DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Warning Letter

Via FedEx
JUL 21 2005

WL: 320-05-03

Mr. Marco Falciani
President
ACS Dobfar
Viale Addetta 4/12
20067 Tribiano
Milan
Italy

Dear Mr. Falciani:

On March 14-24, 2005, the Food and Drug Administration (FDA) conducted an inspection of your sterile pharmaceutical manufacturing facility in Milan, Italy. The inspection by Investigator Susan Bruederle and Microbiologist Richard Friedman revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) Regulations (Title 21 CFR, Parts 210 and 211) in the manufacture of drug products. These deviations were listed on an Inspectional Observations (FDA-483) form issued to you at the close of the inspection. These CGMP deviations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

We have also completed review of your May 18, 2005 response to the FDA-483 observations, as well as the June 9, 2005 response to the meeting on May 23, 2005 and your July 11, 2005 updated response. The CGMP violations discussed below have not been adequately addressed by your responses.

We note that some of the CGMP deviations found during this inspection were similar to those reported in the previous inspection dated May 22-29, 2002. These deviations were found in areas that include[ ]practices,[ ]fills, laboratory controls, environmental monitoring, and validation of sterilization processes. We note that previous corrections had been made in these areas, but our recent review of these areas shows that while individual observations are often corrected a broad review of systems deficiencies with appropriate corrections was not performed. Corrective measures should also be implemented in an attempt to prevent future deficiencies.

[ ]Containment Controls

1. Interim controls for the separation and containment of[ ]and[ ] are inadequate. **21 CFR 211.42 (c)**

   During a meeting on May 23, 2005, we discussed the separation of the[ ] product from the[ ]products manufactured on a campaign basis on the same equipment at your firm. Your long-term goals for separation do not include plans such as dedicated production for the[ ]component of the [ ]product from the equipment used for[ ]production. The controls currently in place are not adequate for separation of production and pose a risk of cross contamination to the[ ]product. No documentation was submitted to show how the[ ]process will be adequately separated or what controls are in place to eliminate or minimize the risk of cross contamination.

   Your plan to move your[ ]API production from[ ]Plant[ ]to a dedicated facility will not take effect until December 2005. We remain concerned about the containment of sensitizing products produced on the same equipment without adequate controls in place in the interim.

2. There is not sufficient documentation to determine the effectiveness of your cleaning agent used between[ ]and[ ] **21 CFR 211.67**

   Your "report for the study of the degradation of[ ]and[ ]by treatment with[ ]was submitted in response to our question regarding[ ]effectiveness as a cleaning agent. Your response did not answer our question in terms of mitigating the original concern of adequate separation as stated on the FDA 483 under observation #1. Also, your report showed that the[ ] is not completely degraded by the[ ]process performed on multi-use equipment. Moreover,[ ] and[ ]do not completely degrade with this process. Your conclusion states that the reductions that occur are from 70% to 100%. Our concern is for those reductions under 100%, and for the potential problems that may be caused by the degradation products which have the potential to contaminate other products processed in the same equipment.

3. Test methods and techniques are not adequate for their intended purposes. **21 CFR 211.160**

   a. Your justification of the use of a swabbing area of[ ]is not adequate. We acknowledge that the USP section[ ]includes a sampling area of[ ]However, this procedure is for a microbiological test, and your sampling is for chemical residues. We recommend using an area of at least 100 cm^2 for this purpose. The swabbing is to detect low-level chemical residues of a sensitizing nature. Smaller sampling areas under these conditions have not been shown to be

sufficient to ensure the detection of low levels of chemical residue in a containment monitoring program.

b. Your response dated June 4, 2005 states that "analytical methods could be used also to detect residual of [ ] in [ ] and of [ ] in [ ] Previous discussions indicated that this was not possible. Please clarify your response and if these methods are available provide us with assurance that the appropriate methods will be implemented.

Investigations

Several observations were made on the FDA 483 regarding deficient investigational practices at your firm. These include:

4. Some batch records did not include complete information relating to the production and control of each batch and deviation reports were not always initiated. **21 CFR 211.192**
5. The quality control unit did not adequately review records to assure that no errors have occurred or, if errors occurred, that they were fully investigated. **21 CFR 211.192**

The above referenced FDA-483 items all relate to the initiation of appropriate investigations. Your response to each of these items was deficient in that only specific incidences were addressed, and no response was given to the overall inadequacy of your procedures for investigations of manufacturing deviations, laboratory OOS results, and customer complaints, as well as the adherence by your staff to these procedures. Several incidences were documented in which your firm's personnel claimed that a procedure was not followed or an investigation was not initiated adequately because the process was too labor intensive. The intensity of an investigation is no excuse for not establishing the cause of the problem and initiating appropriate corrective actions. Also, the relative apparentness of a deficiency or the difficulty in finding a root cause does not negate the need for an investigation and documentation.

