



## WARNING LETTER

VIA FEDERAL EXPRESS

JAN 28 2004

Food and Drug Administration  
Center for Devices and  
Radiological Health  
2098 Gaither Road  
Rockville, MD 20850Linda B. Grable  
Chair and Chief Executive Officer  
Imaging Diagnostic Systems, Inc.  
6531 NW 18<sup>th</sup> Court  
Plantation, FL 33313

Dear Ms. Grable:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at Imaging Diagnostics Systems Incorporated (IDSI). This letter also discusses your written response to the noted violations and requests that you implement prompt corrective actions. Mr. Victor Spagnoli, an investigator from FDA's Florida District Office, conducted the inspection from August 5 through August 18, 2003. The purpose of the inspection was to determine if your activities as a sponsor for the [REDACTED] study complied with applicable FDA regulations. The [REDACTED] is a device defined in Section 201 (h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321 (h)].

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

Our review of the inspection report prepared by the district office revealed serious violations 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 [21 U.S.C. 360j(g)]. At the close of the inspection, Mr. Spagnoli presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations. The deviations noted on the FDA 483 and our subsequent inspection report review are discussed below:

**1. Failure to ensure proper monitoring of the investigational study. [21 CFR 812.25(e) and 812.40]**

Sponsors must monitor studies based on written procedures, and at adequate intervals, to assure that investigators are complying with the signed agreement, investigational plan, and all applicable FDA regulations. The inspection conducted in August 2003 revealed numerous monitoring violations, including the following:

- a. Sponsors are required to include written procedures designed to ensure proper monitoring of the study as part of their investigational plan. You failed to establish

adequate procedures for identifying and addressing discrepancies between the source data and the data submitted in the PMA. In some instances, the data submitted in the PMA did not match the source data. For example, the patient listing for [REDACTED] shows a right [REDACTED] score of 1 while the [REDACTED] shows a score of 4. In addition, the PMA reports the [REDACTED] for patient [REDACTED] while the source document lists the same patient's [REDACTED]. With regard to patient [REDACTED]; the initial and independent second [REDACTED] reading were positive and negative respectively. The reason for the difference is unclear and undocumented.

Monitors also failed to observe that the first enrolled patient's [REDACTED] was assessed with an earlier software version. Because earlier software versions were not equivalent to later versions used in the study, the data should not have been included in the data analysis.

Although your response indicated that these were typographical or transcription errors occurring mainly at the [REDACTED] site, adequate monitoring procedures should detect such discrepancies.

b. You failed to adequately monitor the clinical investigators participating in this study to assure that they were following the protocol. For example, patient logs indicated that 50 of the patients enrolled from November 16, 2001, through June 18, 2002, at the [REDACTED] clinical site did not meet the protocol's enrollment criteria. These patients had [REDACTED] scores of 1, 2, and 5 while the protocol required that only patients with scores of 3 or 4 be included in the study. The patient logs for the [REDACTED] and [REDACTED] sites also indicate that a total of 36 enrolled patients had [REDACTED] scores of 1, 2, or 5. Although the PMA data listings excluded most patients with [REDACTED] scores of 1 or 2, the listing included a total of 29 patients with scores of 5.

The protocol also required that enrolled patients already have scheduled biopsies. At the [REDACTED] sites, there were no biopsies indicated for four patients [REDACTED] and [REDACTED] with [REDACTED] scores of 4 who should have had scheduled biopsies.

We disagree with your response that the [REDACTED] site enrolled all patients with non-qualifying [REDACTED] scores within the first 2 months of the study (November and December, 2001). We note that the [REDACTED] site enrolled 10 patients with [REDACTED] scores of 1, 2, or 5 between January 9 and April 8, 2002. During the post-inspection discussion, IDSI staff informed the FDA investigator that [REDACTED] continued to enroll non-qualifying patients after IDSI informed her that this was a protocol deviation. Your response also does not account for the 36 non-qualifying patients enrolled at the other sites. The response is also unclear about the four patients at the [REDACTED] and [REDACTED] sites with [REDACTED] scores of 4 who did not have scheduled biopsies.

The protocol also required that abnormalities observed on the [REDACTED] be geographically located in the same place as lesions observed on [REDACTED] to permit increases in the [REDACTED] adjunctive scores, and there were specific criteria for determining geographic equivalence of lesions. There is no documentation or evidence that the physician determining geographic equivalence of lesions followed these criteria, and this physician failed to explain to the investigator why there were many unexplained discrepancies between the [REDACTED] and [REDACTED] results. The PMA Patient Listing included 45 subjects with abnormalities on [REDACTED] and increased [REDACTED] scores regardless of biopsy results or lesion location on the [REDACTED].

Your response describes how the investigators calculated the [REDACTED] score; however, the response does not account for the 45 discrepancies noted above. Although investigators did not document that they calculated scores according to the protocol, if they followed the protocol, [REDACTED] results and [REDACTED] scores should correlate with biopsy and lesion results.

