DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

M2875.1

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Via Federal Express

WARNING LETTER

AUG 18 1999

Charles J. Casebeer, M.D.
President and CEO
CRS-USA, Inc.
7898 East Acoma, Suite 210
Scottsdale, Arizona 85260

Dear Dr. Casebeer:

During the period of May 3 through 13, 1999, CRS-USA, Inc. was visited by Mr. Armando (Tony) A. Gonzalez, an investigator from the Food and Drug Administration's (FDA) Los Angeles District Office. The purpose of that visit was to inspect your activities as the sponsor of studies with the [redacted]" for Laser Assisted in situ Keratomileusis (LASIK) for myopia, with and without astigmatism, to determine if they complied with applicable FDA regulations. Excimer lasers are devices 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.

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 were used to evaluate your activities. Our review of the inspection report submitted by the district revealed that deviations were noted during the inspection. These were listed on form FDA-483, "Inspectional Observations," which was presented to and discussed with you at the conclusion of the inspection. Deviations noted included:

- Failure to establish standard operating procedures for study monitoring and integrity review. 21 CFR 812.25(e) requires that the investigational plan include the sponsor's written procedures for monitoring the investigation. Moreover, 21 CFR 812.43(d) requires a sponsor to select monitors qualified by training and experience to monitor the investigational study.

- Failure to properly monitor sites for compliance. 21 CFR 812.46(a) requires a sponsor to monitor investigations for the purpose of securing clinical investigator compliance with the signed investigator agreement, the study protocol(s), and applicable FDA regulations.

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

The inspectional report notes that Mr. Gonzalez discussed a number of other issues with you, including the following:

- There were no procedures for qualifying clinical investigators. 21 CFR 812.43(a) requires a sponsor to select investigators qualified by training and experience to investigate the device. Curriculum vitae (CVs) for all participating investigators are the customary records maintained as evidence that this requirement was met.

- There was no verification that the data submitted by the clinical investigators matched source data at the site. The only data verification was performed by the computer data service, [redacted] and involved scrutinizing the data for such errors as out-of-range data, field entry omissions, exam dates out-of-range, and missing exams. This process could not verify that the data entered into the computer system was an accurate record of the source data at the site. According to 21 CFR 860.7, it is the responsibility of the applicant to assure that FDA receives valid scientific evidence of the safety and effectiveness of a device. 21 CFR Part 814, Premarket Approval of Medical Devices, references section 860.7 as criteria that will be used in deciding whether to approve or deny approval to a PMA.

  It is noted that the protocol for both the initial study and the study expansion states, under Data Reporting Procedures, Access, and Limitations, that "The sponsors have do not assume responsibility for monitoring individual results." (It is assumed that the typographical error is the addition of "have.") Such a statement cannot serve to release a sponsor from their responsibility. Data validation is part of monitoring and, as noted above, Part 812 gives the sponsor the responsibility for assuring that a clinical study is properly monitored.

- Lack of documentation for software validation. Dr. Guy Kezirian, study coordinator, stated to Mr. Gonzalez during the inspection that he has never seen any validation of the software package used by [redacted]. Enclosed is a copy of the FDA guidance document on "Computerized Systems Used in Clinical Trials."

- In discussing problems associated with difficulty in collecting complete and accurate data from [redacted] Mr. Gonzalez was informed that CRS had paid for and provided technical support to remedy the problem, in the form of technical assistance from [redacted]. This does not appear to agree with information gathered by a different FDA investigator who inspected [redacted] Both [redacted] and her study coordinator, [redacted], who was responsible for entering the data into the computer, stated that no one ever visited their site to offer technical assistance. The only visit they received was from Dr. Kezirian, at the time the study was initiated at the site. They stated that CRS requested data corrections from them on several occasions but did not offer suggestions or assistance on how to provide it in a specific manner. It was only after the site had been inspected by FDA, that suggestions were provided regarding means for gathering all the subject data for use by CRS.

The inspectional report also notes that you promised corrections to the items listed on form FDA-483. In that regard, you stated that CRS is in the process of establishing standard operating procedures (SOPs) for study monitoring and integrity review, in compliance with IDE regulations. For assistance in preparing these procedures, a copy of the FDA guidance "Guideline for the Monitoring of Clinical Investigations" has been enclosed.

Within 15 working days of receipt of this letter, please inform FDA of the corrective actions that have been taken with regard to the deviations noted. Please include a copy of the completed monitoring SOPs and send all relevant material 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 can result in further regulatory action without additional notice.

All present and future IDE studies need to include monitoring provisions. Please modify the protocols for on-going studies to reflect this and submit a copy of the pertinent revised section to the address above. These revisions should also be submitted as official supplements to the IDEs in question.

A copy of this letter has been set to FDA's Los Angeles District Office, 19900 MacArthur Boulevard, Suite 300, Irvine, California 92612. 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,

Norma O'Connor, RPh

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

Enclosures

cc:
Guy Kezirian, M.D.
LASIK study coordinator