6. Sterility Complaint investigations failed to:
    a. Address whether fundamental equipment or processing design issues might be a cause. **21 CFR 211.198**
    b. Discuss or extend to other batches that may have been associated with a failure. **21 CFR 211.198**
7. Sterility complaint investigation reports failed to identify and discuss any possible correlation of the sterility test isolate with microorganisms found in your firm's environmental and personal monitoring. **21 CFR 211.198**
8. Specific complaints (claims) of damaged bags or loss of [ ] in bags were not always investigated. **21 CFR 211.198**

The significant number of sterility complaints received by your firm should have been more thoroughly investigated. A template, which gives the same investigation procedures and corrective actions, is not an adequate investigation. These investigations failed to find the cause of contamination but instead concluded that your customers were at fault without significant evidence for that conclusion. Your Quality Assurance Unit was also not effective in ensuring an adequate depth of the investigations, and that documentation was adequate to support the final conclusion. A thorough investigation of the 50 customer complaints regarding sterility was not completed and your response did not address this overall deficiency. The sterility issue cannot be adequately corrected until all causes are determined

[ ]Processing

Several observations were made on the FDA 483 regarding deficient[ ]practices at your firm. **21 CFR 211.113 (b)**

The below referenced FDA-483 items all indicate failure to employ current principles of [ ]technique and the procedures necessary to manufacture sterile drug products, and do not ensure the sterility of your drug products. Your response did not adequately address the following specific observations.

9. The[ ]filling process was not adequately designed to permit unidirectional airflow protection of the bulk sterile drug.

The smoke studies of your[ ]filling operation indicated that unidirectional flow is not achieved in your current design. Documentation of the design of the[ ]you propose to put in place, and information regarding the new layout of the filling area was not submitted. FDA-483 observations that dealt with this area remain a concern. Your response also does not address the dead air space inside the filling cabinet, and the turbulent airflow that can be created by repeatedly opening and closing the cabinet. We acknowledge your long-term goal of installing a[ ]in this area, but you also need to address these short term manufacturing issues.

10. [ ]processing areas were deficient regarding the system for monitoring environmental conditions.

Your response regarding monitoring the environmental conditions does not address the issue of failing to acknowledge and evaluate alert and action limits at the time they occur. It is important to assess an observation at or above established limits to determine if the process is still being performed under[ ]conditions. Also, non-viable monitoring before and after a campaign run does not give an accurate measure of the levels during the multi-week campaign. The "closed" system used to manufacture[ ]is open at the time[ ]is performed, and it is necessary to monitor and control the environment in which this[ ]is performed to ensure[ ]

11. Procedures designed to prevent microbial contamination of drug products purporting to be sterile did not include adequate validation or controls of the sterilization process.

Your response regarding validation of your sterilization processes does not include an assurance that the transfer lines in the system have been adequately[ ]The monitoring of[ ]in your[ ]does not assure the integrity of the entire system. Also, your response does not address hard to reach areas for your [ ]validation. The critical areas of the equipment may not be the hardest to reach and vice versa. The hardest to reach areas were not tested to see if they were indeed reached by the[ ]

12. [ ]fill studies were incomplete and did not provide a fully accurate assessment of the capacity for production of a sterile product throughout manufacture.

Your response does not adequately address the issue of[ ]the appropriate number of[ ]during[ ]fills. You propose to keep the same[ ]scheme changing only the rotation of operators through the filling of the last sub lot of the[ ] fill. This does not account for the many[ ]manipulations (interventions) that could occur throughout the simulation, nor does it qualify all operators to perform those interventions. The minimal amount of[ ]filled along with the manual operation for which you are simulating indicates that the number of units to be[ ]should be at or approaching the full production batch size. This should ensure that all operators and all interventions are covered in the[ ]fill.

Laboratory

13. The sterility test method was not properly executed to ensure detection of contamination. **21 CFR 211.167 (a)**

Your response fails to address the main deficiency cited in the observation. The test method itself is not deficient. Rather, the analyst's failure to follow the procedure was the concern. Your response does not address the issue of following SOPs. Also, your response did not indicate that corrective actions were extended to all analysts who perform this test method.

General Comments

Many of your responses referred to the capacity of chemical agents or processes to degrade drug residues and therefore prevent contamination. If your firm is relying on this, you should provide adequate justification. Otherwise your firm should not rely on the nature of the processing to assure a lack of contamination and sterility assurance. Controls and testing must be put in place to ensure that these agents as well as your process do in fact assure the sterility of your products and prevent cross contamination.

The CGMP deviations identified above or on the FDA-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practices.

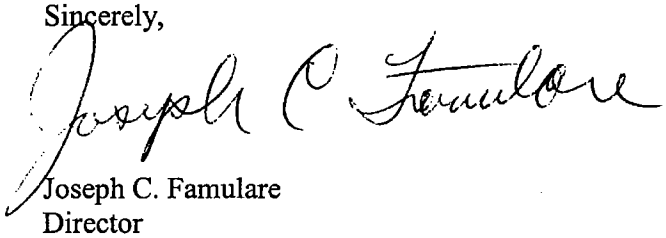
Failure to correct these deficiencies may result in FDA denying entry of articles manufactured by your firm into the United States. The articles could be subject to refusal of admission pursuant to Section 801(a)(3) of the Act in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practices within the meaning of Section 501(a)(2)(b) of the Act.

Please respond to this letter within 30 days of receipt. Your response should include data collected in your correction to the deficiencies cited as well as copies of procedures not already provided. Please identify your response with FEI 3002806297. Until FDA can confirm correction of the deficiencies observed during the most recent inspection, and that this facility is in compliance with CGMP's, this office will recommend disapproval of any new applications listing your firm as the manufacturer of sterile drugs. Please contact Carole Jones, Compliance Officer, at the address and telephone numbers shown below, if you have any questions, written response or concerns regarding these decisions.

U.S. Food & Drug Administration
CDER HFD-325
11919 Rockville Pike
Rockville, MD 20852
Tel: (301) 827-9054; FAX (301) 827-8909

To schedule a re-inspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Field Investigations, HFC-130, 5600 Fisher's Lane, Rockville, MD, 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,



Joseph C. Famulare
Director
Division of Manufacturing and Product Quality
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