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	4/28/2025-5/9/2025*
	FEI NUMBER 3001617666

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Sylvain Thuot, Vice President, Product Supply

FIRM NAME	STREET ADDRESS
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CITY, STATE, ZIP CODE, COUNTRY Richmond Hill, L4C 5H2	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

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.

1. On April 30, 2025, (b) (4) leak tests were attempted on (b) (4) Filling Line (b) (4) and all of them failed. The (b) (4) is used for aseptic filling of (b) (4) products for the US market. Subsequent (b) (4) leak testing on May 1, 2025, identified 34 different locations around the (b) (4) that were leaking. The identification of leaking locations was not thoroughly documented. (b) (4) tests are not documented, but should have been performed at the start of the (b) (4) cycles completed between (b) (4) There has been no investigation into how these tests passed when subsequent (b) (4) leak testing and (b) (4) leak testing identified at least 34 leaking locations.

   Previous identifications of (b) (4) leaks did not include investigations in the quality system to evaluate the cause of the leak or the impact on previously manufactured batches:

   a. Beginning on or around April 17, 2025, there were an unknown number of (b) (4) leak test failures of the (b) (4) in (b) (4) Filling Line (b) (4) per the Production Manager. These leak test failures were not documented. Production personnel performed investigations to identify the location of leaks, including (b) (4) leak testing on at least (b) (4) different occasions per the Production Manager. The results of the (b) (4) leak

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Justin A Boyd, Investigator Wayne D Mcgrath, Investigator	X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 05-09-2025 12:50:04	DATE ISSUED 5/9/2025

tests were not documented as required by procedure SOP-PR-070.004-R "Leakage Testing of Production (b) (4) Method". Per the Production Manager the (b) (4) leak tests identified leaks and resulted in corrective work orders to replace the gasket around the (b) (4) machine, replacement of gaskets on (b) (4) (b) (4) replacement of gaskets on (b) (4) and replacement of gaskets on at least (b) (4) The work orders do not specify which (b) (4) or (b) (4) had gaskets replaced.

The leaks identified during this work were not documented within a quality system investigation to evaluate the cause of the leaks and assess the impact of these leaks on previously filled aseptic products such as (b) (4) batch (b) (4) (US market) filled (b) (4) There is no leak testing performed at the end of commercial aseptic filling.

b. On September 3, 2024, a (b) (4) leak test of the (b) (4) failed as part of a maintenance activity. Subsequently, (b) (4) investigative (b) (4) leak tests were performed to identify leaks on the (b) (4) No documentation was made of the findings from the (b) (4) leak test. A workorder # (b) (4) during this time period was opened to perform corrective actions to fix leakage including the (b) (4) gaskets on the filler, gasket of (b) (4) (b) (4) and a (b) (4) housing that needed to be sealed and aligned. There was no investigation to evaluate the cause of the leaks and assess the impact of these leaks on previously filled aseptic products, including (b) (4) Solution (b) (4) filled (b) (4)

c. On or around September 2, 2023, (b) (4) leak testing was performed on the (b) (4) to identify a leak. No documentation was made of the findings. Workorder # (b) (4) was opened to perform corrective actions to fix leakage by replacing gaskets on (b) (4)

(b) (4) There was no investigation to evaluate the cause of the leaks and assess the impact of these leaks on previously filled aseptic products such as, (b) (4) Solution batch (b) (4) filled (b) (4)

d. Workorder # (b) (4) was opened to fix a leak at (b) (4) on August 7, 2024. The workorder documents the mechanic also applied a seal to the (b) (4) of (b) (4) as production personnel found leaks from corners of the (b) (4) There was no investigation of the leaks or the impact on previously manufactured batches.

e. Notification # (b) (4) identified a (b) (4) leak test failed on July 26, 2024. There was no further documentation of how it was investigated or resolved or whether it impacted the previously filled (b) (4) Solution batch (b) (4) (US submission batch).

f. Workorder # (b) (4) was opened for a failed leak test on May 17, 2024. It identified a leaking (b) (4) There was no investigation of the leak or the impact on previously manufactured batches, including (b) (4) batch (b) (4) (US submission batch).

