DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313)393-8139	10/31/2023-11/15/2023* FEI NUMBER 3005949964

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Scott G. Gunther, Vice President, Quality and Regulatory Affairs

FIRM NAME	STREET ADDRESS
Catalent Indiana, LLC	1300 S Patterson Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Bloomington, IN 47403-4828	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

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

Specifically,

We observed numerous instances in which the Quality Unit did not appropriately exercise its responsibility to ensure that drug products manufactured meet applicable good manufacturing practices and meet established specifications of identity, strength, quality, and purity as is required by A-POL-03-01-001, *Quality Manual*. The observations that follow demonstrate ways in which the Quality Unit:

- Did not always ensure that "if errors have occurred, that errors have been fully investigated" (§5.5.1);
- Did not always ensure that "validation and revalidation activities are appropriately executed and documented" (§5.5.1);
- Did not always ensure operations designed to monitor the output of manufacturing processes that may cause variability in the quality characteristics of pharmaceutical products were performed by appropriately qualified production personnel (namely, qualification of personnel performing manual visual inspection) (§7.5.1); and
- Did not always ensure that "all equipment used in the manufacturing, processing, packaging, or

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holding of Drug Substance, Drug Product, or Medical Devices is maintained in a good state of repair" (§6.3.2.2).

OBSERVATION 2

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. Between 31 OCT 2021 and 31 OCT 2023, there have been approximately 194 deviations discussing (b) (6), (b) (7)(C) (b) (4) failures. These failures are reported across the (b) (4) systems of all (b) (4) filling lines (b) (4)). Of these deviations, nine were identified as requiring new action(s) to prevent recurrence of the issue. Approximately 31 actions were initiated directly from these nine deviations. Six of the nine deviations were identified as requiring checks to ensure the action(s) taken were effective. 171 of these deviations do not identify a definitive root cause; in these cases, for major deviations, governing procedure A-SOP-21-01-054, *Drug Product* (b) (4) *Program*, instructs investigators to indicate a possible/probable root cause as (b) (4) in the deviation's root cause grid. 155 deviations list a possible/probable root cause as (b) (4) .

There are approximately (b) (4) batches associated with these deviations, with approximately (b) (4) batches pertaining to commercial drug and biological drug products. No commercial lots of drug and biological drug products have been rejected due to (b) (4) failures. These batches span across (b) (4) project codes ((b) (4) ,

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(b) (4), and (b) (4)). One example of a recently released lot is project code (b) (4) - lot #(b) (4) released on or around 04 NOV 2023, which was shipped to (b) (4) on (b) (4).

In the same time period, there have been approximately 668 corrective maintenance (CM) actions associated with (b) (4) that failed (b) (4); between the close of the previous FDA inspection on 12 MAY 2023 through 30 OCT 2023, there have been approximately 85 corrective maintenance actions associated with (b) (4). Document TEC-000-300-164, *Drug Product Primary Trending Report Building A, B, and C - Q4FY23 (b) (4) Program*, includes the following statistics:

	(b) (4) Vial	(b) (4) (b) (4) Syringe	(b) (4) Flexi	(b) (4) Vial	(b) (4) Vial	(b) (4) Syringe
# of Failures	(b) (4)					
# of Batches						
Batch Impact Rate						
Avg. Days in Use						

On 31 OCT 2023 during filling of (b) (4) Lot (b) (4), approximately four (b) (4) (b) (4) failed (b) (4); Investigators Tan and Kuo observed three of these failures occur in real time.

B. Since 01 NOV 2021, there have been approximately 170 deviations associated with particles

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found in (b) (4) . These failures are reported across the (b) (4) systems of all (b) (4) filling lines ((b) (4)).

There are approximately 170 batches associated with these deviations. Of these 170 deviations, approximately 38 were identified as requiring new action(s) to prevent recurrence of the issue; approximately 28 deviations were identified as requiring checks to ensure the action(s) taken were effective. Trends are tracked in the existing process for trends associated with deviations; there is not currently a trending program for particles in (b) (4) similar to what's done for trending (b) (4) failures.

