DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Los Angeles District

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Irvine, California 92612-2506
Telephone (949) 608-2900

WARNING LETTER

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

May 17, 2007 W/L 12-07

Edward T. Cleek, CEO
Quantimetrix Corporation
2005 Manhattan Beach Blvd.
Redondo Beach, CA 90278

Dear Mr. Cleek:

During an inspection of your firm located in Redondo Beach, CA on November 27, 2006 through February 6, 2007, investigators from the United States Food and Drug Administration (FDA) determined that your firm manufactures Spinalscopics, Synovialscopics, QuanTscopics, DipandSpins, GlycoHemosure, and the Lipopprint Subfractionation System. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or function of the body.

This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act (21 U.S.C. § 351(h)), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (C.F.R.), Part 820. We received responses from Edward Cleek, CEO and Bernice Navarro, QA/RA Manager and Site Representative dated February 27, 2007 concerning our investigator's observations noted on the Form FDA 483, List of Inspectional Observations that was issued to you and a subsequent progress report dated April 18, 2007. We address these responses below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1) Management with executive responsibility did not ensure that an adequate and effective quality system was fully implemented and maintained at all levels of the organization [21 C.F.R. 820.20]. Specifically,

(a) There was a decision to become an alternate supplier for [redacted] for use in the production of your Spinalscopics, QuanTiscopics, Synovialscopics and

DipandSpin controls. [redacted] were made by R&D using unapproved procedures. The documentation for the [redacted] lots produced by R&D between 2001 and 2003 does not demonstrate that the [redacted] were made to your own procedures; the process was not validated; the accelerated stability studies were not complete; and the assignment of expiration dates was inconsistent with the prepared Component Specification Record and Certificate of Analysis.

(b) Procedures and instructions regarding the recording of test results were not always followed as demonstrated through review of records/laboratory books for the preservative challenge (3/04), the [redacted], the extended expiration date of Spinalscopics (lot #46170), and the design history records of GlycoHemosure.

We have reviewed your response and have concluded that it is inadequate because for observation 1(a) you have not addressed corrective action for product previously distributed and currently in use.

2) Production processes were not developed to ensure that a device conforms to its specifications [21 C.F.R. 820.70(a)]. Specifically, R&D batches of [redacted] were prepared and used in the production of finished devices, Spinalscopics (lot #s 46170, 46160, 46150, 46140, 46130), QuanTscopics (lot #s, 48170, 48180), Synovialscopics (lot #s 38050, 38060, 38070), and Dip & Spin (lot #s 47160, 47170, 47180, 47190, 47200, 47200, 47210, 47220).

We have reviewed your response and have concluded that it is inadequate because you have not addressed corrective action for product previously distributed and currently in use.

3) Not all of the actions needed to correct and prevent the recurrence of nonconforming product and other quality problems were identified. Specifically, your firm documented decreasing [redacted] in Spinalscopics, lot #46170, during the accelerated stability testing for extending the expiration date and there was no nonconformance prepared for the decreasing [redacted] [21 C.F.R. 820.100(a)(3)].

We have reviewed your response and have concluded that it is inadequate because you did not identify the root cause of this deficiency which would be corrected by the additional training.

4) A process, with results which cannot be fully verified by subsequent inspection and test, was not adequately, fully validated and approved according to established procedures [21 C.F.R. 820.75(a)]. Specifically,

(a) [redacted] of the Lipoprint System LDL subfraction kits are manufactured in part by mixing various powders and liquids. Those mixing processes were not validated. This is a repeat observation.

(b) [redacted] are [redacted] for use in Spinalscopics, QuanTscopics, Synovialscopics and Dip & Spin controls. Those processes were not validated.

(c) The acceptance criteria listed under the protocol section in the Preservative Validation Report for the Replacement of [redacted] in Urine Dipstick Products (dated 3/31/04) did not have a clear definition of:

(1) How tubes are rated by presence and concentration of growth.
(2) The set distance for placement of the saturated disks on the plate.
(3) Method for measuring zones of inhibition in millimeters.
(4) Quantified number of bacteria for the acceptance criteria.

