U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Gulf Pharmaceutical Industries 2/23/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-12-08

February 23, 2012

Dr. Ayman Sahli
Chief Executive Officer
Gulf Pharmaceutical Industries
P.O. Box 997
Airport Road, Digdaga Area
Ras al Khaimah, UAE

Dear Dr. Ayman Sahli:

During our September 25 to October 3, 2011 inspection of your pharmaceutical manufacturing facility, Gulf Pharmaceutical Industries, located at Airport Road, Digdaga Area, Ras Al Khaimah, United Arab Emirates, investigators from the U.S. Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP), Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product(s) 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 reviewed your firm's response of October 28, 2011, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited to, the following:

1. Your firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures include validation of the sterilization process [21 C.F.R. § 211.113(b)].

For example,

a) You failed to perform unidirectional airflow pattern studies (i.e. smoke studies) for the ampoule filling line used for the production of **(b)(4)** Lot **(b)(4)**, distributed to the U.S. on July 13, 2010.

This is a repeat observation from the December 2004 inspection at this facility. Our current inspection found that your firm failed to perform smoke studies for the ampoule filling line. Your firm was previously cited in 2004 for a failure to conduct smoke studies for your vial filling line.

Your response of October 28, 2011, is inadequate because you failed to describe the specific steps that you are taking to ensure adequate oversight by the quality unit over critical aseptic operations such as unidirectional airflow pattern studies.

b) The unidirectional airflow studies performed for the vial filling line are inadequate in that the studies do not show unidirectional airflow.

These unidirectional airflow studies showed turbulent airflow in the following areas: above the **(b)(4)** just prior to entry into the filling **(b)(4)**, over the stopper **(b)(4)** adjacent to the filling **(b)(4)**, and over the **(b)(4)** tray filled with partially-stoppered vials during the automatic loading of vials into the **(b)(4)**. We are concerned that your quality unit failed to identify these instances of turbulent airflow.

Although you state in your response that **(b)(4)** will perform complete smoke pattern studies for the ampoule filling line and the vial filling line, you have not proposed the implementation of additional actions or controls needed while you complete smoke studies and demonstrate that these areas are suitable for aseptic manufacturing of sterile drug products. In addition, you failed to provide your risk assessment for all sterile products within expiry that were manufactured under these unacceptable conditions.

c) HEPA air velocity is not evaluated proximal to the working level.

SOP ECPI-021: Calibration Procedure for unidirectional Airflow Unit and Bench is deficient in that it only requires HEPA air velocity checks to be performed **(b)(4)** inches below the filter face, but does not require that the air velocity be evaluated proximal to the working level.

Your response is inadequate because your corrective action for your failure to evaluate air velocity proximal to the working level consisted of providing a revised procedure and training, but you have not yet evaluated the current air velocity at the working level.

d) Your firm demonstrated poor aseptic technique in gowning and production during the manufacture of **(b)(4)** Injection Lot **(b)(4)** on Sept 28, 2011.

During gowning and production operations, investigators observed poor aseptic practices, including, but not limited to, excessive touching of the outside of hood and gown during gowning, exposing aseptic processing equipment and equipment parts in the Class 1000 area prior to introduction into the Class 100 area, disrupting airflow with hands and forearms over the stopper bowl while transferring **(b)(4)** stoppers, and excessive and repeated touching of parts of the filling machine and **(b)(4)** barriers.

Your response references corrective actions through training employees, equipment purchase, and procedural improvements. However, your response fails to specifically address the observed deficiencies in aseptic operations and the impact to the sterility of **(b)(4)** Injection Lot **(b)(4)** and other products.

e) The revalidation of the **(b)(4)** sterilization cycles for machine parts is deficient in that the exact placements of the biological indicators (BIs) and **(b)(4)** are not documented and consequently can not be confirmed as the worst case locations.

Your response indicates that BI locations are now identified in SOP QAS 296 and that retraining has occurred. However, SOP QAS 296, provided in your response, indicates that BIs are not attached with the **(b)(4)** in several locations including, but not limited to, **(b)(4)** of the **(b)(4)**, within the **(b)(4)** attached to the **(b)(4)**, and **(b)(4)** through the **(b)(4)** with **(b)(4)** and **(b)(4)**. Your response is inadequate because it fails to

include your rationale for not routinely placing BIs next to the **(b)(4)** in the areas you have designated as most difficult to sterilize.

