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	10/25-27,30-31, 11/1-2 & 6, 2023 FEI NUMBER 3004664162

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mr. Hideki Fujiwara, Vice President/Head of Hikari Plant	
FIRM NAME Takeda Pharmaceutical Company Limited	STREET ADDRESS Takeda 4720, Mitsui
CITY, STATE, ZIP CODE, COUNTRY Hikari, Yamaguchi, 743-0011 Japan	TYPE ESTABLISHMENT INSPECTED Human 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:

OBSERVATION 1

Written records are not made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications.

Specifically,

A. You have not initiated a comprehensive investigation into the negative trend of critical quality complaints reported on your (b) (4) drug/device product.
B. Without initiating an investigation into the root cause of these continued re-occurring (b) (4) drug/device defect complaints, you have also failed to initiate corrective and preventive actions for these complaints which have been reported. For example, there have been seven complaints received on a lot of (b) (4) mg sterile injectable product and six complaints were reported on another lot for device component issues.

OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy and/or 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. Your SOP no. 225372 "Visual Inspection of Drugs for Injection" describes your visual inspection process which is followed by your AQL evaluation. Your Quality Unit does not initiate or consider additional evaluations of your sterile injectable product when action limits are reached. These

SEE REVERSE OF THIS PAGE	Michele Perry-Williams, Investigator David J. Gomes, Microbiologist	Michele Perry-Williams X David J. Gomes	11/06/2023

negative quality signals are not acted upon with additional visual inspections and/or tightened AQL evaluations until the product is sent through a normal AQL evaluation and defects exceeding that evaluation are exceeded.

B. In your Defect Library dirt is considered as a Major Defect and is classified as an intrinsic defect. In addition, if particulates are experienced on the outside of the drug product (on the vials, (b) (4) etc.) they are not given a classification of intrinsic or extrinsic.

OBSERVATION 3

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

Specifically,

During my review of "EM Risk Assessment and EM Performance Qualification for (b) (4) Manufacturing Line (b) (4) the firm presented to me on 11/06/2023 photos with measurements results showing the non-viable particle counter (b) (4) is approximately (b) (4) away from the (b) (4) used during (b) (4) filling operations.

OBSERVATION 4

Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Specifically,
On 10/31/2023 a microbiologist was observed performing Endotoxin Testing of (b) (4) Lot (b) (4) manufactured on 10/28/2023 using the harmonized compendial JP<4.01>/USP<85> Bacterial Endotoxins Test/ Kinetic Photometric assay. The firm's test procedure H-TM-010803002 Revision 15, Implemented 08/31/2023 requires the measurement of pH value of the sample and sample with LAL reagents after the test run is completed.