DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301) 796-3334 Fax: (301) 847-8738 CDEROSIAB@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	11/13-17/2017
	FEI NUMBER 3002808534

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Masaru Matsui, President and CEO

FIRM NAME	STREET ADDRESS
Yuki Gosei Kogyo Co., Ltd.	Ochiai 788, Joban Nishigo-machi
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Iwaki-shi, Fukushima, 972-8316, Japan	API Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

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

OBSERVATION 1

Laboratory control procedures are not followed.

Specifically, during my review of your firm's Quality Control Laboratory electronic chromatography data, deviations from the firm's written laboratory control procedures were identified. The original injections and/or processed injections are not reported, and no investigation is initiated as required per SOP JHA405, titled "The Procedure for Deviation", effective date 09/15/17 and SOP JHA419, titled "The Procedure for Out of Specification", effective date 09/11/15. Additionally, trial sample analyses are performed prior to the start of the reported sample analysis. The results of these trial sample analyses are not reported in official QC analytical batch records.

1. HPLC

A. Raw Material (b) (4) Lot No. (b) (4) used in manufacture of domestic (Japan) (b) (4) API, testing for related substance and impurities.

-The original analysis was performed on 06/07/17 starting at 11:55 am on HPLC LC030. The result was not reported in the official analytical batch record and no deviation, investigation, or OOS was initiated.

-The official/reported analysis was initiated on 06/07/17 starting at 16:59 (4:59 pm) on LC023.

B. (b) (4) API, Lot No. (b) (4) testing for related substance.

-The original analysis was performed on 07/28/15 starting at 13:45 (1:45 pm) on HPLC LC027. The result was not reported and no deviation, investigation, or OOS was initiated.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Arsen Karapetyan	Arsen Karapetyan, Investigator	11/17/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301) 796-3334 Fax: (301) 847-8738 CDEROSIAB@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	11/13-17/2017
	FEI NUMBER 3002808534

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Masaru Matsui, President and CEO

FIRM NAME	STREET ADDRESS
Yuki Gosei Kogyo Co., Ltd.	Ochiai 788, Joban Nishigo-machi
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Iwaki-shi, Fukushima, 972-8316, Japan	API Manufacturer

-A sequence with approximately (b)(4) injections of Lot No. (b)(4) was performed on 07/28/15, starting at 16:18 (4:18 pm) on HPLC LC027. The results were not reported and no deviation, investigation, or OOS was initiated.

-The official/reported analysis was initiated on 07/28/15 starting at (b)(4) on HPLC LC029.

-Another analysis was performed the next day on 07/29/17 starting at 13:52 (1:52 pm) LC027. The results were not reported and no deviation, investigation, or OOS was initiated.

C. (b)(4) Lot No. (b)(4) testing or related substance, (b)(4) manufactured by your firm, used in industrial and in food additives per your QC Manager.

-An unreported same trial injection for "Lot No. (b)(4) Sample Solution (b)(4)" was performed on 11/10/14 starting at (b)(4) on HPLC LC027. The result was not reported.

-An unreported sample trial injection with sample name as "Blank" was performed on 11/11/14 starting at 11:30 am. This result was not reported.

-Original analysis for Lot No. (b)(4) Lot No. (b)(4) and Lot No. (b)(4) was performed on 11/11/14 starting at (b)(4) These results were not reported.

-An unreported sample trial injection with sample name as "Blank" was performed on 11/12/14 starting at 11:23 am. This result was not reported.

-An unreported sample trial injection with sample name as "Blank" was performed on 11/12/14 starting at 14:17 (2:17 pm). This result was not reported.

-An unreported sample trial injection with sample name as "Blank" was performed on 11/12/14 starting at 14:34 (2:34 pm). This result was not reported.

