



FEB 1 2005

Via Federal Express

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

WARNING LETTER

Veronica Jordan, Ph.D.
President and CEO
Medelle Corporation
29 Sawyer Road
Waltham, Massachusetts 02453

Dear Dr. Jordan:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a recent Food and Drug Administration (FDA) inspection at your firm. This letter also requests that prompt corrective actions are implemented in response to the violations cited. The inspection took place during the period from June 16 through July 1, 2004, and was conducted by Mr. Gary J. Hagan and Mr. Paul P. Geraci, investigators with FDA's New England District Office. Ms. Barbara A. Crowl, a Consumer Safety Officer with FDA's Center for Devices and Radiological Health, participated in the first week of the inspection.

The purpose of the inspection was to determine if your firm's activities as the sponsor of studies used to support [REDACTED] for Medelle [REDACTED] [REDACTED] complied with applicable FDA regulations, published in Title 21, Code of Federal Regulations, Part 50-Protection of Human Subjects, and Part 812-Investigational Device Exemptions [21 CFR 50 and 812]. The products used in the study are devices as that term is defined in Section 201(h) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 321(h)].

The FDA conducted the inspection under a program designed, in part, to ensure that data and information contained in [REDACTED] submissions are scientifically valid and accurate. Another program objective is to ensure that human subjects are protected from undue hazard or risk during scientific investigations.

Our review of the inspection report prepared by the New England District Office revealed violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions. FDA Investigators Hagan and Geraci listed their findings on a Form FDA-483, "Inspectional Observations," and discussed these findings with you and other Medelle staff at the conclusion of the inspection.

The deviations noted on the FDA-483, your written responses to those deviations, and issues from our subsequent review of the inspection report are discussed below.

1. Failure to ensure proper monitoring of the investigation, failure to select appropriately qualified and trained monitors, and failure to secure investigator compliance [21 CFR 812.40, 43(d), and 46(a)].

Responsibilities of Sponsors include ensuring proper monitoring of the investigation [21 CFR 812.40] with appropriately qualified and trained monitors [21 CFR 812.43(d)] in order to secure compliance with the investigational plan [21 CFR 812.46 (a)].

You failed to adhere to the above stated regulations. Examples of these failures include but are not limited to the following:

- a. Medelle had no written monitoring procedures for the three clinical studies: [REDACTED]
[21 CFR 812.25(e)].
- b. Medelle failed to ensure that data for all enrolled study subjects were reported. Specifically, information on two subjects at Site # 001 who were dropped from the [REDACTED] study due to positive bacteriological screens were not included in the firm's submission to the FDA.
- c. Monitoring reports were incomplete and inaccurate. Specifically:
 - i. Initiation, interim, and closeout reports for three study sites had no indication as to which of three studies was being monitored. Sites # 001 and 002 had reports for two studies, and Site # 003 had reports for three studies.
 - ii. Monitoring reports were inaccurate. For example:
 - A Study Closeout Visit form for Dr. [REDACTED] (Site # 001), dated 1/29/04, states 5 participants were enrolled, 5 participants completed the study, and no participants were dropped. However, the study records indicate that 9 subjects were actually enrolled, 5 completed the study, and 4 were dropped (2 for positive bacteriological screens and 2 chose to withdraw).
 - A Study Closeout Visit form for Dr. [REDACTED] site (Site # 002), dated 2/2/04, states 6 participants were enrolled, 6 participants completed the study, and no participants were dropped. However, in your response to the FDA dated July 8, 2004, you stated that "at site # 002, two participants (#3 and #8) of the 8 that originally signed informed consent, were dropped from the study (prior to being subjected to the device) simply because they were not needed.
- d. Monitoring reports indicated that investigators were not compliant with the protocol by enrolling ineligible patients, but there was no documentation of any actions taken by Medelle to secure compliance. For example:
 - i. The Intermediate Monitoring Visit form for Dr. [REDACTED] (Site # 003), dated

1/26/04, states a protocol deviation occurred---“one patient with BMI over 30 was recruited.” This condition was an enrollment exclusion criterion for Protocols 002 and 003. (There is no indication on the form as to which study this report referred.)

