U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Tosoh Bioscience Inc 8/5/16

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Cincinnati District Office
Central Region
6751 Steger Drive
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August 5, 2016

WARNING LETTER **VIA UPS**
CIN 16-505636-19

Yosuke Yamaski
President
Tosoh Bioscience, Inc.
6000 Shoreline Court
Suite 101
San Francisco, CA 94080

Dear Mr. Yamaski:

During an inspection of your firm located at 3600 Gantz Road, Grove City, OHon various days between May 16 – June 28, 2016, an investigator from the United States Food and Drug Administration (FDA) determined that your firm is the initial importer, complaint handling unit, and repacker/relabeler of High Performance Liquid Chromatographs (HPLC) used in the measurement of hemoglobin, Automated Immunoassay Analyzers (AIA) used in the treatment of disease, and laboratory solutions, assays and test-cup reagents. Your firm also manufactures a hemolysis and wash solution used with the HPLC devices. 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 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 (CFR), Part 820. We received a response from Susan Koss, Quality Assurance/Regulatory Manager, dated July 15, 2016, concerning our investigator's observations noted on the Form FDA 483, List of Inspectional Observations (FDA 483) that was issued to your firm. 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 review, evaluate and investigate any complaint involving the possible failure of a device, labeling or packaging to meet any of its specifications, as required by 21 CFR 820.198(c) . Specifically, your "Complaint Handling" procedure, revision 12.0, dated 11/19/2014; and "**(b)(4)** Documentation TSG" procedure, revision 11.0, dated 12/12/2014 do not ensure that all complaints are reviewed, evaluated and investigated. For example:

a) Over 15 Ticket Reports (non-routine service reports) reviewed by the FDA investigator document possible failures of AIA and HPLC analyzers. The Complaint section in your **(b)(4)** database was not completed and Investigation Form, 10-QAG-015-2 was not initiated, as required by section 6.0 of your Complaint

Handling procedure. For example: Ticket number 862-02-000256, dated 9/2/2015, states that the wrong software version was installed with the G8 analyzer; and Ticket number 001-00050034, dated 8/4/2015 states the customer was "Getting error message, and 338 as comm error" and ASM Board was replaced. No investigations were performed.

b) Service calls received on analyzers under warranty are not considered complaints, as defined by your procedures, and no complaint investigation is performed. For example, Ticket Report number 001-00-055919, dated 4/8/2016 for a G8 analyzer, which was installed on or around 1/20/2016, states that the customer was "getting a low pressure error when she runs Pt samples. Your service representative documented that he replaced the defective SV3 valve on the analyzer. The Complaint section in your **(b)(4)** database was not completed and Investigation Form, 10-QAG-015-2 was not initiated, as required by section 6.0 of your Complaint Handling procedure.

Your response is not adequate. Your response states that you are revising your procedures, but it does not address performing a retrospective review of Ticket Reports to determine which reports should have been documented as a complaint, and that these complaints will be evaluated and failure investigations will be performed, if necessary.

2) Failure to establish and maintain adequate procedures for implementing corrective and preventive action that shall include requirements for analyzing processes, work operations, concessions, audit reports, quality reports, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming products, or other quality problems, as required by 21 C.F.R. § 820.100(a)(1). Your "**(b)(4)** Documentation TSG" procedure, revision 11.0, dated 12/12/2014; "Trending Procedure", 10-QAG-019-0, Revision 9.0, dated 12/13/2016; and "Corrections, Corrective Actions, Preventive Actions" procedure, 10-QAG-010-0, Revision 8.0, dated 03/21/2013 are not adequate in that :

a) You have not implemented your above procedures in that you did not initiate a Corrective Action Request Form for the trend found indicating that the AIA-900 Pickup Arm or motor on the pickup arm exceeded your failure rate tolerance limit of ≤ 2%.

b) All sources of quality data are not being analyzed. Specifically,

i) Nonconformances, (i.e. leaking bottles), found during the manufacturing of the Hemolysis and Wash Solution, are not being analyzed to identify existing and potential causes of nonconforming product and other quality problems.

ii) Service and Complaint Ticket Reports opened as "warranty" are not being analyzed to identify existing and potential causes of nonconforming product and other quality problems.

iii) Complaints on "consumable" products such as needles, cups, and analyzer accessory kits are not being analyzed to identify existing and potential causes of nonconforming product and other quality problems.

c) You have not identified appropriate statistical methodology to be employed to detect recurring quality problems. Specifically,

i) Your "Trending Procedure" only applies to devices with an installed base of 100 or more units. For example, service and complaints received on the AIA 1800 analyzers are not analyzed to identify existing and potential causes of nonconforming product because there are less than 100 units in distribution.

ii) The information entered into the Area/Category/Issue sections of your **(b)(4)** database is not standardized and the Type is not always entered so the failure rate per part cannot be accurately calculated. As a result, you are not identifying failure rates per part that are above your thresholds for initiating a CAPA, as described in your "Trending Procedure".

