U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Medefil Incorporated

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Chicago District
550 West Jackson Blvd., 15th Floor
Chicago, Illinois 60661
Telephone: 312-353-5863

June 10, 2010

WARNING LETTER

CHI-08-10

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Pradeep Aggarwal
President & CEO
Medefil, Incorporated
250 Windy Point Drive
Glendale Heights, Illinois 60139-3805

Dear Mr. Aggarwal:

During an inspection of your firm located in Glendale Heights, Illinois from December 1, 2009 through February 11, 2010, investigators from the United States Food and Drug Administration (FDA) determined that your firm manufactures Heparin and Normal Saline I.V. Flush Syringes in various fill sizes for human use. Under Section 201 (h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321 (h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or function of the body.

This inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act (21 U.S.C. § 351 (h)), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at Title 21, **Code of Federal Regulations** (C.F.R.), Part 820. We received a response from Pradeep Aggarwal dated March 8, 2010 concerning our investigator's observations noted on the Form FDA 483, Inspectional Observations, that was issued to you. Your firm's response dated March 8, 2010, was received after 15 business days of the inspection and therefore will not be evaluated in accordance to the information contained in 74 FR 40211-40212. These violations include, but are not limited to, the following:

1. Failure to establish and maintain adequate procedures for implementing corrective and preventive action, as required by 21 CFR 820.100(a). For example, your firm's procedures for managing nonconformance investigations and CAPA's do not contain or make reference to document control for investigations that are initially conducted, but are then cancelled. As a result, CAPA 09-014 and **(b)(4)** were deleted without an explanation of the reason they were deleted, or why no investigation or follow-up was necessary.

2. Failure to establish and maintain adequate procedures for identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(3). For example **(b)(4)** showed that during a customer audit, in November 2008, the temperature excursions occurring in your firm's refrigerator #2 were not investigated. The CAPA's preventive action recommended that management replace the refrigerator and the verification/validation was to qualify and monitor the new refrigerator. However, during the FDA inspection, it was noted that the refrigerator had not been replaced. Further, there was no documented evidence of a summary/follow-up on the report.

3. Failure to establish and maintain adequate procedures for implementing corrective and preventive action which shall include requirements for verifying and validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device, as required by 21 CFR 820.100(a)(4). For example,

Section **(b)(4)** of your firm's SOP **(b)(4)** Corrective and Preventative Actions (CAPA), **(b)(4)** states, "the QA Director (or designee) will verify and document that the corrective or preventative action does not adversely affect the process, product or other related systems." However, your firm's procedure does not adequately address the verification or validation requirements that will ensure that the action is effective and does not affect the finished device.

As a result, the following nonconformance reports (NCRs) containing CAPA investigations for **(b)(4)** caused by **(b)(4)** in the **(b)(4)** did not contain verification or validation to ensure the corrective action would not adversely affect the finished device:

a. **(b)(4)** documented **(b)(4)** in the **(b)(4)** due to a **(b)(4)** lock for supplier's lot 10309302. Your firm notified the supplier's **(b)(4)** QA Manager of the issue. The supplier determined a root cause, which mentioned that the **(b)(4)** becoming loose, causing a **(b)(4)**. The supplier also **(b)(4)**

b. **(b)(4)** (discovered on **(b)(4)** documented **(b)(4)** The NCR also referenced NCR's **(b)(4)** for similar defects in **(b)(4)** Your firm notified the supplier and the supplier's response included a root cause, relating to worn parts used to make the **(b)(4)** a corrective action which included replacing or refurbishing the tool, and preventive measures. The supplier also stated that without these actions, they could not guarantee this defect would be caught prior to release from the **(b)(4)** facility. Your firm's corrective action **(b)(4)** on June 30, 2009) was to order a new **(b)(4)** A **(b)(4)** and **(b)(4)** by the supplier was your firm's method of verification/validation. However, there was no documented evidence in the NCR that ensured such action was effective and did not adversely affect the finished device.

c. **(b)(4)** documented **(b)(4)** discovered July 24, 2009, while manufacturing Haparin I.V. Flush Syringes **(b)(4)** The earlier initiated **(b)(4)** was referenced retrospectively and no additional verification or validation of any corrective or preventative actions was performed regarding this issue.

