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	8/10/2022-8/19/2022*
	FEI NUMBER 3007647000

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Wim Blendeman, General Manager

FIRM NAME	STREET ADDRESS
Catalent Belgium SA	Font Saint-Landry 10
CITY, STATE, ZIP CODE, COUNTRY Brussels, Brussels-Capital Region, 1120 Belgium	TYPE ESTABLISHMENT INSPECTED Finished drug product manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectio nal 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.

The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically, air visualization (smoke) study videos recorded in January 22 on RABs cannot clearly demonstrate that airflow which is supplied by the HEPA filters over the grade A areas, is in sufficient velocity to cover the critical areas of the filling machines (e.g [(b) (4)] Air visualization (smoke) study videos showed that during the interventions, smoke generator rod is held a few inches above the intervention areas and operators' hands to show the airflow. The study could not demonstrate the actual velocity of the air from the HEPA filters over the RABs to the work surface and critical areas.

OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, your investigation and root cause analysis of deviations is deficient. For example, your firm

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has (b) (4) for sterilizing equipment, parts, and tools used in production of drug formulations and (b) (4) filling operations. The validation study protocol and reports demonstrated that these (b) (4) are validated with worst-case load configurations in June 2022. However, (b) (4) these (b) (4) failed to perform properly after a month in July 2022 (Deviation #560932) due to observed (b) (4) on and between the wrappings of the sterilized part. Your investigation stated this issue as an isolated issue with no prior recurrence.

A review of the deviations issued in 2019 to 2022 demonstrated that a few deviations are issued in 2019, 2020, and 2021 for (b) (4) which also included observing (b) (4) on and inside the sterilized parts and tubes. You failed to properly investigate (b) (4) issues and identify the root cause of the problem.

OBSERVATION 3

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.

Specifically, aseptic filling process simulations which are performed in April 2022 after significant changes to the HVAC system and replacing HEPA filters inside the cleanrooms used for filling drug product (b) (4) for the US commercial market is deficient. During these studies, you followed your routine (b) (4) media fill schedule and filled only low fill volume (b) (4) with high filling speed. You failed to consider the major changes to the HEPA filters in grade A and B areas and perform media fill in (b) (4) with larger openings under low filling speed condition as well.

OBSERVATION 4

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

Specifically, qualification studies are deficient.

a (b) (4) (b) (4) cycles qualification performed in June 2022 is deficient in that during requalification of (b) (4) cycles you failed to use the same type of parts which were qualified for that load configuration. For example, during qualification of (b) (4) load cycle for (b) (4) filling line parts in October 2021, you used a (b) (4) µ filter with a larger surface instead of a (b) (4) µ filter with similar surface size that was used for filtration of the drug products before filling the (b) (4) during routine manufacturing operation.

b)You have performed performance qualification studies o (b) (4) ntegrity testers in July 2022 to demonstrate that your (b) (4) integrity testers are capable to detect holes greater than (b) (4) µm under initial pressure of (b) (4) Pa for (b) (4)

b-1) your study results demonstrate that you have performed the study for (b) (4) instead of (b) (4) which was required by your protocol.

b-2) based on the results of the studies on (b) (4) integrity testers for (b) (4) filling lines, initial pressure at lower ra (b) (4) Pa) may provide false negative for the (b) (4) with integrity issues specially when it is performed for (b) (4)

(b) (4) **test run** (b) (4) **integrity testerInitial pressure** (b) (4)				

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±(b) (4) (Pa)Final pressure (Pa) After (b) (4) (b) (4) P = Initial pressure -final pressureSpecification					
(b) (4)					**ΔP (b) (4) Pa**

c)Results of the integrity test on (b) (4) are recorded as Pass or Fail with no value. You do not have a record of the applied initial pressure and final pressure values in (b) (4) RABs (b) (4) during the qualification studies.

d)Equipment clean hold time studies for production equipment is deficient. Your study failed to

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demonstrate the clean hold time after cleaning of dirty equipment and parts. To perform the clean hold time study, you performed a full cleaning on previously washed and cleaned equipment and hold these pieces of equipment for (b) (4) You failed to demonstrate whether or not these pieces of equipment remain clean for (b) (4) after only one cleaning cycle.

