



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

April 26, 2007

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail – Return Receipt Requested
And by Facsimile Transmission

CBER -07- 009

Warning Letter

Mr. Michael Dayton
4608 Rue Bordeaux
Lutz, Florida 33558

MedEnclosure, L.L.C.
c/o CPC of America
6336 17th Street Circle East
Sarasota, Florida 34243

Dear Sponsor:

This letter describes the results of Food and Drug Administration (FDA) inspections of and conversations with clinical investigator [REDACTED] and the [REDACTED] Investigational Review Board [REDACTED] as they relate to the MedClose™ Vascular Closure System (VCS). FDA conducted this investigation under the Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational products. A sponsor inspection of MedEnclosure, LLC was unable to be performed as described below.

The MedClose™ VCS is a combination product subject to regulation under the device authorities of the Federal Food, Drug, and Cosmetic Act, including the Investigational Device Exemption (IDE) regulations (21 CFR Part 812). Under the IDE regulations, compliance with all provisions is required because the product is a significant risk device; the product is not eligible for investigation under the abbreviated requirements.

Recognizing that an IDE was required for this investigation, you filed an (IDE) application for the MedClose™ Vascular Closure System identifying MedEnclosure LLC (MedEnclosure) as the sponsor. FDA identified this application as [REDACTED] (when initially filed at the Center for Devices and Radiological Health [CDRH]) and BB-IDE [REDACTED] when transferred to the Center for Biologics Evaluation and Research [CBER]. On 8/17/05 you submitted a Request for Designation related to this product in which you stated "The sponsor believes that the MedClose VCS should be regulated as a Class III medical device."

By letter dated 3/17/06, signed by officials from both CDRH and CBER, FDA approved your IDE, subject to certain conditions. However, instead of proceeding with that study, and without informing FDA, you initiated a study outside of the IDE regulations. You advised [REDACTED] that this was a non-significant risk device not subject to IDE requirements. You stated to [REDACTED]

The MedClose plug-mediated VCD [sic] as an alternative to manual compression does not present a "significant risk" per 21 CFR 821.3(l)(m) [sic- presumably 21 CFR 812.3(m) was intended] because:

1. the MedClose and the FDA licensed biologic (fibrin plug) does not meet the definition of a "implant" as the fibrin plug is totally resorbed within 10-14 days,
2. the MedClose and the delivered fibrin plug are not intended for use in supporting or sustaining human life,
3. the MedClose and the delivered fibrin plug are not used for the purpose of diagnosing, curing, mitigating or treating disease, or preventing impairment of human health,
4. and use of the MedClose is restricted to a low risk population (diagnostic cases only, males only, no coumadin therapy), the MedClose and the FDA licensed biologic (fibrin plug) do not present a potential for serious risk to health, safety, or welfare of a subject.

Apparently relying on these representations, [REDACTED] allowed a study to proceed as a study of a non-significant risk device. [REDACTED] conducted a clinical study entitled *Randomized, Prospective, Multi-Center Trial of the MedClose™ Vascular Closure System*. When FDA learned of this ongoing study, you then withdrew the IDE application you had filed. On 10/26/06, FDA issued a letter to you reminding you that the product is a significant risk device.

We have determined that you violated the IDE regulations governing the proper conduct of clinical studies involving investigational devices, as published in 21 CFR Part 812 (available at <http://www.access.gpo.gov/nara/cfr/index.html>). The applicable provisions of the CFR are cited for each violation listed below.

1. **You failed to provide investigators with the information they need to conduct the investigation properly and failed to ensure that IRB review was obtained. [21 CFR § 812.40].**
 - A. The FDA inspections of [REDACTED] and the [REDACTED] showed that you provided [REDACTED] and the IRB with misleading information regarding the risk assessment of the MedClose™ VCS. By providing [REDACTED] with misleading information, you interfered with [REDACTED] protection of the rights, safety, and welfare of subjects under his care. Because it received misleading information [REDACTED] was unable to conduct appropriate

review of that study. The provision of misleading information interfered with [REDACTED] protection of the rights and welfare of the human subjects.

The "Risk Evaluation" provided to [REDACTED] represented the MedClose™ VCS as a non-significant risk device. The "Risk Evaluation" stated, "the MedClose and the FDA licensed biologic (fibrin plug) do not present a potential for serious risk to health, safety, or welfare of a subject." You failed to state that the proposed use of Tisseel® VH Fibrin Sealant (Tisseel®) in the MedClose™ VCS is not an approved use, and that the product is not a "licensed biologic" for this use.

Tisseel® is indicated for use as an "adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries due to blunt or penetrating trauma to the abdomen, when control of bleeding by conventional surgical techniques, including suture, ligature and cautery, is ineffective or impractical." The labeling for the approved use identifies a number of risks which would be expected to be present when Tisseel® is used investigational with the MedClose™ device. You failed to provide information to [REDACTED] regarding the risks identified in the prescribing information for the "TISSEEL VH [Fibrin Sealant] Two-Component Fibrin Sealant, Vapor Heated, Kit" dated April 2006. The following risks to human subjects were not disclosed in the informed consent form you provided to the clinical investigator and [REDACTED] even though they were identified by the TISSEEL manufacturer:

- "The prescribing information warns **"Do not inject TISSEEL VH [Fibrin Sealant] directly into blood vessels. Intravascular application or injection of TISSEEL VH [Fibrin Sealant] directly into tissues may result in life-threatening, thromboembolytic events and/or allergic/anaphylactoid reactions."** In the event the MedClose™ balloon is not properly deployed, the thrombin component of Tisseel® may be directly introduced into the blood vessels.
- "There have also been rare reports of fatalities following the misadministration of topical thrombin (bovine origin)."
- "There have been rare reports of serious adverse events such as paralysis and other compressive complications possibly related to the use of fibrin sealant in combinations with resorbable hemostatic agents." "Tisseel VH [Fibrin Sealant] is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses that can cause disease. ...Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the

Creutzfeldt-Jakob disease (CJD) agent....The physician should discuss the risks and benefits of this product with the patient."

