DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
Rockville MD 20857

WARNING LETTER
Via Federal Express

AUG 30 2000

Thomas F. Motter
Chairman & CEO
Paradigm Medical Industries, Inc.
2355 South 1070 West
Salt Lake City, Utah 84119

Dear Mr. Motter:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of your site, discuss your written response to the inspectional observations, and request a prompt reply with regard to the remaining issues. The inspection took place during the period of June 5 and 26, 2000, and was conducted by Ms. Margaret M. Annes, an investigator from FDA's Denver District Office. The purpose of the inspection was to determine if your activities as sponsor of clinical studies of the [redacted] comply with applicable FDA regulations. This system is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notifications [510(k)] are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, Part 50 - Protection of Human Subjects, and Section 520(g) of the Act. You received a form FDA-483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you. We acknowledge receipt of a copy of a response by Mr. Tracy S. Best, Manager, Regulatory Affairs and Quality Assurance, to the form FDA-483 items that was sent to the Denver District Office, dated July 29, 2000. The deviations noted on the form FDA-483 include:

Failure to adequately monitor the study (21 CFR 812.46).
There is no documentation that any of the study sites were monitored prior to January 2000. A review of the case report forms (CRFs) revealed numerous deviations from the investigational plan, including enrollment of subjects who failed

to meet the inclusion/exclusion criteria, follow-up visits outside of the prescribed timeframes, and adverse effects which were not reported. There is no indication that the investigators were informed of these deviations or instructed to come into compliance. Moreover, study subjects at several sites were not properly consented prior to surgery. Limited written procedures titled "Paradigm Clinical Site Audit," dated July 25, 1998, do not have a signature authorizing their implementation or identifying them as study monitoring procedures.

Failure to provide study investigators with the information needed to conduct the study (21 CFR 812.45).
There is no documentation to show that investigators or their personnel were trained in the use of the [redacted], regarding the investigational plan, or in how to complete the CRFs. Information gathered during the inspection indicates that the [redacted] should only be sterilized a maximum of 5 times and then discarded. There is no documentation to show that the investigational sites were made aware of this. Three versions of the study protocol were supplied during the inspection, but there was no documentation that the investigators were provided the revised versions, one of which includes revised CRFs. Review of CRFs indicated that not all sites were using the most recent versions. Moreover, the basis for [redacted] was not explained in the protocol and several investigators used a different system, ranging from [redacted] rather than the [redacted] system indicated in the protocol.

Failure to select qualified monitors [21 CFR 812.43(d)].
None of the individuals listed as monitors during the course of the study had previous experience with clinical trials and/or monitoring. Moreover, only one of the monitors had experience relative to [redacted] procedures.

Failure to maintain accurate, complete, and current records of device accountability [21 CFR 812.140(b)(2)].
There is no documentation of the number of [redacted] and [redacted] manufactured and distributed, the number of copies of the controlling software made, or the disposition of each copy of the software. There are no records showing to which sites the device was shipped or whether the required software was supplied. There is no documentation to show when sites were given keys to turn on and use the [redacted] or when keys were retrieved from sites where the study was reportedly closed. There is also no documentation to show when the modified [redacted] was installed at each site and whether or not this change in any way affected the investigational device.

Failure to obtain signed investigator agreements [21 CFR 812.43(c)].
The original IDE submission contains a statement that the sponsor was responsible for securing investigator compliance with the signed Investigator Agreement. Files reviewed contained only signed Confidential Non-disclosure Agreements.

Failure to maintain accurate records of adverse effects [21 CFR 812.46(b)].
CRFs reviewed during the inspection included adverse effects, both anticipated and unanticipated, which were not reported as such and which were not therefore included under that heading in your submission. Moreover, the inspection report notes that you were not aware that all adverse events that occur to subjects taking part in a study must be recorded and reported, even if it is determined that they are not related to use of the investigational device.

Failure to maintain accurate, complete, and current records of all correspondence with investigators, monitors and the institutional review boards (IRBs) [21 CFR 812.140(b)(1)].
There is no documentation of any site visits prior to the year 2000. There is no documentation to show that the sites were sent revised copies of the protocol or given permission to deviate from the protocol requirement of using an independent laboratory to perform [redacted]. There are also no copies of the progress reports from the investigational sites.

It is also noted in the inspection report that you do not have adequate control over the receipt of study data and its subsequent input into the database. There are no records to show when study data is received and when it is entered into the database. There is also no audit trail for changes made to the database. No data queries or clarifications have ever been generated and sent to the sites to verify missing information or to clarify discrepancies. There is no requirement for dates on the CRFs for follow-up visits and therefore no way to show if they occurred as specified in the protocol. Not all sites are using the same version of the CRFs and there is, therefore, no uniformity of the data submitted across sites. There are no subject enrollment rolls at the sites and you are unable to accurately determine the actual number of subjects who have participated in the study to date.