g. Workorder # (b) (4) dated April 1, 2024, was opened following a failed leak test on the (b) (4) The maintenance personnel changed the seal for (b) (4) but did not document which (b) (4) There was no investigation of the leaks or the impact on previously manufactured batches, including (b) (4) Solution batch (b) (4)

h. Notification # (b) (4) identified a (b) (4) leak test failed on October 5, 2023. There was no further documentation of how it was investigated, resolved, or whether it

impacted the previously filled (b) (4) Solution batch (b) (4) (US market, expiration (b) (4)

2. Analytical method GM-66 Determination of Weight Loss reports (b) (4) bottles, but does not require individual bottles to meet the specification. Individual bottles that exceed specifications for weight loss during stability are identified as anomalous and investigated as a Laboratory Investigation Reports (LIR). These investigations do not evaluate if the anomalous results are indicative of marketed product that is not integral. There is no evaluation of a root cause or assessment of the impact on the stability batch and commercial batches. For example:

   a. (b) (4) Solution, specification NMT (b) (4) % for weight loss.

   LIR # (b) (4) confirmed an anomalous result at the 12-month timepoint for stability batch (b) (4) (US batch, expiration (b) (4) with a weight loss of (b) (4) % on bottle (b) (4) and (b) (4) % on bottle (b) (4) since the initial timepoint.

   LIR # (b) (4) confirmed an anomalous result at the 12-month timepoint for stability batch (b) (4) (Canada batch, expiration (b) (4) with a weight loss of (b) (4) % on bottle (b) (4) since the initial timepoint. At the 18-month timepoint, bottle (b) (4) had a (b) (4) % weight loss since the initial timepoint.

   The LIRs do not evaluate whether the anomalous bottles represent non-integral bottles of a sterile product.

   b. (b) (4) Solution. Specification NMT (b) (4) % for weight loss.

LIR # (b) (4) confirmed an anomalous result at the 6-month timepoint for stability batch (b) (4) (US batch, expiration (b) (4) with a weight loss of (b) (4) % on bottle (b) (4) since the initial timepoint.

LIR # (b) (4) confirmed an anomalous result at the 12-month timepoint for stability batch (b) (4) (US batch, expiration (b) (4) with a weight loss of (b) (4) % on bottle (b) (4) since the initial timepoint. At the 18-month timepoint, bottle (b) (4) had a weight loss of (b) (4) %.

The LIRs do not evaluate whether the anomalous bottles represent non-integral bottles of a sterile product.

c. (b) (4) Spray, specification NMT (b) (4) % for weight loss.

LIR # (b) (4) confirmed an anomalous result at the 12-month timepoint for stability batch (b) (4) (US batch, expiration (b) (4) at the 25°C/60% RH condition, with a weight loss of (b) (4) % on bottle (b) (4) since the initial timepoint. Bottle (b) (4) had a weight loss of (b) (4) % at the 24-month timepoint and (b) (4) % at the 36-month timepoint.

Additionally, bottle (b) (4) had weight loss of (b) (4) % at the 24-month timepoint and (b) (4) % at the 36-month timepoint.

The same batch had a weight loss on bottle (b) (4) in the 2-8°C stability conditions of (b) (4) % at the 24-month timepoint and (b) (4) % at the 36-month timepoint.

d. (b) (4) Spray, specification NMT (b) (4) % for weight loss.

LIR # (b) (4) confirmed an anomalous result at the 12-month timepoint for stability batch (b) (4) (US batch, expiration (b) (4) with a weight loss of (b) (4)% on bottle (b) (4) since the initial timepoint. Bottle (b) (4) visually had a lower level of product than other bottles.

LIR (b) (4) confirmed an anomalous result at the 12-month timepoint for stability batch (b) (4) (US batch, expiration (b) (4) with a weight loss of (b) (4)% on bottle (b) (4) since the initial timepoint. Bottle (b) (4) visually had a lower level of product than other bottles.

e. (b) (4) Spray. Specification NMT (b) (4)% for weight loss.

LIR # (b) (4) confirmed an anomalous result at the 18-month timepoint for stability batch (b) (4) (US batch, expiration (b) (4) with a weight loss of (b) (4)% on bottle (b) (4) since the initial timepoint. Bottle (b) (4) had a weight loss of (b) (4)% at the 24-month timepoint.

