

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

DISTRICT ADDRESS AND PHONE NUMBER 12420 Parklawn Drive, Room 2032 Rockville, MD 20857	DATE(S) OF INSPECTION 11/18/2019-11/26/2019*
	FEI NUMBER 3004664162

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Hideki Fujiwara, Head of Hikari Plant

FIRM NAME Takeda Pharmaceutical Company Limited	STREET ADDRESS Takeda 4720, Mitsui
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CITY, STATE, ZIP CODE, COUNTRY Hikari, Yamaguchi, 743-0011 Japan	TYPE ESTABLISHMENT INSPECTED Sterile Drug Manufacturer
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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:
QUALITY SYSTEM**

OBSERVATION 1

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

Specifically,


a) The Quality Unit failed to provide adequate oversight of production operations, aseptic controls and maintenance of equipment, and failed to identify inadequate practices or deviations from written procedures as evidenced by the observations cited during this inspection.

b) Full-size trial runs of (b)(4) filled with (b)(4) are performed after (b)(4) operations (b)(4) in the filling lines without the documented approval by the quality unit and without batch records to ensure (b)(4) filled with (b)(4) are reconciliated and 100% line clearance, accountability, segregation, and destruction are performed. The diluent used in (b)(4) is also a clear liquid.

OBSERVATION 2

Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product.

Specifically, the quality unit failed to conduct thorough investigations and extend them to other potentially affected batches of (b)(4) when black metal particles were found during visual inspections

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(b) (4) of (b) (4) batches of (b) (4) vials manufactured from May 2019 thru August 2019 after it was determined the root cause of contamination to be metal shavings from the (b) (4) (b) (4) used for vials (TW 60337, 61908, 64716 & 67805).

PRODUCTION SYSTEM

OBSERVATION 3

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

Specifically,

a) No aseptic process simulation (media fill) was conducted in the (b) (4) filling lines after operations (b) (4) period in (b) (4) that included activities such as: HVAC (b) (4) testing and re-qualification; (b) (4) system (b) (4); and manufacturing/sterilization equipment maintenance and calibrations. (b) (4) manufacturing activities was approved by the Quality Unit on 7/18/19 which was not in accordance with SOP H-SOP-PRD-0010, (b) (4) Manufacturing Activities in Aseptic Manufacturing.

b) The design of the aseptic process simulation for the (b) (4) of sterile (b) (4) in a Class A (b) (4) (b) (4) (b) (4) did not represent actual production operations. The process simulation for the (b) (4) of (b) (4) involved (b) (4) containers whereas actual productions can involve up to (b) (4) containers at a time. In addition, the simulation performed on 12/2/2018 failed sterility on 12/17/2018 but the failure was attributed to operators' poor aseptic practices not deemed representative of actual production operations (TW # 63749). Furthermore, operators authorized to perform this critical (b) (4) step are not required to conduct a media fill of this specific process at least (b) (4)

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c) Your firm failed to incubate several integral vials from a media fill without adequate justification. Media fill (b) (4) or (b) (4) filled on 4/29/2019, documented (b) (4) vials that were rejected due to interventions or integrity issues. However, ten (10) of these rejected vials were pulled from the pool of eligible integral units before incubation for other analyses unrelated to the media fill.

d) The washer used to wash, (b) (4) stoppers used in (b) (4) has not been re-qualified for endotoxin removal since its initial qualification in 1997.

e) Written procedures for filter integrity testing (b) (4) of (b) (4) µm filters for (b) (4) are not adequate in that it allows re-testing of the (b) (4) filters up to (b) (4) times with different (b) (4) solutions (b) (4) without conducting any investigations to determine the root cause of the failures. One (1) out of (b) (4) ss validation batches failed filter integrity testing twice with the (b) (4) as the (b) (4) solutions. It was reported that filter integrity tests routinely fail about 50% of the time with the (b) (4) as the (b) (4) solution due to adherence of (b) (4) in the formulation to the (b) (4) however, the integrity testing procedure has not been improved and validated to prevent the high failure rate of the initial test. In addition, the (b) (4) equipment used for filter integrity testing shares the same username and password for all operators.

OBSERVATION 4

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.

Specifically,

a) Controls for the in-house sterilization and replacement of gowns worn in classified areas are not adequate. During the walk-through inspection of the (b) (4) manufacturing area on 11/21/2019 gowns for the Class A & B areas were observed packaged in (b) (4) bags stamped with a sterilization date of 11/18/2019; however, they had not been (b) (4) yet. These gowns were observed in the laundry room without access control in the production floor. It was reported that sterilization was delayed but the date on the packaged clothing would not have been changed if sterilized on a different date than the stamped date; therefore, traceability for the

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sterilization cycle of the gowns would not be possible. In addition, written procedures do not require investigations when tears or holes are found during inspection of gowns after degowning in the (b) (4) and (b) (4) manufacturing areas.

b) On 11/18/2019, operators were observed using poor aseptic technique in the Class A area during the production of (b) (4) lot (b) (4). The operators were observed moving and touching (b) (4) be (b) (4) and opening the (b) (4) to the RABS with their gloved hands without spraying them. Also, an operator was observed performing an extensive intervention while leaning his upper torso inside the RABS.

c) The wipes (b) (4) used in the classified aseptic areas lacked a Certificate of Conformance showing that the wipes were (b) (4) for sterility. Also, the firm lacked written procedures for the receipt and approval of these wipes.

