U.S. Department of Health & Human Services

U.S. Food and Drug Administration

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Inspections, Compliance, Enforcement, and Criminal Investigations

McGuff Pharmaceuticals Inc. 12/28/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Los Angeles District
Compliance Branch
19701 Fairchild
Irvine, CA 92612-2506

Telephone: 949-608-4426
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Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 19-11

December 28, 2010

Ronald M. McGuff
President and CEO
McGuff Pharmaceuticals Inc.
2921 W Macarthur Blvd Ste 142
Santa Ana, CA 92704-7944

Dear Mr. McGuff:

During our May 18 to June 2, 2010 inspection of your pharmaceutical manufacturing facility, McGuff Pharmaceuticals, Inc., located at 2921 W Macarthur Blvd Ste 142, Santa Ana, California, 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 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.

In addition, you distribute unapproved new and misbranded drugs in violation of sections 505(a) and 502(f)(1) [21 U.S.C. §§ 355(a) and 352(f)(1)] of the Act.

We have reviewed your firm's response of June 16, 2010, and note that it lacks sufficient corrective actions.

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

CGMP Violations

1. Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including procedures for validation of all aseptic and sterilization processes [21 C.F.R. § 211.113(b)]. For example:

> a. Your firm has failed to conduct a media fill representative of the different packaging configurations of your drug products for the past two years. Your firm has been using a volume of **(b)(4)** for media fills; however, commercial products are available in **(b)(4)** and **(b)(4)**. In addition, you have not established maximum aseptic fill duration.

In your response, your firm states that you have amended your Standard Operating Procedure (SOP) **(b)(4)** to "bracket" the container sizes by utilizing both the **(b)(4)** and **(b)(4)** volumes. Your response, however, is inadequate because you have not provided a risk assessment that examines the effects of differences between product fill sizes (i.e., fill speed, operating methods, container opening size, mass) to determine if bracketing is appropriate.

> b. Your firm's qualifications of the Getinge Model 4300 autoclave and the Grieve CLE-500 oven are inadequate in that you have not qualified this equipment with representative loads. Your firm's practice is to qualify the equipment using minimum loads as opposed to actual loads during routine operation (e.g., Grieve CLE-500 oven was qualified to depyrogenate glass vials using **(b)(4)** tray when the actual load is a maximum of 60 trays).

In addition, your use of biological indicators and penetration thermocouples in the qualification studies are inadequate. Your firm has not used any penetration thermocouples during the qualification of Getinge Model 4300 since February **(b)(4)**, nor have you incorporated the use of biological indicators. During the maximum load configuration study, your firm only used a **(b)(4)** penetration thermocouple and failed to use any biological indicators.

In your response, your firm commits to evaluate the adequacy of your current procedure, to qualify your minimum and maximum load on each of your manufacturing operations, and to include penetration thermocouples and biological indicators in appropriate areas and in appropriate quantities. However, your response is inadequate because you did not explain how you will determine the appropriate locations and quantities for the thermocouples and the biological indicators. Since your firm is currently manufacturing sterile drug products using unqualified equipment, your response fails to include any additional controls to assure the quality of your drug products while you are evaluating your current procedures.

2. Your firm has not conducted at least one specific identity test and has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals [21 C.F.R. § 211.84(d)(2)].

For example, your firm accepts and relies upon the Certificate of Analysis (COA) from your active pharmaceutical ingredient (API) suppliers without conducting appropriate validation of the supplier's test results. This is of heightened concern since you have not established endotoxin specifications, nor have you performed endotoxin testing on APIs intended to be used in the manufacture of sterile drugs.

In your response, your firm commits to test any APIs with amended specifications in an attempt to correct this deficiency. However, your response fails to explain which specifications are to be amended or which APIs are to be tested. In addition, you do not describe corrective actions regarding products currently in the market manufactured with APIs of questionable quality.

Please note that adequate qualification of suppliers is critical in assuring that your sterile drug products are of the quality intended.

