

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER One Montvale Avenue Stoneham, MA 02180 (781) 587-7500 Fax: (781) 587-7556		DATE(S) OF INSPECTION 11/7/2018-12/4/2018*
		FEI NUMBER 3013438665
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Deborah McHugh, Director, Quality Assurance		
FIRM NAME Fresenius Kabi Compounding, LLC	STREET ADDRESS 20 Dan Rd	
CITY, STATE, ZIP CODE, COUNTRY Canton, MA 02021-2809	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility	

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**

Established laboratory control mechanisms are not followed.

Specifically,

- The firm does not adequately document or investigate all sterility testing invalid assays as required per procedure. Inadequate documentation of invalid sterility tests includes tests conducted for initial process validation lots of potassium chloride injection USP, which were intended to be commercial lots and later reclassified as engineering batches, and commercial lots. For example:
 - During sterility testing of potassium chloride injection USP (20 mEq per 20 mL in 0.9% sodium chloride) Lot 650014, (produced 8-Jun-18 as an intended PV batch) the firm was unable to analyze the sterility sample due to a leak detected in the (b) (4) sterility testing (b) (4). An additional sterility test was conducted for Lot 650014, however, no investigation was conducted or documented into the initial invalid assay.
 - During sterility testing of potassium chloride injection USP Lot 650043 (produced 10-Aug-18 as a commercial lot, product distributed), the firm was unable to analyze the sterility sample due to operator error, as documented in KabiTrack Event Record# 340169. The sterility test was repeated; however, no investigation was conducted, or root

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cause documented for the original invalidated sterility test. The KabiTrack Event Record# 340169 states: "incident only, known operator error. No investigation required". The firm could not explain what error occurred during the current inspection.

- During sterility testing of potassium chloride injection USP Lot 650040 (produced 26-Jul-18 as a PV batch, sterility failure), the firm conducted (b) (4) sterility tests for the lot. The first (b) (4) tests were invalidated due to an exceeded incubation time and missing labeling solution volumes during the testing sessions respectively. The firm failed to adequately document the invalid assays at the time of occurrence. The invalid sterility testing assays were eventually documented as part of the sterility failure investigation for Lot 650040. The sterility failure investigation (KabiTrack Event Record #304043, opened on 13-Aug-18) for Lot 650040 was closed on 29-Sep-18.
- The firm does not investigate or assess potential product impact when errors occur at contract testing laboratories. For example, during endotoxin testing of potassium chloride injection USP (20 mEq per 20 mL in 0.9% sodium chloride), Lots 650014 (produced 8-Jun-18 as an intended PV batch), 650016 (produced 12-Jun-18 as an intended PV batch), and 650024 (produced 27-Jun-18 as an intended PV batch), the (b) (4) samples were (b) (4) for endotoxin analyses by the contract testing laboratory. The firm notified the contract testing laboratory in June 2018 to cease the (b) (4) of endotoxin sample however, the (b) (4) endotoxin samples for the aforementioned lots were evaluated against the same endotoxin limits as (b) (4) (b) (4) samples (b) (4) EU/mL) and the firm never assessed the potential product impact from results obtained using (b) (4) samples.

OBSERVATION 2

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

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Specifically,

- The firm does not investigate all sterility failures as required by procedure - Global Working Instruction gWI -QC-0001 – Sterility Test Failure Investigation. For example, during sterility testing of potassium chloride injection USP (20 mEq per 20 mL in 0.9% sodium chloride), Lots 650024 (produced 27-Jun-18 as an intended PV batch), 650030 (produced 3-Jul-18 as an intended PV batch), and 650031 (produced 6-Jul-18 as an intended PV batch), the firm obtained positive microbiological growth in the negative control of the (b) (4) experiment. No sterility failure investigation was initiated as required per procedure and the firm accepted the passing sterility results for the potassium chloride lots despite the failed negative control.
- The firm has not investigated unknown crystalline material observed between the cap/syringe interface of potassium chloride injection USP syringes (20 mEq per 20 mL in 0.9% sodium chloride). From 11/13/2018 – 11/16/2018, unknown crystalline material was observed between the cap/syringe interface of potassium chloride injection USP syringes from stability samples of Lot 650044 (produced 24-Aug-18 as a commercial lot, product distributed), from QC retain samples of Lots 650066 (produced 3-Oct-18 as a commercial lot, product distributed) and 650070 (produced 9-Oct-18 as a commercial lot), and packaged QA approved Lots 650080 (produced 25-Oct-18 as a commercial lot), 650077 (produced 16-Oct-18 as a commercial lot), and 650079 (produced 24-Oct-18 as a commercial lot). The firm was unaware of the noted unknown crystalline material and could not speak to the material identity.
- The firm has not investigated environmental monitoring excursions associated with QC sterility testing and batch release of potassium chloride injection USP (20 mEq per 20 mL in 0.9% sodium chloride) syringes. For example, personnel monitoring action limits (set as (b) (4) cfu for sterile gloves or sterile sleeves per the firm's procedure) were exceeded by QC analysts performing sterility testing in ISO-5 classified (b) (4) laminar flow hoods for several lots. A personnel monitoring worksheet for Lot 650024 (produced 27-Jun-18 as an intended PV batch) identified a QC analyst with a result of 1 cfu on their left sleeve, a personnel monitoring

