



March 31, 2004

HAND DELIVERED

WARNING LETTER

Ref. KAN 2004-06

Mr. E. Thomas Corcoran, President
Fort Dodge Animal Health, a Division of Wyeth, Inc.
9401 Indian Creek Parkway, Suite 1500
Overland Park, KS 66210

Dear Mr. Corcoran:

On December 1-12, 2003 Food and Drug Administration (FDA) Investigators performed an inspection of your veterinary pharmaceutical manufacturing operation known as Fort Dodge Laboratories, Inc., located at 800 5th Street, N.W., Fort Dodge, Iowa 50501. This inspection revealed serious deviations from the current Good Manufacturing Practice (cGMP) regulations, Title 21, Code of Federal Regulations, Parts 210 and 211 (21 CFR 210 and 211). These deviations 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). Section 501(a)(2)(B) of the Act requires that the methods used in, or the facilities or controls used for, the manufacture, processing, packing, and holding of drugs conform with cGMP to assure that such drugs meet the requirements of the Act as to safety, and have the identity and strength, and meet the quality and purity characteristics, which they purport or are represented to possess.

Deviations observed during the establishment inspection include, but are not limited to the following:

1. The Quality Assurance Auditing Staff failed to fully follow established Standard Operating Procedure (SOP) 81-003-14 with regard to the auditing of personnel working in the aseptic core. The audits performed have not identified deficiencies in the systems designed to prevent microbial contamination of drug products purported to be sterile. [21 CFR 211.22(d)]
2. Employees working in the sterile manufacturing area and sterility suite lack appropriate training in aseptic techniques and aseptic conduct. In addition, these employees have failed to follow established SOPs designed to prevent microbiological contamination of drug products purported to be sterile as evidenced by FDA's numerous inspectional observations. The inspectional observations include an employee entering the Class [REDACTED] filling suite with exposed skin between the hood and mask. This same employee was observed to be wearing safety glasses when the Gowning Procedures for the Parenteral

Sterile Filling Area SOP 14-011-12 specifically states in bold letters that safety goggles are to be worn. Forceps used to remove fallen vials were brought out of the Class [REDACTED] room area into the Class [REDACTED] area and back into the Class [REDACTED] area. Employees in the aseptic filling room exhibited inappropriate aseptic conduct as evidenced by the observation of rapid movement throughout the Class [REDACTED] filling room. An operator was observed to reach over uncovered vials being loaded onto the turntable while he was removing vials that had fallen over. The plastic curtains that surround the Class [REDACTED] area, which are intended to protect the product from contamination, were displaced leaving gaps which could affect air flow in the Class [REDACTED] area. An operator in the sterile filling suite was observed spraying her fingertips with isopropyl alcohol before collecting personnel environmental monitoring samples from her fingertips. The above-referenced observations reveal significant problems in the training of the employees who perform activities in the sterile core. [21 CFR 211.25(a), 21 CFR 211.28(a), and 21 CFR 211.113(b)]

3. The environmental monitoring systems in the small volume parenteral manufacturing and filling areas are deficient in that your firm has not performed a scientific assessment to identify appropriate environmental monitoring sampling sites during the actual manufacturing and sterile filling operations that could pose the most microbiological risk to the products manufactured. Inspectional observations include failure to perform air sampling in the area near the vial turntable to assess the condition of the air during manual loading of vials. Environmental monitoring of personnel was not performed immediately after a significant intervention into the Class [REDACTED] area. Equipment such as forceps, carts, and tools used during the filling operation are not routinely monitored. Isopropyl alcohol was observed being sprayed directly over the [REDACTED] air samplers located in the Class [REDACTED] area during the media fill. This occurred after intervention through the plastic curtains that surround the Class [REDACTED] area and after Rodac sampling of the plastic curtains was performed. Environmental monitoring for viable organisms in the manufacturing area is done in the center of the room at times when there is no activity in the room. [21 CFR 211.113(b)]

4. No evaluation has been performed to show the adequacy and efficacy of the cleaning and disinfection process used in parenteral filling room [REDACTED] as specified by SOP 14-014-08. [21 CFR 211.42(c)(10)(v)]

5. Investigations of a batch failure or any of its components processed in the aseptic processing area did not extend to other drug products that may have been associated with a specific failure or discrepancy. The heat exchanger used in the Small Volume Parenteral manufacturing rooms [REDACTED] and [REDACTED] was found to be contaminating the water for injection (WFI) with bacteria. The failure investigation did not extend to reviewing the possible impact on other previously manufactured drug products. In addition, the heat exchanger continued to be used to manufacture other parenteral products after the equipment was identified as being contaminated. Furthermore, the filter integrity test procedure outlined

in SOP 14-177-01 does not specify a limit on the number of times a filter can be flushed or rewetted. [21 CFR 211.192 and 21 CFR 211.42(c)(10)(vi)]

