DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	4/26/2022-5/9/2022*
	FEI NUMBER 3002809586

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Pradipta Swain, Site Head & Vice President, Operations

FIRM NAME	STREET ADDRESS
Sun Pharmaceutical Industries Ltd.	Halol - Baroda Highway
CITY, STATE, ZIP CODE, COUNTRY Halol, Gujarat, 389350 India	TYPE ESTABLISHMENT INSPECTED Drug 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 WE OBSERVED:

PRODUCTION SYSTEM

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic process.

Specifically,

A. None of the (b) (4) Aseptic Process Simulations (media fills) (Batch #s: (b) (4)) performed for (b) (4) Injectable Suspension USP, (b) (4) mg/mL, (b) (4) mL (b) (4) from April 2020 thru March 2022 accurately represent the actual manufacturing process. This is a high-risk manually intensive dispensing and compounding process that uses sterile API that does not undergo (b) (4) filtration after compounding or before filling. Some of the deficiencies include but were not limited to:

Commercial manufacturing process	Aseptic Process Simulation
About (b) (4) g of sterile API is hand (b) (4) from (b) (4) sealed or previously opened (b) (4) bags into (b) (4) (b) (4) canisters.	About (b) (4) g of sterile (b) (4) is hand (b) (4) from (b) (4) sealed (b) (4) container into (b) (4) (b) (4) canisters. The use of previously

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	opened bags of sterile API has not been simulated.
(b) (4) g of sterile API is hand (b) (4) an unknown number of times (MBR states "*slowly and gradually add*") from (b) (4) canisters into the compounding tank over a time period varying from (b) (4) (outlier) to (b) (4) (including (b) (4) change at times) for (b) (4) batches mfd. from 5/20-11/21. It was reported (not documented) the canisters and tank remained opened during this time.	-About (b) (4) g of sterile (b) (4) is hand (b) (4) from (b) (4) canister into the compounding tank for a period of (b) (4) (b) (4) for the first (b) (4) media fills. Time for last (b) (4) media fills was extended to (b) (4) and (b) (4) (actual or simulated) (b) (4) for a total of about (b) (4) g were added to tank from (b) containers, which is still less manipulation and exposure time of the sterile API than commercial batches. - Failed Media Fill (b) (4) (11/19/21) only simulated the addition of (b) (4) into the compounding tank without actual addition of the (b) (4) (PR No. 1056557).
(b) (4) change occurred during addition of sterile API into compounding tank for batches (b) (4).	No (b) (4) change has been simulated during addition of sterile API.

The same deficiencies apply to (b) (4) Injectable Suspension USP, (b) (4) mg/mL (b) mL vials which share the same compounding process in Room (b) (4) (Block (b) (4)). A total of (b) (4) batches of (b) (4) Suspension USP, (b) (4) mg/mL, (b) mL (b) (4) and (b) (4) batches of (b) (4) Suspension USP, (b) (4) mg/mL, (b)

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mL vials were released and distributed to the U.S. from 7/2020 to 11/2021. Four (4) batches are on hold pending conclusion of media fill failure investigation PR No. 1056557. During the inspection on 5/2/22, a final FAR was submitted to the Agency committing to recall or reject all batches of (b) (4) Suspension USP, (b) (4) mg/mL (b) (4) and vials.

B. During the review of videos of media fills and smoke studies for (b) (4) Suspension USP, (b) (4) mg/mL, (b) mL (b) (4), the following inadequate aseptic practices were observed:

a. Media Fill (b) (4) 4/14/20 video:
   i. The operator is observed hand (b) (4) sterile (b) (4) powder from the original container to the (b) (4) canister while blocking laminar (b) (4) air over the open original container with his arm.
   ii. The operator is observed closing the canister containing the sterile powder by grabbing a large, (b) (4) stopper with his gloved hands and pressing it down until seated. He was observed un-stoppering and stoppering the canister with his gloved hands to hand (b) (4) the powder from the canister to the compounding tank.
   iii. The operator was observed inserting his gloved hand inside the (b) (4) canister a few times to (b) (4) out the sterile powder from the bottom of the narrow and tall canister in order to transfer it to the compounding tank. The (b) (4) used had a short handle. At times, he leaned over the open canister or tilted the container towards his body to (b) (4) out the sterile powder while blocking (b) (4) air.

b. Smoke Study (8/3/21) of the (b) (4) filling station showed the operator transferring a (b) (4) tub containing open sterile (b) (4) (opening facing up) from a (b) (4) to the (b) (4) filling machine by grabbing the front and back of the tub with his gloved hands while blocking (b) (4) air over the sterile (b) (4) with his left arm.

