

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Food and Drug Administration 10903 New Hampshire Avenue Bldg. 51, Room 4225 Silver Spring, MD 20993 Phone: 1-301-796-3206 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION June 13-17, 2016
	FEI NUMBER 3002806840

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Homare Tachiyangi, General Manager

FIRM NAME Sekisui Medical Co., Ltd.	STREET ADDRESS 4-115, Matsuo
CITY, STATE AND ZIP CODE Iwate 028-7305 Japan	TYPE OF ESTABLISHMENT INSPECTED API Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION #1

Failure to maintain and review all raw data.

1. Until 06 June 2016, procedures did not require that all raw data be maintained. Only reported data was maintained. Analysts deleted or did not submit test data that would not be reported. This was done without oversight. Review of electronic files from the HPLC and GC computers found the presence of hundreds of deleted or unreported chromatograms. Deleted files were also observed on the IR-3 system.

Examples of deleted or unused chromatograms included:

a. The computer for GC-4 and GC-6 had deleted individual chromatogram files and deleted folders containing sequences with associated chromatograms in the "Recycle Bin". Deleted data for testing of (b) (4) lot (b) (4) as part of sequence 150909 was restored. It showed an original sequence with 11 injections from 09-10 September 2015. These were deleted on 31 May 2016 without any documented reason. A new sequence for the same lots was repeated on 11 September 2015 and the data was used to report results.

b. (b) (4) testing of batch (b) (4) was started on 28 February 2014 on HPLC 16. The duplicate injections showed a differing peak appearance. The test was repeated again on 02 March 2014, which showed additional abnormal peak appearance. Testing was repeated a third time on 03 March 2014 and instead performed on HPLC 15 with conforming results. Only the data from the third test was reported.

c. In sequences 160309 and 160115 on HPLC 16, individual chromatograms were deleted and then replaced with new chromatograms with the same name as the original file.

2. No raw data could be provided to support the recovery method of the cleaning validation sampling method for (b) (4).

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3. Complete raw data relating to sample preparation times, weights, media lot numbers, and incubators used were not maintained for the microbial testing and endotoxin testing performed during cleaning validation of (b) (4) (b) (4).

OBSERVATION #2

Failure to prevent unauthorized access of changes to data and to provide adequate controls to prevent omissions of data.

1. Electronic GC chromatography data from GC-7, collected prior to March 2016, was not available for review. This instrument was used for release testing of (b) (4) and (b) (4), products for the US market. The stand-alone computers associated with the GC were discarded. Data was backed-up onto an external drive, but could not be restored at the time of the inspection. No tests were conducted to verify the back-up process would work prior to disposing of the computers that contained the source raw data.

2. The data back-up process for the standalone HPLC and GC systems does not include back-up of audit trails associated with the analysis. During the inspection the stand-alone computer associated with HPLC-19 was not functional. Audit trail information could not be retrieved from the back-up.

3. Electronic chromatography data is stored on stand-alone systems for seven of the (b) (4) HPLCs and one of the (b) (4) GCs. There are no controls to prevent deletion of the source data. Analysts reported that they have deleted files directly from the source data on the hard drive of the computer.

4. Only hard copy chromatograms are reviewed. The EZ Chrome generated reports for printing chromatograms are not protected. This software is used for five of the (b) (4) HPLCs. Analysts can change sample identifications or dates on the chromatograms prior to printing.

5. Chromatograms were reviewed that had no corresponding entries in the audit trail records. For example, analysis performed on 03 March 2014 for (b) (4) lot (b) (4) for HPLC 15. The chromatograms are dated 03 March 2014, but there are no entries in the audit trail between 28 February 2014 at 9:27 and 04 March 2014 at 10:09.

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6. Audit trail reviews are limited to only checking the audit trail against the written instrument log.
7. Toximaster software is used to collect data for endotoxin testing of finished API samples. The software does not require username/passwords, there are no audit trails, and electronic data can be deleted.
8. Electronic data for FTIR IR-3 was stored on the hard drive of the associated computer. There were no controls to prevent deletion of data and deleted FTIR data was observed in the computer "Recycle Bin". This system that was used until 19 February 2016 and lacked username/passwords and audit trails.
9. The TOC used for testing water conductivity has an audit trail that is archived by the software (b) (4) and then cleared. The laboratory personnel are unable to access the archived audit trail data. During the inspection no audit trail entries prior to 06 June 2016 could be reviewed.
10. Passwords used to access analytical software are assigned by a manager that also knows the analyst's password.

OBSERVATION #3
 Failure to design and monitor the water system to ensure it is suitable for its intended use.

Non-sterile APIs manufactured in Plant (b) (4) and (b) (4) are intended to be used in the preparation of sterile finished dosage products for the US market.

1. Dead leg sections of piping, where water remains stagnant for extended periods of time, were observed in the (b) (4) water distribution system.
 - a. Below the (b) (4) tank VE-320 in Plant (b) (4) there is a dead leg section of piping at least (b) (4) meters in length. The piping is used to deliver (b) (4) water to (b) (4) tank RE-301, used for (b) (4) manufacturing.
 - b. Inside of the Plant (b) (4) cleanroom, there is a dead leg section of piping approximately (b) (4) inches in length in the water distribution system to deliver (b) (4) water to the (b) (4) (b) (4) -301. This section of piping never gets

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sanitized.

