DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAY 9 2007

# WARNING LETTER

VIA FEDERAL EXPRESS {AND FACSIMILE}

Yoshihiko Nagata, Ph.D.
Plant Manager, Diagnostic Reagents Production
TOSOH AIA, Inc.
2, Iwasekoshi-Machi
Toyama City, Japan

Dear Dr. Nagata:

During an inspection of your firm located in Toyama City, Japan on December 4, 2006 through December 7, 2006, investigator(s) from the United States Food and Drug Administration (FDA) determined that your firm manufactures AIA-PACK PA PSA Assay and ST AIA-PACK PA PSA. 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, current procedure concerning electronic data storage in the 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 a response from Charles P. Gill, RA/Quality Assurance Manager dated December 22, 2006 concerning our investigator's observations noted on the Form FDA 483, List of Inspectional Observations that was issued to you. We address this response below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1. Failure to perform design verification to confirm that the design output meets the design input requirements, as required by 21 CFR 820.30(f).

For example: the protocol entitled "Verification Method Protocol" requires that the samples [redacted] containing the monoclonal antibodies, derived from the bioreactors, be stored at [redacted]C and [redacted]C for [redacted] and [redacted] days; however, the final report entitled "Design Process Change Verification" document revealed that the samples were placed in an incubator at [redacted]C at [redacted] relative humidity suggesting that the humidity was neither monitored nor recorded; you failed to document the storage details such as the initial placement, any movement and/or the identification of the refrigerators in which the samples were stored at [redacted]C and tested at months [redacted] and [redacted] as required by their established stability protocol [redacted] you failed to adhere to the requirements established by the stability protocol [redacted] in that, the method for tracking (i.e. Microsoft Excel) the number of samples placed in the incubator was unauthenticated.

We have reviewed your response and have concluded that it is inadequate because although, sections "7.3 Design and Development", "7.5.1.2 Storage of Record" and "List of Quality Record" of the "Quality System Procedure" were revised to ensure that relevant data is explicitly included and controlled in the procedure, you failed to verify that the design outputs met the desired inputs. Secondly, the format of the equipment control ledger for refrigerators and incubators; as well as, the new record format used in the validation study have been revised and implemented to fully document design validation activities; however, no documentation was provided to demonstrate that measurable design outputs were adequately defined to complete design validation activities.

2. Failure to store records so as to minimize deterioration, prevent loss and back up of automated data processing systems as required by 21 CFR 820.180.

For example: the electronic data did not correlate with the paper records; you had not established an electronic data back-up procedure; and finally, data was copied onto the server from one system to the next via floppy; therefore, no limited access or data protection had been established.

We have reviewed your response and have concluded that it is inadequate because you failed to encrypt and/ or physically secure your data back-up system to comply with the requirements to prevent deterioration or deletion of the analyzer data. Your revision to the current "Quality System Procedure", with regard to the electronic data storage, to include: a data back-up system using CD-R (non-rewritable CD); as well as, to require the most responsible person to make photocopies of the serial paper print out and maintain an electronic file has been noted.

3. Failure to adequately validate the intended use of this PC and its software, as required by 21 CFR 820.70(i).

For example: the dedicated PC [redacted] attached to the [redacted] was not secure in that access to the data on [redacted] was not granted by a unique username and password or equivalent method; there was no documentation associated with the electronic data for whom was responsible for collection of the analytical results as several quality control personnel have access to the [redacted], no software changes in the study data could be detected as there was no audit trail capability; and finally, the electronic data did not correlate with the paper records.

We have reviewed your response and have concluded that it is inadequate because no system validation was conducted to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

A follow up inspection will be required to assure that corrections are adequate. We will contact the appropriate people and request an establishment re-inspection. An FDA trip planner will be in touch with you to arrange a mutually convenient date for this inspection.

You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action, which may include detaining your devices without physical examination upon entry into the United States until the corrections are completed. Section 801(a) of the Act (21 U.S.C. § 381(a)) Also, U.S. 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 violation(s), or similar violation(s), 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. If the documentation is not in English, please provide a translation to facilitate our review.

Your response should be sent to: James Woods (HFZ-440), 2098 Gaither Road, Rockville, MD 20850. If you have any questions about the content of this letter please contact: Cecily Jones at 240-276-0493 or 240-276-0652.

Finally, you should know that this letter is not intended to be an all-inclusive list of the violation(s) at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violation(s) 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 violation(s), and take prompt actions to correct the violation(s) and to bring your products into compliance.

Sincerely yours,

S. Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Office of In Vitro Diagnostic
Device Evaluation and Safety
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