- ii. The Intermediate Monitoring Visit form for Dr. [REDACTED] (Site # 002), dated 2/2/04, states three protocol deviations occurred---“1 patient with an abnormal pap smear was recruited. 2 patients with BMI over 30 were recruited.” These conditions were enrollment exclusion criteria for Protocols 002 and 003. (There is no indication on the form as to which study this report referred.)
 - iii. Another Intermediate Monitoring Visit form for Dr. [REDACTED] (Site # 002), also dated 2/2/04, states two protocol deviations occurred---“1 patient was overweight (BMI of 33). Another patient had an abnormal pap smear.” Both of these conditions were enrollment exclusion criteria for Protocols 002 and 003. (There is no indication on the form as to which study this report referred.)
- e. Medelle did not ensure that investigators maintained complete, accurate, and current records of the investigators’ participation in an investigation. For example:
- i. Raw data, including original laboratory worksheets for the sterility testing [REDACTED] [REDACTED] “Assessment of Sterility of [REDACTED] [REDACTED]”), had been discarded by [REDACTED] [REDACTED] Laboratory. Although the Study Director, [REDACTED], indicated in the study report summary that none of the 10 [REDACTED] showed any contamination, there was no way to verify the data.
- Included in your response dated July 8, 2004, you provided correspondence and attestations from [REDACTED] Lab investigators that the report accurately reflected the data, based on their “recollection” of the test results. You have also included an undated and unsigned “preliminary report” as documentation of the laboratory results.
- The inability of the sponsor to provide the raw data to corroborate the laboratory staff’s “recollections” of the sterility testing results raises questions of accuracy and reliability of this data.
- Your response letter to the FDA, dated September 24, 2004, stated that Medelle will implement an SOP covering retention and utilization of outside testing facilities, and the SOP would be completed and released within 2-3 weeks of that date. Please include a copy of this SOP with your response to this letter.
- f. There were inconsistencies between the records and the data submitted to FDA. For example:
 - i. The sterility testing laboratory report indicated that the devices from 4 subjects,

(001, 002, 007, and 008) from Site # 003 (Dr. [REDACTED]) were tested for the [REDACTED]. However, the Case Report Forms for [REDACTED] for Site # 003 list 8 subjects in the [REDACTED] study.

- ii. During the inspection, the FDA investigators were told that 4 of the 8 subjects from Site # 003 (003A, 004, 005A, and 006A) were actually in the [REDACTED]. However, there is nothing in the Case Report Forms to indicate this. In fact, the Case Report Forms do not specify which type of device these 8 subjects received ([REDACTED]), so it is impossible to tell which subjects were actually enrolled in the [REDACTED].
- iii. In addition to the issues noted above, the FDA investigators found that Medelle had re-numbered the study subjects when analyzing the study data. This resulted in inconsistencies in the study data and confusion among your own staff during the FDA inspection as to which study subjects were enrolled in the [REDACTED]. Dr. Tulchinsky identified study subjects 3A, 4, 5A, and 6A as being enrolled in the [REDACTED], while the hand-written [REDACTED] results from the laboratory identify subjects 1, 2, 7, and 8 as being in the [REDACTED].

The lack of accuracy regarding lot number documentation, accountability of the devices shipped to investigators, and inconsistencies regarding which subjects were enrolled in the studies raise numerous questions regarding the reliability and validity of the study data submitted to the FDA.

- g. Medelle failed to use monitors qualified by training and experience. Dan Tulchinsky, MD, Medical Director for Medelle, was the study monitor for the clinical studies. In a letter to Carl DeMarco, dated 9/24/04, you stated “In hindsight, the Company recognizes that, while Dr. Tulchinsky is an accomplished infertility specialist, he does not have the appropriate regulatory background for clinical monitoring. Medelle has now implemented a formal Clinical Monitoring SOP on which employees of Medelle (and future employees and/or contractors) involved in clinical studies have been (will be) trained...Medelle will also be providing outside training in good clinical practices for its employees involved in clinical studies”. The letter also noted “Dr. Tulchinsky has recently chosen to resign from his employment at Medelle and re-resume his prior role as a consultant for medical input. He will no longer monitor clinical studies”.

These deficiencies in the monitoring of the three clinical studies used to support [REDACTED] for Medelle [REDACTED] raise issues regarding the reliability and applicability of the data submitted to the FDA.

To address these monitoring deficiencies, Medelle prepared a standard operating procedure (SOP), “Monitoring of Clinical Studies Procedure,” and provided a copy to the FDA investigators during their inspection closeout visit. The SOP was subsequently revised and included with your response dated July 8, 2004. Ms. Crowl, of the FDA, reviewed this SOP and provided feedback to you and Kathleen Karloff. You stated you plan to immediately implement the SOP, and that all individuals who have responsibilities in this area, including clinical investigators, would be

trained (and documented) prior to any clinical activities. In your response to the FDA, dated September 24, 2004, you stated that the Clinical Monitoring SOP has been implemented, Medelle personnel have been trained, and new employees/contractors will be trained to this SOP. Further, your response letter stated that training of all Medelle employees on the new Clinical Monitoring SOP was completed on 7/11/04.

FDA agrees that proper implementation of the SOP and adequate training should help to minimize the recurrence of the types of deficiencies seen during the inspection. You should also ensure that all study monitors are qualified by training and experience.