Failure to submit annual progress reports to the reviewing IRBs [21 CFR 812.150(b)(5)].
According to the inspection report, you have not submitted any annual progress reports to the reviewing IRBs during the course of the study.

Failure to collect and maintain financial disclosure records for all clinical investigators [21 CFR 812.140(b)(3)].
21 CFR Part 54 – Financial Disclosure by Clinical Investigators was published as final regulations in the Federal Register in February 2, 1998, after the initiation of your study. These records are required for all studies supporting applications submitted after that date.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. It is your responsibility as a sponsor to ensure that the investigation is conducted in accordance with applicable FDA regulations.

The inspection report also notes that you have not filed the required [redacted] reports for the investigational device. Ms. Corrine Tylka of the Office of Compliance (OC) was informed about this omission and has been in touch with you in this regard.

As noted above, a change was made to the [redacted] of the [redacted]. Since this change affects the [redacted] for both the [redacted] and [redacted] functions of your device, it would appear that a premarket notification should have been submitted. Our records do not reflect that a premarket notification was submitted for this change. Failure to submit a 510(k) at least 90 days prior to offering this device for sale in interstate commerce, and obtaining the necessary FDA clearance, results in the device being misbranded within the meaning of 502(o) of the Act. Furthermore, because this device has not yet been found substantially equivalent to a predicate device through the review of a 510(k) submission, this device is also adulterated within the meaning of section 501(f)(1)(B) of the Act. This is based on the fact that it has been offered for sale in interstate commerce for the first time after May 28, 1976, thereby statutorily classifying it as a Class III device. It does not have, as required under section 515(a), an approved application for premarket approval (PMA) and it is not exempt from such requirement under an Investigational Device Exemption (IDE) (section 520(g)).

For information concerning when it is necessary to submit a 510(k) for a change to a marketed device please refer to the guidance document Deciding When to Submit a 510(k) for a Change to an Existing Device, which can be found at http://www.fda.gov/cdrh/ode/510kmod.html.

Your present plans to assume manufacturing responsibilities, originally contracted to [redacted] may also require submission of a 510(k). Please consult the guidance referred to above and the reviewing division in ODE before production of the [redacted] at your site is initiated. If it is determined that a 510(k) is needed, you may also need to be inspected with regard to the good manufacturing practice requirements specified in the Quality System Regulation (21 CFR 820), i.e. a GMP inspection, prior to a clearance decision.

The July 29, 2000, response to the form FDA-483 items by Mr. Best includes a number of corrective actions taken and/or proposed, including: suspension of the on-going clinical trial until corrective actions are made and a new protocol version, with revised CRFs, is approved; auditing of all sites by an independent auditor; hiring of a qualified, trained clinical trial monitor; development and initiation of SOPs for the control of clinical studies both at the sponsor and at the clinical sites; and creation of device accountability records after an inventory of current devices and their locations is completed. Included in the response are finalized SOPs for control of all aspects of a clinical study and a revised protocol and CRFs. Also included are copies of signed investigator agreements for a number of the study investigators and copies of Federal Express receipts for those investigators who have not yet returned their agreements.

21 CFR 812.43(d) requires a sponsor to select monitors qualified by training and experience to monitor the investigational study in accordance with applicable FDA regulations. To facilitate communication with and an understanding of the problems of the clinical investigators, study monitors should also have knowledge and experience in the appropriate medical field, in this case [redacted]. Please forward us, at the address given below, the curriculum vitae of your clinical trials monitor once chosen.

The protocol included in Mr. Best's response is in a text/paragraph format. Please revert to the format used in the other versions of your protocol. We suggest that you make appropriate additions and/or changes to your most recent version, dated August 26, 1999. As evidenced in the version of the protocol included in the response, additions would include a clear statement that all study subjects, those treated with both the [redacted] and [redacted] need to go through the informed consent process before enrollment in the study. (Informed consent is a process and involves more than simply signing an informed consent document.) Other additions evident in your proposed protocol include a definition of the [redacted] system to be used and a description of the randomization method for assigning subjects to the different devices. Your inclusion/exclusion criteria are also expanded to require pre-operative [redacted] or better and exclude those with a history of [redacted] The requirement for [redacted] to be made by an independent laboratory has been deleted and the need for this measurement limited to the pre-operative and 2- and 3-month post-operative visits.