LIR # (b) (4) confirmed an anomalous result at the 12-month timepoint for stability batch (b) (4) (Australia batch, expiration (b) (4) 2-8°C, with a weight loss of (b) (4)% on bottle (b) (4) since the initial timepoint. Bottle (b) (4) had a weight loss of (b) (4)% at the 18-month timepoint and (b) (4)% at the 24-month timepoint. The same batch stored at 25°C/60% RH had a weight loss in bottle (b) (4) of (b) (4)% at the 24-month timepoint.

3. Investigations into out of specification results in stability weight loss tests were not thoroughly investigated and expanded to other batches.

   a. On August 18, 2022, LIR # (b) (4) was opened for an OOS weight loss result for (b) (4) (US market) 12-month, 25°C/60% RH when the (b) (4) weight loss of

the (b) (4) bottles was (b) (4) % compared to a specification of not more than (b) (4) %. (b) (4) of the (b) (4) individual bottles had weight loss of more than (b) (4) % and these (b) (4) bottles visually had a lower level of fill. Additionally, the LIR investigated anomalous individual results above the specification from the 2-8°C storage samples for this same batch (b) (4) anomalous results), the 12-month 2-8°C samples for (b) (4) anomalous results), and the 12-month 25°C/60%RH samples for (b) (4) anomalous results). The LIR confirmed the results as valid.

Deviation #1336797 was opened August 18, 2022. The investigation identified the root cause as the commercial packaging (b) (4) causing (b) (4) the product to (b) (4) leak out. The investigation stated these units would (b) (4) concentrating the product and increasing the assay.

An October 8, 2022, inspection of stability samples identified leaking samples from (b) (4) bottles) and (b) (4) bottles), which were both packaged into (b) (4) packaging. (b) (4) of (b) (4) stability samples inspected from batch (b) (4) were found to be leaking.

Despite identifying the bottles were not integral for multiple stability batches packaged in the (b) (4) configuration, an October 17, 2022, Escalation Committee meeting concluded no market action was required for the product within expiry on the US market represented by the leaking stability samples.

The site continued to release (b) (4) Spray in the (b) (4) configuration identified to be responsible for leaking stability samples on multiple batches. Batch (b) (4) was the last batch released using this (b) (4) packaging configuration on (b) (4) It was placed on stability. At the 12-month time point bottle (b) (4) had an

anomalous result in the weight loss test of (b) (4)%. No reassessment of the decision to leave the impacted batches on the market was made. At the 24-month timepoint bottle (b) (4) has a weight loss of (b) (4)%.

On May 5, 2023, deviation investigation #1437225 was opened to investigate OOS weight loss results for batches (b) (4) that identified the (b) (4) packaging as the root cause. The investigation concluded there was no impact to other distributed batches.

On September 7, 2023, LIR # (b) (4) was opened at 12-month for an anomalous result on bottle (b) (4) of (b) (4)% weight loss for batch (b) (4) which was packaged in the (b) (4) configuration.

Substantiated market complaints were made for leaking product packaged in the (b) (4) configuration including:

PR ID #1341174, batch (b) (4) opened 31 August 2022 and closed 05 May 2023.
PR ID #1428311, batch (b) (4) opened 14 April 2023 and closed 13 June 2023.
PR ID #1465951, batch (b) (4) batch opened 14 July 2023 and closed 11 August 2023.

All three complaints were attributed to leaking due to the (b) (4) packaging. No action was taken to address the distributed batches within expiry on the US market.

b. During stability sample examination on October 8, 2022, a leaking sample was observed from batch (b) (4) Spray batch (b) (4) (US market, expiration (b) (4) which is not packaged in the (b) (4) configuration. No investigation was opened.

Subsequently, deviation #1368683 was opened November 15, 2022, for batch (b) (4) (b) (4) labeled expiration date) at the 24-month stability timepoint. There were OOS results for assay (b) (4) with a result from bottle (b) (4) %), bottle (b) (4) (b) (4) %), and bottle (b) (4) %), that fell outside the (b) (4) % criteria. Additionally, the lot was OOS for (b) (4) weight loss with (b) (4) % compared to a limit of NMT (b) (4) %. Individual bottles had weight loss of (b) (4) % (bottle (b) (4) and (b) (4) % (bottle (b) (4) The root cause was identified as (b) (4) due to variation in bottles resulting in leaking bottles.

