U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Uriel Pharmacy, Inc 8/18/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Minneapolis District Office
Central Region
250 Marquette Avenue, Suite 600
Minneapolis, MN 55401
Telephone: (612) 334-4100
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August 18, 2011

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Refer to MIN 11 – 47

Mark S. McKibben
President
Uriel Pharmacy, Inc.
N8464 Sterman Road
East Troy, Wisconsin 53120

Dear Mr. McKibben:

During our October 18 to November 1, 2010, inspection of your pharmaceutical manufacturing facility, Uriel Pharmacy, Inc., located at N8464 Sterman Road, East Troy, Wisconsin, 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 (21 CFR 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.

In addition, FDA reviewed your firm's labeling and marketing information found on your website at the internet address http://urielpharmacy.com [1]. Based on our review of your labeling and website, you market drugs that are misbranded in violation of sections 502 and 301 of the Act, 21 U.S.C. §§ 352 and 331.

We have reviewed your firm's response received November 23, 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, 21 CFR 211.113(b). For example:

   a. Your firm has failed to validate your **(b)(4)** cycles to demonstrate their effectiveness at rendering your products sterile. Your firm also does not document the parameters (e.g., time, temperature and pressure) used to sterilize your products (i.e., 10ml vials and eye drops).

   b. Your firm uses distilled water that does not meet the specifications of water for injection (WFI), USP, to manufacture sterile injectables and sterile eye drops.

   c. Your firm has failed to validate the use of a **(b)(4)** sterilizing filter with your products and processes, and does not conduct integrity testing. Your firm uses a sterilizing filter that is labeled only for laboratory use by the filter manufacturer in the manufacture of your sterile drug products.

In your response, your firm states that you: (1) will modify batch record sheets to document the completion of keys steps in the manufacturing process; (2) have now validated your **(b)(4)** cycles; (3) will use a sterilizing filter validated for human use by the filter manufacturer; and (4) will use only sterile WFI to manufacture ampules and eye drop products. Your response, however, is inadequate because your firm has not addressed the necessary training to ensure that operators complete pertinent documentation. Further, your firm has not provided any documentation (e.g., a protocol and report) to demonstrate your **(b)(4)** cycles are validated. In addition, you have not explained the adequacy of the parameters previously used to **(b)(4)** your sterile drug products or a scientific justification for allowing these lots to remain on the market.

Your response is also inadequate because you have not clarified whether your new sterilizing filter is intended for pharmaceutical use or how and when you will validate its use with your products and processes to ensure filter capability. In addition, you have not stated whether you will use sterile WFI to manufacture your sterile 10ml vials and your justification for allowing sterile drug products manufactured using distilled water to remain on the market.

2. Your firm has failed to sterilize drug product containers and closures to remove pyrogenic properties and to assure that they are suitable for their intended use, 21 CFR 211.94(c).

For example, your firm has failed to validate the depyrogenation process (i.e., heating to 350°F in a convection oven) to demonstrate that any glassware used in the manufacture of your sterile injectables are rendered non-pyrogenic.

In your response, your firm states that you use pyrogen-free containers and closures, and that your Standard Operating Procedure (SOP) S2.171 follows the United States Pharmacopeia (USP) recommendation to use **(b)(4)** to demonstrate pyrogen-free containers and closures. Your response further states containers and closures will be depyrogenated according to SOP S2.170. At this time, we cannot determine the adequacy of your response because your response is unclear. Please clarify whether you are purchasing pyrogen-free materials and/or depyrogenating materials in-house. Also, please provide details regarding the depyrogenation cycles and other controls utilized to prevent contribution of endotoxin load.

3. Your firm has not established written procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product, 21 CFR 211.110(a). For example:

   a. Your firm has failed to have adequate control procedures that describe the in-process controls, tests, or examinations to be conducted in ensuring the ampule **(b)(4)** is operating properly. As a result of **(b)(4)**, particulates (believed to be glass) were discovered in your 1 ml ampule products causing your firm to initiate a recall of 52 lots in October 2010.

In your response, your firm states that at the time of inspection you provided a new SOP that outlines the proper operating procedures for the **(b)(4)** and staff training. In addition, your firm states that you currently conduct **(b)(4)** inspection of ampules, but you will establish acceptable quality limits as a result of our concerns. Further, your **(b)(4)** inspection will now incorporate **(b)(4)**. Your response, however, is inadequate because it is not apparent what routine in-process examinations or tests your operators will conduct to ensure that the ampules are filled and closed properly. In addition, your response does not clearly describe, in

sufficient detail (e.g., procedures, etc.) whether you intend to conduct **(b)(4)** inspection.

Please note that the document that was provided to our investigators entitled "Ampule filling and closing machine" appears to be an operating manual as opposed to a standard operating procedure that can be easily followed by your operators.

b. Your firm has failed to have control procedures that describe the in-process controls, tests, or examinations to be conducted in ensuring your mixing processes are adequate. At the time of inspection, your firm stated **(b)(4)** in your manufacturing process.

In your response, your firm states SOP S2.120 entitled "**(b)(4)** " is being reviewed and updated and will be available to production operators for mixing. In addition, your firm will modify batch record sheets to clearly delineate the completion of key steps in the manufacturing process. Your response, however, is inadequate because you have not provided a copy of your revised batch record sheet (i.e., sterile product checklist) documenting all in-process controls and significant steps, including samples tested, **(b)(4)** inspection results in the manufacture of your drug products.

4. Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity, 21 CFR 211.160(b).

For example, your firm does not have documentation to demonstrate that your in-house method, **(b)(4)** is appropriate for testing the sterility of your drug products for release. In addition, your firm has not provided documentation (e.g., a written procedure with the sample preparation and plan) to demonstrate that the confirmatory sterility testing conducted by your contract testing laboratory is appropriate.

In your response, your firm states no further ampules will be released before sterility test results are completed. Further, your SOP S2.020 entitled "Final Product Check" will be revised to require adequate USP third party testing for sterility prior to release. In addition, your Quality Assurance (QA) Director will now review all batch records to ensure that final specifications are met. Your response, however, is inadequate because you have not: (A) identified the sterility method used by your third party laboratory; (B) provided documentation to demonstrate that your third party laboratory's sterility method is validated; and (C) provided assurance that all sterile drug products (not just ampules) will undergo and complete the necessary testing prior to release. In addition, you have not addressed whether your prior sterility test method was adequate, nor have you provided any scientific justification for allowing any of the lots tested using this method to remain on the market.

5. 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 CFR 211.192. For example:

a. Your firm failed to initiate an investigation concerning visible particulates in ampules until October 27, 2010 (after the start of the inspection), even though your firm identified that there was problem with the **(b)(4)** on October 15, 2010.

In your response, your firm states that the inspection delayed the documentation of the event and implementation of the action plan. In addition, your firm was in the process of hiring a QA Director with the responsibility of responding to discovered manufacturing errors. Your response, however, is inadequate because your firm has failed to ensure, as described under 21 CFR 211.25(c), that your firm has an adequate number of qualified personnel to perform daily operations (which includes the initiation of investigations).

In addition, it appears that your firm may have been aware of a problem with the **(b)(4)** prior to October 15, 2010, because at least **(b)(4)** lots manufactured from September 3 to October 11, 2010, were **(b)(4)**. It is unclear as to why these lots were **(b)(4)** , but statements by your Pharmacy Technician during the inspection noted that ampules are **(b)(4)**. Your response is also inadequate because you have not described your retrospective review to ensure thorough investigations have been conducted.

A review of batch production records also determined that lot 100309, Arnica/Rosa 7ml Drops (manufactured March 9, 2010), and lot 100421, Hepar/Magnesium 4X ampules (manufactured April 21, 2010), were **(b)(4)** prior to the installation of your **(b)(4)**. Please provide the rationale for the **(b)(4)** and your findings.

b. Your firm failed to adequately investigate a July 22, 2010, complaint received concerning a bottle of Aquavit Etheric Energizer Liquid (lot 100118) that exploded when opened. The complaint was also not documented in your customer complaint log.

In your response, your firm states that only one bottle from the batch in question had a problem and you will retrain employees to check that closures are sealed tightly prior to labeling. Your response, however, is inadequate because you have failed to provide any details regarding your investigation including your determination that a single bottle from one lot was affected and whether there is need for a second verification of the closure inspection. Also, your response is inadequate because you have not provided any details as to how you determined the observed fermentation in the bottle (as stated on your product return form) was due to an improper seal as opposed to microbiological contamination prior to sealing.

Misbranded Drugs

FDA reviewed your firm's labeling information for products including, but not limited to: "Arnica Rosa," "Stibium 6," "Stannum 5 Cream," "Bryophyllum Argentum," and "Arnica Plumbum Mel." These products are misbranded in violation of sections 502 and 301 of the Act, 21 U.S.C. §§ 352 and 331.

