DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
ORA OPQO HQ, Room #2032 12420 Parklawn Drive, Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	10/23/2023-10/27/2023 FEI NUMBER 3003943727

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
Mr. Toshikatsu Konishi, Manager Kaizuka Plant and Production Team

TO: FIRM NAME	STREET ADDRESS
Sumitomo Osaka Cement Co.,Ltd.	8-1, Nishikinakacho, Kaizuka-shi,
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Osaka, 597-0093 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 OBSERVED:

OBSERVATION 1

Cleaning Validation Program is deficient, Specifically

The firm manufactured and shipped (b) (4) API products for the US market in the past three years each with a different particle size as listed below:

Product Name	Product Type	NDC
		(b) (4)

The firm performed three cleaning validations to establish successful product change over cleaning as detailed below for (b) (4) and (b) (4) product changeovers:

Reference	Date of completion	Content	Result
CL-001	9/22/2014	A washing amount of (b) (4) or more is required. (b) (4) products → (b) (4) products, (b) (4) products → (b) (4) products)	Validated
CL-001-4	6/5/2018	A washing amount of (b) (4) or more is required. (b) (4) products → (b) (4) products, (b) (4) products → (b) (4) products)	Validated
CL-001-5	2/26/2018	A washing amount of (b) (4) or more is required. (b) (4) product→ (b) (4) product)	Validated

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Lata Mathew	Lata C. Mathew, Ph.D., Drug Specialist /Pre-Approval Manager	10/27/2023

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However, there is no assurance that the cleaning validation was successful. Approximately nine out of specification investigations were initiated after completion of the three successful cleaning validations for failure of Specific Surface Area (BET) results after cleaning as listed below:

Date of OOS	OOS Number	Name of the product	Batch No.	Specific Surface Area (BET) Specification m^2/g	Result	Root Cause
3/14/2018	OOS18008				(b) (4)	Line cleaning insufficient
5/26/2018	OOS18014					
6/4/2018	OOS18015					
7/24/2018	OOS18018					
9/18/2018	OOS18026					
11/15/2018	OOS18029					
11/25/2018	OOS18030					
2/26/2019	OOS19005					
3/26/2019	OOS19006					

No OOS investigations were initiated after 3/26/2019 and the quantity of discard was further increased to (b) (4) since June 11, 2019, if the cleaning results failed and was therefore not documented as OOS. However, the SOP for product changeover cleaning (GMP-SOP-M-006 revision 7, titled Product Switching Procedure Manual) was updated to include rejection of additional quantity of product on cleaning failure and made effective on 10/23/23 (the first day of inspection).

OBSERVATION 2

Out of Specification investigation (OOS) is deficient and further no CAPA is initiated to prevent recurrence. Specifically,

1. OOS investigation OOS21001 was initiated on 3/3/2021 to probe the failure of (b) (4) Assay (b) (4) %) in (b) (4) API batch (b) (4) against a specification of (b) (4) to (b) (4) % using Ion chromatograph. The root cause of failure was attributed to error in the first standard preparation without any scientific justification or comparison with historical area response obtained for standard.

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The firm prepared a second standard and calculated the result of the original sample, and the results met the specification (b) (4)%). The firm then prepared a new sample and measured against the second standard and the results met the specification (b) (4)%). The firm invalidated the original result based on passing result from the single new sample and new standard (second). No CAPA was initiated.

2. OOS investigation OOS22002 was initiated on 5/10/2022 to probe the failure of (b) (4) Assay (b) (4)%) in (b) (4) API batch (b) (4) against a specification of (b) (4) to (b) (4)% using Ion chromatograph. The root cause of failure was attributed to error in standard preparation. The firm invalidated the original result based on passing result (b) (4)%) from the single new sample and new standard preparation. The CAPA (CP-22001) did not consider error in the weighing of the standard and instead stated that the failure is possibly due to spillage of standard solution while preparation without any scientific evidence.

3. OOS investigation OOS23001 was initiated on 1/30/2023 to probe the failure of static (b) (4) (b) (4) in (b) (4) API batch (b) (4) (process validation batch) against a specification of (b) (4) to (b) (4) (b) (4) No root cause was identified and the original sample from the lab and fresh sample from the warehouse was reanalyzed and the results met the specification (b) (4) and (b) (4) The original result was invalidated and no CAPA was initiated.