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OBSERVATION 2

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically, your Quality Unit failed to identify the following manually intensive operations for environmental sampling as high-risk for microbial cross-contamination in SOP 027928 "Microbiological Monitoring of Parenteral Manufacturing Area" and Protocol SUN/S-EM/005 "Justification for Microbial Monitoring Sampling Site Selection for Aseptic Area (Filtration and Filling Room) of (b) (4) Parenteral Manufacturing Area ((b) (4)) Block-(b) (4) ":

A. Manual dispensing ((b) (4)) and weighing operations of the sterile API (b) (4) (b) (4) from (b) (4) bags into (b) (4) canisters carried out on a perforated surface (b) (4) located in a corner within the Grade A filling room for (b) (4) ((b) (4)). The SOP does not require any viable and non-viable environmental monitoring (e.g., air and surface sampling) in this location.

B. Manual transfer ((b) (4)) of sterile API (b) (4) from (b) (4) to the compounding tank through a funnel by (b) (4) operators. This transfer operation lasts approximately (b) (4) . No environmental sampling has been performed close to this operation in the Grade-A (b) (4) filling room.

C. Personnel monitoring of fingertips is not performed immediately after handling sterile (b) (4) API during dispensing and compounding. The product is not (b) (4) sterilized after this high-risk manually intensive operation.

This sterile API is used for (b) (4) Suspension USP, (b) (4) mg/mL, (b) mL (b) (4) (b) (4) and vials.

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FACILITIES & EQUIPMENT SYSTEM

OBSERVATION 3

Equipment and utensils are not cleaned, maintained and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, the production equipment used to manufacture (b) (4) dosage (b) (4) drug products is not adequately cleaned, maintained, and sanitized to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug products.

Significant deficiencies were observed during the inspection of various (b) (4) Equipment (equipment ID: (b) (4) 1, (b) (4) 4, (b) (4) 5, and (b) (4) 6) on 5/2/2022. All of this equipment is shared-use equipment and was tagged as "Clean" after completion of the product changeover "Type-B Cleaning". During the inspection of these (b) (4) we observed foreign matter, residue (that appeared white, (b) (4), and black colored), round pellets (that appeared as drug product), and small shiny fragments (that appeared as metal shavings) on product contact surfaces. There is no assurance that the products manufactured by this equipment are free from contaminants.

This equipment is used to manufacture the following products:

Equipment Name	Equipment Code	Product Name	No of Batches
(b) (4)	(b) (4) T239	(b) (4) for (b) (4) Tablets (b) mg	(b) (4)

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(b) (4)	1			
			(b) (4) Pellets (b) (4) (b) (4) % W/W	(b) (4)
			(b) (4) Pellets (b) (4) (b) (4) % W/W	(b
			(b) (4) Pellets (b) (4) % W/W	(b
			(b) (4) Pellets (b) (4) % W/W	(b) (4)
			Total	(b) (4)
(b) (4)	(b) (4) 4	T358	(b) (4) Pellets (b) (4) (b) (4) % W/W	(b
			(b) (4) Pellets (b) (4) % W/W	(b) (4)
			(b) (4) Pellets (b) (4) % W/W	(b) (4)
			(b) (4) Pellets (b) (4) %	(b) (4)
			(b) (4) Pellets (b) (4) % W/W	(b
			Total	(b) (4)
(b) (4)	(b) (4) 2	TC182	(b) (4) tablets (b) (4) mg	(b) (4)
			(b) (4) for (b) (4) Tablets (b mg	(b
			(b) (4) Pellets (b) (4) W/W Professed Standard	(b
			(b) (4) Tablets (b mg	(b
			(b) (4) tablets (b) (4) mg	(b