2. Monitoring of the (b) (4) water system does not include sampling at all of the use points that deliver water to the production process or for cleaning equipment. Plant (b) (4) has (b) (4) use points, but only (b) (4) are included in the water monitoring sampling plan. There are (b) (4) use points in Plant (b) (4), but only (b) (4) are included in the water monitoring sampling plan.

For example, in Plant (b) (4) there is no sampling at the point of use for the (b) (4) tank RE-301, at the point of use for the (b) (4) tank in the clean room, at the (b) (4) (b) (4) -301 inside of the clean room, or at all of the use points in the clean room that supply water for cleaning equipment in the (b) (4) steps of the API production.

3. Validation of the water system has never included increased sampling from all points or at frequency more often than (b) (4) times per (b) (4) for microbial tests and (b) (4) per (b) (4) for endotoxin.

4. In the Plant C (b) (4) water system, a leak was observed from the pump at the distribution loop. Beneath this area of the water system there was standing water on 14 June 2016 due to this leak. The leak and standing water were still present on 17 June 2016.

5. In the Plant (b) (4) (b) (4) water system, leaks were observed from the pipe taking (b) (4) water from the (b) (4) unit to the holding tank and from the pipe taking water from the holding tank to the distribution loop pump. A leak was also observed from a valve in the use point (point not identified) near the clean room (b) (4).

6. During water sampling, samples are taken directly from valves on the loop. During routine use, these valves always have flexible hoses, up to (b) (4) meters in length, connected to them. No data has been collected to evaluate whether these hoses affect the quality of the (b) (4) water where it is actually used.

7. Permanent piping supplying (b) (4) water from the loop to the (b) (4) tanks in Plant (b) (4), which are used for (b) (4), are never sanitized.

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- The (b) (4) water system is not monitored for objectionable organisms.
- A city water supply line inside of the clean room was observed to be leaking.

OBSERVATION #4
Failure to ensure cleaning procedures are effective.

- Cleaning validation for the equipment used in Plant (b) (4) did not include microbiological or endotoxin evaluation. The equipment is used to manufacture (b) (4) for the US market, which is a non-sterile API used for the preparation of sterile finished drug products. The cleaning process includes rinsing with purified water, but no sanitization steps.
- Maximum campaign lengths for (b) (4) have not been established.

OBSERVATION #5
Equipment is not maintained and cleaned.

- (b) (4) sheeting is taped to the (b) (4) of tanks in the clean room of Plant (b) (4) to protect them from rusting. The (b) (4) is left in place during production campaigns. On 14 June 2016 this (b) (4) sheeting was observed to hold stagnant water that was (b) (4) in color and had suspended solids in it (b) (4) tank RE-4002.
- Tape was put over the (b) (4) water lines in the Plant (b) (4) clean room to protect the piping from product powder. Deposits of what was identified to be product was observed under this tape on 14 June 2016.
- Tape is used throughout the clean rooms to make repairs or protect equipment.
- (b) (4) applied to equipment and surfaces in the clean room is not smooth and cleanable.
- The floor was not adequately sealed under the recovered (b) (4) receiving tank RE-303 in the Plant (b) (4) clean room. Pieces of the floor were chipping off and could be observed at a floor drain on 14 June 2016.

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6. The (b) (4) (b) (4) -4002 in the clean room of Plant (b) (4) had rust stains.

OBSERVATION #6

Process validation has not demonstrated the process is in a state of control.

1. Process validation studies have not included statistical evaluation of variability within a batch or between batches. Studies have not included statistically sound sampling plans. A (b) (4) sample from (b) (4) batch is taken during process validation batches.
2. (b) (4) process reviews lack complete trending of critical testing results and process monitoring results.
3. Actions are not taken to adjust established limits as a result of ongoing process verification. Specifically, acceptable yield ranges do not reflect historical data. As a result, when there are variations in yield results, these are not identified and further investigated.

OBSERVATION #7

Failure to establish scientifically sound and appropriate test procedures.

1. The impurity methods used for stability testing of APIs for the US market have not been shown to be stability indicating. For example, (b) (4), (b) (4), and (b) (4). No forced degradation studies have been conducted.
2. Total aerobic count and yeast and mold test performed on the finished APIs for the US market have not been validated.
3. Manual integration is commonly used by analysts processing data from the Chromeleon software. There are no procedures to describe when manual integration is permitted, how to perform it, or how it will be reviewed.
4. Only hard copy chromatograms are printed for review. The printed chromatograms do not allow for adequate

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review of the integration being performed.

OBSERVATION #8
 Failure to ensure the APIs meet established specifications for quality and purity.

(b) (4) batches with unknown peaks present in the residual solvent chromatograms were released without further investigation. Unidentified peaks were observed with a retention time of approximately (b) (4) - (b) (4) minutes, in some, but not all (b) (4) batches. For example, review of a sequence performed on 12 April 2016 showed extra peaks at this retention time in approximately 7 of the 20 batches tested.

An additional peak present with a retention time of approximately (b) (4) minutes is present at varying levels in all batches. This peak has not been identified and is not described in the impurity profile.

OBSERVATION #9
 Failure to establish impurity profiles.

Complete impurity profiles have not been established for the US market API products.

OBSERVATION #10
 Failure to establish a system to control the issuance of documents.

The production department prints blank copies of GMP forms, including batch records. The laboratory department prints analytical worksheets for documenting analyses. Issuance, use, and reconciliation of these GMP records are not documented.

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