Failure to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether the batch has already been distributed. Specifically,

a. Standard Operating Procedure STB-QA-0010, Deviation Management, v21 classifies deviations as minor, major or critical based on the calculation of a risk priority number, with a HEPA filter failure within a Grade A environment often classified as minor. Specifically, Deviation 327567 (Date of occurrence 04 March 2021) was for a HEPA filter failure on the fill line, with a breach at the HEPA filter frame. The location of the HEPA filter was with a settling plate in the near vicinity having recoveries of CFU/plate. Your product quality impact assessment included within the deviation investigation failed to provide a comprehensive and detailed impact assessment for all products produced and distributed to the United States for the time period the Grade A environment was compromised and to prevent a recurrence of the failure. Commercial products manufactured within the compromised Grade A environment and distributed to the United States include the following:

i. Batch

ii. Batch

iii. Batch

iv. Batch

b. You failed to adequately investigate multiple HEPA filter failures that were observed for the fill line Grade A space, Grade A/B space, and Grade B surrounding area, with the following filters replaced based on velocity (average speed) measurement not meeting the acceptance criteria of m/s to m/s, filter integrity for DOP test and differential pressure:
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRIBUTION OFFICE ADDRESS AND PHONE NUMBER
Division of Biotechnology Manufacturing
10903 New Hampshire Avenue; White Oak Building 51,
Room 2269, Silver Spring, MD 20993
Email: OPFBLAInspection-483Responses@fda.hhs.gov
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION
10/18/2021 - 10/26/2021

FEI NUMBER
3007647000

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Wim Blendeman, General Manager

FIRM NAME
Catalent Belgium S.A.

STREET ADDRESS
Font Saint Landry 10

CITY, STATE AND ZIP CODE
Brussels, BRU, B-1120

TYPE OF ESTABLISHMENT INSPECTED
Drug Product Manufacturer

May 2017, Filter GTA02-LAF-0265.02-FA-02, Grade A, Root Cause DOP and Average Speed
May 2017, Filter GTA02-LAF-0265.02-FA-01, Grade B, Root Cause Average Speed
May 2017, Filter GTA02-LAF-0265.01-FA-13, Grade A/B, Root Cause Average Speed
May 2017, Filter GTA02-LAF-0265.01-FA-14, Grade A/B, Root Cause Average Speed

January 2018, Filter GTA02-LAF-0265.02-FA-02, Grade A, Root Cause Average Speed
January 2018, Filter GTA02-LAF-0265.02-FA-01, Grade B, Root Cause Average Speed

August 2018, Filter GTA02-LAF-0265.02-FA-02, Grade A, Root Cause Average Speed
August 2018, Filter GTA02-LAF-0265.02-FA-01, Grade B, Root Cause Average Speed

March 2019, Filter GTA02-LAF-0265.02-FA-02, Grade A, Root Cause Average Speed

August 2019, Filter GTA02-LAF-0265.02-FA-01, Grade A, Root Cause Average Speed
August 2019, Filter GTA02-LAF-0265.01, Grade B, Root Cause DOP
August 2019, Filter GTA02-LAF-0265.02, Grade B, Root Cause DOP
August 2019, Filter GTA02-LAF-0265.03, Grade B, Root Cause DOP

March 2020, Filter GTA-LAF-0265.02-FA-02, Grade A, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.02-FA-01, Grade B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-13, Grade A/B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-14, Grade A/B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-15, Grade A/B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-16, Grade A/B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-17, Grade B, Root Cause Delta P
March 2021, Filter GTA-LAF-0265.01-FA-08, Grade A, Root Cause Average Speed

A single commercial product produced on the fill line for United States distribution is

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SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE
Wayne Seifert, Consumer Safety Officer
Lindsey Brown, Microbiologist

DATE ISSUED
10/26/2021
Other GMP manufacturing areas have a similar elevated level of HEPA filter failures, with the root cause of the HEPA filter failures unknown. There is no CAPA in support of correction action. Your firm failed to ensure your investigations identify appropriate root causes and you failed to implement sustainable corrective action and preventive action (CAPA).

c. You failed to adequately investigate numerous environmental monitoring excursions for the GMP drug product manufacturing areas. Specifically,

In the calculation of environmental monitoring recovery rates for rooms in Grade B space from September 2020 to August 2021 (available data), a long term trend was observed where the acceptance limit was consistently exceeded, recovery rates $\geq (0.4)\%$. The trend includes the following areas: Area 297 Corridor; Room $09(4)$ Women's Exit; Room $09(4)$ Women's Entry; Room $09(4)$ Men's Entry; Room 0403C, Personnel Exit, Men and Women; and Room $09(4)$.