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worksheet for Lot 650037 (produced 13-Jul-18 as a PV batch) identified a QC analyst with a result of 1 cfu on their left glove and 1 cfu on their right glove, and a personnel monitoring worksheet for 650042 (produced 3-Aug-18 as a commercial lot, product distributed) identified a QC analyst with a result of 1 cfu on their right sleeve. Even though action limits were exceeded, no investigations or corrective actions were conducted or implemented as required per procedure.


- The firm has not adequately investigated all discrepancies associated with aseptic process simulation (media fill) PR-18-00519. For example, personnel monitoring action limits (set as (b) (4) cfu for sterile gloves or sterile sleeves per the firm's procedure) were exceeded by an operator performing the media fill. A personnel monitoring worksheet for media fill Lot 18-024 identified an operator with a result of 1 cfu on their left sleeve. The firm failed to investigate or evaluate this discrepancy as required per their media fill protocol and environmental monitoring procedures.

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,

The firm's process validation for potassium chloride injection USP (20 mEq per 20 mL in 0.9% sodium chloride) was inadequate in that it failed to consistently produce a product that met its predetermined specifications (sterility). The firm's process validation initially included the following lots: 650037 (produced 13-Jul-18 as a PV batch), 650038 (produced 25-Jul-18 as a PV batch), 650040 (produced 26-Jul-18 as a PV batch, sterility failure). Lot 650040 was later rejected by the firm due to a sterility failure and excluded from the process validation study. The firm subsequently produced lot 650044 (produced

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24-Aug-18 as a commercial lot, product distributed), which passed sterility testing and was then incorporated into the process validation. The firm's investigation into the sterility failure included three potential root causes in which one potential root cause was attributed to a tubing failure and subsequent leaking of the product during the manufacturing process. The investigation indicated that this discrepancy had no impact to the product or process validation; however, the investigation also indicated that the discrepancy could not be ruled out as adversely impacting the batch and a possible cause of the sterility failure. In addition, the firm also stated that the justification for the exclusion of the failed batch from the process validation was due to the fact that none of the potential root causes were attributed to problems with the manufacturing process.

OBSERVATION 4

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

Specifically,

- The firm utilized unapproved draft versions of the following procedures: 14-01-00-0126 (b) (4) Control, 14-01-00-0127 (b) (4) Software Operational Procedure, 14-01-00-0128 (b) (4) Software Administration Procedure, 14-01-00-0129 (b) (4) Microscope Operational Procedure, and 14-01-00-0130 (b) (4) Sterility Test Method. The procedures were utilized during sterility release testing of approximately (b) (4) lots including Process Validation lots 650037 (produced 13-Jul-18 as a PV batch), 650038 (produced 25-Jul-18 as a PV batch), 650040 (produced 26-Jul-18 as a PV batch, sterility failure), and 650044 (produced 24-Aug-18 as a commercial lot, product distributed).
- Review of the firm's investigations revealed that the Quality Unit failed to consistently document preventative actions as part of the investigations. For example: Event 351288 was opened on 10/24/2018 for an operator failing to turn on particle counter during operations;

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Event 338223 was opened on 10/04/2018 for an operator utilizing a pipettor after the calibration due date had passed for endotoxin release testing; and Discrepancy 20 of PR-18-00536 which was opened to document the growth of microorganisms on a settle plate utilized during the production of Lot 650031 (produced 6-Jul-18 as an intended PV batch). The firm determined that the potential root cause was attributed to the settle plates being dropped on the floor and then utilized by the firm's operators. No documentation of preventative actions was provided.