2. Failure to maintain accurate, complete, and current records relating to an investigation [21 CFR 812.140(b)]

As per regulation, a sponsor shall maintain all correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, as well as records of shipment and disposition and the signed investigator agreements. Examples of your failure to satisfy these requirements include, but are not limited to, the following:

- a. Complete device accountability records were not maintained. The firm's device shipping records for the [REDACTED] clinical studies with the Medelle [REDACTED] were incomplete and lacked sufficient information to track all study devices shipped to the investigational sites. Specifically:
 - i. The shipping documents maintained by the sponsor did not identify the study for which the devices were to be used.
 - ii. The shipping documents did not always identify the lot numbers of the devices sent to each investigator. For example:
 - A Record of Shipment and Disposition for Dr. [REDACTED] indicates 16 devices of lot number "A5" were shipped on 11/10/2003; a Record of Shipment and Disposition for [REDACTED], MD indicates 10 devices of unknown lot number were shipped on 5/16/2003; a Record of Shipment and Disposition for Dr. [REDACTED] indicates 10 devices of unknown lot number were shipped on 5/19/2003.
 - The test report ([REDACTED]-Report [REDACTED]) identifies the lot number of the test article used as "Lot 031203 A6". However, none of the Records of Shipment and Disposition for devices sent to the study sites lists this lot number.
 - iii. Not all devices shipped to a site were accounted for. For example:
 - A Record of Shipment and Disposition for [REDACTED], MD indicates 16 "dummy" devices were shipped on 11/10/2003. The record indicates 10 unused devices were returned, but there is no accounting for the other 6

devices. In addition, there is no Signature of Investigator under the record of disposition section on the form.

- A Record of Shipment and Disposition for Dr. [REDACTED] indicates 10 devices were shipped on 5/19/2003. The record indicates 8 used devices were returned, but there is no accounting for the other 2 devices. In addition, there is no Signature of Investigator under the record of disposition section on the form.
 - A Record of Shipment and Disposition for [REDACTED], MD indicates 4 devices were shipped, but there is no date or signatures for shipment or receipt. The record indicates 4 used devices were returned, but there is no Signature of Investigator under the record of disposition section on the form.
- iv. There are inconsistencies in shipping records related to “dummy devices”, a term which you stated to the FDA investigators applied to devices of Lot 030403, and were shipped to assist the clinical investigators to become familiar with the devices but were never used in study patients. For example:
- A Record of Shipment and Disposition for [REDACTED], MD (Site # 001) indicates 16 “dummy” devices of Lot 030404 were shipped on 11/10/2003. However, this Lot number is identified in the final reports submitted to the FDA as being the lot number used for the [REDACTED].”
 - The study reports submitted to the FDA indicate Dr. [REDACTED] (Site # 002) enrolled 10 subjects into the [REDACTED] and 6 subjects into the [REDACTED], for a total of 16 subjects. However, the only records of devices shipped to Dr. [REDACTED] were 10 devices of an unknown lot and 8 “dummy devices” of Lot 030403. It is impossible to tell from the records if the “dummy devices” were actually used for study patients, since there is a discrepancy of 6 devices.
 - The study reports submitted to the FDA indicate Dr. [REDACTED] (Site # 003) enrolled 9 subjects into the [REDACTED], 4 subjects into the [REDACTED], and 4 subjects into the [REDACTED], for a total of 17 subjects. However, the only records of devices shipped to Dr. [REDACTED] were 10 devices of an unknown lot, 4 devices of Lot 031203A5R, and 5 “dummy devices” of Lot 030403. It is impossible to tell from the records if the “dummy devices” were actually used for study patients, since there is a discrepancy of 4 devices.

In addition, you failed to notify the FDA within 10 working days that records custody and responsibility were transferred from Dr. [REDACTED] study site (site 001) to you, the Sponsor. During an inspection of Dr. [REDACTED] clinical study site, FDA investigators found that all study records for the [REDACTED], including original case histories and informed consents,

were missing. However, these records were later found at your site during the Sponsor inspection. (EIR page 9) Federal regulations require Clinical Investigators to maintain all records related to research. The Regulations also state that an investigator may withdraw from the responsibility to maintain records for the required period and transfer custody of the records to any other person who will accept responsibility for them. Notice of transfer of the records shall be given to FDA no later than 10 working days after the transfer occurs.

Because notification of records custody was not performed as required, the FDA Investigators were unable to perform the required Data Audit at Dr. [REDACTED] study site in order to verify the accuracy of the clinical data being reported to the FDA by the Sponsor.

The above-described deviations are not intended to be an all-inclusive list of deficiencies found in your clinical studies. When conducting clinical investigations of products regulated by FDA, it is your responsibility to adhere to each requirement of the Act and all applicable federal regulations.

Within 15 working days of receiving this letter, please provide additional written documentation of any additional corrective actions you have implemented or will implement to prevent the recurrence of similar violations in current and future studies. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you.

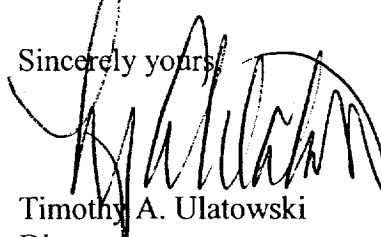
Please respond in writing to:

Food and Drug Administration
Center for Devices and Radiological Health, Office of Compliance
Division of Bioresearch Monitoring, Special Investigations Branch (HFZ-311)
2094 Gaither Road, Rockville, Maryland 20850
Attn: Mr. Michael Marcarelli, Director, Division of Bioresearch Monitoring.

A copy of this letter has been sent to FDA's New England District Office, One Montvale Ave., 4th Floor, Stoneham, MA 02180. We request that a copy of your response also be sent to that office.

Please direct all questions concerning this matter to Michael Marcarelli at (240) 276-0125.

Sincerely yours,



Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health