C. REC 723587, Short Description "*Pest found in* (b) (4) *System* (b) (4) *Room 880, MBR* (b) (4) - (b) (4) , *Lot* (b) (4) *', WO: 5519936/ 5519935*", discusses the discovery of a pest inside (b) (4) System (b) (4) (Syringe Line (b) (4) on 14 JUN 2023 during teardown activities of product code (b) (4) lot #(b) (4) . At the time, a (b) (4) was underway: lot # 4) was filled (b) (4); lot #(b) (4) was filled (b) (4). (b) (4) lots were rejected. When discussing possible scenarios by which the pest may have entered the (b) (4) this investigation (REC 723587) did not consider nor discuss a (b) (4) failure for (b) (4) (b) (4), which was observed to have a (b) (4) (REC 723577).

D. Deviation #730619, opened 29 JUN 2023, was opened in response to retain samples of product (b) (4) lot#(b) (4) failing (b) (4) (b) (4)) (b) (4) (b) (4) , reported result 13N). The scope of this investigation did not extend to all batches of (b) (4) known to have a failure reported for (b) (4) (b) (4) (namely, lot #(b) (4)). This investigation did not identify a root cause.

E. (b) (4) queries are not always ran with appropriate scopes. Examples include, but are not limited to, the following:

1. Deviation #730619, opened 29 JUN 2023, included review of the lots of stoppers and

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syringes used to produce product (b) (4) lot (b) (4) . (b) (4) queries for the lots of stoppers (b) (4) and (b) (4)) and lots of syringes (b) (4) , (b) (4)) were limited to supplier complaints, as opposed to any (b) (4) record (deviation, LIR, CAPA, change control, etc.) that includes the aforementioned lots of components.

2. Deviation #749638, opened 09 AUG 2023, included a query to determine if other records included the words "unfilled" and "syringes". This query was limited to customer complaint records, as opposed to searching through any record that may indicate additional instances of unfilled syringes.

F. The investigation for complaint #764722 is inadequate in that the expiry date for project code (b) (4) lot #((4 was not documented nor were retain samples inspected.

OBSERVATION 3

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

Specifically,

A. The designs of Vial Line (b) (4) (b) (4) systems (b) (4)), Vial Line (b) (4) (b) (4) system (b) (4)), Flexible Fill Line (b) (4) system (b) (4)), Syringe Line (b) (4) (b) (4) system (b) (4), and Syringe Line (b) (4) (b) (4) system (b) (4) do not allow all (b) (4) to be (b) (4) with (b) (4) (b) (4) . These include, but are not limited to, the following:

- (b) (4) (Vial Line (b) (4) (b) (4) (b) (4) and (b) (4)
- (b) (4) (Vial Line): (b) (4)

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- (b) (4) (Flexible Filling Line): (b) (4) (b) (4) , and (b) (4)
- (b) (4) (Syringe Line (b) (4)): (b) (4) (b) (4) , and (b) (4)
- (b) (4) (Syringe Line (b) (4)): (b) (4) (b) (4) and (b) (4)

Qualification of the (b) (4) decontamination cycles for (4) lines did not always include biological indicators (BIs) placed in the (b) (4) furthest away from airflow to demonstrate that the (b) that are not (b) (4) during (b) are sufficiently decontaminated.

B. The design of the (b) (4) systems for Vial Line (b) (4) (b) (4) systems (b) (4) , Vial Line (b) (4) ((b) (4) system (b) (4)), Flexible Fill Line (b) (4) system (b) (4), Syringe Line (b) (4) (b) (4) system (b) (4)), and Syringe Line (b) (4) ((b) (4) (4)) all require all environmental monitoring (EM) plates to be transported to a central location. To do this, operators enter numerous (b) (4) (b) (4) to form a (b) (4) and proceed to pass EM plates through the (b) (4) to the centralized location. Airflow visualization studies do not include visualization of these interventions in their entirety; only the action of changing plates is visualized, and not the transport of new plates from and old plates to the central location.