No action was taking for this stability batch or marketed product represented by this stability study. There was no thorough investigation of other batches that may have been impacted.

Subsequently, deviation #1423953 was opened April 4, 2023, for OOS weight loss at the 24-month timepoint for batch (b) (4) with a (b) (4) result of (b) (4) % weight loss. Bottle (b) (4) had an individual loss of (b) (4) % from the initial to the 24-month timepoint. The investigation identified the same root cause as (b) (4) due to variation in bottles, resulting in leaking bottles. The investigation was not extended to marketed product represented by this stability batch that may have similarly had leaking units.

4. On 17 June 2024, your firm found (b) (4) residue under the cap of a bottle of (b) (4) (b) (4) solution USP, (b) (4) mg/mL, (b) (4) mL bottle, batch number (b) (4) during the 18-month time point stability testing. Your firm filed a field alert report with the US FDA for this issue on 20 June 2024. Your firm determined the root cause of the (b) (4) residue was (b) (4) of the (b) (4) by the product due to the product and (b) (4) being

incompatible, which resulted in product leakage.

Your firm performed a risk assessment for this event (under deviation PR ID 1587361), which you concluded was "High risk". Based on your investigation and risk assessment, your firm decided to destroy all remaining product still under your control, but you did not take any action on the products still on the US market and within expiry at the time. In addition, you identified (b) (4) solution (b) (4) mg/mL, (b) (4) mL bottle, was also at risk of adverse interactions between the product and the (b) (4) in the (b) (4) but your firm took no action on this product on the US market. Your investigation found multiple batches of impacted products on the US market including, but not limited to, the following:

- (b) (4) solution USP, (b) (4) mg/mL, (b) (4) mL bottle, batch number (b) (4) manufactured on 22 December 2022.

- (b) (4) solution USP, (b) (4) mg/mL, (b) (4) mL bottle, batch number (b) (4) manufactured on 07 January 2023.

- (b) (4) solution (b) (4) mg/mL, (b) (4) mL bottle, batch number (b) (4), manufactured on 25 April 2023.

Your firm performed a health hazard assessment (HHA) on 09 July 2024 for this event and concluded there was no additional risk to the patient. However, the HHA only focused on the patient's exposure to (b) (4) Your firm did not perform any testing on the (b) (4) residue found on the (b) (4) or consider what impurities may be generated by the

degradation of the (b) (4)

Your firm created a corrective and preventive action (CAPA) report for this issue on 07 October 2024 (PR ID 1627777), which was closed on 07 March 2025. Your firm closed this CAPA without having a new (b) (4) in place to avoid incompatibility issues with these drug products. Your firm stopped manufacturing (b) (4) solution USP, (b) (4) mg/mL, (b) (4) mL bottle, in (b) (4) but you continue to manufacture (b) (4) solution (b) (4) mg/mL, (b) (4) mL bottle, using the same (b) (4) with a (b) (4)

According to your records, the following (b) (4) batches of (b) (4) solution (b) (4) mg/mL, (b) (4) mL bottle, are currently on the US market and within expiry: (b) (4) (b) (4) These batches have a range of expiration dates from (b) (4) to (b) (4) Also, (b) (4) solution USP, (b) (4) mg/mL, (b) (4) mL bottle, batch number (b) (4) is on the US market with an expiration date of (b) (4)

5. On May 17, 2022, deviation #1305427 was opened for (b) (4) Spray batch (b) (4) when the assay (b) (4) failed with an individual result for bottle (b) (4) of (b) (4) % assay for the (b) (4) sample. The investigation identified void volumes in the (b) (4) and (b) (4) (b) (4) as the root cause. Batch (b) (4) was destroyed, but other batches that used the same batch of (b) (4) including US market batch (b) (4) were released. No CAPA actions were implemented.

   Subsequently, on September 10, 2024, deviation #1617267 was opened for (b) (4) Spray stability batch (b) (4) at the 3-month timepoint. The batch was OOS for assay (b) (4) with an individual result for bottle (b) (4) of (b) (4) % assay for the (b) (4) sample. The

investigation identified the root cause as large voids along the (b) (4) for bottle (b) (4) that could trap API particles that are later released causing the high assay (b) (4) The investigation concluded there was no impact on other batches, but the same lot of (b) (4) were used in US market batches (b) (4) expiration (b) (4) expiration (b) (4) and (b) (4) expiration (b) (4)

No evaluation was done on other lots of (b) (4) received from the same vendor to determine if they contained (b) (4) with similarly large voids along the (b) (4) or (b) (4) (b) (4) No incoming check for (b) (4) batches has been implemented to detect for the presence of large voids or (b) (4) The (b) (4) vendor has not yet implemented equipment changes to address the formation of excessive voids.