--The official/reported analysis was initiated on 11/13/14 starting at (b)(4) on HPLC 027.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
		Arsen Karapetyan, Investigator	11/17/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301) 796-3334 Fax: (301) 847-8738 CDEROSIAB@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	11/13-17/2017
	FEI NUMBER 3002808534

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Masaru Matsui, President and CEO

FIRM NAME	STREET ADDRESS
Yuki Gosei Kogyo Co., Ltd.	Ochiai 788, Joban Nishigo-machi
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Iwaki-shi, Fukushima, 972-8316, Japan	API Manufacturer

2. GC

A. Lot No. (b) (4) Lot No. (b) (4) Lot No. (b) (4) and Lot No. (b) (4) for residual solvent test for (b) (4) API for domestic market (Japan).

- Loose unidentified analytical scale printouts for Lot No. (b) (4) Lot No. (b) (4) Lot No. (b) (4) and Lot No. (b) (4) testing for residual solvent via GC, for drug substance (b) (4) manufactured for domestic (Japan) market. These printouts were not reported in official analytical batch records because the samples were retested, with no deviation or explanation as to why at the time.

-Residual solvent testing for (b) (4) API based on the above printouts were performed on 01/24/17, at approximately 15:12 (3:12 pm) and ending on 01/25/17 at approximately (b) (4). The results were not reported and no deviation, investigation, or OOS was initiated.

--The official/reported analysis was initiated on 01/28/17 starting at (b) (4) on GC019 and ending on 01/28/17 around (b) (4).

OBSERVATION 2

Records associated with drug substance production and within the retention period for such records, were not made readily available for authorized inspection.

Specifically, on 11/13/17 during my walk-through inspection of your firms Administrative/Quality Assurance Unit building, I randomly selected different rooms and different QA personnel desks to observe and review records, starting around 1:15 pm. Later in the afternoon, during my walk-through inspection of your firm's QC building on 11/13/17, upon entering the second floor QC test room # 1, around 2:20 pm I observed through the glass portion of the door several analysts moving in quick manner, with one analyst specifically near a window. This analyst appeared to close the window and with the other analysts quickly separated from one another, all of which was observed through the glass portion of the door before I entered the room. Upon entering the room, I questioned

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Arsen Karapetyan, Investigator	11/17/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301) 796-3334 Fax: (301) 847-8738 CDEROSIAB@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	11/13-17/2017
	FEI NUMBER 3002808534

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Masaru Matsui, President and CEO

FIRM NAME	STREET ADDRESS
Yuki Gosei Kogyo Co., Ltd.	Ochiai 788, Joban Nishigo-machi
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Iwaki-shi, Fukushima, 972-8316, Japan	API Manufacturer

the analyst near the window and he stated that the window was opened prior to my arrival due to a foul odor, which he was closing when I observed him. After approximately 40 minutes on the second floor, and reviewing contents of randomly selected analyst desks in the QC office which is next to QC test room # 1 with its own entrance and exit, I proceeded to QC first floor near the meeting/break room to get drinking water. When I asked if we could sit inside the meeting/break room, firm personnel opened the door, at which point I noticed 2 other firm personnel inside with records in front of them. As I took a seat, I noted the presence of approximately 4 plastic bags, with approximate 8-12 inches high documents in each bag and approximately 5 bins full of approximately 55 reagents and test batch samples scattered on the floor and chairs within your firm's QC building meeting/break room. For the next approximate 4 hours, I interviewed and went through each document with at least (b)(4) analysts. Per the analysts, their desks were "not organized and messy" and they did not want me, the FDA investigator, to see this. In all, I spent approximately 7 hours of inspectional time with respect to this incidence. The contents of documents and items identified within the room are described in Observation 1, Observation 4, and Observation 5.

In addition, on 11/14/17 and 11/16/17, during my review of HPLC raw data for approximately 11 hours of inspectional time, and my subsequent interviews with analysts responsible for performing the tests, I encountered significant time delays in receiving analytical batch records with all accompanying relevant records and due to asking the same question many different ways due to incomplete answers by analysts.

OBSERVATION 3

Supervisory oversight over the laboratory electronic systems and data is deficient.

Specifically,

The current versions of HPLC and GC systems used by your firm for testing are Open LAB CDS Chemstation Edition A01.04 network software system and more than 7 standalone HPLC and GC systems.

