

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER 12420 Parklawn Drive, Room 2032 Rockville, MD 20857	DATE(S) OF INSPECTION 01/15/2024-01/19/2024
Industry Information: www.fda.gov/oc/industry	FEI NUMBER 3002807025

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Tetsuaki Nishinaga, Senior Managing Director

FIRM NAME Fukuzyu Pharmaceutical Co., Ltd.	STREET ADDRESS 48 Hagiwara
CITY, STATE AND ZIP CODE Toyama, Toyama Prefecture, 939-8261, Japan	TYPE OF ESTABLISHMENT INSPECTED API manufacturer

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

OBSERVATION 1

The quality unit does not always conduct thorough investigations for out-of-specification results and critical deviations.

Specifically,

A) Your firm opened OOS 220202-1 on 02/02/2022 to investigate the OOS result for (b) (4) assay in reprocessed (b) (4) API batch (b) (4) lot (b) (4). One of the (b) (4) initial results was (b) (4)%, which exceeds the (b) (4) API specification of (b) (4)%. The investigation indicated the most likely root cause of the OOS was weighing error caused by static electricity or vibration, but there was no written scientific justification to support this conclusion. The weigh tickets attached to the testing record indicate the correct amounts or materials were used. There is no explanation how static electricity contributes error to an analytical balance, quantification of the error, and a determination that the error could cause the OOS result observed. Your firm opened CAPA 220209-1 to install an ionizer that would reduce static electricity without adequate scientific justification to support implementation of this change as a corrective action. Your firm invalidated the original OOS result and then distributed (b) (4) API batch (b) (4) lot (b) (4) on about (b) (4).

B) Your firm opened OOS 211221-1 on 12/21/2021 to investigate the OOS result for DMF residual solvent in (b) (4) API, batch (b) (4). The initial result was (b) (4) ppm, and the (b) (4) API specification is (b) (4) ppm. The investigation identified residual DMF was not uniform in the (b) (4) API drums (3 of (b) (4) drums were OOS), and the conclusion indicates inadequate (b) (4) as the likely root cause. Your firm reprocessed the OOS batch (b) (4) as batch (b) (4) lot (b) (4) without adequate investigation and follow-up.

i. Your firm opened deviation 211228-1 and CAPA 220323-1 in response to the OOS investigation 211221-1. The deviation and CAPA did not include a thorough investigation of the potential impact the identified root cause of inadequate (b) (4) had on previous lots of (b) (4) API that were (b) (4) for the same amount of time and

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used the same parameters as the OOS batch. Previous lots include batch (b)(4) lot (b)(4) batch (b)(4) lot (b)(4) batch (b)(4) lot (b)(4) and also the most recent batch (b)(4) lot (b)(4)

ii. Your firm conducted a (b)(4) uniformity study using (b)(4) API batch (b)(4) lot (b)(4) in 2013. CAPA 220323-1 appeared to increase the ability to detect inadequate (b)(4) for future batches, but deviation 211228-1 did not investigate the need to perform a new or more thorough (b)(4) uniformity study.

iii. Your firm did not take adequate corrective and preventive action after a DMF residual solvent IPC result for batch (b)(4) exceeded the (b)(4) API specification of (b)(4) ppm. Additionally, records indicate all four (b)(4) batches I reviewed that were manufactured since 2019 failed to meet the residual DMF IPC target of (b)(4) ppm. API include batch (b)(4) (reprocessed to (b)(4) batch (b)(4) batch (b)(4) (reprocessed to (b)(4) and batch (b)(4)

OBSERVATION 2

Shared production equipment is not always cleaned and maintained in a manner suitable to prevent cross-contamination of non-hazardous API by hazardous substances.

Specifically,

A) On 01/16/2023, I observed apparent residue and particulates inside the (b)(4) housing of (b)(4) S-7 and the product (b)(4) of (b)(4) 17. This equipment was designated clean after cleaning verification with rinse samples, swab samples, and visual inspection was completed. (b)(4) are the (b)(4) processing steps before (b)(4) filling and packaging. Equipment use logs indicate your firm used this equipment to manufacture (b)(4) API and other hazardous and non-hazardous substances. (b)(4) API include batch (b)(4) lot (b)(4) batch (b)(4) lot (b)(4) batch (b)(4) lot (b)(4) and batch (b)(4) lot (b)(4)

B) Your cleaning procedures are not validated to inactivate all the hazardous substances manufactured using shared equipment. Your firm does not have a written procedure to evaluate the ability of cleaning procedures to remove residues of (b)(4) and (b)(4) API produced using equipment shared with commercial API. Equipment use and cleaning logs indicate operators used (b)(4) S-7 to process a (b)(4) API before

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(b) (4) batch (b) (4) lot (b) (4) Your firm distributed this batch on about (b) (4)

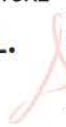
C) Standard Solution (b) (4) and Standard Solution (b) (4) both failed to meet the solution stability acceptance criteria of (b) (4) (b) (4) listed in the approved cleaning validation protocol PYR-2015-02 during the initial test and during the retest with newly prepared standard solutions. Solution (b) (4) was stable for (b) (4) and Solution (b) (4) was stable for (b) (4) during the initial test. Solution (b) (4) was stable for (b) (4) and Solution (b) (4) was stable for (b) (4) during the retest. Your firm approved the cleaning validation report for PYR-2015-02 using the linearity, LOQ, and range data from the first set of standard solutions combined with the solution stability data from the second set of standard solutions. There was no investigation, no scientific justification to accept data from standards that failed stability, and no written justification to accept sample stability that did not meet the acceptance criteria. Your firm relies on cleaning verification samples to detect and prevent cross-contamination between hazardous and non-hazardous API.

OBSERVATION 3
Validation of analytical methods is incomplete.

Specifically, your firm did not provide records during this inspection that documented analysts in your laboratory performed method validation, verification, or transfer for the in-house gas chromatography (GC) residual solvents method used to analyze samples for release testing of (b) (4) API. Your firm used results from this method to release all (b) (4) API, including batch, (b) (4) lot (b) (4) that was distributed on about (b) (4)

OBSERVATION 4
Appropriate procedures are not established and followed for control of computerized systems and electronic records in the QC laboratory.

Specifically,
A) The Vice Manager of QA is the sole administrator for Empower 3 software used to collect and process data

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from multiple chromatography instruments in your laboratory. On 01/18/2023, I observed the Vice Manager of QA login to the software as the administrator and then access system policies, audit trails, and stored data for (b)(4) API. The list of permissions for the Administrator user type indicated the user has unlimited ability to change or delete electronic records. The Vice QA Manager is responsible for oversight of API release. Your firm used Empower 3 software to process chromatographic data used to release (b)(4) batch (b)(4) lot (b)(4)

B) The Shimadzu C-R8A Chromatopac integrator connected to GC-06, asset number QC-0011, does not have features to enable robust data integrity. There is no forced data saving and no audit trail. The system erases electronic files when it is turned off, and I observed the system was not powered on during my review of the laboratory. Analysts use floppy disks to transfer files from the system to an unsecure file on a computer accessible to all QC staff as a backup. There is inadequate assurance quality personnel review all QC records produced by this system prior to making release decisions. Your firm used this system to perform residual solvents analyses and release (b)(4) API batch (b)(4) lot (b)(4) batch (b)(4) lot (b)(4) and batch (b)(4) lot (b)(4)

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