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			(b) (4) Pellets (b) (4) % w/w	(b
			(b) (4) Pellets for (b) (4) Capsules (b mg, (b) (4) mg, (b) (4) mg, (b) (4) mg	(b
			(b) (4) Capsules USP (b) (4) mg	(b) (4)
			Total	(b) (4)
(b) (4)	(b) (4) 3	TC-217	(b) (4) Pellets (b) (4) %W/W	(b) (4)
			(b) (4) Capsules USP (b) (4) mg	(b) (4)
			Total	(b) (4)
(b) (4)	(b) (4) 5	TC-352	(b) (4) tablets (b) (4) mg	(b
			(b) (4) for (b) (4) Tablets (b mg	(b) (4)
			(b) (4) Pellets (b) (4) w/w	(b
			(b) (4) Pellets ((b) (4)) (b) (4) % W/W	(b) (4)
			(b) (4) Pellets (b) (4) %	(b) (4)
			(b) (4) Pellets (b) (4) % W/W	(b
			Total	(b) (4)
(b) (4)	(b) (4) 6	TC353	(b) (4) Pellets (b) (4) % W/W	(b) (4)
			(b) (4) Pellets (b) (4) %W/W	(b) (4)
			(b) (4) Pellets (b) (4) % W/W	(b
			(b) (4) Pellets (b) (4) % w/w	(b
			(b) (4) Pellets for (b) (4) Capsules (b	(b

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			mg, (b) (4) mg, (b) (4) mg, (b) (4) mg	
			Total	(b) (4)
Grand Total				(b) (4)

The site has about (b) (4) equipment to manufacture (b) (4) drugs for the U.S. market. Since January 2020, the firm received about nineteen (19) consumer complaints pertaining to foreign material, stains, specks, and spots in the drug products manufactured at the site. Eleven (11) out of nineteen (19) complaints were later confirmed during the complaint investigation.

OBSERVATION 4

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use and cleaning and maintenance.

Specifically,

From Nov. 2019 thru Dec. 2020, a total of nine (9) manufacturing investigations were opened to investigate abnormal appearance on the external surface of various (b) (4) belonging to (b) (4) in vial filling machine (SH-184) in Room (b) (4) (Block (b) (4)), which at times cross-contaminated the filled vials of (b) (4) injection (b) (4) mg/mL (b) mL vial batches with metal particles generated during filling from the friction of the (b) (4) with the (b) (4). In some cases, the filled solution appeared blackish from the contamination.

The root cause investigations attributed this friction and damage to the (b) (4) to variability in the quality of these parts supplied by the equipment manufacturer. The equipment manufacturer evaluation reported: "*The supplied* (b) (4) *are having close tolerance and the liquid handled is*

viscous…Due to such viscous liquid and close tolerance and during the production friction is generated between (b) (4) *and* (b) (4) *which would be the cause of blackening*." CAPA 700858 was approved on 9/26/20 to procure (b) (4) from a new manufacturer; however, the current MBR for (b) (4) injection USP, (b) (4) mg/mL (b) mL vial approved on 4/5/22 still lists the following seven (b) (4) that were previously identified in these investigations as damaged (scratches & dents) or discolored (abnormal appearance): H106, H102, H105, H156, H168, H169 & H170 as approved equipment. Your Quality Unit failed to establish adequate controls to prevent the usage of damaged equipment and has not conducted a thorough retrospective investigation of all distributed batches manufactured with damaged or poorly designed (b) (4). Of the nine (9) impacted batches in these investigations, five (5) were released to the U.S. market.

OBSERVATION 5

Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to aseptic processing of drug products.

Specifically,

A. The design of the Grade-A (b) (4) room where high-risk dispensing/weighing operations of sterile API (b) (4) and compounding process of (b) (4) Suspension USP, (b) (4) mg/mL, (b) mL (b) (4) and vials does not provide adequate protection (e.g., physical barrier) between the sterile API and the operators.