1. There is no data integrity program in place to include a statistically sound representative review of all electronic data (network and standalone) by the Quality Unit to ensure completeness, consistency, and accuracy of all chromatographic raw data generated by the Quality Control (QC) laboratory. In addition, your firm's QC

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
		Arsen Karapetyan, Investigator	11/17/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301) 796-3334 Fax: (301) 847-8738 CDEROSIAB@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	11/13-17/2017
	FEI NUMBER 3002808534

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Masaru Matsui, President and CEO

FIRM NAME	STREET ADDRESS
Yuki Gosei Kogyo Co., Ltd.	Ochiai 788, Joban Nishigo-machi
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Iwaki-shi, Fukushima, 972-8316, Japan	API Manufacturer

electronic review procedure for analytical test data worksheets associated with final API was recently implemented approximately 1 month prior to the start of this inspection. Finally, your firm has not performed a statistically sound representative review of retrospective electronic data. During the current inspection, deviations from your normal laboratory procedures with respect to data integrity were observed.

2. Administrator role for computer systems, which includes your firm's computer laboratory electronic system, is assigned to your firms QA Manager, as of one month ago. Under the QA Manager, there are (b) (4) System Managers who belong to the QC Unit. During the inspection, on 11/16/17, I observed a System Manager from the QC Unit instructing your system administrator during my request for a demonstration of how users and created and deleted. This administrator has the authority to create and delete names, conducts data backup activities, delete data, and access to raw data for Open LAB CDS Chemstation and other testing programs, and as such, should be independent of the QC Unit. Additionally, on 11/13/17, I observed a QC Analyst transfer raw data from the Network Server to the C Drive of the LC30 equipment, where it was available to view on the LC30 Open LAB interface.

3. During the inspection of your QC Test Room # 1 on the second floor of the QC building, where multiple electronic balance scales are located, I observed several Shimadzu and Sartorius electronic scales with functional printers. It was discovered that the password function for date/time was not locked and restricted from QC personnel. Printouts from these electronic scales are used as original records to document weighing of materials and samples and are attached to analytical batch records. Per your firm, 12 out of (b) (4) electronic scales do not have a password function option for date/time to be locked.

OBSERVATION 4

The Quality Unit lacks adequate control of expired laboratory reagents, samples to be tested and finished batches. Specifically, during the inspection, on 11/13/17, I noted the presence of approximately: 25 uncontrolled expired reagents to be discarded, 11 unopened reagents and 17 samples with respect to manufacturing operations to be tested, located in your firms meeting/break room in the QC building.

Additionally, on 11/15/17, during my walk-through of the (b) (4) plant, I observed two unidentified (no labels) drums located on the top shelf, in an approximate (b) (4) square foot shed with a rollup tarp. Firm personnel, were

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
		Arsen Karapetyan, Investigator	11/17/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301) 796-3334 Fax: (301) 847-8738 CDEROSIAB@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	11/13-17/2017
	FEI NUMBER 3002808534

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Masaru Matsui, President and CEO

FIRM NAME	STREET ADDRESS
Yuki Gosei Kogyo Co., Ltd.	Ochiai 788, Joban Nishigo-machi
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Iwaki-shi, Fukushima, 972-8316, Japan	API Manufacturer

not able to bring down these drums due to their weight, however, the very next day on 11/16/17, your firm identified these two drums as containing (b)(4) lots of (b)(4) ((b)(4) manufactured on or around May 2013 and February 2014 for validation of product composition.

OBSERVATION 5

The Quality Unit lacks adequate controls of GMP documents.

Specifically, during the inspection, I noted the presence of uncontrolled records for a number of cGMP records purported to be controlled under your document control program outlined in SOP JHA408, titled "YGMP Document Control", effective date 03/10/2017, among other procedures. A summary of documents/records identified in the QC building, meeting/break room area during the inspection is as follows:

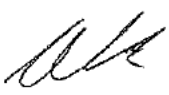
1. On the Job training records with worksheets and chromatograms and documentation of training records belonging to at least (b)(4) analysts.
2. Recently completed analytical testing batch records that were being "double checked" by a second analyst.
3. Blank laboratory analytical batch records for items such as reagent preparation activities.
4. Loose unidentified analytical scale printouts for Lot No. (b)(4) Lot No. (b)(4) Lot No. (b)(4) and Lot No. (b)(4) esting for residual solvent via GC, for drug substance (b)(4) manufactured for domestic (Japan) market. These printouts were not reported in official analytical batch records because the samples were retested, with no deviation or explanation as to why at the time.