The proposed protocol also changes the windows for the post-operative visits and stresses the need for recording of all complications (adverse events) that occur during the study. However, follow-up visits should not be according "to the protocol established by each participating physician," as stated. A list of the minimum measurements/observations to be made at each visit should be included, as presently in the August 26, 1999, version. These should coordinate with the items on the revised CRFs and the CRFs should be included as an appendix to the protocol. For your information, in the box titled Adverse Events/Reactions on your CRFs, the note that follows consistently has a typographical error, with the word redactions in place of reactions.

Once the August 26 protocol is revised as proposed, please submit it to the Division of Ophthalmic and Ear, Nose, and Throat Devices (DOED) in ODE as a supplement to the present IDE. That division must approve the supplement before it can be implemented. Please send us a copy of this protocol as well, to the address given below.

The SOPs included in the July 29 response include ones to cover all aspects of a clinical trial as well as some aspects of the quality systems regulations. In reviewing those related to clinical trials it was noted that all relate to medical device studies. Your present products, both marketed and investigational, fit into this category.

However, if you anticipate possible expansion into pharmaceuticals, you should write your SOPs in more general terms. Moreover, while the SOPs include general terms such as "test article" and "equipment log," product-specific terms appear in several places. For example, under SOP-100-500, the second bullet under 3.4.2 talks about the need for informed consent prior to surgery. Not all medical devices would require a surgical procedure. Moreover, references to [redacted] and [redacted] are found in several places, including the inclusion/exclusion criteria in sections 3.3.2 and 3.4.2 of SOP-100-500. Such product-specific terms should be eliminated.

SOP-100-600, **Monitoring a Clinical Investigation**, includes a specific frequency for site visits and audits in section 3.1.3. SOPs should be written in general terms in this regard. Frequency of visits needs to be tailored to the individual study and may even be modified during the course of a study as subject accrual rates and specific problems are identified. Also, please include in the reference list in Part 4 of this SOP the FDA guidance document, Guideline for the Monitoring of Clinical Investigations, a copy of which is enclosed.

Electronic records, the subject of SOP-100-720, **Electronic Database Maintenance**, are subject to 21 CFR Part 11 – Electronic Records; Electronic Signatures, as well as to the recordkeeping regulations found in 21 CFR 812.140. A guidance document regarding this regulation, Computerized Systems Used in Clinical Trials, dated April 1999, is available at http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm. (There is an underline between compliance and ref which is hidden by the general underlining of this address.)

In SOP-100-110, **Pre-Investigation Sponsor Activities**, 3.8.1 prohibits the use of a local IRB by a clinical investigator who is a member of the IRB. While this is your prerogative, regulations [21 CFR 56.107(e)] only require that an IRB member not participate in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. Also, section 3.11 of this same SOP states that the sponsor will ensure that sites do not commence a study until IRB approval is obtained. Please include an explanation of how this will be accomplished. One method is to require receipt of a copy of IRB approval of the study before shipping the investigational product to the site.

Several SOPs refer to records kept by the sponsor or at the clinical sites. These all state that required records must be maintained for two years following the completion of the study. 21 CFR 812.140(d) more specifically states that records are to be maintained for a period of two (2) years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

A bullet in section 3.2 of SOP-100-160, **Documentation of Sponsor Study Activities**, states that the sponsor will maintain copies of the investigator reports to the IRB, if offered. The progress reports required of clinical investigators by 21 CFR 812.140(a)(3) are to be sent to the sponsor, the monitor, and the reviewing IRB and should be one and the same report to all.

On Friday, August 4, 2000, a teleconference took place regarding the independent data audit. FDA's Carl DeMarco, Integrity Office for ODE, lead the discussion, which also included ODE reviewer Richard Felten and Jean Toth-Allen from the Division of Bioresearch Monitoring (DBM), OC. Mr. Best and [redacted] represented Paradigm and [redacted] and [redacted] represented [redacted], the independent auditor you have hired. [redacted] and Mr. Best agreed to FDA's requests concerning the nature of the audit, including the fact that the report will come directly to FDA without being filtered through Paradigm.

Within 15 working days of receipt of this letter please inform us of the present progress of the corrective actions described in the July 29 response. Please include the results of your inventory of the number and location of all investigational products as well as all information requested above that is presently available. For materials not presently available, please estimate when we can expect to receive them. Please send this information to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Jean Toth-Allen, Ph.D. Failure to respond could result in further regulatory action, such as civil money penalties, without additional notice.

A copy of this letter has been sent to FDA's Denver District Office, 6th & Kipling Street, Denver, Colorado 80225-0087. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Jean Toth-Allen, Ph.D. at (301) 594-4723, ext. 141.

Sincerely yours,

for Steven M. Niedelman
Acting Director
Office of Compliance
Center for Devices and Radiological Health

Enclosure