(4)** cup on the floor of an ISO 7 area (Grade B) to collect water **(b)(4)** from a **(b)(4)** unit. As operators set up ISO 5 (Grade A) filling line, they used the cup contents to wet the mechanical assembly in the piston drive.

b. Operators crawled on the floor on their hands and knees under the filling line during routine aseptic filling operation activities.

c. An operator directed vials to the **(b)(4)** with his hand located directly above open vials.

d. During set up, an operator moved un-bagged sterilized tools from the ISO 7 to the ISO 5 area, which he placed in the filling area near the stoppering equipment.

e. During **(b)(4)** unloading in the ISO 7 area, an operator dropped a sterilized lid from a **(b)(4)** container onto the floor, which he then picked up and placed it back on the container.

f. Before performing aseptic filling activities in the filling room during aseptic setup, operators wore goggles on their foreheads and exposed skin.

g. Operators opened **(b)(4)** barrier **(b)(4)** to adjust or remove vials from the line with bare hands, instead of wearing Restricted Access Barrier Systems (RABS) **(b)(4)**.

h. Operators carried unprotected sterilized RABS **(b)(4)** from the **(b)(4)** ISO 5 area, to the ISO 7 area, and then to the mobile Laminar Air Flow (LAF) ISO 5 area.

Your procedure BRD/GEN/011/08, *Behavior and Aseptic Practices in Classified Areas,* restricts operators from touching the floor or leaning over opened vials. The above examples show that your operators engaged in these practices.

Poor Sterilization Practices
Although your Validation Report PRD/PQ/107-04 REP-07 references the RABS **(b)(4)** loading pattern that should have been followed, the inspection also documented that operators did not follow the validated loading pattern configuration for RABS **(b)(4)** during the **(b)(4)** cycle. For example, the RABS **(b)(4)** were **(b)(4)** inside a **(b)(4)** and not properly configured in the **(b)(4)** to ensure appropriate sterilization of the **(b)(4)** surfaces, as described in the procedure.

Facility Design
Your facility design may represent an additional contamination risk to the products you manufacture. For example, we observed an employee crawling under filling equipment to get to the area where he performed other critical operations. Collecting **(b)(4)** water from the bottom of the filling machine to lubricate equipment, as mentioned above, also raises concerns about the design and qualification of your equipment.

Your response is inadequate because it is limited to a review of video recordings reviewed by FDA and referenced on the FDA Form 483. Your response does not include an evaluation of all available videos to identify all batches that could be affected by poor aseptic practices and associated risks.

In response to this letter, list the batches manufactured from November 2014 to the end of the inspection. Include your independent third party's evaluation of these recordings, and their findings. Also include a detailed action plan describing the revisions made to your procedures, the content of employee training, and how video recordings are evaluated and by whom.

2. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

Unreliable Environmental and Personnel Monitoring
Your environmental monitoring (EM) and personnel monitoring (PM) data are not reliable because of the materials and procedures you use to conduct EM and PM tests. Multiple elements of these programs are scientifically unsound, including the following.

a. Our investigators observed dried media plates you used for surface and personnel monitoring in the **(b)(4)** facility incubators. We documented that 36 of **(b)(4)** plates inside the Plant **(b)(4)** incubator showed signs of dryness and desiccation.

Your response indicated that you initiated a study to assess the signs of desiccation in **(b)(4)** plates. You committed to switch to outsourcing **(b)(4)** and **(b)(4)** plate supplies. However, your use of dried **(b)(4)** plates in prior testing was not scientifically sound, and compromised your results.

In response to this letter, indicate steps you have taken to determine whether products made under these conditions meet limits. Also explain how you will improve laboratory controls to prevent use of unsuitable media in the future.

b. Your EM data for the filling areas did not specify the sampling location of the RABS **(b)(4)** used during filling and **(b)(4)** operations. SOP QCD/MIC/034-10 *Procedure of Surface Monitoring by Swab* does not require sampling from predetermined **(b)(4)** locations identified as critical risk points of your filling and **(b)(4)** operations. Instead, the procedure permits individual operators to determine the location to be sampled. Additionally, you only collected a **(b)(4)** swab sample from **(b)(4)**, and failed to sample other **(b)(4)** used in daily aseptic operations.

According to your response, you will increase the sampling frequency for your RABS **(b)(4)** tests. However, you failed to specify whether you will ensure sampling of **(b)(4)** used in daily aseptic operations.

In response to this letter, specify **(b)(4)** locations in the RABS and your improved sampling procedures.

c. Your firm lacked personnel monitoring data for aseptic operations on line **(b)(4)**. Documents generated in the laboratory for personnel monitoring did not identify specific employees involved in filling operations.

According to your response, it was difficult to accurately locate plates corresponding to specific operators, because the plates were not uniquely identified. You indicated that operators were trained in aseptic practices; practices we observed were "deviations" that you "considered serious lapses by the facility management." Furthermore, you acknowledged serious gaps "especially with respect to the suspected data integrity and falsification" in data generated in your environmental monitoring program.