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,

- The firm has not adequately investigated all sterility failures that occurred during the validation of the (b) (4) sterility test method to properly identify the sources of the contamination. For example, out of (b) (4) drug product samples tested during product suitability testing, the firm obtained failing sterility results for 4 of the samples. Despite the test failing acceptance criteria for sample sterility, the firm accepted the results as part of the (b) (4) method validation and attributed the failures to the use of a non-sterile (b) (4) during testing. Subsequently, during method suitability testing for the (b) (4) sterility test method validation, 3 of (b) (4) negative controls failed to meet acceptance criteria for sterility. The non-sterile (b) (4) (b) (4) was not utilized during the (b) (4) testing, and instead the firm attributed the failures to cross-contamination with positive controls.
- The firm's sterility suite (room 165) is not adequate for conducting the (b) (4) sterility assay. The (b) (4) sterility assay is sensitive to ambient light and room 162 has numerous windows

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which allow ambient light from adjacent areas to pollute the sterility suite. On 11/13/2018, what appeared to be aluminum foil and tinted shields were noted to be taped to the sterility suite windows. During the (b) (4) sterility test method validation, the firm documented 16 discrepancies that occurred during testing to include a discrepancy noted during analyst qualification in which the analyst was unable to confirm all (b) (4) events due to ambient light pollution. The firm's temporary corrective action to the ambient light pollution (aluminum foil and tinted shields taped to the windows) is inadequate.

OBSERVATION 6

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

Specifically,

- There is no assurance that all environmental excursions, including mold excursions, are adequately investigated. For example, on 26-Jul-18, the firm performed active air sampling of ISO-7 classified (b) (4) room 145 as part of the firm's environmental monitoring program during production activities of potassium chloride injection USP (20 mEq per 20 mL in 0.9% sodium chloride) syringes, Lot 650040 (produced 26-Jul-18 as a PV batch, sterility failure). Action limits are set as (b) (4) cfu/m³ for viable molds recovered via volumetric air sampling of ISO-7 classified areas per the firm's environmental monitoring procedures. Identification of a microbial isolate recovered from ISO-7 classified room 145 during environmental monitoring conducted on 26-Jul-18 showed growth of 1 cfu of *Penicillium rubens* (mold). The firm failed to document or initiate an investigation regarding this mold recovery, and as a result the excursion was not considered during the sterility failure investigation of Lot 650040 (KabiTrack Event Report #304043 dated 13-Aug-2018).
- Surface sampling of critical surfaces inside the ISO-5 classified (b) (4) laminar flow hoods (b) (4) is not conducted appropriately to provide meaningful information on the quality of the aseptic processing environment. On November 14, 2018, production personnel were observed

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performing cleaning of critical surfaces inside the (b) (4) with (b) (4), with a (b) (4) dwell time, and (b) (4). Immediately following the cleaning, QC personnel were observed performing surface sampling of critical surfaces inside the (b) (4). The firm's environmental monitoring procedures do not prohibit this practice and firm management identified this practice as common.

- The firm's personnel monitoring program is not well-defined to evaluate personnel practices as a potential route of microbial contamination. Operators and QC analysts performing filling (b) (4) activities and sterility testing inside ISO-5 classified (b) (4) laminar flow hoods (b) (4) conduct personnel monitoring upon the completion of hood activities. The firm's procedures do not include specific instructions describing proper techniques for operators to follow when performing gloved fingertip monitoring or sleeve monitoring. On November 14, 2018, personnel monitoring of gloved fingertips was observed to be conducted inappropriately. Operators touched all five finger tips onto a (b) (4) plate at one time, instead of rolling each finger pad individually to ensure adequate contact.
- The firm failed to provide data to support the environmental monitoring sampling locations within the ISO-5 classified (b) (4) laminar flow hood (b) (4). Settle plates are placed in the (b) (4) and (b) (4) of the (b) (4), away from conducted aseptic activities.

OBSERVATION 7

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room to produce aseptic conditions.

Specifically,

- The firm utilizes the cleaning agent (b) (4) within the ISO-5 classified (b) (4) Laminar

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Flow Hoods and on the surfaces of the firm's classified rooms. (b) (4) is a non-sterile cleaning agent and is (b) (4) by the firm via a (b) (4). The firm has failed to perform (b) (4) of any of the (b) (4) utilized in the sterilization of the (b) (4) (b) (4) cleaning agent.

- Cleaning of the (b) (4) Laminar Flow Hoods (b) (4) are conducted by the firm's employees and documented via the (b) (4) Cleaning Logbooks. Inspection of the (b) (4) cleaning logs revealed that the none of the cleaning records from August of 2018 to November of 2018 had been reviewed by either Manufacturing or Quality Assurance as required by the firm's procedure. In addition, cleaning of the firm's classified areas is conducted by the firm's contract cleaning company and documented via the Cleanroom Cleaning Logs for Zones (b) (4). Inspection of the room cleaning logs revealed that the Quality Unit failed to perform an adequate review of the logs to ensure the accuracy of the recorded information as required by the firm's procedure.
- On November 8, 2018, a contract cleaner was observed mopping ISO-7 classified room 142. The operator failed to clean under several carts located in the room and the mop did not always appear to be adequately soaked with cleaning agent, (b) (4). Room 142 supports ISO-7 classified room 140, which contains (b) (4) ISO-5 classified (b) (4) used to produce sterile products such as potassium chloride injection USP (20 mEq per 20 mL in 0.9% sodium chloride) syringes.