6. During the filling of (b) (4) Spray batch (b) (4) (US market, expiration (b) (4) on June 7, 2023, the batch record comment log and associated workorder # (b) (4) document the presence of foreign black particles found on the (b) (4) and under (b) (4) and (b) (4) There was no identification of the particles, investigation into the source of these foreign particles, or evaluation of how they may have impacted previously filled bottles. Following cleaning of the area, filling of the batch resumed.

OBSERVATION 2

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

1. On May 1, 2025, during filling of (b) (4) Spray batch (b) (4) (US market) on filling line (b) (4)

   a. There was a build-up of unidentified (b) (4) particles on equipment surfaces beginning

at the (b) (4) The (b) (4) had visible wear on its (b) (4) parts. The (b) (4) had worn edges and larger pieces of (b) (4) that appeared to be hanging off the ends of the (b) (4) The product (b) (4) directly contact the (b) (4) and equipment surfaces with visible (b) (4) particles before they are placed directly into bottles of (b) (4) Spray.

b. We observed apparent metal shavings approximately seven (7) inches (b) (4) the cleaned bottle conveyor. (b) (4) spray, batch number (b) (4) was currently in process on this line, but it was not running during our walkthrough. Your firm initiated a deviation investigation for this event (PR ID 1707664) and confirmed the apparent metal shavings were metal particles being generated from a (b) (4) on a (b) (4) coming into contact with the (b) (4) frame.

c. The valve between the (b) (4) tank and the filling machine had (b) (4) residues on it that appeared to be coming from a leaking seal on the valve.

2. On 28-29 April 2025, we observed the following discrepancies in the Grade A space of your (b) (4) on the (b) (4) line, which had been cleaned on 26 April 2025 and was in the final set up stages, including conducting the (b) (4) cycle, and filling process of batch number (b) (4) of (b) (4) solution (b) (4) mL:

-The gasket between the housing pieces (b) (4) the (b) (4) was degrading.
-The white plastic tool used for jammed bottle interventions was discolored.
-Two rips on the seal between the (b) (4) and the (b) (4) frame (b) (4) the filler section.
-Apparent splash residue (b) (4) on the (b) (4) of the filler housing, (b) (4) the filler

(b) (4)
-Apparent splash residue (b) (4) on the (b) (4) of the (b) (4) housing. (b) (4)
(b) (4)
-Tape on all (b) (4) of the (b) (4) covers used during (b) (4)
-Degrading gaskets on the (b) (4) covers at locations (b) (4) (by (b) (4) and (b) (4) by (b) (4)
-Numerous dents and scratches on the (b) (4) floor in the section (b) (4)
-Discoloration and scratches on the (b) (4) between the (b) (4) and the filler.
- (b) (4) discoloration around the feet of the (b) (4) the filler.
-Numerous dents and scratches on the (b) (4)
-Excess sealant around the center of the (b) (4) which created a rough surface.
-Apparent adhesive residue on the (b) (4) of the (b) (4) number (b) (4)

In addition, on 02 May 2025, during (b) (4) integrity testing, we observed discoloration on the (b) (4) of the (b) (4) at (b) (4) numbe (b) (4) which are by the (b) (4)

3. On April 29, 2025, during set-up for aseptic filling of (b) (4) Solution batch (b) (4) (US submission batch), valve (b) (4) was observed to have crusted residues on its external surfaces. Additionally, there were wet drops forming on the bottom of valve and dripping to the floor. This valve is located on the (b) (4) (b) (4)

4. On May 1, 2025, during filling of (b) (4) Spray batch (b) (4) (US market) on (b) (4)

a. There is a (b) (4) based (b) (4) material installed around the cap bowls. The material did not appear to be easily cleanable. There were holes in the (b) (4) with missing pieces near the open caps that are placed on to the bottles of (b) (4) Spray.

b. There were loose screws and bolts in a tray on the base of the machine that had not been removed following maintenance activities.