OBSERVATION 6

Document control of laboratory testing records by the Quality Unit is inadequate.

Specifically,

The Quality Assurance Unit lacks adequate control over the issuance of laboratory batch records and QA related records purported to be controlled under the following procedures: SOP JHA424, titled "Manufacturing Operation Procedure", effective date 11/1/17; SOP JHA420, titled "YGMP Document and Record Generation Procedure",

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
		Arsen Karapetyan, Investigator	11/17/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301) 796-3334 Fax: (301) 847-8738 CDEROSIAB@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	11/13-17/2017
	FEI NUMBER 3002808534

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Masaru Matsui, President and CEO

FIRM NAME	STREET ADDRESS
Yuki Gosei Kogyo Co., Ltd.	Ochiai 788, Joban Nishigo-machi
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Iwaki-shi, Fukushima, 972-8316, Japan	API Manufacturer

effective date 11/01/17; and SOP JHAS08, titled "Analytical Testing Execution Procedure", effective date 11/01/17. The QA unit lacks adequate control over the issuance of laboratory analytical testing worksheets, in that during the inspection it was observed that analytical batch records for API manufactured by the firm are issued by QC personnel, who have direct interest in all raw data generated during testing. Additionally, uncontrolled laboratory batch records/worksheets, chromatograms, and weight scale printouts were observed during the walk-through of the inspection on 11/13/17 with several different analysts.

OBSERVATION 7

Equipment used in the manufacture or holding of drug components is not of appropriate design to facilitate operations for its intended use and maintenance.

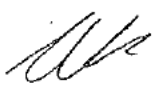
During the walk-through of your firms (b) (4) manufacturing plant I observed an approximate (b) (4) tall, (b) (4) cubic meters (b) (4) Liters) tank used for holding of solution (b) (4) process. Your firm explained that there was a leak in the original tank, ID # T-503, on or around 08/23/17. On or around 08/23/17 your firm moved a temporary Intermediate holding tank to the (b) (4) Plant in order to resume production operations. As of the start of the current inspection, your firm has not performed Installation Qualification, Operational Qualification, and Performance Qualification for this temporary intermediate holding tank. Since installation of this temporary holding tank, your firm has manufactured approximately (b) (4) lots of (b) (4), which could be sold as API.

OBSERVATION 8

Each lot in shipment received was not identified with a distinctive code for each container or grouping of containers for components.

Specifically,

Your firm does not assign a unique lot number for each lot in shipment received for all components used in the manufacture of drug substances. Currently, your firm uses the lot number assigned on the component manufacturers Certificate of Analysis. In addition, there are no adequate procedures for assigning unique lot

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
		Arsen Karapetyan, Investigator	11/17/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301) 796-3334 Fax: (301) 847-8738 CDEROSIAB@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	11/13-17/2017
	FEI NUMBER 3002808534

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
TO: Mr. Masaru Matsui, President and CEO	
FIRM NAME Yuki Gosei Kogyo Co., Ltd.	STREET ADDRESS Ochiai 788, Joban Nishigo-machi
CITY, STATE AND ZIP CODE Iwaki-shi, Fukushima, 972-8316, Japan	TYPE OF ESTABLISHMENT INSPECTED API Manufacturer

numbers for drug components received.

OBSERVATION 9

Equipment used during laboratory operations and production of an intermediate or API are not appropriately identified.

Specifically,

1. An empty functional refrigerator located in QC instrument room on the first floor with no status. Per your firm's QC Manager, this refrigerator is for backup purposed, in case another refrigerator is not functional.

2. Temporary Intermediate holding tank, located in the (b) (4) Plant in order to resume production operations after original tank was found to have a leak on or around 08/23/17.

This is a repeat observation from the last USFDA inspection, dated 09/2016.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Arsen Karapetyan	Arsen Karapetyan, Investigator	11/17/2017