U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Ribbon SRL 5/27/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

May 27, 2010

Ms. Maria Gobbi
General Manager
Ribbon Pharmaceutical and Chemical Products
Via San Leonardo 23
Villadose, Rovigo
Italy

WL: 320-10-006

Dear Ms. Gobbi:

During our December 8 - 15,2009 inspection of your pharmaceutical manufacturing facility, Ribbon Pharmaceutical and Chemical Products located at Via San Leonardo 23, Villadose, Rovigo, Italy, investigators from the Food and Drug Administration (FDA) 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 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 December 31, 2009, 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 appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)].

   For example, the process simulations (media fill) do not represent actual production operations for your sterile API. The process simulation performed by your firm in July 2009 failed to include simulation of the routine interventions performed in a typical campaign of 13 batches.

   Your response indicates that the revised media fill protocols now include the routine interventions in a 13-batch campaign and were performed on January 4, 2010. Your response is inadequate because it does not include the results of the repeated process simulations performed. In your response to this letter, provide the finalized protocol and the summary report for all data generated during the execution of process simulations.

   In addition, the process simulation procedures your firm used to evaluate state of control of sterile API manufacture are inadequate because they do not accurately simulate aseptic manufacturing operations. In addition, the test material and the validation procedures used by your firm compromise the recovery of microbial contaminates. For example:

   a. Placebo mediums should be evaluated for their ability to support growth. Your response states that the placebo used in the process simulation is sodium phosphate in different forms (solution and anhydrous) and sodium chloride solution (l %). The principle of using simulation media is to create conditions representing the greatest possibility of recovering existing contaminants. Your response does not provide scientific evidence and documentation that the placebo medium (solution and anhydrous) used during process simulation adequately supports growth promotion of viable organisms. In your response to this letter, provide the rationale and the supporting study summary report for using each of the placebo growth media (including the medium in its anhydrous state) in your process simulations.

   b. Placebo mediums should be evaluated for their inhibitory effect on microorganisms. Your response does not indicate that your firm uses beta-lactamase to inhibit the effect of antibiotic residue in the production line during process simulation. Media used in process simulation, sterility testing, and environmental monitoring should be evaluated for the use of beta-lactamase to neutralize antibiotics produced at your manufacturing facility. Neutralization of media makes it possible to recover the viable microorganisms that may contaminate the product. Media for environmental monitoring and microbiological testing (including process simulation) should be tested for sterility and growth promotion. You should also assure all media includes antibiotic neutralizing agents. In your response, provide documentation to support that your firm uses beta-lactamase in the media used for the environmental monitoring programs during the process simulations. Provide a copy of the test procedures for beta lactamase in media.

   c. Gases used during process simulation should be evaluated for their inhibitory effect on microorganisms. Your response states that the nitrogen used in the process simulation is removed by the test membrane during filtration. Most contaminants likely to be present in pharmaceutical manufacturing environments metabolize aerobically. The creation of anaerobic conditions in the headspace above the media would decrease the probability of recovering these aerobes. Inert gas used in the process simulations should be replaced with compressed air to create worst case condition. Your response is inadequate because it does not include scientific evidence to ensure that the use of nitrogen during process simulations does not inhibit growth of aerobic organisms.

2. Controls to prevent contamination in defined (critical and support clean) areas are deficient regarding operations related to aseptic processing of product [21 C.F.R. § 211.42(c)(10)].

   For example, there are no dynamic smoke study evaluations to demonstrate that the personnel activities during aseptic filling do not compromise the sterile API. The activities conducted during your documented smoke studies are not representative of actual operations.

   According to your response, smoke studies were to be completed within the first two weeks of January 2010. Your response is inadequate because it does not provide an update on all airflow pattern findings and your evaluation of these study results. An in situ air pattern analysis should be conducted at all critical areas, under dynamic conditions, to demonstrate unidirectional airflow and sweeping action at critical work areas. These studies should evaluate the impact of aseptic manipulations (e.g. interventions) and equipment design, and include documentation for the activities performed with written conclusions. Provide a copy of the smoke study recordings that can be read using Windows Media Player (as an mpeg file, for example) along with supporting documentation. Please also identify the different videos by file name to indicate what is being presented in each file.

3. Your firm does not clean and maintain equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 C.F.R. § 211.67(a)].

   During the inspection, cleaned multi-use hoses used in the production of cephalosporin intermediates had white residue or brown rust-like

residue on the connection surface and the interior of the transfer hose. The presence of rust, deterioration, and debris in product-contact equipment used to manufacture sterile drug products is unacceptable.

We acknowledge the training you provided on your procedure, PRO-SOP-010/02 "General rules of cleaning," and the associated training records. However, your response does not provide the controls implemented to ensure that contaminated hoses are not used in manufacturing. Your response also does not include evidence of corrective actions taken to remove the presence of rust, deterioration, and debris from your product-contact equipment and transfer hoses.

In your response to this letter, provide the production process steps where these hoses are used. Additionally, provide documentation to support that your firm's cleaning procedures are adequate to prevent contamination of your products. Lastly, provide the investigation report with your findings including the cleaning methods performed, as well as the corrective and preventive actions.

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, failure to correct these violations may result in FDA refusing admission of articles manufactured at Ribbon Pharmaceutical and Chemical Products located at Via San Leonardo 23, Villadose, Rovigo, Italy into the United States. 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)].

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 Ceftriaxone Sodium Sterile, Cefuroxime Sodium Sterile, Cefoxitin Sodium Sterile, and Ceftazidime Buffered Sterile, and provide the dates and reasons you ceased production. Please identify your response with FEI #3005479678.

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

U.S. Food and Drug Administration
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International Compliance Branch
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Sincerely,

/s/

Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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