6. All established procedures for production and process control for manufacturing of pharmaceuticals are not followed and documented at the time of performance. For example, during the filling procedures for Factrel®, Lot 431334, the [REDACTED] air sampler was not placed in the location designated by SOP 14-017-21. In addition, the Package and Product Integrity Examination established in SOP 14-059-10 specifies that each vial will be visually examined to assure the integrity of the filled and sealed products. During the establishment inspection, one of the analysts assigned to perform the visual inspection was observed to look away from the line on several occasions thus allowing other vials to pass the inspection site. [21 CFR 211.100(b)]

It is our assessment that the deviations listed above and discussed with your firm's senior management are significant and are a reflection of weaknesses in one or more of the systems designed to control the manufacture of veterinary pharmaceuticals purported to be sterile.

The cGMP deviations noted during the December 2003 establishment inspection, where the firm's employees failed to follow Standard Operating Procedures, do not appear to be isolated events. On November 12, 1999, your firm recalled a lot of Synovex Plus (Trenbolone Acetate and Estradiol Acetate) because it was released for distribution despite failing content uniformity testing. On or about April 30, 2002, Fort Dodge Animal Health sent a letter to FDA's Center for Veterinary Medicine's (CVM), Division of Compliance requesting the rework of one lot of Synovex H (Testosterone Propionate, Estradiol Benzoate) because the release assay showed that the product potency was approximately 10% below the labeled claims.

It should also be noted that similar rework requests were made for products manufactured at the Fort Dodge Laboratories, Riverside Drive location. On or about April 15, 2002, Fort Dodge Animal Health sent a letter to CVM's Division of Compliance requesting rework of one lot of Torbutrol Tablets (Butorphanol Tartrate) because the tablets failed average weight testing. The firm had made a similar request during November 1999 to rework a previous lot of Torbutrol Tablets for a similar failure. On or about May 2, 2002, Fort Dodge Animal Health sent a letter to CVM's Division of Compliance requesting rework of one lot of EtoGesic Tablets (Etodolac) due to tablet chipping and cracking. The firm made a similar request for three other lots of EtoGesic Tablets on or about May 30, 2001.

The commonality regarding the above referenced reworks is that the firm's requests stated that personnel training and experience were factors in the product quality as well as failure to follow Standard Operating Procedures.

We reviewed your firm's response to the FDA-483 observations dated January 14, 2004 and signed by Michael Mlodzik, Associate Director, Pharmaceutical Regulatory Affairs. We acknowledge that your firm has made some changes and provided additional training to your Quality Assurance Auditing Staff as well as to the employees that work in the sterile core in response to FDA's inspectional observations. Your firm has revised twenty-two SOPs associated with the sterile core operation, personnel aseptic conduct, environmental monitoring, microbial testing for the water for injection (WFI) system, filter integrity testing, packaging, and product integrity visual examination. Several of the aforementioned SOPs are viewed as critical to achieve cGMP compliance for an aseptic pharmaceutical manufacturing facility. The proposed corrections will be verified during the next establishment inspection.

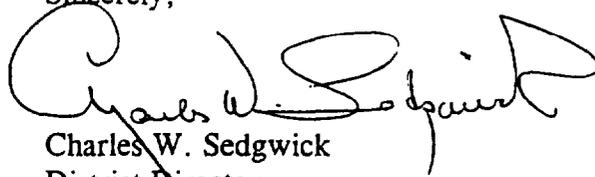
The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Act and its implementing regulations. Deviations from the cGMP regulations were noted on a FDA Form 483 that was issued to and discussed with Dr. Vickie L. Hall, M.S., Ph.D., Vice President of the Iowa Operations and other members of the staff at the Fort Dodge location during a close-out meeting held on the final day of the inspection. A copy of the FDA Form 483 is enclosed for your information.

You should know that these violations might result in FDA taking regulatory action without further notice to you. These actions include, but are not limited to, seizure and/or injunction. Also, other federal agencies are informed about certain Warning Letters issued by FDA so they may consider this information when awarding government contracts.

Please inform this office, in writing, within fifteen (15) working days of receiving this letter of the steps you are taking to correct these deviations. If the corrective actions are going to extend past fifteen days, please include in your response a detailed and specific timeline for the completion of your actions. In addition, please contact the District Office to schedule a meeting regarding your response to this letter. The written response should be delivered at the meeting. At this meeting, it is anticipated that discussion will be held regarding corrective actions taken by your firm, the effectiveness of these actions, and the status of sterile drug products manufactured under the conditions found during the inspection.

You should direct your reply to Ralph J. Gray, Compliance Officer, at the above address.

Sincerely,



Charles W. Sedgwick
District Director
Kansas City District

Enclosure

Cc (Certified - Return Receipt Requested):

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