Your response is inadequate. Despite your claim that your operators were appropriately trained, video recordings of your manufacturing operations clearly showed that your employees were not following proper aseptic techniques.

These violations posed a significant risk to the sterility of your products. You may wish to review FDA's guidance **www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.htm (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.htm)** to help you improve your manufacturing of sterile products. You are responsible for ensuring that your quality and production management organizations oversee critical operations in your facility. We acknowledge your decision to cease production during the FDA inspection and **(b)(4)**.

Inadequate Visual Inspection Program

In addition to the inadequacies of your EM and PM programs, our inspection documented that your visual inspection program is unreliable. Your qualification and re-qualification of operators did not include determining the operator's ability to detect and identify known product defects for **(b)(4)** products or products filled in amber vials.

For example, one inspector failed to correctly identify major defects as defined in your SOP PRD/VAL/003 -05 *Qualification of Visual Inspection Operators*. Your inspector incorrectly identified three of **(b)(4)** vials containing fiber material, one of **(b)(4)** vials containing particles, and one of **(b)(4)** vials that had the incorrect volume from the Kit **(b)(4)** challenge set. A second inspector also failed to correctly identify two of **(b)(4)** units containing fiber, 2 of **(b)(4)** units containing particles, and one of **(b)(4)** units that had the incorrect fill volume from the **(b)(4)** Kit **(b)(4)** challenge set.

Your SOP PRD/OPN/065-09 *Visual Inspection of Vials* permits inspectors to classify defects such as fragmented glass subjectively, as critical or major. Your SOP has no objective criteria for these classification decisions.

According to your response, you will revise the qualification procedure for visual inspections and requalify your inspectors. However, you did not include the revised SOP or your schedule for completing re-qualification.

In your response to this letter, provide a detailed summary of improvements you have made to your visual inspection qualification program. Include training you have provided and will continue to provide to your visual inspectors. Also indicate how you will determine the effectiveness of your visual inspection training program, how you will improve your defect classification, and what you will do if visual inspectors are unable to correctly discriminate between critical and major defects.

In addition to details on the training and re-qualification of your visual inspectors, indicate how you will ensure that no batches with critical defects were released to the market, given that your visual inspection program relied on subjective determinations of criticality by visual inspectors who were unable to correctly classify defects during the inspection. Conduct and provide the results of a risk assessment of products that were visually inspected by unqualified employees and released for distribution. Indicate steps you have taken to ensure that patients have not been, or will not be, exposed to products with critical defects.

3. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

During our inspection, we observed multiple examples of incomplete, inaccurate, or falsified laboratory records.

a. EM records for active air monitoring of the aseptic filling area reported samples as being collected when they were not actually collected, and some records documented purported EM results of zero colony forming units (CFU) even when the samples for which those results were reported were not actually collected. Contemporaneous video recordings that FDA reviewed during the inspection showed that such EM samples had not been collected, even though your laboratory records reported results for those samples. Our investigators observed your firm's practice of falsifying EM results for samples that were not collected for multiple drugs, including **(b)(4)** injection USP lot **(b)(4)** and **(b)(4)** injection lot **(b)(4)**.

Although your laboratory records for these products and lots indicated that you collected active air samples, the video we reviewed during the inspection demonstrated that operators did not actually collect the samples. During the inspection, your microbiologist confirmed that these EM samples were never collected. Additionally, two microbiologists informed the investigator that media plates were labeled and submitted for incubation as though they had been exposed to the environment. However, these media plates were never actually exposed to the environment. Your microbiologist indicated that this practice was routine and due to "work pressure." Because the EM results for samples were falsely reported as having been collected and/or as having produced no CFU growth, you lack assurance that

the injectable drugs your firm produced in this area were sterile at the end of the aseptic filling process.

b. Our review of EM records from January 2014 through September 2014 found that no samples had exceeded the action levels for any of the **(b)(4)** filling lines in your **(b)(4)** plant, or for the filling line in Plant **(b)(4)**. However, we observed 12 microbiological plates in the incubator showing EM results that required further action during our inspection of your laboratory.

These EM records provide critical data on environmental trends and whether environmental control is maintained during aseptic filling of a batch. Environmental monitoring should promptly identify potential routes of contamination, allowing for implementation of corrections before product contamination occurs.

In your response, you stated “there have been serious gaps in the management, oversight and execution of the environmental monitoring program, especially with respect to the suspected data integrity and falsification of data concerns.” Your response also indicated that you revised procedures, provided training, and reviewed documents from March 2013 to January 2015. Your investigation confirmed that EM samples were not collected and “the data was fraudulent.” You acknowledged these problems in your response and took some corrective actions. However, your response is inadequate because you have not demonstrated how you can ensure that EM records generated before the inspection were reliable and accurate, or how the falsification of some of your reported EM data may have affected the quality of your products.