5. On 05 May 2025, we observed apparent (b) (4) product residue on the supporting structures under the filler on Line (b) (4) which is used for (b) (4) drug products. According to your cleaning and usage logbook for this line, it was cleaned on (b) (4) and (b) (4) since it was last used for manufacturing (b) (4) Solution (b) (4) MG/ML (b) (4) ML, batch number (b) (4) (EU market), on (b) (4) Both cleaning activities were checked and signed off with no comments.

6. Preventive maintenance schedules do not include timeframes for proactively changing parts necessary to ensure the (b) (4) used for aseptic filling does not have leaks, including gaskets on (b) (4) These items are changed when there are leak test failures or visual inspection determines the change is necessary.

OBSERVATION 3

Written procedures are not established that describe the tests and examinations to be conducted on appropriate samples of in-process materials of each batch.

1. Your firm does not perform 100% visual inspection on filled bottles of (b) (4) solutions manufactured on your (b) (4) line. This line fills (b) (4) bottles for some drug products,

including, but not limited to, (b) (4) solution (b) (4)% (b) (4) mL and (b) (4) (b) (4) solution (b) (4) mL. Your firm lacks an SOP requiring 100% visual inspection for bottle defects and particulates.

2. Your firm does not perform acceptable quality limit (AQL) inspections on commercial batches of (b) (4) drug products manufactured on your (b) (4) line. Your firm's AQL SOP, number SOP-QA-150.001-R, only requires AQL inspections to be performed on incoming materials/components and during investigations.

3. Your firm does not perform any in-process or finished product container closure integrity testing on (b) (4) drug products manufacturing on your (b) (4) solution line (b) (4) Your firm exclusively relies on your (b) (4) specification of (b) (4) on your (b) (4) but only bottles with a (b) (4) below the lower limit are rejected. The (b) (4) line is used for manufacturing (b) (4) drug products including, but not limited to, (b) (4) (b) (4) solution (b) (4)%, (b) (4) solution (b) (4)%, and (b) (4) solution (b) (4)%.

OBSERVATION 4

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

1. Procedure SOP-PR-080.001-R "Approved Interventions on the (b) (4) Filling Line" permits filling to continue following a breach of a (b) (4) The (b) (4) is tagged not to be used, but filling can continue. For example, during batch (b) (4) of (b) (4) Solution (b) (4) ML (released to US market, expiration (b) (4) a 6mm hole was observed in (b) (4) The (b) (4) was tagged not to be used, but the filling continued with an additional (b) (4) unit filled after identification of the hole in the (b) (4)

2. On 28 April 2025 and on 07 May 2025, during the [redacted] cycle on your [redacted] on the [redacted] line, we observed numerous [redacted] on the [redacted] including, but not limited to, [redacted] at the [redacted] by the [redacted] and the filler [redacted] Your [redacted] decontamination cycle procedure, number SOP-PR-381.003-R, states "[redacted]" on section 8.2.17.5.

OBSERVATION 5

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

1. Your firm does not incubate all integral units during media fills. For example, during media fill, batch number [redacted] you performed fill volume checks on [redacted] units which were initially integral, but an employee opened and emptied the units to perform fill volume checks. Your firm did not incubate approximately [redacted] units used for fill volume checks for each media fill performed in the past three years.

2. On your [redacted] solution line, [redacted] while conducting Intervention [redacted] Due to lack of filling operations during the inspection, we observed this process in a smoke study video performed in June 2023. Your Specialist of Quality Validation stated blocking the first air was required during this intervention during commercial manufacturing. Your approved interventions for [redacted] procedure, number SOP-PR-080.001-R, states "While performing the intervention, avoid approaching the intervention from [redacted] or allowing the [redacted]" The [redacted] line is used for manufacturing [redacted] drug products including, but not limited to, [redacted] solution [redacted]%, [redacted]

(b) (4) solution (b) (4)%, and (b) (4) solution (b) (4)%.

OBSERVATION 6

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

1. The (b) (4) HMI is used to control and monitor the aseptic filling (b) (4) The software uses a shared username and password for the (b) (4) production operators and has no audit trail capabilities that could document changes to recipes for (b) (4) filling, or (b) (4) of bottle caps.