B. Manual loading of tubs of sterile (b) (4) onto the filling (b) (4) does not provide adequate protection between the open (b) (4) and the operator.

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LABORATORY CONTROL SYSTEM

OBSERVATION 6

The written stability testing program is not followed.

Specifically, the QC Lab failed to test more than 200 stability samples within the time frame defined as per stability control procedure (SOP 027980, Version: 3.0). Many samples pertaining to the long term stability studies (for representative batches in the market) were not tested for more than six (6) months. Some examples include:

Product Name	Batch No.	Stability Station	Condition	No. of Days Delayed	Country
(b) (4) Injection, (b) (4) mg/ml, (b) (4) ml	(b) (4)	15M/LT108/ S19/04/3721	Long Term	221	US
(b) (4) Injection, (b) (4) mg/ml, (b) (4) ml	(b) (4)	16M/LT108/ S19/04/3771	Long Term	188	US
(b) (4) injection, (b) (4) mg/vial	(b) (4)	3M/CRT_7/ S20/06/5591	Long Term	187	US

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(b) (4) Injection, (b) mg/ml, (b) (4) ml	(b) (4)	18M/LT108/S19/04/3721	Long Term	181	US
(b) (4) Injection, (b) mg/ml, (b) (4) ml	(b) (4)	20M/LT108/S18/11/3057	Long Term	179	US
(b) (4) Injection, (b) mg/ml, (b) (4) ml	(b) (4)	15M/LT108/S19/04/3771	Long Term	175	US
(b) (4) Injection USP (b) mg/ (b) (4) ml, (b) (4)	(b) (4)	17M/LONG12/S19/03/3502	Long Term	172	US
(b) (4) Injection, (b) (4) mg/ml, (b) (4) , (b) (4) ml	(b) (4)	1M/ACC../S20/04/5435	Accelerated	166	US
(b) (4) injection, (b) (4) mg/vial	(b) (4)	12M/INT_05/S19/10/4667	Intermediate	163	US
(b) (4) Injectable Suspension USP, (b) (4)	(b) (4)	12M/CR/S19/09/4571	Long Term	162	US

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mg/ml , (b) ml vial					
(b) (4) injection, (b) (4) mg/vial	(b) (4)	12M/CRT_7/S19/10/4667	Long Term	160	US
(b) (4) injection, (b) (4) mg/vial	(b) (4)	12M/CRT_7/S19/10/4666	Long Term	160	US
(b) (4) injection, (b) (4) mg/vial	(b) (4)	12M/INT_05/S19/10/4666	Intermediate	160	US
(b) (4) injection, (b) (4) mg/vial	(b) (4)	12M/CRT_7/S19/10/4668	Long Term	160	US
(b) (4) injection, (b) (4) mg/vial	(b) (4)	12M/INT_05/S19/10/4668	Intermediate	160	US
(b) (4) injection, (b) (4) mg/vial	(b) (4)	12M/CRT_7/S19/10/4669	Long Term	159	US
(b) (4) CAPSULES (b) MG	(b) (4)	1M/ACC	Accelerated	158	US
(b) (4) Capsules (b) mg	(b) (4)	1M/ACC	Accelerated	156	US
(b) (4)	(b) (4)	23M/CRT4/	Long Term	151	US

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Injection, (b)(4) mcg/(b)(4) ml, (b) ml (b)(4) (US)	(b)	S19/02/3368			

The firm reported confirmed out of specification results for about 147 samples (out of 215 stability samples that were not tested on time). About thirty-six (36) samples with the confirmed out of specification results were delayed stability testing for more than hundred (100) days.

OBSERVATION 7

Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically, your Quality Unit failed to implement adequate controls to prevent cross-contamination of microbiological samples prior to or during testing. Some examples include:

A. Failed sterility results (investigation PR791952) observed on 1/19/21 for (b) (4), 22-month CRT stability batch (b) (4) (non-U.S. product) were invalidated due to inadequate cleaning and sanitization of laboratory surfaces and sample handling deviations by laboratory personnel.