4. Failure to establish and maintain adequate procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 CFR 820.198(a). For example, **(b)(4)** of your firm's Customer Complaint procedure, **(b)(4)** states, "Complaints may arise from any source via...MedWatch...All complaints will be process in a timely manner...a potential complaint...will be given over to the Quality Assurance (QA) Director or designee...All potential complaints will be investigated at a Level I Failure Investigation ..." However, the procedure does not clearly define "timely manner" or specifically state who the designee will be. As a result, there is no documentation of an investigation for the following complaints:

a. A MedWatch report was generated regarding an adverse event **(b)(4)** involving **(b)(4)** of several patients following use of your firm's Normal Saline I.V. Flush syringes. The complaint was reported to your firm's Sales and Marketing VP (VP) by Risk Management at the user facility in April, 2009. Although your firm's VP discussed these issues with the user facility, there is no documentation that an investigation was performed, per your firm's procedure. Further, the "designee" for handling the complaint was not clearly established.

b. A MedWatch report regarding device malunctions **(b)(4)** reported on January 7, 2009 involving **(b)(4)** entering from the **(b)(4)** The hospital tested other Medefil Syringes that resulted in the same problem. The product was removed from use and the facility reported the problem/complaint to Medefil in February 2009. However, there is no documentation that an investigation was performed, per your firm's procedure. Further, the "designee" for handling the complaint was not clearly established.

c. Your firm's complaint **(b)(4)** was related to a complainant's concern regarding your firm's syringe label. Issues mentioned in the complaint included, the potential for injecting the syringe contents without ever **(b)(4)** as well as tbe package insert on-line instructions, which instruct" ...**(b)(4)** present." However, the complamt did not include or reference an investigation into the syringe label obstructin the view of the syringe contents, including any **(b)(4)** or fully address the directions for use. The investigation conclusion only stated that all syringes manufactured by Medefil contain a **(b)(4)**

5. Failure to establish and maintain adequate complaint handling procedures for the prompt review, evaluation, and investigation of any complaint that represents an event which must be reported to FDA under part 803, as required by 2 CFR 820.198(d). For example, customer complaints **(b)(4)** relating to patient adverse events and associated with your firm's marketed device recall of Heparin I.V. Flush Syringes in March 2008 **(b)(4)** of heparin **(b)(4)** were not investigated until August 18, 2009.

6. Failure to establish and maintain adequate procedures to control product that does not conform to specified requirements, as required by 21 CFR 820.90(a). For example, your firm's procedures for managing nonconformance investigations do not contain or make reference to document control for investigations that are initially conducted, but are then cancelled. As a result, **(b)(4)** and **(b)(4)** were deleted without an explanation of the reason they were deleted, or why no investigation or follow-up was necessary.

7. Failure to establish and maintain adequate procedures to adequately control environmental conditions, as required by 21 CFR 820.70(c). For example, **(b)(4)** of your firm's procedure, number **(b)(4)** Personnel Microbial Monitoring, Revision 005 states, "Remove the plates from incubator, and check if there is any growth of microorganisms on the medium...Record the results on the Microbiological Monitoring of Personnel form (Attachment 710-1)." However the tota plate colony count was not completely documented on the Microbiological Monitoring of Personnel form dated December 30, 2009.

8. Failure to establish and maintain adequate procedures to ensure that sampling methods are adequate for their

intended use and to ensure that when changes occur the sampling plans are reviewed as required by 21 CFR 820.250(b) For example, your firm's procedure **(b)(4)** Sampling of Finished Products, Revision **(b)(4)** describes the requirements for collecting samples of the finished product. However, the procedure does not discuss sampling for additional testing to overcome a failure of the finished product, other than to say that an investigation shall be conducted. As a result, the **(b)(4)** which is integrity testing, was used to release lots of prefilled syringes when defects affecting the container closure integrity were found after or during manufacturing. Sampling for **(b)(4)** consisted of **(b)(4)** regardless of the size of the prefilled syringe lot. In some cases this size was as low as **(b)(4)** of the lot. Your firm released the followin lots of I.V. Flush Syringes on the basis of **(b)(4) p**er your firm's, **(b)(4)**

a. **(b)(4)**
b. **(b)(4)**
c. **(b)(4)**

9. Failure to establish and maintain adequate procedures to control all documents, as required by 21 CFR 820.40. For example,

a. Your firm has no procedures for controlling laboratory worksheets including changes to worksheets, issuance oflaboratory worksheets, and reconciliation of laboratory worksheets.

b. The worksheet "Internal Communication - Batch Release Information" by the warehouse, which is used to identifY released product, was created after **(b)(4)** documented release of finished product for Heparin I.V. Flush Syringes and Normal Saline I.V. Flush Syringes prior to obtaining media fill results. This sheet is used to communicate batch release information to warehouse operations. Use ofthis sheet is not documented in any Medefil procedure nor is control over this sheet documented.

c. Training of employees on **(b)(4)** 'Customer Complaints" was performed on March 10, 2009, using an expired version **(b)(4)** of this SOP when revision **(b)(4)** was effective on December 23, 2008. Copies of revision **(b)(4)** should have been removed and archived and should not have been available for training.