2. Your firm has not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, or quality of the drug product [21 CFR § 211.67(a)].

You do not have data to show that your equipment cleaning procedure is adequate to prevent cross-contamination. Specifically, your firm has not conducted cleaning validation, cleaning verification, or swab recovery studies for non-dedicated equipment used in the production of **(b)(4)** Ampoules and **(b)(4)** Injection.

In your response, you commit to conduct cleaning validation studies and swab recovery studies. However, your response is inadequate because the cleaning validation protocols you have provided do not include an evaluation of swab recovery from **(b)(4)** surfaces (**(b)(4)** tubing) that will be sampled as part of your cleaning validation. In addition, your validation protocol for the filtration assembly and filling machine parts (CVPJII-003) indicates that swab sampling points will be **(b)(4)**cm² but failed to describe how equipment surfaces with smaller surface areas are sampled (e.g., filling needles with a surface area of less than **(b)(4)**cm² in size). Also, you failed to provide your risk assessment for all sterile products within expiry that were manufactured in multi-use equipment without validating your cleaning procedures..

3. Your firm fails to follow written production and control procedures in the execution of the various production and process control functions [21 CFR § 211.100(b)].

For example,

a) Your firm fails to follow SOP QCS-107 entitled Monitoring of Personnel Hygiene which requires personnel (gowning) monitoring **(b)(4)** per shift at minimum.

During the filling of **(b)(4)** Injection lot **(b)(4)** on September 28, 2011, the microbiologist failed to sample the personnel gowns for the **(b)(4)** operators involved in the filling operations. Your response indicates corrective action through procedural improvements and retraining of all analysts. However, your response is inadequate because it fails to describe how this and other sampling will be documented to ensure all necessary samples are taken. In addition, production operators were not involved in the retraining to ensure they do not dispose of their gowns at the end of the shift prior to having samples taken. Also, you have not evaluated the impact of this deficiency on **(b)(4)** Injection lot **(b)(4)**.

b) Operators fail to follow the diagram of the validated **(b)(4)** load configuration provided in SOP QAS-296 entitled Validation/Re-validation of Sterilization Cycles in the **(b)(4)** and SOP PGSI-087: Injectables Machine Parts Preparation Before Sterilization and Batch Processing.

SOP QAS-296 entitled Validation/Re-validation of Sterilization Cycles in the **(b)(4)** and SOP PGSI-087: Injectables Machine Parts Preparation Before Sterilization and Batch Processing provide a diagram of the load configurations; however, our inspection found that the operator performing this function for the parts to be used in the production of **(b)(4)** Injection lot **(b)(4)**, can not follow this load pattern due to insufficient space on the **(b)(4)** trolley. The current **(b)(4)** load configuration used by production operators to **(b)(4)** sterilize filling machine parts has not been validated.

Your response states, "The subject employee inadvertently did not follow the validated load pattern for **(b)(4)** sterilization of filling machine parts." It should be noted that your firm's personnel explained that the failure to follow the validated load pattern was not inadvertent, but was the prevailing practice. Your response indicates an incident report was raised, all operators were retrained, and a sign-off sheet for load configuration was added to the batch record. However, your response is inadequate because it fails to address the disposition of **(b)(4)** Injection lot **(b)(4)** as well as any other batches that may have been impacted by this failure to follow validated sterilization load configurations.

c) Your firm fails to perform gowning qualification for operators prior to working in aseptic processing areas, and all operators are not requalified for gowning on an annual basis as required according to Report QR-103: Report for Aseptic Gowning Qualification Program for Cleanroom Personnel.

Your response states that you issued and implemented SOP QAS-406: Procedure for Gowning Qualification/Requalification of Clean Room Personnel and you revised re-qualification protocols to include all staff entering Class 100 areas. Your response is inadequate in that it does not address how you will prevent individuals who have not undergone the appropriate gowning qualifications from accessing cleanroom areas. Your response also refers to the personnel monitoring conducted during media fill operations and states, "we were under the impression that including the operator for media fill & intensively monitoring the gown is enough to re-qualify a personnel…". With this statement, you disregard your firm's failure to follow your existing SOPs which state that all personnel entering the cleanrooms will be re-evaluated for gowning qualification annually as per a written protocol. It is your quality unit's responsibility to ensure that the established program to regularly assess conformance of personnel to aseptic manufacturing requirements is followed.

