Inspections, Compliance, Enforcement, and Criminal Investigations

Pharmaceutical Company Jelfa SA 7/14/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-016

July 14, 2011

Mr. Marek Wojcikowski
President of the Board
Pharmaceutical Company Jelfa SA
21 Wincentego Pola Str., 58-500
Jelenia Gora, Poland

Dear Mr. Wojcikowski:

During our October 2010 inspection of your pharmaceutical manufacturing facility, Pharmaceutical Company Jelfa SA located at 21 Wincentego Pola Str., 58-500, Jelenia Gora, Poland, 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 November 12, 2010, 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 thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192]. For example,

The inspection documented that **(b)(4)** Injection, batch # **(b)(4)**, failed the sterility test. Your quality control unit repeated the test on a new sample to confirm the original result prior to initiating an investigation. The quality control unit's decision to perform a retest without conclusive assignable laboratory cause is not in accord with USP <71> and is an unacceptable practice.

The retest again revealed non-sterility. Although the lot was eventually rejected, there is no assurance that other lots manufactured and filled in the same production line were not contaminated. The inspection found that the results were valid and that no laboratory error was identified. However, no investigation of the manufacturing process and facility controls was performed to identify the root cause of the sterility failure. This information from the failure investigation also helps determine how many additional other batches may be affected.

Please note that when microbial growth is observed, a lot should be considered nonsterile and an investigation conducted. An initial positive test would be invalid only in an instance in which microbial growth can be unequivocally ascribed to laboratory error. Only if conclusive and documented evidence clearly shows that the contamination occurred as part of testing should a new test be performed. When available evidence is inconclusive, batches should be rejected as not conforming to sterility requirements. After considering all relevant factors concerning the manufacture of the product and testing of the samples, the comprehensive written investigation should include specific conclusions and identify corrective actions.

Please include in the response to this letter a copy of your final sterility failure investigation report for **(b)(4)** Injection, batch # **(b)(4)**. Your response should include a detailed explanation of your root cause analysis and the corrective actions implemented to prevent recurrence of the event(s) that lead to the contamination of the lot. Your firm should also indicate if a media fill was conducted as part of your sterility failure evaluation. If so, provide a copy of the media fill protocol and report as part of your response to this letter. Also include a list of all lots of sterile drug products manufactured at your facility that initially failed the sterility test, and that were released based on a passing re-sample or re-test result. Provide the product name, original test and re-test date, microorganism isolated and product destination.

We noted during our review that SOP No. JZ-V/JV-051: "Proceeding in case of unexpected result obtainment" references the FDA Guidance for Industry: Investigating Out-of-Specification Test Results for Pharmaceutical Production. Please note that the scope of this guidance is intended for chemistry-based laboratory testing of drugs regulated by CDER, and not for microbiological testing investigations. For information on sterility testing, see Section XI of the *FDA's Guidance on Sterile Drug Products Produced by Aseptic Processing.*

Your response includes procedural corrections and training of your analyst. Please describe in your response to this letter the specific training offered and corrections made.

2. 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,

a. During the aseptic filling of two injection batches on filling line **(b)(4)**, where **(b)(4)** injection for the U.S. is filled, employees were observed following poor aseptic techniques. Specifically, movements inside the class A area were not slow and deliberate; operators and an engineer were observed with exposed facial skin during the filling operation; and a forcep was observed in a class B (ISO 6) area and was then used to remove fallen ampoules from the aseptic processing line in the class A (ISO 5) area.

b. Employees who perform critical duties in your aseptic filling line **(b)(4)** did not participate in an **(b)(4)** line qualification (process simulation) during 2010, 2009, and 2008.

c. The tubing ends used to connect the solution tanks to the filling line **(b)(4)** are not protected prior to sterilization to reduce the potential of contamination after sterilization, and prior to the aseptic connection.

d. The disinfectant efficacy studies have not been completed for three of the **(b)(4)** disinfectants used to sanitize surfaces in the sterility testing suite and production aseptic core filling line **(b)(4)**.

Your response indicates corrective action through training employees, equipment purchase, and procedural improvements. However, your response fails to specifically address the observed deficiencies and whether the products already distributed have been evaluated.

3. The quality control unit does not adequately exercise its responsibilities to approve procedures or specifications that may impact the identity, strength, quality, and purity of the drug product [21 C.F.R. § 211.22(c)]. For example,

There was inadequate oversight of the media fill process conducted for batch #**(b)(4)**. Furthermore, the "responsibility" section of procedure JZ-V/JK-053, Validation of Aseptic Manufacturing and Filling Process Using the PST (media fill), makes no mention of the quality control unit having an active role in the oversight of media fill studies.

Your response indicates that procedural corrections will be implemented. Please provide more information in your response regarding how the quality control unit's role has evolved including describing its function relating to observation and approval of media fills (e.g., recent March 2011 media fills).

We note that the CGMP violations listed in this letter include similar violations to those cited in the previous inspection in February 2008, and in our letter to you dated July 17, 2008. For example, 1) unqualified operators involved in aseptic filling operations (no media fill participation), 2) inadequate environmental monitoring practices, 3) failure to adequately conduct disinfectant efficacy studies, and 4) inadequate quality control unit oversight.

We remind you that it is your responsibility to implement sustainable corrective actions to ensure that you firm's drug manufacturing operations are in compliance with the applicable requirements, including the CGMP regulations. FDA expects Pharmaceutical Company Jelfa SA to undertake a comprehensive assessment of the manufacturing operations to ensure that drug products conform to FDA requirements.

We are particularly concerned with your firm's failure to implement a robust Quality System. Repeat citations from prior inspections indicate that your quality control unit is not exercising its responsibilities, and may not have the appropriate authority to carry out its responsibilities. Due to continuing CGMP issues at your firm, we recommend you engage a third party consultant having appropriate CGMP expertise to assess your firm's facility, procedures, processes, and systems to ensure that your drug products consistently meet standards for identity, strength, quality, and purity.

In addition to the items listed above, this inspection identified other worrisome deficiencies. These deficiencies include, but are not limited, to: inadequate vendor qualification of your API suppliers and inadequate smoke study results for aseptic filling line **(b)(4)**.

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 Pharmaceutical Company Jelfa SA, 21 Wincentego Pola Str., 58-500, Jelenia Gora, Poland 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. Please identify your response with FEI #3004680543.

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

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Sincerely,
/S/
Steven Lynn
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