e)your firm's (b) (4) qualifications of the climate-controlled chambers (stability chambers, refrigerator, and incubators) that are used for storing drug products for the US market, is deficient. The initial qualification studies on these chambers which are conducted between 10 to 15 years ago demonstrated that temperature recovery studies are performed by shutting off the power for (b) (4) however the recovery time is not recorded. You failed to perform temperature and humidity recovery time on climate-controlled chambers to determine the recovery time and to ensure that raw materials and finished products stored in these chambers are not impacted by long recovery time.

f)Control over your instruments in the laboratory is deficient. QC instruments and equipment used for analysis of drug products and raw materials are not protected from manipulation and data integrity. You even have a procedure for changing the time and date in QC equipment and QC analysts can change date and time in the instruments following the the instructions in these procedures and/or equipment manuals. For example, procedure # STB-QC-0039, "Procédure d'utilisation d'entretien et de vérification périodique d du QC et des masses certifies", has detailed instruction for changing the date and time in QC balances. These balances are used for measuring raw materials and finished products samples for QC analysis. Similarly, balances and QC measuring devices which are used for testing in-process products in production area, are not protected from changing the date and time by the operators.

OBSERVATION 5

Input to and output from the computer are not checked for accuracy.

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Specifically, you are not performing electronic data review on raw electronic data generated by the computerized system. For example, HPLC, UPLC, IR and UV-Vis are used in the QC laboratory for analysis of the raw materials and finished drug products samples. Your do not have a procedure for electronic data review and review of audit trails and your QC reviewer stated that she never visits the QC instruments to review analytical data or audit trails on the instrument. She confirmed that she only performs paper review of the printed test data which are provided to her by QC analysts.

OBSERVATION 6

Backup data is not assured as exact, complete and secure from alteration, erasure or loss through keeping hard copy or alternate systems.

Specifically, QC raw data generated by stand-alone QC analytical instruments (IR, UV-Vis, etc.) after analysis of samples, are backed up in GMP folder by IT at QC, however backup data are not verified for completeness and whether they can be restored.

OBSERVATION 7

The design history file was not established.

Specifically, your firm has neither a procedure for receiving and control of customer designs and specifications, nor a device history file for customer's designs and specifications.

OBSERVATION 8

Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established.

Specifically, your purchasing process control is deficient in that:

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a)your purchasing procedure STB-SC-0001," Procédure de traitement des commandes" does not have a requirement for communicating materials specifications and designs with suppliers.

b)your purchase order does not have a reference to the material specification/design with the revision numbers. Your purchase order information for the material being purchased is limited to the item number (internal part #), quantity required, and date required.

c)The QC inspection procedures for inspecting incoming materials are not followed. For example, STB-OC-0148-F1," Rapport de controle des (b) (4) for receiving inspection of (b) (4) requires dimensional measurements be performed on the (b) (4) Three areas with measurements are defined on the (b) (4) ' drawings. However, during QC inspection and release, only (b) (4) ' height are measured. Your firm failed to perform measurements on all three areas.

OBSERVATION 9

Quality audits have not been performed.

Specifically, your internal audit procedure, STB-QA-0012, "Procédure de gestion des audits internes" is deficient for a combination drug/device manufacturer. Your procedure only requires a drug GMP audit with no indication to the device regulation or requirements. Your firm's management confirmed that your internal audits process always followed this procedure and were performed per drug GMP regulations.

***DATES OF INSPECTION**

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8/10/2022(Wed), 8/11/2022(Thu), 8/12/2022(Fri), 8/16/2022(Tue), 8/17/2022(Wed), 8/18/2022(Thu), 8/19/2022(Fri)

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Annotations to Observations

Observation 1: Not annotated

Observation 2: Not annotated

Observation 3: Not annotated

Observation 4: Not annotated

Observation 5: Not annotated

Observation 6: Not annotated

Observation 7: Not annotated

Observation 8: Not annotated

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Annotations to Observations

Observation 9: Not annotated

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