4. Your firm has not established appropriate controls over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Your firm also fails to maintain a backup file of data entered into the computer or related system [21 CFR § 211.68(b)].

For example,

a) There is no system in place to ensure that all electronic raw data from the laboratory is backed up and/or retained.

During the inspection, you informed our investigators that electronic raw data would not exist for most HPLC assays over two years old because data is not backed up and storage space is limited.

Data is deleted to make space for the most recent test results. You also informed our investigators that printed copies of HPLC test results are treated as raw data.

Printed copies of HPLC test results from your firm's systems do not contain all of the analytical metadata (for example: instrument conditions, integration parameters) that is considered part of the raw data. We acknowledge that your response indicates that you have created a procedure in order to implement the back-up and retention of HPLC data. This electronic HPLC data supports testing, disposition, and other significant quality control decisions, and it is essential that you maintain this information for each batch. In your response, please provide a detailed update on your firm's implementation of this correction. Also describe your firm's policy for retaining HPLC raw electronic data associated with pending applications.

b) You have not implemented security control of laboratory electronic data. All laboratory analysts share the same password for the HPLCs in the QC analytical chemistry lab and Omnilog in the microbiology lab. In addition, analysts have access to the HPLCs which allow them to create and/or modify validated methods.

Your response indicates that SOP EDS-084: Procedure to Assign User Access Levels and Privileges for Computerized Analytical System has been issued and training has been provided. Please clarify in the response to this letter how you define the levels of authorization or the user access and privileges for analysts. Your response also explains that analysts now have their own passwords and that changes will be captured by audit trail. We also note that your SOP does not have provisions for any audit trail reviews to ensure that deletions and/or modifications do not occur. Please provide an explanation of your firm's procedures regarding audit trails.

We recommend that you conduct a complete and extensive evaluation of your overall quality and manufacturing controls to ensure that all finished dosage drugs manufactured at your facility meet the quality and purity characteristics they purport to possess. We highly recommend that you hire a third party auditor, with experience in detecting data integrity problems, who may assist you in evaluating your overall compliance with CGMP.

On September 27, 2011, investigators identified pre-dating on the Manufacturing Document Compliance Declaration forms, which are attached to the batch production records, for **(b)(4)** lot **(b)(4)** and **(b)(4)** lots **(b)(4),** and **(b)(4).** Pre-dating is an unacceptable practice and raises doubt regarding the validity of your firm's records. Investigators also identified misleading dating practices concerning the completion of the QC Department Visual Inspection Report, used to document personnel practices in the aseptic filling area during filling operations. Although **(b)(4)** lot **(b)(4)** was filled on September 28, 2011, the QC Department Visual Inspection Report document was not completed at that time. This document was completed and provided to investigators on October 2, 2011, but was dated September 28, 2011, which is not the date that the document was completed and is therefore misleading. Your response indicates that the Visual Inspection Record will now be made contemporaneously. However, you have not evaluated whether these records were not completed contemporaneously for other batches already manufactured and distributed, nor have you described any investigation into other manufacturing documents that are not being completed contemporaneously.

The lack of reliability and accuracy of data generated by your firm is a serious CGMP deficiency that raises concerns with all data generated by your firm. While we acknowledge the commitment in your response to improve quality assurance, we remain concerned that your investigation is not

comprehensive enough to determine the extent and impact of the problem. A review of the batch records that were listed in FDA form 483 is not sufficient. In your response, provide a complete corrective action plan that includes a retrospective review of the analytical data and batch records for all products manufactured at your facility that remain within expiration. In addition, provide the actions taken to prevent recurrence of the problem. Your investigation should be expanded to all other products manufactured at this site and include the establishment of a comprehensive training program for each person engaged in the manufacturing, processing, packaging, or holding of drug products. This plan should include training to all managers, supervisors, and quality unit personnel in detecting data manipulation and questionable practices.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

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, until such time as your manufacturing practices are verified to comply with CGMPs, your firm will remain under FDA Import Alert, and FDA will continue to refuse admission of all articles manufactured at Gulf Pharmaceutical Industries located at Airport Road, Digdaga Area, Ras Al Khaimah, United Arab Emirates into the United States. Because your firm is currently under Import Alert, 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 Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

If, as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov in order to ensure that your action(s) does not adversely affect the public health.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3004006043.

If you have questions or concerns regarding this letter, contact Maan S. Abduldayem, Compliance Officer, at the below address and telephone number.

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Sincerely,

/Steven Lynn/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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