(d) There was no raw data to substantiate all computer generated tables generated for the Preservative Validation Report for the Replacement of [redacted] in Urine Dipstick Products (dated 3/31/04).

(e) There was no protocol or documentation that the validation for the [redacted] filling machine has been performed. This equipment was used to fill vials of finished devices.

(f) There was no protocol or documentation that the validation for cap torquing has been performed. Your firm received [redacted] complaints for product leakage ([redacted]).

We have reviewed your response and have concluded that it is inadequate because for observation 4(a) you have not addressed why this repeat observation had not been corrected after the 2003 inspection; for observation 4(b) you have not addressed product currently on the market; and for observations 4(c) and 4(e) you have not explained the length of time until completion which appears to be excessive.

5) Employee training was not fully documented [21 C.F.R. 820.25(b)]. Specifically,

(a) There was no documented training for the CEO, President, or Quality Control Manager in the firm's current quality manual (includes the firm's quality policy), Revision F.

(b) There was no documented training for the Lead Auditor [redacted] or 2006 auditors, [redacted] and [redacted], in the firm's Internal Audit Procedure, QSP-17, Revision C.

Your response to this observation appears to be adequate.

6) Employees were not adequately trained [21 C.F.R. 820.25(b)]. Specifically,

(a) Only 16 out of approximately 60 employees received training in cGMP on 1/11/05 and no additional group training was held in 2006.

(b) Out of 11 initial training records reviewed, only 1 person ([redacted]) was documented as receiving cGMP training on 1/11/05 and again on 9/9/05. This employee was not documented as receiving the group training on 1/11/05.

(c) Employees were not always trained on changes to procedures and records.

(d) SOP-01-031, Quantimetrix Personnel Training indicates management follow-up in the effectiveness of training is to be performed via an oral/written examination with the results documented. Out of 11 plus training files reviewed, there were no documented training examination results maintained.

Your response to this observation appears to be adequate.

7) Employees were not made aware of device defects that could occur when they improperly perform their jobs [21 C.F.R. 820.25(b)(1)]. Specifically,

(a) A correction was made to the percentage of recovery on 10/3/05, from [redacted]% to [redacted]% that caused [redacted] at [redacted] degree C not to be within the [redacted]% specification. There was no nonconformance prepared.

(b) During real time stability, inaccurate recordings of WBC and RBC counts for Spinalscopics, Level 1, lot #46151 caused the product to be outside the 1-10 [redacted] ranges. There was no nonconformance prepared for the out of [redacted] ranges.

(c) During real time stability, inaccurate recordings of [redacted] and [redacted] for Spinalscopics, Level 1, lot #46161 caused the product to be outside the [redacted] range for [redacted]. There was no nonconformance prepared for the out of [redacted] range.

(d) Single [redacted] recordings for [redacted] and [redacted] for devices in the firm's real time stability program (Spinalscopics, lot #s 46161, 46152) are not made in accordance with the stability procedure, which requires recording the averaging of [redacted] units at each test interval.

We have reviewed your response and have concluded that it is inadequate because you have not addressed why the nonconformances were not prepared; we are therefore unable to evaluate your corrective action.

8) Quality audits were not conducted at sufficient regular intervals as prescribed by internal procedure to verify that the quality system is effective in fulfilling the quality system objectives [21 C.F.R. 820.22]. Specifically, the Internal Audit Procedure states the audit schedule is based on ensuring all elements of ISO 13485, IVD Directive and CMDCAS ISO 13485 are audited for not less than [redacted] per year.

(a) The Quality Control Department is scheduled for auditing during the lst quarter of a year. No auditing of this department was conducted in 2006. The last documented audit of this department occurred on 3/28/05.

(b) Sales & Marketing is scheduled for auditing during the 3rd Quarter of a year. No audit of this department was done in 2006.