B. Environmental monitoring (EM) excursion investigation (PR#1001344) was opened on 9/25/21 to investigate settle plate counts that exceeded the action limit in three (3) separate locations within the Grade A (b) (4) vial filling line (b) (4) (Block (b) (4)) during filling operations of (b) (4) Injection, (b) (4) mg/mL, (b) mL vials, batch (b) (4). Each sample site had a count of 1 CFU/mL of *Chaetonium globosum* (fungus). The

environmental excursions were attributed to "*un-noticed moisture at edges of exposed media plates and lapse in aseptic practices (i.e., touching of the media plate after contacting with less sanitized surface at the time of operation of the* (b) (4) *system) during handling of the media plate by the EM operator at the time of exposure or collection of media plate.*" This batch was released by your Quality Unit.

C. Environmental monitoring investigation (PR#571630) was opened on 4/22/20 to investigate multiple environmental monitoring excursions in Grade A/B locations in Room (b) (4) (Block (b) (4)) during Media Fill batch (b) (4) of (b) (4) . Excursions were attributed to inadequate handling of sampled media plates at the QC Microbiology lab and inadequate sanitization of trays used for sample incubation.

QUALITY SYSTEM

OBSERVATION 8

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically, your Quality Unit failed to fulfil its key responsibilities assigned as per SOP 030295, Version: 2.0, "Key Responsibilities of Quality Unit". For example:

A. The list of objectionable conditions document that personnel may not have the necessary skill sets/training, experience, and/or scientific knowledge with respect to investigations & deviations, training, environmental monitoring, aseptic processing, stability testing, visual inspection, equipment cleaning & maintenance, facility design, and related systems in order to adequately

assess the cGMPs and the impact on the finished sterile and non-sterile products.

B. Quality Unit failed to take market actions as listed in "Drug Product Recall SOP 030153" for non-conforming batches on long-term stability, or the market action was taken when the batches were about to expire. For example:

   a. Out of specification investigation OOS 1048015 was initiated on 11/20/2021 when (b) (4) representative batch of (b) (4) Tablets, (b) (4) mg batch (b) (4) (Mfg. Date: 02/2020; Exp Date: (b) (4); long-term stability, 18-month interval) failed to meet dissolution specifications in Level 1, Level 2, and Level 3 stages and the OOS results were confirmed. A Field Alert Report (FAR) was submitted on 11/23/2021. Your quality unit failed to recall the non-confirming batch from the market. The impacted batch (b) (4) was the representative batch for about (b) (4) commercial batches of (b) (4) Tablets in the market and your Quality Unit did not fully evaluate all of these distributed batches to ensure conformance to specifications. Instead, the retain samples from only six (6) batches were tested.

   b. Out of specification investigation OOS 715576 was initiated on 10/14/2020 when four validation batches (also (b) (4) representative batches, long-term stability, 12-month interval) of Pantoprazole Sodium Injections (batch # JKU3595A, JKU3596A, JKU3597A, and JKU3629A) failed to meet specifications for related compounds (b) and (b) when tested for impurities analysis. The original OOS results were confirmed. The firm submitted the field alert report on 10/16/2020. These four validation commercial batches were manufactured in September 2019 (expiration date: February 2021). The quality unit failed to recall these batches in a timely manner. Instead, the firm recalled the impacted batches four months later in February of 2020; the month when all four batches were expiring.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	4/26/2022-5/9/2022*
	FEI NUMBER 3002809586

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Pradipta Swain, Site Head & Vice President, Operations

FIRM NAME	STREET ADDRESS
Sun Pharmaceutical Industries Ltd.	Halol - Baroda Highway
CITY, STATE, ZIP CODE, COUNTRY Halol, Gujarat, 389350 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