   The system is not configured to save electronic data or print all activities and alarms. For example, (b) (4) leak tests and leak tests associated with the (b) (4) cycle, including failing leak tests, are only visible on the screen and are not captured in the electronic data and the data cannot be printed. Alarms occurring on the system not specifically associated with a batch are not printed or maintained electronically.

2. The (b) (4) software is used to perform leak testing of the (b) (4) The software has no audit trail capability. The user performs tests, can see progressing results, and has the ability to end the test before completion. If the test is ended before its completion, the retest overwrites the aborted test with no record in the electronic or printed records.

3. The (b) (4) Integrity Tester is used to test (b) (4) including product (b) (4) The software uses a shared username and password for the (b) (4) production operators. The operators are relying on paper printouts as the raw data. Quality personnel do not perform a review and reconciliation of the data stored electronically and what is printed for reporting. For example:

b. On April 9, 2025, at (b) (4) there was a failing (b) (4) test identified as "Pretest" that was not documented or explained in the reported records.

b. On April 9, 2025, at (b) (4) and (b) (4) there were error results associated with batch (b) (4) that were not included in printed data.

c. On April 16, 2025, there were 14 results identified as "Test" that were not documented or explained in the reported records, including a failing result, error results, and an aborted test.

4. The notification system documents requests for higher level access of passwords. There were approximately 404 notifications with this request in the past two years. The requests were granted without always documenting why they were needed or whether changes were made. Requests for higher level access included systems with no audit trail capabilities, including the HMI for the (b) (4) and filling machine.

5. The (b) (4) used for sterilizing product contact parts used in the aseptic (b) (4) (b) (4) does not save electronic data and has no audit trails. The printouts are considered the raw data and intended to be sequentially numbered by the equipment.

   On April 28, 2025, a printout indicating a process failure during a leak test from April 21, 2025, was found in a storage room, not archived with the printed records. Additionally, there were missing sequential printouts listed in the logbook.

6. The non-viable particle counters used to monitor the (b) (4) use a shared username and password.

7. Empower software is configured to allow chemists to view the quantitation fields in the review window. This permits chemists to see area counts for the (b) (4) before choosing whether to save changes made to integration processing methods.

8. The audit trial review procedure is general, without any specific details for different software describing what the reviewer needs to review or identification of what information in the audit trail is relevant.

OBSERVATION 7

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

1. There is no non-viable particle monitoring inside the aseptic filling (b) (4) conducted near the (b) (4) bowl, or near the (b) (4) of the (b) (4)

   There is only (b) (4) non-viable particle counter inside the (b) (4) located near the filling machine. On April 29, 2025, during set-up for (b) (4) Solution batch (b) (4) (US submission batch), the probe was angled away from the filling machine.

2. There is no viable monitoring performed from the end of set-up to the start of filling. During this time there are exposed (b) (4) closures including bottles and (b) (4) and product contact surfaces like (b) (4) Interventions for filling start-up occur during this time period.

3. Viable air monitoring in the area where the open (b) (4) closure bottles are located in a (b) (4) bowl, and track, is only limited to (b) (4) for (b) (4) monitoring.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	4/28/2025-5/9/2025* FEI NUMBER 3001617666

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Sylvain Thuot, Vice President, Product Supply	
FIRM NAME Apotex Inc.	STREET ADDRESS 380 Elgin Mills Rd E
CITY, STATE, ZIP CODE, COUNTRY Richmond Hill, L4C 5H2	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

OBSERVATION 8

Procedures describing the handling of written and oral complaints related to drug products are.

1. Your firm has not implemented adequate corrective and preventive actions (CAPAs) for approximately 492 market complaints related to hard to open bottles of (b) (4) drug products in the past three years. The products include, but are not limited to, (b) (4) (b) (4) solution (b) (4)%, (b) (4) solution (b) (4)%, and (b) (4) (b) (4) solution (b) (4)%.

   On 01 September 2022, your firm opened a CAPA (PR ID 1341808) to address (b) (4) variation on your (b) (4) filling line (b) (4) and it was closed on 12 September 2023 after your firm optimized the process and (b) (4) parameters. However, your firm did not implement an upper limit for (b) (4) on the (b) (4) line and only bottles with (b) (4) below the lower limit of (b) (4) (b) (4) are rejected. Your firm has received approximately 73 complaints related to hard to open bottles of (b) (4) solution since the CAPA was closed in September 2023.