LABORATORY CONTROL SYSTEM

OBSERVATION 5

Drug products failing to meet established specifications are not rejected.

Specifically, two (2) batches of (b) (4) (same as (b) (4) for the U.S.), lots (b) (4) failed sterility testing on 9/21/2018. *Bacillus subtilis* was identified for both batches. Investigation report TW 62064 documented that both tests were invalidated because the analyst filtered the (b) (4) into (b) (4) vials; however, the investigation lacked evidence to support this root cause. These lots were manufactured in the Hikari plant and tested at the firm's sister plant in Osaka. On 11/8/2018, the Quality Unit released these lots based on re-test passing results.

FACILITIES AND EQUIPMENT SYSTEM

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OBSERVATION 6

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

Specifically, (b) (4) (ID: (b) (4) 5350) used to (b) (4) sterilize the diluent in the (b) (4) has not been properly maintained to prevent malfunctions. For example,

a) Increased (b) (4) (b) (4) time was observed randomly at least eight (8) times from May 2018 thru May 2019 resulting in the rejection of eight (8) batches of (b) (4) due to product exposed to excessive (b) (4). According to Investigation TW 66192 dated 5/9/19, the increased (b) (4) time was due to "an imbalance between (b) (4) due to inadequate adjustment of the (b) (4) (b) (4) which was the same root cause identified in the previous investigation in February 2019 (TW 64796). The (b) (4) was changed for the first time in 20 years on 12/13/2018 due to erosion observed upon insp

b) The maximum (b) (4) during (b) (4) has been monitored since 2/12/2019 during production. On 8/26/2019, a specification of ≤ (b) (4) established for the (b) (4) as a (b) (4) maintenance inspection criterion; however, monitoring data from 2/12/2019 thru 9/30/2019 shows the (b) (4) varying greatly from - (b) (4) to (b) (4) (b) (4). No reasonable explanation was provided for the random variability in (b) (4) which was reported as (b) (4) at least 23 times.

c) The (b) (4) used to measure the (b) (4) was reported as defective and a purchase order was approved for replacement on 2/28/19; however, a new (b) (4) has not been received and replaced to this date. On 3/20/2019, an Incident Report was issued for discrepancies in the (b) (4) reading, but according to Quality Assurance Deviation (QAD) 19-286 engineering found no issues and the report was closed. However, variability in (b) (4) readings continued.

This (b) (4) failed the (b) (4) B.I. challenge re-qualification on 10/28/2019. The ongoing investigation (TW 69280) identified the most likely root cause as the use of an inappropriate B.I. (b) (4) challenge and criteria due to inability to obtain the correct BI (b) (4). However, the re-qualification has not been repeated yet.

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OBSERVATION 7

Written procedures for cleaning and maintenance fail to include maintenance and cleaning schedules, description in sufficient detail of methods, equipment and materials used, description in sufficient detail of the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance and instructions for protection of clean equipment from contamination prior to use.

Specifically, the controls of sterilized gloves used for Class A aseptic operations are not adequate to prevent microbiological cross-contamination. These gloves are (b)(4) in a Class A (b)(4) (b)(4) to (b)(4) sterile (b)(4) as well as in the RABS filling line to fill (b)(4) into (b)(4). For example,

- a) During the review of a video of (b)(4) manufacturing operations on 11/18/19, we observed an operator unloading black gloves from a rack pulled out of the (b)(4) shortly after sterilization with his gloved hands while touching the outer surfaces of the sterilized gloves before placing them inside a (b)(4) (b)(4). The operator was observed walking through (b)(4) between the Class A and B areas and touching (b)(4) handles before handling the sterilized gloves with minimal sanitization of gloves. SOP H-WP-PRD-6150 does not provide instructions to unload the gloves and (b)(4) them in the (b)(4) and (b)(4) in a manner to prevent cross-contamination.
- b) The leak test for pinholes in gloves described in SOP H-WP-PRD-6150 is not adequate to accurately detect integrity issues. The SOP only state: “perform visual check and put (b)(4) n (b)(4) gloves to check any existence of pinhole or tear.”
- c) When pinholes or tears are found during inspections of gloves, they are simply replaced as per the SOP without conducting investigations to determine the impact to the sterility of the filled drug product.

***DATES OF INSPECTION**

11/18/2019(Mon), 11/19/2019(Tue), 11/20/2019(Wed), 11/21/2019(Thu), 11/22/2019(Fri), 11/25/2019(Mon), 11/26/2019(Tue)

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X Steven M Weinman
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