3. 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, your firm failed to conduct adequate investigations into action level excursions. Your investigations (e.g., **(b)(4)**) of growth in a media fill did not include a review of the batch records, equipment logs, or HVAC system by the most responsible personnel (e.g., a microbiologist reviewed a batch record). Further, the Quality Assurance Unit did not review and approve the investigation. Finally, your firm failed to implement the corrective/preventative action identified in the investigation.

In your response, your firm states that: 1) your SOP will be revised to require a formal investigation by the Quality Assurance Unit when environmental monitoring action levels are exceeded and 2) retrospective investigations into previous excursions were conducted. You also commit to re-investigate **(b)(4)** and that any impact on aseptic operations will be assessed by the Quality Assurance Unit. Your response, however, is inadequate because you have not described how you will assess the potential impact on products that have already been distributed.

Unapproved New Drug and Misbranding Violations

In addition to violating CGMPs, you manufacture and market unapproved new drugs in violation of sections 505(a) and 502(f)(1) [21 U.S.C. §§ 355 (a) and 352(f)(1)] of the Act. Based on the information your firm submitted to FDA's Drug Registration and Listing System and the information collected during the inspection of your facility, you manufacture the following prescription drugs, including, but not limited to:

- Ascor L 500, Ascorbic Acid Injection, USP, 500 mg/mL in 50 mL vial (McGuff Pharmaceuticals)
- Ascorbic Acid Injection, USP, 500 mg/mL in a 50 mL vial (**(b)(6)**)
- Ascor L NC, Ascorbic Acid Injection, USP, Non-Corn Source (500 mg/mL in 50 mL vial) (McGuff Pharmaceuticals)
- Magnesium Chloride Injection, 200 mg/mL, in 50 mL Multi-Dose vial (McGuff Pharmaceuticals)
- Magnesium Chloride Injection, 200 mg/mL, in 50 mL Multi-Dose vial (**(b)(6)**)
- Vitamin B-Complex 100 Injection, 30 mL Multi-Dose vial (McGuff Pharmaceuticals)

These products are drugs within the meaning of section 201(g) of the Act, [21 U.S.C. § 321(g)] because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. Further, they are "new drugs" within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for their labeled uses. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)] a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the drug. Based on our information, you do not have any FDA-approved applications on file for these drug products. The marketing of these products, or other applicable products, without an approved application constitutes a violation of these provisions of the Act.

Additionally, because the above products are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for them so that a layman can use this product safely for its intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses, causing it to be misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)] Because your products lack required approved applications, they are not exempt under 21 C.F.R. § 201.115 from the requirements of section 502(f)(1) of the Act. The introduction or delivery for introduction into interstate commerce of these products therefore violates sections 301(a) of the Act [21 U.S.C § 331(a)].

You should discontinue manufacturing and distributing all of your unapproved drugs at all facilities immediately. For questions about the regulatory status of your drugs, contact Kathleen Joyce, at 301-796-3329. For assistance in communicating with the FDA concerning the application process for your unapproved drug(s), contact FDA's unapproved drugs coordinator, Dr. Sally Loewke, at 301-796-0710.
To ensure that all drugs marketed in the U.S., prescription and over-the-counter, have been shown to be safe and effective, FDA published a Compliance Policy Guide (CPG) Section 440.100, Marketed Unapproved Drugs, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf[1]. FDA expects manufacturers of products requiring approval to submit applications to the agency showing that their products are safe and effective. The CPG describes the very strict criteria under which the Act permits drugs to be marketed without approval. The CPG also outlines the Agency's enforcement policies aimed at efficiently and rationally bringing all drugs requiring approved applications into the approval process.

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. It is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

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. For discontinued products, you must update the Drug Listing files in accordance with 21 C.F.R. § 207.30(a)(2).

Your reply should be sent to the following address: Food and Drug Administration, Attention: Blake Bevill, Director Compliance Branch, 19701 Fairchild, Irvine, California 92612-2445.

Sincerely,
/S/
Alonza E. Cruse
District Director

Links on this page:

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf