U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Dakota Laboratories, Llc 3/17/11

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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March 17, 2011

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Refer to MIN 11 - 1

Charles L. Voellinger
President and CEO
Dakota Laboratories, LLC
9735 Green Park Industrial Drive
St. Louis, Missouri 63123

Dear Mr. Voellinger:

During our June 22 – 24, 2010, inspection of your pharmaceutical manufacturing facility, Dakota Laboratories, LLC ("Dakota"), located at 1022 North Main Street, Mitchell, South Dakota 57301, an investigator 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 CGMPs.

FDA reviewed your firm's labeling information for products including, but not limited to, "Ring Relief Ear Drop" and "Iwise Pink Eye." Based on our review of the labeling for these products, these products are misbranded under sections 503 and 301 of the Act, 21 U.S.C. §§ 353 and 331.

We have reviewed your firm's response of July 9, 2010, and note that it lacks sufficient corrective actions.

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

CGMP

1. Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile per 21 CFR 211.113(b). For example,

   a. Your firm released several batches of sterile ophthalmic eye drops without adequately validating your aseptic process. According to your raw materia specification sheets and your list of batches manufactured, your aseptically manufactured products are filled into 15mL bottles; however, your process **(b)(4)** bottles which did not represent the products that would be manufactured.

In your response, your firm states that **(b)(4)** were successfully completed by the time the product was shipped to the customer. Your response is inadequate because you have not provided any assurances that your aseptic process was in a state of control during the manufacture of sterile drug products which were subsequently distributed.

   b. Your firm has not established written and approved specifications to assure suitability of each lot of the **(b)(4)** filters used for sterilization.

In your response, your firm provided a draft specification sheet for the **(b)(4)** sterilizing filter. Your response, however, is inadequate because your firm has failed to provide a justification for the specifications (e.g. **(b)(4)**) listed for each filter. In addition, we note that your specification sheet allows for the use of multiple filter manufacturers. The validation of each approved model of sterilizing filter should be assessed and documented.

2. Your firm failed to establish time limits for the completion of each phase of production to assure the quality of the drug product per 21 CFR 211.111. For example,

   a. Your firm has failed to provide a justification for the hold times (i.e., **(b)(4)**) used in current batch records for sterile ophthalmic eye drop products.

In your response, your firm provided a report entitled " **(b)(4)** Study Report" to justify your use of a **(b)(4)** day hold time. This report, however, is inadequat because your study tested lots on Day **(b)(4)** that did not correspond to or match the lots tested on Day **(b)(4)** Your study should compare the same lot for microbial recovery on Day **(b)(4)** to Day **(b)(4)** to determine whether the bulk products originally tested still had levels of bioburden within your validated sterilization ranges.

   b. In addition, your response failed to address the inadequate investigations for those batches where the hold times of the bulk product exceeded your hold time limits.

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, as per 21 CFR 211.192. For example,

   a. You failed to investigate environmental monitoring data recorded in your aseptic processing suite, which failed to meet your established limits.

Your response states that you have revised your environmental monitoring form to allow space for explanation when needed; however, your response is not adequate. You have not investigated the cause of the environmental monitoring results that exceeded the limits on your "Performance Qualification Data HVA(Validation" and "Routine Environmental Monitoring" worksheets, nor have you justified your assessment of the product impact caused by those excursions.

   b. Your firm failed to investigate the failure to sample and test water used in the manufacture of Ortho-K Eye Drops (batch 021008) and Women's Eye Drops (batch 031011).

Your response states that there is no microbial requirement in the USP for purified water as a reason for not testing water for microbial quality. Routine evaluation of the acceptability of the quality of water used in the manufacture of drug products is a fundamental part of good manufacturing practices. In addition, we also note that your procedures require the microbial testing of your purified water. Your response is inadequate because you failed to identify corrective actions to prevent a recurrence.

4. Your firm does not have an adequate system for monitoring environmental conditions in aseptic processing areas, as per 21 CFR 211.42(c)(10)(iv)]. For example,

a. Your firm does not have written procedures for environmental monitoring during aseptic processing, including sampling frequency, sampling locations, or procedures for alert and action levels.

In your response, you state that you have revised your environmental monitoring form to include a place for explanations and that you are developing an environmental monitoring procedure. You also state that your acceptance criteria currently listed on your worksheets is your action limit. You are required to ensure all sampling locations, sampling frequency, and alert and action levels are justified by a scientific rationale. We request you provide your alert levels. If these levels have not already been established, provide the timeframe within which they will be established.

Misbranding [§§ 503(b)(4) and 301(a)]

According to their labeling, the above listed products are intended to cure, mitigate, treat, or prevent diseases, or to affect the structure or function of the body. Your product labeling documents the intended uses of your products including, but not limited to the following:

Ring Relief Ear Drop: "Ringing, Buzzing, Noises in Ears ** Pain and Discomfort ** Tinnitus."

Iwise Pink Eye: "Intended for inflamed, red eyes and eyelids."

Based on the above labeling and claims, these 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.

Section 503(b)(1) of the Act, 21 U.S.C. § 353(b)(1), identifies criteria for determining the prescription status of a product. The products listed above are prescription drugs within the meaning of section 503(b)(1) of the Act because they are intended to treat diseases that require diagnosis and treatment by a physician or are intended to provide treatment for symptoms usually caused by an underlying disease process that requires diagnosis and treatment by a physician. Because they may be dispensed only by prescription of a licensed practitioner, these products are misbranded under section 503(b)(4) of the Act, 21 U.S.C. § 353(b)(4), in that their labels fail to bear the symbol "Rx only."[1] Your marketing of these misbranded products violates sections 301(a) and (k) of the Act, 21 U.S.C. §§ 331(a) and (k).

We recognize that these products are labeled as homeopathic drugs with active ingredients measured in homeopathic strengths. 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. One of those conditions is compliance with section 503(b) of the Act. Under the CPG, only homeopathic products intended solely for self-limiting disease conditions amenable to self-diagnosis (of symptoms) and treatment may be marketed OTC. Homeopathic products offered for conditions not amenable to OTC use must be marketed as prescription products. [2]

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.

Based upon the nature of the CGMP violations identified at your firm, we recommend you engage a third party consultant having the appropriate CGMP expertise to assess your firm's facility design, procedures, processes, and systems, including your aseptic processing capabilities, to ensure that your sterile drug products have their appropriate identity, strength, quality, and purity.

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.

Your reply should be sent to Compliance Officer Demetria Lueneburg at the following address: Food and Drug Administration, 250 Marquette Avenue, Suite 600, Minneapolis, MN 55401.

If you have any questions concerning this letter, you may contact Ms. Lueneburg at (612) 758-7210.

Sincerely,

/s/

Gerald J. Berg
Director
Minneapolis District

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[1]The Agency's guidance, "Conditions Under Which Homeopathic Drugs May be Marketed (CPG 7132.15)," states that, in accordance with § 503(b)(1) of the Act, homeopathic drug products offered for conditions that require diagnosis or treatment by a licensed practitioner must bear the prescription legend "Caution: Federal law prohibits dispensing without prescription." This guidance was issued by the agency in 1988. In 1997, Congress enacted the Food and Drug Administration Modernization Act (FDAMA); section 126 of FDAMA amended § 503(b)(4) of the Act to require that the label of a prescription drug must bear the symbol "Rx only."

[2] We note that the CPG also states that if the HPUS specifies a distinction between nonprescription (OTC) and prescription status of a product based on strength (e.g., 30X), and that distinction is more restrictive than section 503(b) of the Act, the more stringent criteria (i.e., the HPUS criteria) will apply. It follows from this that if the HPUS specifies a distinction between OTC and prescription status based on strength, and that distinction is less restrictive than section 503(b) of the Act, the section 503(b) criteria will apply regardless of the HPUS distinction.

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