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Telephone (201) 331-2910

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

December 26, 1996

WARNING LETTER

CERTIFIED MAIL-
RETURN RECEIPT REQUESTED

Mr. Walter Zywottek
President and CEO
EM Industries, Inc.
7 Skyline Drive
Hawthorne, NY 10532

RELEASE

REVIEWED BY JPR 12/27/96
C.O. DATE

Dear Mr. Zywottek:

File No: 97-NWJ-09

During an inspection of your firm located at 480 S. Democrat Rd., Gibbstown, NJ, between September 16 and October 17, 1996, our investigators determined that your firm manufactures Liquid Sodium Bicarbonate-Chloride Concentrate for Hemodialysis, labeled as "non-pyrogenic" and various in-vitro diagnostic reagents. The In-Vitro Diagnostics and Hemodialysis Dialysate are medical devices as defined by section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act).

The above-stated inspection revealed that the IVD devices are adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage or installation are not in conformance with Good Manufacturing Practice (GMP) for Medical Device Regulations, as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as follows:

1. Your firm failed to have stability data for distributed lots of ~~XXXXXX~~ Quick Start Amylase Clinical Chemistry Reagents having a 12 month expiration date. For example, EMS lot numbers #6030, Exp. 2/97; #6160, Exp. 6/97; and #6225, Exp. 8/97.
2. There have been no stability studies conducted since 1993 for the following products: Albumen, Lactate Dehydrogenase (LDH); Creatine Kinase (CK) and Direct Bilirubin. There has been no stability studies conducted since 1994 for Urea Nitrogen (BUN), nor Glucose.
3. Your firm lacks adequate data to support reconstituted storage periods for the Lactate Dehydrogenase, Urea Nitrogen, and Systemate Plus Direct Bilirubin. For example:

- A. The reconstituted stability period for Direct Bilirubin was extended in January 1994 from seven days to thirty days based upon a September 1993 stability test which was conducted on only one bottle of Direct Bilirubin, lot #2260.
 - B. Since September 1993, all finished product release and stability tests have been conducted on Direct Bilirubin, which was reconstituted and held for a maximum period of ten days.
 - C. The reconstituted stability period for Lactate Dehydrogenase (LDH) and Urea Nitrogen (BUN) at 21 days and 28 days, respectively, could not be confirmed. In both instances, your firm could only confirm 10 day reconstitution claims.
4. Failure to conduct stability testing in accordance with written procedure, "Stability Shelf Life Studies," which states that all QC finished product release procedures will be used as the basis for all stability testing. For example: Amylase stability testing did not include pH testing, although pH testing is done for final release testing. Your firm's investigations into consumer complaints, revealed that, "pH is highly correlated with recovery values and that relatively small changes in reagent pH will result in measurable differences in apparent sample activity."
 5. There were no preservative effectiveness studies conducted for Direct Bilirubin, which contains [REDACTED]. Furthermore, there is no microbial testing of in vitro diagnostics upon release nor during stability testing.
 6. Shelf life stability studies consist of testing one lot per year at expiration, only. There is no data to show product stability at 0, 3, 6, 9, 12, 24, and 36 months.
 7. There is no assurance that your deionized water system and components of your water system, used in the manufacture of In Vitro Diagnostics, (IVD's), are capable of providing a device which conforms to applicable specifications. For example:
 - A. Water system sampling is not representative of water drawn for use in production. For example: sampling procedures require a [REDACTED] minute flush prior to collection, yet water drawn for use in production is not flushed.

- B. The bioburden test method for water has not been validated.
 - C. Microbial testing of water did not include the use of positive controls, although positive controls are required by your "Water System Validation Protocol."
8. Your firm has no water system sanitization procedure in place to aid in the removal of biofilm buildup and to eliminate bioburden. For example:
- A. On March 4, 1996, incoming city water contained 0 cfu/ml. After deionization, water samples collected noted bacteria levels as TNTC.
 - B. On October 2, 1996, incoming city water contained 0 cfu/ml. After deionization, water samples collected noted bacteria levels as TNTC.
 - C. A water sample collected on February 20, 1996 containing 116 cfu/ml was speciated and found to contain *Acinetobacter baumannii*, a gram-negative rod. Your firm has failed to sanitize the system, subsequent to these findings.

Furthermore, this inspection revealed that the Hemodialysis Dialysate products manufactured by EM Science are adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage or installation are not in conformance with Good Manufacturing Practice (GMP) for Medical Device Regulations, as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

We recognize that in August 1996, EM Science recalled 41 lots of Liquid Sodium Bicarbonate-Chloride for Hemodialysis, from the market place, due to bioburden and endotoxin levels detected in retain samples.

On November 14, 1996, EM Science informed FDA, New Jersey District, that you would discontinue the manufacture of hemodialysate solutions. EM Science produced four(4) lots (6243, 6248, 6249, and 6254) of Liquid Sodium Bicarbonate-Chloride for Hemodialysis, subsequent to the recall. We understand that these lots, produced just prior to the FDA inspection which found non-conformance with medical device cGMP's, were not distributed and are on hold within your company. It was further discovered during the inspection, through EM Science finished product testing, that lot number 6243 contained various Bacillus organisms and that lot number 6249 contained Salmonella.

The agency is in receipt of your written response, dated October 28, 1996, and November 14, 1996, to the FDA 483 issued to your firm on October 17, 1996. We acknowledge your firm's commitment to further evaluate the deionized water system for use in production of products other than hemodialysate solutions.

We also noted from your response that if your firm decides to manufacture hemodialysate in the future, that FDA New Jersey District would be notified and that those cGMP deviations (FDA 483 items #1-#14) pertaining to the manufacture of hemodialysate would be corrected prior to commencement of dialysate manufacturing. The FDA is also interested in your further disposition of Liquid Sodium Bicarbonate-Chloride for Hemodialysis, lot numbers 6243, 6248, 6249 and 6254.

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 regulations. The specific violations noted in this letter and in the FDA 483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for devices to which the GMP deficiencies are reasonably related will be cleared until the violations have been corrected. Also, no requests for Certificates For Products for Export will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include, but are not limited to seizure, injunction, and/or civil penalties.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the Food and Drug Administration,
New Jersey District Office, 10 Waterview Blvd., 3rd Floor,
Parsippany, New Jersey 07054, Attention: Vincent P. Radice,
Compliance Officer.

Very truly yours,



MATTHEW LEWIS
District Director
New Jersey District Office

VPR:slw