OBSERVATION 9

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A. Two (2) manufacturing Investigations PR 949445 & PR 949338 were opened on 7/27/21 to investigate OOT and OOS results for related substances for (b) (4) Injection USP (b) (4) mg/mL, (b) mL vials, batches (b) (4) and (b) (4) respectively. The root cause for the increased unknown impurities was identified as "*extraneous matter present*" in (b) (4) API, batch (b) (4), which increased product filtration time exceeding the NMT (b) (4) ((b) (4) for batch (b) (4)) specified in the master batch record and changed the color of the (b) (4) µm (b) (4) filter (b) (4) from (b) (4) *to* (b) (4)." The identity or source of the extraneous matter could not be identified by the API or product manufacturers, but it was noted that Loss on Drying (LOD) test result for this API batch was higher than historical API batches. These two finished product batches ((b) (4) & (b) (4)) were rejected; however, another two (2) finished product batches ((b) (4) and (b) (4)) were also manufactured with partial additions of this (b) (4) API, batch (b) (4), but were released based on passing finished product results and historical stability data for this drug product. Even though these batches were included in the investigation, your quality unit failed to thoroughly assess the impact to the purity, quality and safety of these batches manufactured with potentially contaminated API with an unknown extraneous matter before release.

B. Two (2) manufacturing investigations were opened on 5/21/21 and 12/3/21 to investigate water leaks coming from the LAF ceiling of filling area (b) (4) (Block (b) (4)) as follows:

a. PR 890889: On 5/20/21, during filling machine set-up operations of (b) (4) injectable suspension USP, (b) (4) mg/mL, (b) mL vial, batch

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Saleem A Akhtar, Investigator Ileana Barreto-Pettit, National Expert Jose M Cayuela, Investigator - Dedicated Drug Cadre	X Saleem A Akhtar Investigator Signed By 2001638440 Date Signed 05-09-2022 18 43 07	5/9/2022

(b) (4), water was observed dripping from the LAF ceiling to the Grade A (b) (4) filling area close to the (b) (4) stopper station. Filling operations resumed the following day (5/21/21) after re-cleaning and sterilization of filling equipment and sanitization of the filling room; however, the batch was rejected as the filtered bulk solution exceeded the hold time of (b) (4). The root cause of the water leak was identified as an old (b) (4) (b) (4) for the (b) (4) located in the utility floor above the filling room that was leaking and was replaced; however, it was not known for how long this equipment had been leaking. A visual check of the replaced (b) (4) during the FDA inspection revealed this equipment was located approximately 23' away from the ceiling leak location in the filling room and personnel stated there was a lot of water on the utility room floor that spilled over the area. A review of maintenance records for the (b) (4) (b) (4) during the inspection revealed this equipment was last inspected on 3/22/21 (2 months earlier) but the investigation did not provide these details and the Quality Unit failed to extend this investigation to other batches that were manufactured in this filling line during this time frame and could have potentially been impacted.

b. PR 1059368: On 12/3/21, another water leak was observed in the same room from the ceiling in the Grade B area outside of (b) (4) vial filling line before resuming filling operations of (b) (4) injection USP (b) (4) mg/mL (b) mL vials, batch (b) (4) (b) (4), after (b) (4) change. The investigation reported this issue had not occurred within the last year in this room even though it had occurred at least once 7 months earlier (PR 890889). The root cause was identified as water dripping from an unused (b) (4) water pipe with damaged insulation that accumulated on the utility floor above the filling line and leaked thru the ceiling. Filling operations continued and the repair was performed in the utility room. This batch was released based on satisfactory environmental monitoring and finished product testing results. Your investigation did not include an inspection of the (b) (4) LAF ceiling for water damage and gaps/cracks that could allow dirty water ingress from the utility room and crawl space into the aseptic filling room and extend the

investigation to other potentially impacted batches.