We have reviewed your response and have concluded that it is inadequate because you have not addressed the lack of audits in 2006 and have not planned the corrective action for completion until the third quarter of 2007.

9) Individuals who conduct quality audits have direct responsibility for the matters being audited, in violation of 21 C.F.R. 820.22. Specifically, one ([redacted]) of the individuals who audited manufacturing on 3/6/06 had direct responsibility over the area he audited.

We have reviewed your response and have concluded that it is inadequate because you have not addressed how [redacted] was assigned to audit an area he had direct responsibility for and how management will correct that from happening in the future.

10) The Design History File was not established or maintained for the Liproprint LDL and HDL Subfraction System [21 C.F.R. 820.30(j)].

We have reviewed your response and have concluded that it is inadequate because you have not explained why it will take one year for correction.

11) The Design History File does not demonstrate that the design was developed following the approved design plan and the design control requirements of 21 CFR 820. Specifically, the design history file (DHF) for GlycoHemosure, Hemoglobin Alc (HbAlc) Control is incomplete or procedures were not followed. [21 C.F.R. 820.30(j)].

(a) The designated project leader did not maintain or update the file as required by your firm's design control procedure. There were unsigned computer generated copies for design activities (e.g. approval of design output, approval of 12/31/03 minutes for release of device to market). [21 C.F.R. 820.30(a)].

(b) The Design Input procedure for defining design inputs was not followed for the design inputs approved on 6/20/03. [21 C.F.R. 820.30(c)].

(c) Design outputs did not include test methods and a device master record. [21 C.F.R. 820.30(d)].

(d) The risk analysis is incomplete in that the risk analysis report dated 4/17/04, risk analysis for GlycoHemosure HbAlc Control Level 1 and 2 did not include the risks of microbial growth or contamination within the product. Additionally the risk analysis was not performed according to established procedures, SOP-12-007, Risk Analysis Procedure, which requires the risk analysis to be performed

utilizing the [redacted] approach but was not conducted or documented in this manner. [21 C.F.R. 820.30(g)].

(e) Acceptance criteria were not defined prior to performance of verification activities. For example, the GlycoHemosure device was developed for use on immunoassay or HPLC instruments. There is no acceptance criteria defined for the DCA 2000 instrument. [21 C.F.R. 820.80].

(f) Not all design reviews identified the independent person (e.g. 8/8/03, 9/29/03 and 12/31/03). [21 C.F.R. 820.30(e)].

(g) The 8/8/03 dated Meeting Minutes states a validation report (manufacturing process) will be based on three production batches by 12/31/03. No validation report has been written because only [redacted] production lots have been manufactured ([redacted]. [21 C.F.R. 820.75].

Your response to this observation appears to be adequate but we are concerned that the corrections are scheduled for completion in the third quarter of 2007. Your response should explain the need for this length of time.

12) The Design History File does not demonstrate that the design was developed following the approved design plan and the design control requirements of 21 CFR 820. Specifically, the firm's design control procedures were not followed for the Spinalscopics Control. There was no design plan in the DHF, there were no approved design inputs, and the risk analysis was not performed according to the firm's procedure, which requires the use of the [redacted] approach. The DHF also lacks documentation of design verification, design validation, design review, and design transfer activities.

Your response to this observation appears to be adequate but we are concerned that the correction is scheduled for completion in the third quarter of 2007. Your response should explain the need for this length of time.

13) Acceptance records did not include the results of certain acceptance activities [21 C.F.R. 820.80(e)(1)]. Specifically, real time stability tests are not conducted according to the firm's Stability Procedure. For example,

(a) The most recent production lot of [redacted] 32202) has not been entered into the firm's real time stability program.

(b) The most recent production lot of [redacted] has not been entered into the firm's real time stability program.

(c) No real time stability testing was performed at the [redacted] interval month because reagents were not on hand to perform the stability test (Worksheet for Dipper, lot #44391).

(d) No real time stability testing was performed on GlycoHemosure, lot #13010 at the [redacted] month interval because the firm did not retain a sufficient amount of product in inventory to perform the stability testing.