The monitors failed to assure that the investigators signed and dated their [REDACTED] readings on the assessment sheets. Additionally, the sheets contained alterations and inconsistent use of checkmarks to record data. According to IDSI's monitoring procedures described in Standard Operating Procedure (SOP) 500007, investigators must "correct errors in logbooks by drawing a line through the entry, initialing/dating, and entering the correct information alongside." The procedures also state that investigators should initial and date [REDACTED] entries. As the study sponsor, you had an obligation to monitor the investigators' activities under the study and assure their compliance with these requirements. Your response indicates that you are aware of this responsibility.

c. The monitors failed to assure that investigators maintained accurate, complete, current records as required in 21 CFR 812.140 (a)(3). The monitors also failed to follow IDSI's monitoring procedure to assure that monitoring reports documented efforts to obtain missing source records or document the reasons that these records were missing. Many records remained missing from several sites at the time of the inspection. Examples included missing [REDACTED] and pathology reports for biopsies at the [REDACTED] site and a missing pathology report for case [REDACTED] reported as positive and included in the PMA Patient Listing. There was no biopsy report for patient [REDACTED], also reported as positive in the PMA.

Your response indicates that monitors used spreadsheets to generate reports of missing items and followed up with calls/emails to obtain the missing information. However, there was no documentation available during the inspection to verify that you used these procedures. Not only must your SOPs clearly describe your monitoring procedures, you must also document that you carry them out and account for any missing records.

d. Monitors failed to assure that clinical investigators complied with the requirements for obtaining informed consent. Clinical investigators at the [REDACTED], and [REDACTED] sites used informed consent forms that did not contain all of the basic elements of informed consent as required by 21 CFR 50.25(a). Specifically, the informed consent forms used at these sites failed to mention that patients would be required to have a biopsy before undergoing a [REDACTED].

The monitoring report for the [REDACTED] site failed to address the absence of [REDACTED] measurements required in the informed consent form approved at this site. Furthermore, IDSI management was unaware that the consent form included the [REDACTED] measurement requirement.

We note that your corrective action plan includes revising your monitoring procedures to assure that all participating sites adhere to approved language in the informed consent documents. Your corrective action plan should also assure that sites use complete documents containing all required elements.

e. The monitor failed to verify that clinical investigators reviewed the seven adverse events reported in the PMA. The Adverse Event Reports collected by the monitors lacked clinical investigators' signatures and dates indicating that investigators had reviewed the reports, evaluated the patients, and concurred with the assessment. Your response indicates that you recognize the need for investigators to document that they have reviewed all adverse events regardless of their significance and have evaluated the patients.

## **2. Failure to select qualified investigators [21 CFR 812.43]**

Sponsors are also responsible for selecting investigators qualified by training and experience to investigate the device. The protocol required testing the clinical investigators' proficiency in [REDACTED] interpretation prior to interpreting cases submitted in the IDE. No documentation is available to verify that investigators received adequate training and demonstrated [REDACTED] interpretation proficiency prior to study participation. Your response indicates that you agree that investigators' training should have been documented in writing.

As part of their training, investigators received only small numbers of normal and abnormal scans to interpret. The adequacy of such a limited number of cases to develop proficiency is questionable. The number of discrepancies with a tendency toward high numbers of false positive [REDACTED] results is evident. For example, [REDACTED] received only four abnormal scans. Of these, both the first and second readings for cases [REDACTED] and [REDACTED] were positive whereas the biopsy result was negative. At the [REDACTED] site, there were nine cases of positive [REDACTED] readings with corresponding negative biopsies. There was no follow up to assess these results.

Additionally, agreement among investigators reading the same [REDACTED] was poor, and in only five of the six cases did one or more investigator agree that there was an

abnormality; in no instance did all of the investigators agree. There is no indication that there was follow up to determine if additional training was needed or to assess the quality of the scans. These observations failed to support the sponsor's statement in the PMA that "post-market diagnostic accuracy will be consistent among different users."

We note that you are investigating these observations and will respond later.

**3. Failure to secure compliance from a non-compliant investigator [21 CFR 812.46 (a)]**

When sponsors discover that investigators are not complying with the signed investigator agreement, the investigational plan, the requirements of applicable FDA regulations, or any conditions of approval imposed by FDA or the reviewing Institutional Review Board (IRB), the sponsor must promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. Both clinical monitoring visits and reports from your monitors indicated that several participating clinical investigators repeatedly failed to follow the protocol during the clinical investigation (examples noted above in section one). However, there was no indication that you obtained prompt correction and compliance or that you terminated these investigators' participation in the study as required by regulation.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a sponsor to assure adherence to each requirement of the Act and all applicable federal regulations.

Within 15 working days after receiving this letter please provide written documentation of the additional, specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to: 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: Sybil Wellstood, Ph.D.

We are also sending a copy of this letter to FDA's Florida District Office, 555 Winderley Place, Suite 200, Maitland, FL 32751, and request that you also send a copy of your

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response to that office. If you have any questions, please contact Dr. Wellstood by phone at (301) 594-4723, ext. 140, or by email at [saw@cdrh.fda.gov](mailto:saw@cdrh.fda.gov).

Sincerely yours,

A handwritten signature in black ink that reads "Michael E. Marcano". The signature is written in a cursive style with a large initial 'M'.

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