DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Dallas District
4040 North Central Expressway
Dallas, Texas 75204-3145

April 27, 2005

Ref: 2005-DAL-WL-15

WARNING LETTER

CERTIFIED MAIL
RETURNED RECEIPT REQUESTED

Mr. Terry L. Crabtree, President
Inoveon Corporation
800 North Research Pkwy, Ste 370
Oklahoma City, Oklahoma 73104-3698

Dear Mr. Crabtree:

During an inspection of your establishment located in Oklahoma City, Oklahoma, on December 7- 21, 2004, our Investigator determined that your firm manufactures the Diabetic Retinopathy 3DT ™ System intended for early detection, staging, and monitoring of diabetic eye diseases, e.g., diabetic retinopathy, macular degeneration, and glaucoma. Your firm designs, installs, and operates the 3DT™ System at a number of clinical sites in Oklahoma, St. Louis, Missouri, and Denver, Colorado. The 3DT™ system includes a retinal image acquisition subsystem, an image enhancement and reading subsystem, and an analysis algorithm subsystem. The Diabetic Retinopathy 3DT ™ System is a device as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for their manufacturing, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation for medical devices, as specified in Title 21, Code of Federal Regulations (CFR), Part 820. Significant deviations include, but are not limited to, the following:

1. Failure to establish and maintain adequate procedures for validating the device design to ensure that the device conforms to user needs and intended uses and include risk analysis, as required by 21 CFR 820.30(g) [FDA 483, Item 15]. For example, a formal risk analysis of the original system design and software changes to correct software bugs that caused incorrect functionality or performance problems, and to

enhance the product, has not been documented. Although your software release notes briefly describe the nature of unresolved software bugs in a particular software version, they do not explain the impact of these software bugs on user needs and intended uses. For example, in the workflow release notes, dated 6/24/04, software version 2.0tr17 described that "the scores for the left eye and right eye was reversed, and the macular edema value used previously was confusing."

2. Failure to establish and maintain adequate procedures to ensure formal documented reviews of the design results are planned and conducted at appropriate stages of the design development, as required by 21 CFR 820.30(e). For example, although the software release notes describe what software bugs were known, resolved or not resolved, the results of design reviews were not documented to (a) indicate how design reviews are linked to the software release notes; (b) indicate who attended the design reviews and the date of review; and (c) explain the impact of unresolved or known software bugs, and any other action items.

3. Failure to establish and maintain adequate procedures for the identification, documentation, validation or verification, review, and approval of design changes before their implementation, as required by 21 CFR 820.30(i) [FDA 483, Item 9]. For example:

   a) Status of design changes was not documented to explain why certain design changes were not implemented to correct software bugs. For example, the [redacted] report, queried on 12/8/04, showed Item 405 and 406 for "iScore report modification (evidence of glaucoma) - glaucoma screening", Item 109 for "to close "99" loophole in the analysis algorithm", and Item 678 for "Analysis Application Testing." These software bugs remained open and not assigned;

   b) Your firm was not able to explain what changes had been made to the device design validation document (e.g., Commissioning Validation Plan) when the document version was changed from v0.91 to v0.96;

   c) The "Workflow Release Notes by [redacted]" has no status information or discussion of the test releases of software versions v2.0tr36 through v2.0tr40. These software versions were released for use at the [redacted]

   d) Design change testing to release software version 2.0tr38 contains unclear explanation of the software validation test results to document what exact functionality or performance problems were detected during testing and to explain the impact of these problems. For example, Test No. 4.1.2 for ETDRS (Early Treatment Diabetic Retinopathy Severity Scale) data commented "ETDRS data

appears to be correct" under the Comment section, and "There have been a number of recommendations offered. We should consider addressing them in subsequent releases" under the Issues/Problems section. Test No. 4.2.1 for Diagnostic Report commented "looks good", and "There have been a number of recommendations offered. We should consider addressing them in subsequent releases." See [redacted] System Functional Tests, test dated 10/27/04;

e) Design change testing to release software version v2.0tr38 showed Test No. 4.2 for "Print iScore Report" feature failed. A workaround to resolve this software bug was not clearly explained. For example, the Issues/Problems section reported " *** found a problem where the recommendation in the Print email did not match the follow-up recommendation on the iScore ***", and the Workaround section reported "iScore is the official source for follow-up recommendation; however, if someone uses the print email for decision making, having an inconsistent recommendation would be very bad." See [redacted] System Functional Tests, test dated 10/27/04.