Your response is not adequate. Your response states that you are revising your procedures, but it does not address performing a retrospective analysis of all data sources to determine if corrective action and preventive action should be opened and investigations of existing and potential causes of nonconforming product and other quality problems will be initiated.

3) Failure to verify and validate corrective and preventive actions to ensure that such actions are effective and do not adversely affect the finished device, as required by 21 CFR 820.100(4).

Your response cannot be assessed at this time. You response states that you will be revising your CAR form Template and reviewing CAR #20015-005 by August 30, 2016. Please provide an update regarding your corrective action.

4) 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. Specifically

a) Your "Supplier Quality System Review and On-Site Audits" procedure, 05-SCM-003-0, revision 7.0, dated 8/21/2015 does not describe your requirements, including quality requirements, for the three supplier risk levels (High, Moderate and Low).

b) Your 2016 Supplier Review did not ensure that your suppliers are adequately evaluated and monitored. Tosoh has received complaints on 2 of the 11 suppliers reviewed by the FDA Investigator. Your 2016 review of these 2 suppliers stated "No recorded complaints".

Your response is not adequate. Your response states that you will revise your procedures. It does not address reevaluating your suppliers to assure they meet all specified requirements.

5) Failure to establish and maintain schedules for the adjustment, cleaning and other maintenance of equipment to ensure that manufacturing specifications are met, as required by 21 CFR 820.70(g)(1). Specifically, your "Equipment Preventive Maintenance" schedule, 07-SRG-005, revision 4, is not being implemented in that:

a) The schedule states for the **(b)(4)** Water, which is used to purify the water used in manufacturing the Hemolysis and Wash Solution, to "Replace Cartridges and sanitize bowl/heads 1 yr or if pressure becomes too high". Your procedure does not specify a pressure limit but the **(b)(4)** instruction manual states the cartridge should be changed "with a membrane cartridge installed in Bowl #4, and the pressure differential between #3 exceeds 10 psi". Device History Records for Lots HW-389-JU and HW-380-JU each showed a 20 psi pressure differential. The cartridge has not been replaced.

b) The schedule states for the Main Warehouse Refrigerator to "Inspect quarterly (TSMD log)". There are only 3 "WALK IN COOLER/FREEZER" forms completed in 2015 and there are no forms/records of inspection for 2016.

Your response cannot be assessed at this time. You state that you will revise your procedures to reference the appropriate documentation for the **(b)(4)** system in use; and will review your procedures for the Refrigerator Maintenance and assure the PM is completed by August 30, 2016. Please provide an update regarding your corrective action.

6) Failure to establish and maintain procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system, as required by 21 CFR 820.22.

Specifically, your "Quality System Audits and Auditor Training" procedure, 02-QAG-006-0, revision 7, dated 7/17/2015 does not address reaudits of deficient matters, and your Manager of Regulatory Affairs and Quality Assurance stated that reaudits are not performed.

Your response is not adequate. Your response states that you will revise your audit procedure to include reaudits, but it does not address reviewing previous audits to determine if reaudits of deficient matters need to be completed and conducting and documenting these reaudits.

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.

We are requesting that you submit to this office, according to the schedule below, certification by an outside expert consultant that he/she has conducted an audit of your establishment's manufacturing and quality assurance systems relative to the requirements of the device quality system regulation (21 CFR Part 820). You should also submit a copy of the consultant's report, and certification by your establishment's Chief Executive Officer (if other than yourself) that he or she has reviewed the consultant's report and that your establishment has initiated or completed all corrections called for in the report. The initial certifications of audit and corrections should be submitted to this office by the following date:

- Initial certification by consultant and establishment – February 1, 2017.
- Subsequent certification – February 1, 2018.

Additionally, please contact the compliance officer listed below to schedule a regulatory meeting to discuss the deficiencies found during the inspection and your corrective action plan.

Please notify this office in writing within fifteen working days from the date you receive this letter of the specific steps that 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: Ms. Gina Brackett, Compliance Officer, Food and Drug Administration, 6751 Steger Drive, Cincinnati, Ohio 45237. If you have any questions about the content of this letter please contact Ms. Brackett at (513) 679-2700, ext. 2167, or by facsimile at (513) 679-2773.

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 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 Yours,
/S/
Steven B. Barber
District Director
Cincinnati District

More in 2016 (/ICECI/EnforcementActions/WarningLetters/2016/default.htm)