"Arnica Rosa," "Stibium 6," "Stannum 5 Cream," "Bryophyllum Argentum," and "Arnica Plumbum Mel" are all labeled as "Homeopathic" and contain the indication "Use according to standard homeopathic indication." Therefore, the above products are drugs under section 201(g)(1)(B) of the Act, 21 U.S.C. § 321(g)(1)(B), because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man, and under section 201(g)(1)(C) of the Act, 21 U.S.C. § 321(g)(1)(C), because they are intended to affect the structure or any function of the body.

We recognize that these products are identified as homeopathic drugs with active ingredients measured in homeopathic strengths.[1] The definition of "drug" in section 201(g)(1) of the Act, 21 U.S.C. § 321(g)(1), includes articles recognized in the official Homeopathic Pharmacopeia of the United States (HPUS), or any supplement to it. Homeopathic drugs are subject to the same regulatory requirements as other drugs; nothing in the Act exempts homeopathic drugs from any of the requirements related to adulteration, labeling, misbranding, or approval. We acknowledge that many homeopathic drugs are manufactured and distributed without FDA approval under enforcement policies set out in the Agency's Compliance Policy Guide entitled "Conditions Under Which Homeopathic Drugs May be Marketed (CPG 7132.15)" (the CPG). As its title suggests, the CPG identifies specific conditions under which homeopathic drugs may ordinarily be marketed. Thus, in order to fall under the enforcement policies set forth in the CPG, a homeopathic product must meet the conditions set forth in the CPG.

According to the labeling collected by FDA during the inspection, it appears that many of your products including, but not limited to, "Arnica Rosa," "Stibium 6," and "Stannum 5 Cream," are not labeled for any over-the-counter (OTC) indications.[2] In fact, the labeling collected by FDA during the inspection only states: "Use according to standard homeopathic indications." Under section 502(f)(1) of the Act, 21 U.S.C. § 352(f)(1), a drug is misbranded unless its labeling bears adequate directions for use. Under section 201.5 of FDA's regulations (21 CFR 201.5), "adequate directions for use" means directions under which a lay person can use a drug safely and for the purposes for which it is intended. Further, the CPG states that "[t]he labeling for those products offered for OTC retail sale must bear at least one major OTC indication for use, stated in terms likely to be understood by lay persons." If the labeling for an OTC drug product does not contain any OTC indications for use, then a lay person cannot use the drug for the purposes for which it is intended, and it therefore fails to bear adequate directions for use. Accordingly, "Arnica Rosa," "Stibium 6," and "Stannum 5 Cream" are misbranded under section 502(f)(1) of the Act, 21 U.S.C. § 352(f)(1).

In addition, section 502(a) of the Act, 21 U.S.C. § 352(a), states that a drug is misbranded if its label is false and misleading in any particular. The labeling of a drug product may be misleading if it features inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation, 21 CFR 201.10(c)(4). You list "Mel" as an inactive ingredient, but this ingredient is prominently displayed in the "Arnica Plumbum Mel" product name. Similarly, you list "Bryophyllum e fol" as an inactive ingredient, but this ingredient is prominently displayed in the "Bryophyllum Argentum" product name. Including an inactive ingredient in the product name creates the impression of value greater than the functional role of the ingredient. Therefore, your products "Arnica Plumbum Mel" and "Bryophyllum Argentum" are misbranded under section 502(a) of the Act, 21 U.S.C. § 352(a), because their labeling is false and misleading.

Your marketing of these misbranded products violates section 301(a) of the Act, 21 U.S.C. § 331(a).

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.

It is your responsibility, as a drug manufacturer, to assure that drug products manufactured in your facility comply with all CGMP regulations and the Act as to safety, identity, strength, quality, and purity. Based upon the nature of the violations, we recommend that you engage a third party consultant with appropriate CGMP expertise to assist in your efforts to achieve and maintain compliance prior to manufacturing sterile drug products.

Within 15 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 15 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 dates and reasons you ceased production.

Your reply should be sent to Compliance Officer Demetria L. Lueneburg at the address indicated in the letterhead. If you have questions regarding any issues in this letter, please contact Ms. Lueneburg at (612) 758-7210.

Sincerely,

/s/

Gerald J. Berg
Director
Minneapolis District

[1] For example, "Arnica Rosa" includes the ingredient "Argentum nitricum 6X."
[2] According to the CPG, homeopathic drug products offered for retail sale must bear adequate directions for use in conformance with section 502(t) of the Act and 21 CFR 201.5.

Links on this page:

1. http://urielpharmacy.com/