Our inspection also revealed that your Heparin I.V. Flush Syringes are misbranded under Section 502(t)(2) of the Act, 21 U.S.C. 352(t)(2), in that your firm failed or refused to furnish material or information respecting the device that is required by or under Section 519 ofthe Act, 21 U.S.C. 360i, and 21 C.F.R. Part 803 - Medical Device Reporting (MDR) regulation. Significant deviations inelude, but are not limited to, the following:

1. Failure to have adequate procedures in place that provide for timely and effective identification, communicatio and evaluation of events that may be subject to MDR requirements, as required by 21 CFR 803.17(a)(1).

a. For example, your firm's **(b)(4)** includes reporting requirements for medical device reporting under 21 CFR Part 803 and adverse experience reporting under 21 CFR Part 600. It does not clarify how your firm will determine when to report a medical device event to the Center for Devices and Radiological Health (CDRH) and a drug event to the Center for Drug Evaluation and Research (COER).

b. For example, the scope of the current MDR procedure is defined "for meeting the legal responsibility under the provisions of the Safe Medical Devices Act of 1990." (SMDA). This definition neglects to mention the regulations implemented since 1990 as part of Food and Drug Administration Modernization Act (FDAMA) of 1997 and Medical Device User Fee and Modernization Act (MDUFMA) of 2002. Thus, your curren procedure does not meet current MDR reporting responsibilities.

2. Failure to have adequate procedures in place that provide for documentation and recordkeeping requirements, as required by 21 CFR 803.17(b).

a. For example, your SOPs **(b)(4)** fail to describe how your finn will comply with the requirements of 21 CFR 803.18 and 21 CFR 803.18 (b)(i) and (ii), (c), and (e), as required by 21 CFR Part 803.17(b).

b. For example, **(b)(4)**" of your firm's SOP **(b)(4)** fails to require retention of MDR files for two years from the date of the event or a period of time equivalent to the expected life of the device, whichever is longer.

c. For example, your firm's SOP **(b)(4)** provides no guidance on:

1) Documentation requirements for deliberations and decision-making processes,
2) Assurance that your MDR files will be prominently identified as MDR reportable events when kept with your complaint files, as indicated in **(b)(4)**

3. Failure to either submit complete information on a report, or alternatively provide a statement explaining why this information was incomplete and the steps you took to obtain the information, as required by 21 CFR 803.50(b)(3).

a. For example, MDR # **(b)(4)** submitted per FDA Form 3500A did not indicate in Block H the type of reportable event and did not include an explanation of why the required information was not provided and the steps taken to obtain such information.

b. For example, MDR # **(b)(4)** submitted per FDA Form 3500A did not include in Block H an explanation of why Block B 1-3 of FDA Form 3500A was not complete and did not include an explanation of why the required information was not provided and the steps taken to obtain such information.

4. Failure to submit an MDR report within 30 days ofreceiving or otherwise becoming aware of information, from any source, that reasonably suggests that a marketed device may have caused or contributed to a death or

serious injury, as required by 21 CFR 803.50(a)(1).

a. For example, your firm failed to report to FDA no later than 30 calendar days after the day that they received or otherwise became aware of information, from any source, that reasonably suggests that a device that you market may have caused or contributed to a serious injury events as reflected in com laint number: **(b)(4)**

b. For example, your firm failed to report to FDA no later than 30 calendar days after the day that you received or otherwise became aware of information, from any source, that reasonably suggests that a device that you market may have caused or contributed to a death event, as reflected in complaint numbers **(b)(4)**.

5. Failure to submit an MDR report within 30 days of receiving or otherwise becoming aware of information, from any source, that reasonably suggests that a marketed device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur, as required by 21 CFR 803.50(a)(2).

For example, your finn failed to report that a device that they market has malfunctioned and this device or a similar device that you market would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur, as reflected in complaint numbers **(b)(4)**

You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Also, 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, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. 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 response should be sent to: Lorelei Jarrell, Compliance Officer, Food and Drug Administration, 550 W. Jackson Blvd., 15th floor, Chicago, IL 60661. If you have any questions about the content of this letter, please contact Ms. Jarrel at 312-596-4216.

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of th inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Sincerely,
/S/
Scott J. MacIntire
District Director

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