C. Written procedures designed to prevent microbiological contamination of products purporting to be sterile during aseptic processing are not adequate. For example, the following was observed:

1. On 31 OCT 2023, we (Investigators Tan and Kuo) observed operators' bare face/skin and gowns touching (b) (4) while performing interventions (b) (4) start-up and at end of fill (b) (4) system (b) (4) (Grade A) and Grade C areas in Room 820). One operator was observed blowing air from his mouth (not masked) into the surrounding environment while his face was touching (b) (4) during an intervention that he

was performing.

2. (b) (4) appear stained/soiled. For example, (b) (4) (b) (4) on Vial Line (b), (b) (4)(b) (4) on Vial Line (b) (4) (b) (4) (b) (4) and (b) (4) on Syringe Line (b), and (b) (4) (b) (4) on the Flexible Fill (Flexi) line were observed with apparent ink over the (b) (4). Additionally, (b) (4) (b) (4) on Flexi and (b) (4) (b) (4) on Syringe Line (b) were observed to have an apparent brown residue.

3. On 31 OCT 2023, we (Investigators Tan and Kuo) observed operators performing aseptic connection of the product storage bag to the filling line. We observed that after connection of the connectors to the fill line outside the (b) (4) the unused backup connector outlets were hanging down towards the floor and contacting a (b) (4) Barrier that was used and stepped over by operators during the aseptic connection process.

4. On 01 NOV 2023, during aseptic set-up of the stopper bowl on Vial Line (b) (4) prior to (b) (4), we (investigators Tan and Kuo) observed that the operators appeared to have difficulty in removing the (b) (4) cover off the installed stopper bowl, potentially causing unnecessary perturbations of the unidirectional air flow in the (b) (4)

5. On Oct 31, 2023, Investigator Kuo observed that on one of the staging carts in Filling Room 820 Grade C area, one of the wheels of the cart was observed to have (b) (4) materials lodged within and around the (b) (4) wheel, which may prevent adequate sanitization.

OBSERVATION 4

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

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Specifically,

For visual inspection of drug products and biological drug products purporting to be sterile, operators are qualified on (b) (4) vials; doing so allows operators to inspect (b) (4) , and (b) (4 vials. Justification provided for why this is allowable (document A-VPPQ-00316-S-VL-016AUG23, (b) (4 *Visual Inspection Process* (4 *Vials) Test Method Validation (TMV) Summary Report, VL-016AUG23*) is inadequate in that the justification appears to attempt to validate a (b) (4) process and the document's qualification methodology was not designed to mimic the conditions of the individual inspector qualifications (§3.2).

OBSERVATION 5

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

Specifically,

There is a failure to validate the endotoxin sample storage of drug products under project code (b) (4) at (b) (4) up to (b) (4) prior to the testing. A (b) (4) hold study or low endotoxin recovery data demonstrates that the hold period at (b) (4) does not negatively affect the endotoxin recovery from samples to ensure the microbial contamination is under control.

OBSERVATION 6

Written procedures are not followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

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Work Orders (WOs) 1004043 and 1004053 were opened on 26 OCT 2023 and 27 OCT 2023, respectively, pertaining to incidences of the (b) (4) malfunctioning on System (b)(4) (Syringe) (4) Visual Inspection) in Building D, Room 141, used for visual inspection of Project Code (b) (4) - Pre-Filled Syringes. Both WOs failed to contain any information documenting the incidences nor log statements as required by the written procedure, A-SOP-07-01-015: Performing Maintenance and Calibration, Version 44, Effective 2023-08-28. Corrective actions were not performed to address these WOs and subsequently, on 31 OCT 2023, recurrences of this same issue of (4) malfunctioning were apparent. During walkthroughs on 31 OCT 2023, this malfunction was observed in real time during the visual inspection of Project Code (b) (4) Lot (b) (4) .

***DATES OF INSPECTION**

10/31/2023(Tue), 11/01/2023(Wed), 11/02/2023(Thu), 11/03/2023(Fri), 11/06/2023(Mon), 11/07/2023(Tue), 11/08/2023(Wed), 11/14/2023(Tue), 11/15/2023(Wed)

Rafeeq Al Habeeb
2002600606
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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."