OBSERVATION 3

Reports of analysis from component suppliers are accepted without establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. Specifically,

Raw material suppliers of (b) (4) the raw material utilized in the manufacturing of (b) (4) API for US (b) (4) and (b) (4) were qualified without establishing complete reliability of supplier's certificates of analysis (COA) through confirmatory testing. Results of vendor and firm were not comparable for multiple quality attributes. Your written procedure for supplier qualification process, SOP GMP-SOP-S-017, revision 2 on Purchasing / subcontractor management

procedure manual is deficient and does not specify the number of batches required to be tested for verification of vendor COA during vendor qualification of raw materials. Additionally, your current practice of reduced testing from one vendor does not include verification of [(b) (4)] assay, a critical quality attribute and instead only an identification test for [(b) (4)] is performed using x-ray fluorescence and verification of weight variation of the [(b) (4)] bag received is performed for release, which are not specific to identification of [(b) (4)] The acceptance and release criteria from a second vendor includes only confirmation of [(b) (4)] and no other critical quality attribute for [(b) (4)] is verified for release. The current tests performed for release of [(b) (4)] does not follow the tests recommended in [(b) (4)] [(b) (4)] USP monograph.

The change control (KC-152) permitting reduced testing for acceptance of [(b) (4)] was approved on December 8, 2022. However, it was observed that the firm was conducting reduced testing for [(b) (4)] batches as early as January 2022 (for [(b) (4)] Batches [(b) (4)] and [(b) (4)] and July 2022 (for [(b) (4)] Batches- [(b) (4)] respectively.

OBSERVATION 4

The roles and responsibilities of the quality unit is not fully followed. Specifically,

1. During the review of OOS investigations, it was observed that about ten confirmed OOS was reported for failure of specific surface area (SSA-BET) in API batches and the root cause was attributed to fluctuation in [(b) (4)] of raw material [(b) (4)] However, no CAPA was initiated.

2. During the review of OOS investigations, it was observed that about 13 confirmed OOS was reported for failure of specific surface area (SSA-BET) in API batches and the root cause was attributed to insufficient cleaning of lines after product changeover cleaning. However, no CAPA was initiated.

3. The BET method validated in 2014 (VDR-A-001) for testing of specific surface area in [(b) (4)] API shipped for US failed to meet the acceptance criteria. The firms QA Manager (from [(b) (4)] site) stated that the method was not revalidated (validation report- A-001) until August of 2023 because the

firm did not have any OOS associated with the test. However, it was observed that about ten confirmed OOS was reported for failure of specific surface area (SSA-BET) in API batches.

4. Deviation DV22002 and DV22003 was initiated for excursions in humidity (74%) for (b) (4) and for temperature and humidity (35.8°C and 70.4% RH) for (b) (4) in the 25°C/60%RH (b) (4) stability chamber. However, no CAPA was initiated.

5. The analytical method for (b) (4) the raw material used in the manufacturing of (b) (4) API is not verified. The firm does not perform testing of assay and instead confirm assay with the COA of supplier to ensure if the results meet the firms' specification.

6. The operating (b) (4) of the (b) (4) (Id # APK-002) utilized in (b) (4) of (b) (4) raw material to manufacture (b) (4) and (b) (4) API is (b) (4) to (b) (4) However, the calibration of the old (b) (4) was performed between (b) (4) to (b) (4) in September 2022 (Certificate# FK 610003-1-8) and between (b) (4) to (b) (4) (Certificate# FK 600446-1-8) in July 2022 for the new (b) (4) thus not covering the entire operating range.

7. The firm does not monitor appearance and assay of (b) (4) (critical quality attributes) on stability samples of all (b) (4) API for US (b) (4) and (b) (4) and instead monitors residue on ignition, conductivity and specific surface area. The firm has shipped approximately (b) (4) API batches to US since 2019.

8. Your Training Procedure GMP-SOP-S-005 states to include CGMP training in the (b) (4) training plan. However, no documentation was available for any employee of the firm for the year 2021 and 2022.

9. No method equivalency is established between the (b) (4) XRF method (X-ray fluorescence) and the USP Ion Chromatography method used for the determination of (b) (4) in (b) (4) raw material.

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OBSERVATION 5

Review of audit trail for analytical data generated by your firm is inadequate. Specifically,

Review of the electronic audit trails from the Specific surface area measuring machine (BET)- Macsorb HM-model 1201 (ID-RK062 for API samples and ID-RK131for raw material samples) indicated repeated events of 'Measurement error', 'Measurement interruption', 'Measurement warning' and 'File delete'. For example, during the test runs, the following incidents were observed between September 2022 and September 2023:

Instrument ID/ Errors	RK131	RK062
Measurement error	2	
Measurement interruption	6	
Measurement warning	4	
File delete		5
File move		1
File rename		15
File save with different name		18

However, your quality unit did not initiate deviation for these instances to assess what may have caused these events. You also failed to investigate what those interruptions are and why the files were deleted. Your Audit Trail Review -SOP GMP-SOP-S-046 is deficient in that it does not cover system errors such as the ones listed in the table above. This limits your ability to review, document, and investigate all electronic data and is a gap in your Data Integrity Program.

***DATES OF INSPECTION**

10/23/23 (Mon), 10/24/23 (Tue), 10/25/23 (Wed), 10/26/23 (Thu) and 10/27/23 (Fri)

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