OBSERVATION 8

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release.

Specifically,

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The firm's visual inspection procedures utilized for final release of sterile products, and as identified on the certificates of analysis for already distributed batches of potassium chloride injection USP (20 mEq per 20 mL in 0.9% sodium chloride) syringes, are deficient for the following reasons:

- Established defect categories such as particles and/or precipitation inside the syringe, leakage from syringe, crack or break on any portion of syringe or missing flange, tamper evident cap is missing or damaged, incorrect volume reading, or incorrect syringe size, do not include relevant action levels.
- Defects are not classified for criticality or significance of risk to product quality. For example, defects such as particles and/or precipitation inside the syringe or leakage from syringe are not identified as critical. Particulates were found during 100% visual inspection or AQL for the following lots 650057 (produced 6-Sep-18 as a commercial batch, sterility failure), 650063 (produced 12-Sep-18 as a commercial batch), 650065 (produced 2-Oct-18 as a commercial batch), and 650077 (produced 16-Oct-18 as a commercial lot). Leaking syringes or leaking caps were found during the 100% visual inspection or AQL for the following lots 650070 (produced 9-Oct-18 as a commercial batch), 650078 (produced 16-Oct-18 as a commercial batch, sterility failure), 650079 (produced 24-Oct-18 as a commercial lot), and 650080 (produced 25-Oct-18 as a commercial lot).
- Investigations are not required to be initiated for any defects identified during 100% visual inspection regardless of quantity or criticality. For example, on 24-Oct-18 during 100% visual inspection of potassium chloride injection USP syringes Lot 650079 (produced 24-Oct-18 as a commercial lot), the firm rejected 3 syringes due to leaking. On 11/15/18, unknown crystalline material was observed between the cap/syringe interface of rejected syringes from Lot 650079.
- The firm's visual inspection qualification process fails to adequately consider any rejects likely to be deemed as critical, such as particles and/or precipitation inside the syringe or leakage from syringe. The defect kit used for visual inspection and AQL qualification includes (b) (4) and

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(b) (4) ((b) (4)) and (b) (4) and (b) (4)
(b) (4)). Nine of the firm's (b) (4) technicians and QC staff who perform 100% visual inspection and AQL were found to have been deemed qualified by the firm's Quality Assurance even though they failed to identify both (b) (4) and (b) (4) in the defect kits.

OBSERVATION 9

Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

Specifically,

There is no assurance of the integrity of the container closure system used for potassium chloride injection USP (20 mEq per 20 mL in 0.9% sodium chloride) syringes. The firm's container closure integrity tests do not include equivalence studies utilizing potassium chloride to demonstrate tamper evident tip caps with different configurations and from different manufacturers are suitable and can be used interchangeably.

OBSERVATION 10

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

Specifically,

The firm's air pattern analysis (smoke study) conducted for the ISO-5 classified (b) (4) Laminar Flow

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Hoods (b) (4) was inadequate in that the dynamic smoke studies failed to incorporate all aspects of the firm's production process. For example, the firm failed to include a balance within the (b) (4) or demonstrate the airflow patterns around the balance.

OBSERVATION 11

The labels of your outsourcing facility's drug products are deficient.

Specifically,

The following information is not found on the drug product labels:

- The statement "This is a compounded drug"

Examples of product labels that do not contain this information:

- Potassium Chloride 20mEq per 20mL

***DATES OF INSPECTION**

11/07/2018(Wed), 11/08/2018(Thu), 11/13/2018(Tue), 11/14/2018(Wed), 11/15/2018(Thu),
11/16/2018(Fri), 11/19/2018(Mon), 11/26/2018(Mon), 11/27/2018(Tue), 12/04/2018(Tue)

X Sean R Marcsisin
Investigator
Signed By: Sean R. Marcsisin -S
Date Signed: 12-04-2018 08:43:57

X Erik W Koester
Investigator
Signed By: Erik W. Koester -S
Date Signed: 12-04-2018 08:44:35

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE John P Mistler, Investigator Erik W Koester, Investigator Sean R Marcsisin, Investigator	John P Mistler Investigator Signed By: John P. Mistler -S Date Signed: 12-04-2018 08:43:10 X	DATE ISSUED 12/4/2018