C. Environmental monitoring (EM) investigation PR 812342 was opened on 2/14/21 to investigate EM excursions during filling operations of (b) (4) Injectable (b) (4) (b) (4), batch (b) (4) in Grade A Room (b) (4) (Block (b) (4)) on 2/7/21 as follows:

Location	Type of Sample	Count	Organism ID
(b) (4) VTLP (viable tub loading point)	Active air	3 CFU/m3	*Staphylococcus walneri* *Micrococcus luteus*
(b) (4) B (under LAF near (b) (4) stoppering)	Settle plate	1 CFU/plate	*Bacillus circulans*

The investigation concluded that location (AA (b) (4) VTLP) was "*situated outside of filling* (b) (4) *under LAF where product is not directly exposed*." It also stated that any lapse in aseptic practice (frequent men/material movement) during the tub loading & tub unloading time, led to the viable excursion. However, the impact assessment did not identify that the tub loading location is a high-risk manually intensive operation where the operator loads tubs of open sterile (b) (4) facing up ((b) (4) /tub) with his gloved hands and a total of (b) (4) tubs were loaded for filling during the active air plate exposure time that had the excursion. This batch was released by your Quality Unit without rejection of any filled (b) (4) due to EM excursions in Grade A.

D. Out of specification investigation OOS 993797 was initiated on 9/17/2021 when (b) (4) representative batch (b) (4) of (b) (4) Tablets USP (b) (4) mg, (9-months, long-term stability; manufacturing date: 11/2020, expiration date: (b) (4)) failed to meet the dissolution specifications. The dissolution test for this product is performed by using (b) (4)

unit tablets and the dissolution samples are collected manually after 1, 2,3 and 10 hour time points. During the test Unit 1 at 1 hour interval yielded the value of (b) (4) % and failed to meet the specs of (b) (4) - (b) (4) %. The Quality Head stated the dissolution apparatus that was used for this analysis comprised of (b) (4) dissolution vessels. (b) (4) vessels containing the dissolution media (0.05M Phosphate Buffer, pH 6.8) were used for the test by dropping (b) (4) tablet in each of these (b) (4) vessels. The remaining (b) (4) vessels were filled with (b) (4) only. The QC Lab concluded that the tubing of the auto sampler was not connected properly, and the analyst pulled the samples for Unit 1 from the vessel containing the (b) (4) only (with no (b) (4) tablet). The QC Lab invalidated the original results, analyzed the new samples and reported the conforming results.

If the suspected samples were pulled from the vessel containing only the (b) (4) (no product) as claimed by the QC Lab; then no (b) (4) content should be observed in the samples pulled at 1, 2, 3, and 10 hour time points. However, the (b) (4) content was observed with an increasing trend for all the samples i.e., 1 hour ((b) (4) %), 2 hour ((b) (4) %), 3 hour ((b) (4) %), and 10 hour ((b) (4) %). The firm shipped this batch to the U.S. on (b) (4).

E. From November 17, 2020, to January 6, 2021, the firm received nine (9) confirmed customer complaints for (b) (4) Tablets, (b) (4) mg batch (b) (4) regarding (b) (4), dirty, and/or black specks in the tablets. The firm failed to conduct thorough investigations of these complaints because only the tablets received from the first complaint (PR# 741288) were sent to the laboratory for identification or characterization of the (b) (4) inclusions. All the other eight (8) complaint investigations failed to include laboratory identification and/or characterization test results for the inclusions or specks observed in the tablets. Instead, your Quality Unit assumed that the identification of the specks found on the tablets from the other eight (8) complaints of (b) (4)

(b) (4) mg tablets were of the same nature and identity as the specks found in complaint PR# 741288. Additionally, as part of the above investigations, the Quality Unit inspected in-house control (retain) samples; however, it failed to include the identify and/or characterization with laboratory testing of the black specks also observed in the control (retain) samples for the (b) (4) Tablets, (b) (4) mg batch numbers (b) (4).

F. Complaint investigation PR# 468068 regarding (b) (4) and (b) (4) Tablets USP (b) (4)/(b) (4) mg, batch (b) (4) having (b) (4) specks all through the tablets, failed to include laboratory identification and/or characterization test results for the (b) (4) specks observed in the complaint sample and in the in-house control (retain) sample. Your Quality Unit concluded that the identification of the specks found on the tablets came from the (b) (4) material used in the manufacturing of the product without scientific evidence.

Your Quality Unit failed to conduct adequate root cause analyses of these complaints in order to take corrective and preventive action to ensure the quality and purity of your drug products.