Furthermore, a similar trend for recovery rates not meeting the acceptance criteria was observed from March 2020 to June 2021 (available data) for Grade C Manufacturing, Grade C $09(4)$ Shared Grade C space, and Grade D space, with the acceptance criteria for recovery rates Grade C and Grade D, $\leq (0.4)\%$ and $\leq (0.6)\%$, respectively.

Corrective actions not limited to a procedural update, change control and CAPAs starting in October 2020 have failed to bring the recovery rates within the acceptance limit.

Observation 2:

Failure to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess. Specifically,

Your firm did not adequately validate the process used to manufacture the drug product and drug product stains on the exterior of the and drug product solution found in the stopper cavity is associated with dripping during manufacture on the fill line. You have not demonstrated that the filling process for the drug product is under control to ensure the prevention of contamination of drug product by...
Observation 3:

Validations, designed to prevent microbial contamination of the drug product purporting to be sterile, have not been adequately established. Specifically,

a. Rapport Validation Plan Equipment 131909-N Annex 4, 09 March 2008 for the RAB integrity tester includes a performance qualification where testing was conducted with a 75 mm micrometer breach, with the purpose of the test to evaluate the functionality of the instrument. The performance qualification failed to determine the breach limit of detection based on validation for the fill line.

Furthermore, the integrity testing frequency for the is conducted. The frequency is inadequate as it does not access the status of each batch that may be impacted by failure.

b. The minimum load for sterilization is not reflective of the worst-case equipment item as determined from the maximum load (lowest acquired lethality item), but is based on a theoretical worst-case equipment assembly. Change control 151393 has been open since 18 November 2020 for a sterilization optimization study that includes a minimum load assessment based on the maximum load worst-case load item, with the sterilization studies still pending completion.

c. There is a failure to establish an equipment clean hold validation pending sterilization.

d. According to procedure STB-QA-0061, Methodologie de validation des procedures de nettoyage, v11, Effective date 08 Jan 2021, cleaning validation for vessel (tanks) includes rinsate samples, with swab samples excluded. Though rinsate samples may provide a good indication of cleanliness, it should not be used as a substitute for not performing swabbing on equipment that may present and elevated challenge in removal of product residues.

Observation 4:

A written procedure designed to prevent contamination of products during aseptic processing is not adequate.
Specifically,

Procedure STB-MFG-0026, Generale Zone A/B, v10, Effective date 21 September 2021 contains instructions to sanitize, spray onto the RAB in Grade A space. On 20 October 2020, we observed your employee repeatedly spraying steriele within the RAB (Grade A space) during manufacture of to sanitize the RAB. The practice occurred in close proximity to exposed stoppers within the stopper bowl and environmental monitoring that included a settling plate. A product quality impact assessment has not been performed to address the risk associated with the use of during manufacturing operations.

Observation 5:

Equipment and facilities used in the manufacture of drug product are not adequately maintained or appropriately designed to facilitate operations for their intended use. Specifically,

a. The filling machine RAB that extends to ceiling level and is system was observed with the barrier system damaged at a number of RAB points. The root cause of the damage is missing. Furthermore, two black lines were observed on a mechanical piston system for the near open You indicated the cause of the black material is unknown.

b. Sinks in Room Grade C space include used in production equipment manual cleaning operations, with the sink drain line not containing in mitigation of water backup.

c. Analytical balance BAL93 used in weight checks for the fill line was observed with the shield glass broken, with the broken glass secured by tape.

d. Deteriorated surface finish sealant was observed within the following GMP suites: and Local Storage at the ceiling.

Wayne Seifert, Consumer Safety Officer Lindsey Brown, Microbiologist

10/26/2021
Observation 6:

Your laboratory analytical method for endotoxin has not been adequately validated. Specifically,

Procedure STB-QC-0048, Reception des essai aux QC, v20, Effective date 06 August 2021 provides up to 4 hours for the drug product in-process control endotoxin test. There is no validation to support the sample storage time of 10 days.

Observation 7:

Standard operating procedures are not followed or are deficient. Specifically.

a. Standard operating procedures for visual inspection of the media fill SB-QC-0079 "Mirage des milieux de culture et MFT" v6.0, Effective date 30 Jan 2019 does not include instructions for mixing of samples prior to visual inspection.

b. Sample Logbook Suivi du Transfer des Echantillons, STB-QC-057-21, v2 was observed incomplete, with the date and hour for all entries, removal of material not completed. Procedure SOP-STB-QC-0057, Prelevement des Echantillons au Department Manufacturing, v7, Effective date 30 December 2020, Section 5.3.4 Transfert des echantillons, indicates to document transfers by logbook. The procedure was not followed.

Furthermore, Logbook Archivage Cycle Lancer, STB-MFG-0046-F3, v6, Effective date 23 March 2020 and Logbook D'Utilisation des au Department MFG, STB-MFG-0119-F1, v1, Effective date 25 September 2019 were not completed for Visa Paraphe Supervisor as required.