2. Your firm did not identify foreign matter found in your drug products on multiple occasions, including, but not limited to, the following:

   c. On 29 September 2022, you received a complaint for a small black object floating in a bottle of (b) (4) solution (b) (4) mL (PR ID 1351915). Your microbiology laboratory identified the black object as a hyphae like structure with spores similar to mold. However, you did not perform any microbial identification on the microorganism in the drug product as part of the investigation.

   b. On 20 October 2023, you received a complaint for black particles floating in a bottle of

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[(b) (4)] solution [(b) (4)] mL (PR ID 1503292). The complaint sample was received approximately 25% full and your microbiology laboratory observed the black particles and determined they were not viable cells, but stated further confirmation was required to identify the type of particles. However, your firm did not perform any additional testing and concluded the contamination was caused by customer's mishandling of the product.

3. Your firm did not examine retain samples as part of the investigation for multiple complaints related to leaking product, including, but not limited to, the following:

PR ID 1407999, [(b) (4)] Solution [(b) (4)] mL USA (batch # [(b) (4)] received on 21 February 2023.

PR ID 1398998, [(b) (4)] Solution [(b) (4)] mL USA (batch # [(b) (4)] received on 31 January 2023.

PR ID 1367470, [(b) (4)] Spray [(b) (4)] mL (batch # [(b) (4)] received on 09 November 2022.

PR ID 1323100, [(b) (4)] Spray [(b) (4)] mL (batch # [(b) (4)] received on 08 July 2022.

OBSERVATION 9

Your firm failed to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess.

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Sylvain Thuot, Vice President, Product Supply	
FIRM NAME Apotex Inc.	STREET ADDRESS 380 Elgin Mills Rd E
CITY, STATE, ZIP CODE, COUNTRY Richmond Hill, L4C 5H2	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

The (b) (4) Spray is a (b) (4) product this is (b) (4) during filling. The batch record instructions allow line stoppages of up to (b) (4) without any actions required to (b) (4) filling machine during the line stoppage. There is no data to support the bottles filled after restarting will meet all quality specifications. For example, during batch (b) (4) of (b) (4) Spray (US market, expiration (b) (4) there was a line stoppage of (b) (4) (b) (4) with no documented (b) (4)

OBSERVATION 10

Established sampling plans and test procedures are not followed and documented at the time of performance.

1. On 01 May 2025, during a (b) (4) leak test of the (b) (4) on the (b) (4) line, the (b) (4) was fluctuating between (b) (4) and (b) (4) Your (b) (4) leak test procedure, number SOP-PR-070.004-R, instructs the (b) (4) to be (b) (4) to (b) (4) in section 7.8. In addition, we observed an Operator holding the (b) (4) on the frames of the (b) (4) for approximately (b) (4) per location, but your procedure requires (b) (4) of contact time for each location in section 7.12.

2. Documentation of environmental monitoring of the aseptic filling (b) (4) is not documented accurately and contemporaneously. The sampling personnel collect all samples from (b) (4) consecutively before making any documentation. The documentation they eventually enter into LIMS contains specific times of sampling that were not recorded at the time of sampling.

    d. On April 30, 2025, at 4:19 pm the operator was observed entering in the sampling time of 3:45pm, when the sampling time had not been recorded contemporaneously, during surface monitoring after (b) (4) Solution batch (b) (4) (US submission batch).

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b. On January 24, 2025, during (b) (4) fill monitoring with settle plates for batch (b) (4) Solution batch (b) (4) (US market), some sampling start times were not entered into LIMS until more than one hour after they times they were documented to start.

***DATES OF INSPECTION**

4/28/2025(Mon), 4/29/2025(Tue), 4/30/2025(Wed), 5/01/2025(Thu), 5/02/2025(Fri), 5/05/2025(Mon), 5/06/2025(Tue), 5/07/2025(Wed), 5/08/2025(Thu), 5/09/2025(Fri)

X Wayne D Mcgrath
Investigator
Signed By: 2001897192
Date Signed: 05-09-2025 12:50:26

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	Justin A Boyd, Investigator Wayne D Mcgrath, Investigator	X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 05-09-2025 12:50:04	5/9/2025