G. From Jan 2020 thru April 2022, your firm has received at total of 811 complaints for crystallization of (b) (4) injectable USP, (b) (4) mg/mL, (b) & (b) (4) mL vials. Inspection of the complaint samples to confirm crystallization, check the vials for integrity (i.e., stoppering, leaks and cracks) and re-dissolve the crystals in warm water bath is performed by the laboratory of your sister company in NJ that only tests (b) (4) dosage forms and for which you lacked documentation of their training and qualification to perform these inspections. In addition, as per Protocol No: SUN/S-EMC/531/01 approved on 7/16/19, your Quality Unit discontinued warming the complaint crystallized samples to redissolve the crystals because all (b) (4) previously tested samples had dissolved as per labeling instructions which state: "*Warming*

and shaking the vial should redissolve any crystals that may have formed during storage at temperatures lower than recommended." However, you lacked raw data to confirm crystals in these complaint samples adequately re-dissolved in a timely manner. According to consumer complaints PR260646 & 238781 received in Feb/March 2019, complaint samples took over 5 hours in a water bath (35-40°C) to re-dissolve the crystals; however, your complaint investigations concluded that there were no issues with the batches and the product was acceptable.

OBSERVATION 10

Employees engaged in the manufacture and processing of a drug product lack the training required to perform their assigned functions.

Specifically, employees engaged in the manufacturing and processing of parenteral and (b) (4) dosage drugs lack adequate training to perform visual inspection of the drugs manufactured at the site. For example:

A. On 4/27/2021, a qualified operator (b) (6) was challenged to detect the known defects (critical and major) in (b) (4) vials (presented to her from vial kit ID: PMA/LYV/006/00) under real conditions. She failed to detect defects in all of the (b) (4) vials. The operator (b) (6) has been performing visual inspection of the filled vials since 2014. Discrepancies were also observed pertaining to the records of her routine eye exams (operator, (b) (6)) that were conducted during the last two years.

   During the last two years, operator (b) (6) performed 100% visual inspection of many injectable/non-injectable sterile drugs including (b) (4) injections, (b) (4) injections, (b) (4) injections, (b) (4) injections, (b) (4) injections, (b) (4) injections, (b) (4) injections, (b) (4)

solution, and (b) (4). The firm shipped (b) (4) batches of these products into the U.S. since Jan 2020. Twenty-one (21) batches (out of these (b) (4) batches) were visually inspected by the operator (b) (6). There is no assurance if these distributed batches were effectively inspected for critical and major defects. Since January 2020, the firm received about seventeen (17) consumer complaints pertaining to foreign material, stains, spots, and specks in the injectable drugs shipped to the US from this site.

B. There is no assurance how the manufacturing and QA visual inspectors are qualified to identify defects (i.e., critical, major, and minor) in tablets. The firm could not provide the visual inspection kit, which should include physical samples with defects that may be found in finished product batches that the manufacturing and QA visual inspectors would be required to inspect in real-time for training and qualification. According to your management, the visual inspection kit is destroyed after the qualification process.

C. The visual inspection process of (b) (4) Tablets, (b) (4) mg batches (b) (4) failed to detect black specks in the tablets prior to release the products to the U.S. market. These black specks were detected during the complaint investigation (PR# 741288) and inspection of control (retain) samples.

D. The visual inspection process of (b) (4) Tablets, (b) (4) mg batches (b) (4) and (b) (4) manufactured in July 2020 and October 2020 failed to detect black spots observed in complaints PR# 882709 and PR# 883690.

***DATES OF INSPECTION**

4/26/2022(Tue), 4/27/2022(Wed), 4/28/2022(Thu), 4/29/2022(Fri), 5/02/2022(Mon), 5/03/2022(Tue), 5/04/2022(Wed), 5/05/2022(Thu), 5/06/2022(Fri), 5/09/2022(Mon)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	4/26/2022-5/9/2022*
	FEI NUMBER 3002809586

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Mr. Pradipta Swain, Site Head & Vice President, Operations

FIRM NAME	STREET ADDRESS
Sun Pharmaceutical Industries Ltd.	Halol - Baroda Highway
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
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DATE ISSUED
5/9/2022