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Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

FEDERAL EXPRESS

WARNING LETTER

JUL 23 1998

Mr. William Dow
President/CEO
PLC Medical Systems, Inc.
10 Forge Park
Franklin, Massachusetts 02038

Dear Mr. Dow:

During January 21-February 6, 1998, Mr. Gary J. Hagan, an investigator with the U.S. Food and Drug Administration (FDA), New England District Office, visited your facility. The purpose of that inspectional visit was to determine whether your firm's activities as the sponsor of the investigational study of the PLC Medical Heart Laser™ CO2 Surgical Laser System (PMA P950015, IDE G900099) complied with applicable FDA regulations. This product is a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

Our review of the inspection report, as well as the reports of FDA-conducted data audits at several of your clinical investigator (CI) sites and inspections of the nonclinical laboratories whose studies supported the research or marketing applications of the device, revealed violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions and 21 CFR Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies.

The findings from the FDA inspection conducted at your firm were listed on the form FDA-483, Inspectional Observations, which was presented to and discussed with you at the conclusion of the inspection. The following list of violations is not intended to be an all-inclusive list of the problems encountered during our review:

- (1) Failure to ensure proper monitoring of the clinical investigation as required in 21 CFR 812.40.

Records indicate that [REDACTED] monitored the clinical studies from

May 1, 1991, to November 6, 1992, and by [REDACTED] from February 22, 1993, to January 31, 1997. [REDACTED] PLC Medical Systems, Inc. (PLC) [REDACTED] had written procedures describing the process by which the clinical investigations were to be monitored nor how compliance with the investigational plan and regulations would be assured.

As a result, monitoring reports failed to include basic information such as whether informed consent was obtained from all study subjects; whether there were deviations from the approved protocol, amendments, or FDA regulations; and whether corrections to case report forms were made and the reasons documented.

- (2) **Failure to monitor to the extent necessary to secure compliance of clinical investigators with the investigational plan as required in 21 CFR 812.46(a).**

Records obtained from our audits of Drs. [REDACTED] and [REDACTED] revealed that these clinical investigators failed to follow the investigational plan and maintain complete and current records and reports.

- (3) **Failure to properly obtain agreements with clinical investigators as required by 21 CFR 812.43(c)(4).**

PLC did not have valid signed investigator agreements prior to enrolling and treating subjects. In fact, [REDACTED] of the [REDACTED] Phase II clinical investigators did not sign investigational agreements until after the first patient surgery.

- (4) **Failure to maintain accurate, complete, and current information as required in 21 CFR 812.140(b).**

You failed to maintain records of all on-site monitoring visits. For example, the reports for the initial site visits for two study sites and the monitoring visit for another study site were not available.

Study records were inadequate in that they failed to provide for accurate device accountability, including device shipment, device histories, and service records of the investigational devices used at study sites. For example, shipment records could not identify the clinical investigators receiving the devices and the serial numbers of all devices shipped to clinical sites. Disposition records did not identify the circumstances surrounding the removal of devices from the study sites.

FDA requested that you develop and conduct an independent assessment of the angina class on all surviving study subjects in Phase III with an independent interviewer with controls to limit study bias. Contrary to PLC's prescribed plan to limit bias, there were ten or more cases where the "independent reviewer" was not blinded to the treatment group into which the subject was assigned. In addition, the interviews were not adequately documented in that at least 100 questionnaires had no verifying signatures of the interviewer(s).

(5) Failure to follow good laboratory practices for nonclinical laboratory studies as required by 21 CFR 58.

You failed to maintain complete and accurate records of a preclinical study in that the documentation of your bench testing verifying the laser output and determining the depth of penetration of the laser in animal heart muscle were not retained. The study results were used to determine the approximate energy required in the clinical investigation (IDE). Federal regulation 21 CFR 58.195(b)(2) requires you to retain these records for a period of at least five years in support of an application for a research or marketing permit.

Also, PLC Medical Systems indicated in the PMA submission that the following nonclinical studies were conducted in compliance with 21 CFR part 58: "Recovery and Viability of an Acute Myocardial Infarct after Transmyocardial Laser Revascularization" [REDACTED]; "The Long- and Short-term

Effects of Transmyocardial Laser Revascularization in Acute Myocardial Ischemia" [REDACTED]
Our review of the records obtained during our audits of these testing facilities and PLC Medical Systems indicate that the studies were not performed in accordance with this regulation. Additionally, these testing facilities were not instructed to conduct their studies in compliance with 21 CFR Part 58. Federal regulation 21 CFR 58.10 requires that the sponsor notify any contracted laboratory that the studies must be conducted in accordance with Part 58 when the results of a nonclinical laboratory study are intended to be submitted to or reviewed by the FDA.

We have reviewed your March 11, 1998, and March 30, 1998, correspondence in response to the observations identified during the FDA's January 21-February 6, 1998, inspectional visit. Your response includes a corrective action plan, which describes corrections already accomplished, or a plan to implement corrective action, which includes proposed completion dates. When fully implemented, this plan should prevent the recurrence of the types of violations noted during the current inspection. Your responses appear to satisfy most concerns and inspectional observations. These corrective actions may be verified during a future inspection.

It is your responsibility to ensure adherence to each requirement of the Act and regulations. Should you choose to respond to this letter, or have any questions concerning this matter, please contact Mr. Kevin Hopson at (301) 594-4720, ext. 128.

Your response may be directed to the U.S. Food and Drug Administration, Center for Devices and Radiological Health,

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Office of Compliance, Division of Bioresearch Monitoring,
Program Enforcement Branch I (HFZ-311) 2098 Gaither Road,
Rockville, Maryland 20850, Attention: Kevin Hopson.

A copy of this letter has been forwarded to our New England
District Office, One Montvale Avenue, Stoneham,
Massachusetts 02180. We request that a copy of your
response be sent to that office.

Sincerely,

A handwritten signature in cursive script, appearing to read "Lillian J. Gill, RA".Handwritten initials "LJG" in cursive script.

Lillian J. Gill
Director
Office of Compliance
Center for Devices
and Radiological Health