4. Failure to establish and maintain procedures for analyzing processes, work operations, concessions, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems, as required by 21 CFR 820.100(a)(1) [FDA 483, Item 1]. For example:

   a) Your firm has not analyzed quality data from your [redacted] (software issues), service reports, and Help Desk in the last 12 months;

   b) Your [redacted] system is used to record customer complaints reported by the readers at the reading center after product releases as well as internal non-conformances detected by the software engineers during their software design validation testing prior to product releases. The [redacted] tracking of submitted items dated 12/8/04, lacked information to identify which product issues are related to either customer complaints or internal non-conformances detected during testing;

   c) Your [redacted], dated 12/8/04, recorded certain nonconforming items as either "closed" or "closed (verified)". Your firm has not defined procedures clarifying the possible meaning of "closed" and "closed (verified)" in order to explain whether or not and how these nonconforming items are resolved;

   d) In a 12/14/04 e-mail explaining your firm's trend analysis of quality data during the inspection, your firm provided a numerical count of product defects, nonconformities, and product enhancements. Your firm has not categorized the

types of product enhancements. Your firm trended product defects and nonconformities into six types of categories but has not clearly explained their specific nature and impact on product functionality or performance. In addition, your firm has not defined what and how product issues are classified as "defects" or "nonconformities." For example, your firm recorded 103 defects and 361 enhancements for software version 1.x, and 190 nonconformities and 159 enhancements for software version 2.x; and

e) Your firm's Quality Manual requires that a quality report discussing customer satisfaction/complaints/consults, quality indicators, quality audits, and proficiency testing is to be prepared on a scheduled basis for review by the Quality Council and Executive Committee. In spite of the software defects, nonconformities, enhancements mentioned above, your firm reported that no quality report has been generated at the time of inspection.

5. Failure to implement and record changes in methods and procedures needed to prevent and correct identified quality problems, as required by 21 CFR 820.100(a)(5). For example:

   a) In your firm's executive summary concerning patients who have a pre-existing condition, Pan-Retinal Photocoagulation (PRP), prior to undergoing an examination by your 3DT system, your firm reported that once the PRP has been performed, one can not determine the EDTRS level in the eyes prior to the PRP and that fields with PRP scars are usually scored as ungradable. Your firm further reported that there were (538) eyes from (360) patients with visible PRP scars noted, and (50) eyes were misclassified as having an ETDRS level below 53 (including several 10s). A number of these patients received a referral recommendation of "return for reevaluation" or a "technical referral." Your firm then recommended implementing an alternative algorithm and other solutions to fix the bug in the Analysis Application Program that produces spurious scores when some lesions are scored individually as "Can't Grade." At the time of our inspection, your firm had not documented whether your recommended alternative algorithm was implemented or justified the reasons for not implementing the algorithm. See OFI_AltAlgB-PRP.09, effective dated 3/24/04; and

   b) In your firm's executive summary concerning an unacceptably high disagreement rate between the readers on the classification of cases of ungradable eyes, your firm identified that the root cause is that there is no clearly stated procedure for deciding how to grade fields that are clearly sub-standard but which may have some lesions that can be graded. Your firm then recommended that the readers and software engineers get together to develop an alternative grading questionnaire and analysis algorithm that can provide a long-term improvement.

At the time of our inspection, your firm had not documented whether corrective actions were implemented. See EC OFI-200312-Ungradable.09, effective dated 3/24/04.

6. Failure to establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices is not released for distribution until all the requirements are completed as required by 21 CFR 820.80(d) [FDA 483 item 3]. For example, your firm has not documented the signature(s) of approval needed to release 3DT software versions 1.1, 1.2, 1.3, and 2.0 for distribution.

7. Failure to establish and maintain procedures for adequate installation and inspection, as required by 21 CFR 820.170(a) and document the installation activities and inspection results, as required by 21 CFR 820.170(b) [FDA 483 Item 5]. For example, your firm's device installation procedure was in the draft form at the time of our inspection, and your firm has not maintained records of installation activities and inspection results of the retinal image acquisition subsystem of the 3DT system at the clinical sites.

8. Failure to maintain device master records, as required by 21 CFR 820.181, and to ensure that each device master record is prepared and approved in accordance with 21 CFR 820.40 [FDA 483 items 3, 5, 6, 7, and 14]. For example, your firm has not established a device master record index referencing or identifying all the necessary specifications and procedures for the three subsystems of the 3DT system: (a) Retinal image acquisition (retinal photography) subsystem at the clinical sites, (b) Image enhancement and reading subsystem at the evaluation center, and (c) analysis algorithm subsystem at the business center.

