U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Laboratorios L.O., Oftalmi, C.A. 5/12/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-10-004

May 12, 2010

Mr. Jose Ruscica, Plant Director
Laboratorios L.O., Oftalmi, C.A.
Calle 6, Centro Empresarial RS
Zona Industrial de La Urbina
Caracas 1061 – A
Venezuela

Dear Mr. Ruscica:

During our February 22 – 26 and March 1 – 2, 2010 inspection of your pharmaceutical manufacturing facility, Laboratorios L.O., Oftalmi, C.A. located at Calle 6, Centro Empresarial RS, Zona Industrial de La Urbina, Caracas 1061-A, Venezuela, 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.

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 [21 C.F.R. § 211.113(b)]. For example,

a. Your media fill studies suggest that your manufacturing process is not under control. The presence of contaminated units found in four of the six media fills conducted during 2008 and 2009 is an indication of serious breaches to assure sterility of the ophthalmic drug products manufactured at your facility. Your failure to document the evaluation of media fill units after 14 days of incubation, and to identify the organisms in contaminated media fill units, is also unacceptable. Adequate records of media fill unit examinations and identification of the contaminating microbes are essential to any investigation into the origin of the media fill failures.

b. Operators involved in the filling operations for the sterile ophthalmic drug products manufactured at your facility do not practice adequate aseptic techniques to prevent product contamination. Deficient practices include, but are not limited, to: operators that directly contacted sterile bottles with their gloved hands during filling operations, improper movements and actions, and operators who reach over sterilized open bottles and (b)(4) on the filling line. These practices are unacceptable. We expect that operators who conduct operations within aseptic processing areas be properly trained and monitored to ensure that proper aseptic techniques are utilized during all operations, especially filling operations.

c. Your environmental monitoring program does not give assurance that environmental contaminants are reliably detected. Your deficient procedures and practices include, but are not limited, to: failure to collect active (viable) air samples during filling operations, failure to collect non-viable particulate samples during filling operations, collecting non-viable particulate samples near the HEPA-filter unit, and inadequate sampling frequency for other classified areas.

An adequate environmental monitoring program needs to be established by your firm. It should capture meaningful data and act as an early warning system to detect possible environmental contaminants that may impact the sterility of the ophthalmic drug products manufactured at your facility that purport to be sterile.

2. Your firm does not thoroughly investigate 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, you do not conduct adequate evaluation of out-of-specification (OOS) test results during investigations. Specifically, your practice of invalidating initial OOS results without justification is unacceptable. Under CGMP, your firm must perform an adequate investigation into the OOS results. The investigation should include an appropriate evaluation of events associated with the laboratory analysis that scientifically supports any determination that the OOS result is caused by laboratory error. Strong evidence and science-based justification is necessary for your quality unit to permit invalidation of an initial OOS result.

3. Your firm has not established separate or defined areas or such other control systems as necessary to prevent contamination or mix-ups during aseptic processing. [21 C.F.R. § 211.42(c)]. For example,

a) Your firm lacked an adequate assessment of the cross-contamination risks posed by the manufacture of several potentially hazardous compounds (e.g., beta lactam antibiotic and steroid products) at your facility. Deficiencies were observed in the shared manufacturing areas where you manufacture potentially hazardous compounds and sterile ophthalmic drug products intended for the U.S. market. You should ensure that a

documented justification and a well-designed contamination prevention strategy has been put in place to minimize the possibility of contamination. FDA encourages sound risk assessment approaches to address hazard identification, exposure consequences, and implement controls designed to prevent and detect cross-contamination. To achieve an acceptable level of risk requires sound and risk-based assurance that one drug does not contaminate another drug.

b) There was no documentary evidence of in-situ air pattern analysis (e.g., smoke studies) conducted at critical areas to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. Please note that proper design and control prevents turbulence and stagnant air in the critical area. It is crucial that airflow patterns be evaluated for turbulence that can act as a channel for air contamination. The studies should be well documented with written conclusions, and evaluate impact of aseptic manipulations (e.g., interventions) and equipment design.

c) You do not have a procedure or documentation for monitoring differential pressure within the aseptic processing areas.

It is vital for rooms of higher air cleanliness to have an appropriate and substantial pressure differential relative to adjacent rooms of lower air cleanliness. Pressure differentials between cleanrooms should be monitored continuously throughout each shift and frequently recorded. All alarms should be documented and deviations from established limits should be investigated.

In addition to the items listed above, the results of this inspection include other deficiencies that increase our serious concerns regarding the quality of the sterile ophthalmic drug products manufactured at your facility. These deficiencies include, but are not limited, to: inadequate procedures for deviation investigations, lack of an ongoing stability program, and failure to validate **(b)(4)** procedures and **(b)(4)** cycles intended to sterilize equipment and utensils used in the aseptic processing operations.

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, FDA will be refusing admission of articles manufactured at Laboratorios L.O., Oftalmi, C.A., Calle 6, Centro Empresarial RS, Zona Industrial de La Urbina, Caracas, Venezuela 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 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 # 3003571292.

If you have questions or concerns regarding this letter, contact Douglas Campbell, 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,
/Richard L. Friedman/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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