(e) Real time stability testing was not performed on GlycoHemosure Control, lot #13020 in a timely manner at the [redacted] months interval and no testing was performed during the [redacted] months interval. However, the expiration date was extended to 3/06.

(f) No real time stability testing of open and closed vials was performed on Spinalscopics, lot #46170 at the [redacted] months interval. Accelerated stability on closed vials (only) was performed in 10/06 to support the extended expiration date of 11/07.

We have reviewed your response and have concluded that it is inadequate because you did not explain why the nonconformance in observation 13(c) was not issued so that your corrective action could be evaluated; you did not explain your logic that allows the conclusion that the expiration date extension in observation 13(e) was appropriate; and for observation 13(f) you have not addressed product potentially on the market with inadequately supported expiration dates.

14) Software used as part of the production quality system was not validated for its intended use according to an established protocol [21 C.F.R. 820.70(i)]. Specifically,

(a) Spreadsheets intended to check for outliers and calculate mean, SC, % CV, value assignments for finished devices.

(b) Complaint handling software

(c) Quantrol database program

Your response to this observation appears to be adequate but we are concerned that the corrections are scheduled for completion in the fourth quarter of 2007. Your response should explain the need for this length of time.

15) Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements were not established [21 C.F.R. 820.50]. Specifically, independent laboratories evaluated production lots for the purpose of contributing to the device value assignments. Those laboratories were not on the approved vendor list.

Your response to this observation appears to be adequate but we are concerned that the correction is scheduled for completion in the third quarter of 2007. Your response should explain the need for this length of time.

16) Corrective and preventive action activities were not documented, including the actions needed to correct or prevent recurrence of nonconforming product and other

quality problems, and implementation of corrective and preventive actions [21 C.F.R. 820.100(b)]. Specifically,

(a) In 9/2000, the packaging of Lipoprint System LDL kits was changed by adding [redacted] in the [redacted] There were no records of the corresponding packaging validation. The corrective action is incomplete in that the packaging validation did not show repeatability, did not identify how many tubes were included in the transport stress test performed during the validation, and did not specify the shipping details, i.e., weight of the shipping carton. This is a repeat observation.

(b) Temperature recording charts for [redacted] indicated temperatures were outside the acceptable range on at least four (4) occasions. The corrective action required investigating the effect of temperature fluctuations on the product when the freezers were not within the acceptable range. This evaluation was not performed.

(c) Release testing results for Lipoprint lot #96350A were outside the acceptable range. There were no records indicating that the department supervisor was notified and there was no documentation of investigation/analysis for root cause. The firm's corrective action included retraining employees in cGMP practices. There is no documentation to show training of all employees.

Your response to this observation appears to be adequate but we are concerned that the corrections are scheduled for completion in the fourth quarter of 2007. Your response should explain the need for this length of time. Also, you have not addressed why observation 16(a) was not corrected after the 2003 inspection.

17) There was no corrective and preventive procedure to determine when verification can be conducted in lieu of validation [21 C.F.R. 820.100(a)(4)]. Specifically, Corrective and Preventive Action Procedure, QSR-14, effective 7/14/06, Rev J requires the QA/RA Department to determine the need for validating an action only. The procedure does not address verifying actions.

Your response to this observation appears to be adequate.

18) Appropriate sources of quality data were not adequately analyzed to identify existing and potential causes of nonconforming product and other quality problems [21 C.F.R. 820.100(a)(1)]. Specifically, trend reports, presented during management reviews, for data sources (e.g. power points of technical supports, complaints) from May 2005-May 2006 were not problem/product specific.

Your response to this observation appears to be adequate but we are concerned that the correction is scheduled for completion in the third quarter of 2007. Your response should explain the need for this length of time.

19) A justification for not reporting the correction or removal action to FDA that included conclusions and reviews by a designated person was not included in the correction or removal records [21 C.F.R. 806.20(b)(4)]. Specifically, there was no justification maintained for not reporting to FDA:

(a) A June 19, 2006 technical update suggesting the [redacted] dilution of [redacted] controls for use with the Icon 25 hCG kits due to possible partial or inhibition of reactivity, presenting as a weak positive or a false negative.