9. Failure to establish and maintain procedures to ensure that device history records for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the device master record, as required by 21 CFR 820.184 [FDA 483, Items 3 and 8]. For example, your firm has not established procedures defining the specific types of information and acceptance records needed to be included in the device history records to demonstrate that the 3DT system is manufactured in accordance with the DMR and other requirements of the Quality System Regulation.

10. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, as required by 21 CFR 820.50 [FDA 483, Items 10, 11, 12, and 13]. For example, your firm has not (a) evaluated the suppliers for their ability to meet your firm's requirements; (b) defined the quality requirements that each supplier must meet; (c) defined the frequency of supplier evaluations; and (d) documented supplier evaluations.

11. Failure to establish procedures for quality audits and conduct such audits to assure that your firm's quality system is in compliance with the established quality system requirements, as required by 21 CFR 820.22 [FDA 483, Item 4]. For example, although your firm has used past third-party audits for the purpose of supporting your firm's clinical study effectiveness and operational integrity of the 3DT system, your firm has not conducted any internal audits of your firm's quality system requirements in the last five years.

Additionally, the above-stated inspection revealed that your devices are misbranded under section 502(t)(2) of the Act, in that your firm failed or refused to furnish any material or information required by or under section 519 respecting the device and 21 CFR Part 803 – Medical Device Reporting (MDR) regulation. Specifically, our inspection documented your firm's failure to develop, maintain, and implement written medical device reporting (MDR) procedures as required by section 519 of the Act and 21 CFR 803.17. See FDA 483 Item 16. Your firm provided the Investigator with MDR procedures during the inspection, however the following deficiencies were observed:

a. Item # 2, page 1 of 2, "Scope" fails to mention the MDR malfunction reporting requirement. This requirement is also missing from Item # 3.1.1.1., page 1.

b. Item # 3.1.1.2. does not reflect the definition of a serious injury.

c. Item # 3.1.2.1. states that "MedWatch forms must be typed or completed with FDA provided software instead of handwritten". This statement is not correct. FDA prefers that forms be typed and using MedWatch software is optional. However, the forms must be completed in English.

d. Item # 3.1.4. should be revised to reflect the two types of five day reports under 803.53(a) and 803.53(b).

e. Item # 3.1.6. concerning Annual Reports--A Medical Device Reporting Annual User Facility Report, should be removed as it is a requirement that applies to medical device user facilities- not manufacturers.

f. Item # 4.1.6., page 2, does not mention that MDRs must be investigated, as well as evaluated, according to 21 CFR Part 803.50(b)(2), 21 CFR Part 803.17(a), and other applicable sections of the MDR regulation.

g. Your procedures must describe how to determine whether incoming complaints meet the criteria for an MDR reportable death, serious injury or malfunction in accordance with 803.17(a)(2).

We acknowledge receiving your firm's letter, dated January 7, 2005, responding to the Form FDA 483, Inspectional Observations, issued to you at the conclusion of our inspection on December 21, 2004. You indicated that your firm will correct the Quality System regulation observations, outline a general corrective action plan with time frames for completion ranging from January through May, 2005, and complete a comprehensive baseline audit of your firm's quality system conducted by a third party consultant in late June, 2005.

With regard to the Quality System regulation issues, your firm's response is incomplete until your firm provides FDA with update reports outlining the specific steps addressing the specific FDA 483 observations and issues identified in this letter, complete all the corrective actions by May 2005, and provide FDA with the auditor certification report upon the completion of the third party baseline audit after June, 2005.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and the regulations. The specific violations noted in this letter and in the Form FDA 483 issued at the close of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. You also must promptly initiate permanent corrective and preventive action on your quality system.

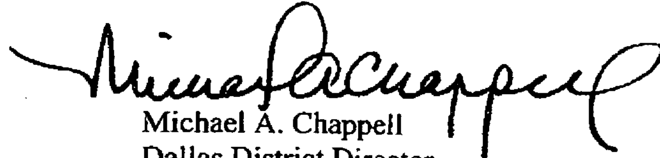
Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for Class III devices to which the Quality System regulation deficiencies are reasonably related will be cleared or approved until the violations have been corrected. Also, no requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within 15 working days of receipt of this letter of the specific steps you have taken, or will take to identify and correct the noted violations, including (1) the time frames within which the corrections will be completed, (2) any documentation indicating the corrections have been achieved, and (3) an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to ensure that similar violations will not recur.

Your reply should be directed to Thao Ta, Compliance Officer, at the address indicated on the above letterhead.

Sincerely,



Michael A. Chappell
Dallas District Director

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