- "Some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women or immune-compromised individuals. Symptoms of parvovirus B19 infection include fever, drowsiness, chills, and runny nose followed about two weeks later by a rash, and joint pain. Subjects should be encouraged to consult their physician if such symptoms appear."
- B. You failed to disclose to [REDACTED] that you applied to FDA for an IDE, which FDA had conditionally approved, and that you had not disclosed to FDA that you were asking [REDACTED] to conduct a study outside the IDE requirements.

**2. You failed to provide accurate, complete, and current information about aspects of the investigation, when requested by FDA.
[21 CFR § 812.150(b)(10)]**

In letters dated 5/11/06, 8/8/06, and 8/11/06 FDA specifically requested that MedEnclosure provide accurate, complete, and current information pertaining to investigation of the MedClose™ VCS as required under 21 CFR § 812.150(b)(10). MedEnclosure failed to provide the requested information. Additionally a meeting between MedEnclosure and FDA was scheduled for 7/27/06 however, MedEnclosure declined to participate.

We note that you may contend that MedEnclosure did not initiate a clinical trial under the IDE conditionally approved by FDA and that, accordingly, no reports were due to FDA. However, you did sponsor a trial conducted by [REDACTED]. If that trial was not pursuant to the IDE you submitted to FDA, then you failed to submit an IDE to FDA for that trial, as required under 21 USC §§ 331(a),(b),(q)(1)(A), 351(f), 360j(g), 21 CFR § 812.20 and 812.40.

**3. You failed to grant access to permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted, or where records of results from use of devices are kept.)
[21 CFR § 812.145(a)].**

On 10/12/06, FDA Investigator Ernest Clausnitzer went to the address for MedEnclosure LLC listed in the IDE application, 6636 17th Street Circle E, Sarasota, Florida. The building bore a logo for CPC of America, Inc. (CPCA). MedEnclosure, LLC is a subsidiary of CPCA. The door was not answered in response to Investigator Clausnitzer's knock. On 10/13/06 Investigator

Clausnitzer returned to this address and was informed that an individual who is Chairman, President, Chief Executive Officer, Chief Financial Officer, and Secretary of CPCA, maintains an office at this location but resides outside of the state. Investigator Clausnitzer made a telephone call to that individual. The call was answered by an answering machine. Investigator Clausnitzer left a message requesting a return call. The phone call was not returned.

On 10/13/06 Investigator Clausnitzer attempted to visit the address of the sponsor contact listed in the IDE application, Michael P. Dayton, Biomed Research, Inc. The 4608 Rue Bordeaux, Lutz, Florida address was located in a gated community which the investigator could not access. On 10/16/06 Investigator Clausnitzer left a voice message requesting a return phone call from Mr. Dayton. On 10/17/06 Investigator Clausnitzer reached Mr. Dayton who directed him to speak to another representative.

On 10/17/06 Investigator Clausnitzer and his supervisor Virginia Meeks contacted that representative regarding the inspection of the MedClose sponsor. He informed them that MedEnclosure had submitted a letter to FDA on 10/16/06 that would impact the MedClose™ VCS application. That 10/16/06 letter withdrew the IDE application MedEnclosure had filed. Although MedEnclosure withdrew the IDE, 21CFR § 812.140(d) requires that records of the investigation are to be maintained for a period of two years after the date that records are no longer required for purposes of supporting a pre-market approval application. FDA may enter the establishment and inspect the records in accordance with 21 CFR § 812.145 (a) and (b).

To date, you have not permitted FDA access to the sponsor's establishment and/or records pertaining to the MedClose™ Vascular Closure System.

The deviations listed above are not intended to be an all-inclusive list of deficiencies. It is your responsibility as a sponsor to adhere to applicable regulations.

This Warning Letter is issued to you because of the serious nature of the violations described above. Please be advised that failure to implement effective corrective action may result in the initiation of enforcement action(s) without further notice.

We request that you identify the location of the establishment where the MedClose™ Vascular Closure System products are held and where records are maintained, so that FDA employees may inspect and copy records pursuant to 21 CFR § 812.145 (a) and (b) and 21 USC 374.

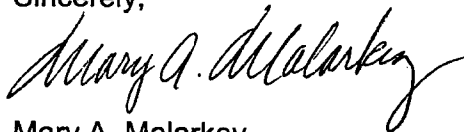
We also request that in accordance with 21 CFR § 812.150(b) you immediately identify any clinical investigators who have conducted or are currently performing clinical studies involving the MedClose™ VCS in the United States and any IRBs that have reviewed those studies.

Please provide your response to this letter, in writing, within fifteen (15) working days. You may send your response to:

Christine J. Drabick
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1448
Telephone: (301) 827-6323

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,



Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Emma R. Singleton
Florida District Director
Food and Drug Administration
555 Winderley Place, Suite 200
Maitland, Florida 32751