We acknowledge your **(b)(4)** after the inspection, your management changes, and your engagement with consultants. However, your investigation was not extended to all systems and areas that may have been affected by your questionable practices. You have not provided data sufficient to demonstrate that all products released for distribution were manufactured with the appropriate environmental controls in place during aseptic filling operations.

Furthermore, data falsification and manipulation, and your reliance on incomplete records to release product to the market, are repeat violations. A February 2014 inspection of solid **(b)(4)** dosage operations at this same facility also reported data manipulation and falsification of test results generated by your firm, along with other deficient laboratory practices that also resulted in products being recalled from the U.S. market.

In your 2014 response, you made a similar commitment to hire a third party auditor to conduct a comprehensive audit of all laboratory electronic and hard copy data for tests conducted for all release and stability finished product. Our 2015 inspection found continuing practices of data falsification and manipulation at your facility, indicating that previous corrections were ineffective.

c. Our investigators observed poor documentation practices during production and in-process testing.

i. Media fill batch **(b)(4)** documented a “check by” operation performed by an operator who was not present at the facility. This operator signed “checked by” for 63 out of **(b)(4)** individual **(b)(4)**. In addition, during this media fill, a Quality Assurance (QA) individual signed “checked by” for observing the intervention “**(b)(4)** of conveyor belt” from **(b)(4)** to **(b)(4)** on December 2, 2014, but the QA individual was not present in the filling room when this intervention was performed, and did not view it.

Your response admitted that the individual signing the QA “checked by” column was not present during that portion of the media fill **(b)(4)** to **(b)(4)** on December 2, 2014.

ii. Disinfection of the filling machine was not completed before filling of **(b)(4)** injection USP batch **(b)(4)** (aseptically filled, **(b)(4)**, and distributed to the U.S. market). Records were made for cleaning on November 13, 2014, from **(b)(4)** to **(b)(4)**, but review of videos show that cleaning did not match records.

Your response confirms that the cleaning and disinfection did not occur on November 13, 2014.

iii. On January 29, 2015, an operator performed in-process weight checks for **(b)(4)** during the filling operation performed at 13:30. This activity was not documented until 14:15. In addition, another weight check operation performed at **(b)(4)** had not been documented on the record when reviewed at **(b)(4)** by the inspector.

Your response indicated that activities that occurred on January 29, 2015, are deviations.

iv. Cleaning of the **(b)(4)** and parts of the filling machine was not completed before filling **(b)(4)** injection USP batch **(b)(4)** (aseptically filled, **(b)(4)**, and distributed to the U.S. market). Records were made for cleaning on November 26, 2014, from 08:57 to 09:26, but videos show that cleaning did not match records.

Your response indicates that the cleaning and sanitization of the conveyor **(b)(4)** was missed on one side.

Your investigation into this issue is inadequate because it did not consider other in-process tests, or whether the operator(s) have been involved in the same poor documentation practices for others batches. Your response lacks an assessment of your documentation practices to determine the extent of the problem in your facility.

Conclusion
Violations cited in this letter are not intended to be an all-inclusive list. You are responsible for investigating and determining the causes of the violations identified above, for preventing their recurrence, and preventing other violations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm’s compliance with CGMP, FDA may withhold approval of any new 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 Emcure Pharmaceuticals Limited, Plot No. P-1, IT BT Park Phase II, MIDC, Hinjwadi, Pune 411 057, Maharashtra, India, into the United States. Under Section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3), articles may be refused admission because manufacturing methods and controls do not appear to conform to CGMP within the meaning of Section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

Within 15 working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations. In addition to the specific requests noted above, supporting documentation should include your third party assessment of the following.

1. A comprehensive evaluation of the extent of the inaccuracy of your recorded and reported data. Include a detailed action plan to fully investigate the extent of your deficient documentation and data management practices.

2. A risk assessment of the potential effects of observed failures on the quality of your drug products, including the effects of deficient documentation and data management practices, aseptic processing breaches, and inadequate environmental

monitoring program. Determine the effects of your failures on the quality of drug products released for distribution and the data supporting all associated submissions.

3. A management strategy for your firm that includes the details of your corrective action and preventive action plan. Describe the actions you will take, such as contacting your customers, recalling drugs, conducting additional testing and/or adding lots to your stability programs, or other steps to assure the quality of your drugs manufactured under the deficient conditions discussed above. Also indicate measures you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other actions to prevent the recurrence of CGMP violations, including breaches of data integrity.

Provide copies of supporting documentation. If you cannot complete corrective actions within 15 working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the drug products at issue, provide the date(s) and reason(s) you ceased production. Send your reply to:

Maan Abduldayem
Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing Quality
Division of Drug Quality I
White Oak Building 51, Room 4212
10903 New Hampshire Ave.
Silver Spring, MD 20993
USA

Please identify your response with FEI# 3005151215.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

More in 2016 (/ICECI/EnforcementActions/WarningLetters/2016/default.htm)