(b) A March 31, 2006 technical update limiting the use of The Dipper, Dropper, and Dropper Plus controls with pregnancy test kits.

(c) A January 26, 2006 technical update revising the QuanTest Human Protein Standards product insert changing the referenced NIST from SRM 927a (obsolete) to NIST SRM927c.

(d) A March 24, 2005 technical update reporting errors in the product insert in the values and ranges for the International System of Units for the HDL Plus Control.

(e) A July 26, 2006 technical update correcting errors in the Visual table used with The Dipper, The Dropper and The Dropper Plus Visual Examination.

(f) A January 11, 2006 technical update correcting the expected range for specific gravity for The Dipper, The Dropper, and The Dropper Plus.

(g) A June 16, 2006 technical update revising the expected range of [redacted] and [redacted] for the Dip and Spin control material.

(h) A November 8, 2006 technical update revising the expected range for [redacted] in response to customer inquiries concerning the [redacted] for Spinalscopics: Spinal Fluid Cell Count control.

(i) A January 6, 2006 technical update revising the reporting units from mg/dL to mg/L for Microalbumin using The Dipper, Dropper, Dropper Plus, and DipandSpin urine dipstick control material.

(j) A January 9, 2006 technical update correcting errors in the product insert for the Dip & Spin.

We have reviewed your response and have concluded that it is inadequate because you have not directly addressed the issue of why the justifications you provided in your response were not part of the record required by 21 C.F.R 820.20. Furthermore, the agency disagrees that the corrections referenced in observations 19(a) and (h) are not reportable because of serious consequences that could result from the incorrect validation

of pregnancy test kit performance in 19(a) or the potential need for an additional spinal tap in 19(h).

20) Complaint handling procedures for complaints were not implemented [21 C.F.R. 820.198(a)]. Specifically, [redacted] of [redacted] complaints reviewed exhibited failures of the device, its labeling, or packaging to meet specifications. These complaints were not investigated. [redacted] of [redacted] complaints did not include the reason for no investigation.

We have reviewed the documentation you submitted in your progress report and concluded it is not adequate because not all of the complaints covered by this observation were addressed. Furthermore, you have provided documents dated prior to the inspection which were not available during the inspection. You should explain why they were previously unavailable.

21) Records of a complaint investigation did not include appropriate corrective action [21 C.F.R. 820.198(e)(7)]. Specifically, microbial testing of Synovialscopics Control was performed on 4/19/05 as part of an investigation into a complaint of microbial contamination. Although there were no positive/negative controls run when the microbial test was performed, no corrective action was taken.

We have reviewed the documents submitted in your progress report and note the changes made to the manufacturing record. Your response to this observation appears to be adequate and we will confirm the adequacy of those corrections at your next inspection.

22) Written MDR procedures were not developed [21 C.F.R. 803.17]. Specifically, SOP 12-004, Medical Reporting, effective date 04/04/06, was developed to comply with reporting to the Competent Authority, not to FDA.

Your response to this observation appears to be adequate.

23) Schedules for the adjustment, cleaning and other maintenance of equipment were not implemented [21 C.F.R. 820.70(g)(1)]. Specifically, two instruments S/N 973496 and S/N 9847, used during testing of finished devices were observed on 11/27/06 as requiring preventative maintenance.

Your response to this observation appears to be adequate.

You should take prompt action to correct the violations addressed in this letter. 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 money penalties. Also, 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, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have

been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to:

Pamela B. Schweikert
Director, Compliance Branch
United States Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2506

If you have any questions about the content of this letter please contact: John J. Stamp, Compliance Officer at 949-608-[redacted].

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Sincerely,

Alonza E. Cruse
Los Angeles District Director

cc: Department of Health Services
Food and Drug Branch P.O.
Box 997413, MS-7602
Sacramento, CA 95899-7413