DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214)253-5200 Fax:(214)253-5314	3/9/2018-3/22/2018* FEI NUMBER 3004483441

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. James L. McCarley, CEO

FIRM NAME	STREET ADDRESS
Cantrell Drug Company	7321 Cantrell Rd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Little Rock, AR 72207-4144	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

Investigations of an unexplained discrepancy did not extend to other drug products that may have been associated with the specific failure or discrepancy.

A. Your quality control unit has not adequately investigated EM excursions and trends as follows:

i. Between December 2017 and February 2018, three viable organism recoveries were identified within ISO-7 production areas on laptop keyboards used by compounding assistants. Assistants were observed placing and removing materials to/from ISO 5 hoods on 13 March 2018. No adequate corrective action has yet been determined and nearby product in ISO-5 hoods are not rejected by the Quality Unit. Organisms and counts are as follows:

7-Dec-17	8	Aspergillus spp.
24-Jan-18	7	Staphylococcus auricularis
9-Feb-18	TNTC	Staphylococcus spp.

ii. Between 19 December 2017 and 9 March 2018, at least 22 viable organisms were identified from employee gown samples (who work in ISO-7 areas). There is no adequate trending or root cause analysis for these recoveries. It should be noted that smoke studies (August 2017) confirm turbulent flow and stagnant air in ISO-7 class gowning rooms where air returns are co-located with HEPA air supply fixtures in the ceiling (room (b) (4) and (b) (4)). It should also be noted that technicians wear "street" shoes inside the clean room which are covered with a fiber cloth shoe

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cover and inside sterile polyester gowning.

iii. Between 1 June 2017 and 18 March 2018, at least five viable organism recoveries were identified within ISO-5 production area laminar flow hoods that are used (b) (4) for processing sterile injectable drug products. While responses include destruction of affected product, no root cause has yet been identified. It should be noted that a plenum space above the ISO 7 cleanroom ((b) (4)) is not periodically cleaned or disinfected. Organisms include Staphylococcus hominis, Talaromyces rugulosus, and Sclerotinia sclerorotiorum.

B. Your firm contracted a 3rd party consultant (beginning in December 2017) for conducting a review of your compounded sterile finished drug batch records and associated documents. While the contractor makes suggestions to documentation changes and provides an initial disposition of the batch, there is no internal protocol or mechanism to track and trend the results of this process to determine if process changes are occurring or needed.

You Director of Quality reported the 3rd party consultant provided recommended approving/release memorandum as part of all sterile finished drug product batch records. Your firm's Regulatory Administrative Assistant & Batch Record Reviewer reported your firm fails to include email communications and/or reference the location of received from your 3rd party consultant identifying deficiencies found during their secondary review.

C. Your firm failed to follow written procedure P&P 4.170, Revision 1, 6/30/2015: Change Control for Processes and Policies and Procedures, when changes were made to the differential pressure monitoring system for ISO 7 clean rooms where drug products are produced. Your equipment qualification ((b) (4) (b) (4) Report, dated 8/3/2017) for your firm's "(b) (4)" electronic system used in the measuring and monitoring of temperature, differential pressure, and relative humidity shows changes to your firm's (b) (4) were made. Your IT Manager stated this change was made to enhance (b) (4) performance when poor (b) (4) was observed, but no change control document was completed.

D. Your firm's procedure, Temperature, Humidity, Pressure Differential Monitoring of the Classified and Controlled

Areas, P&P No. 3.010, Revision 10, 2/23/2018, Subsection 8.5.2.2, states "Control Charts will be reviewed on a (b) (4) basis to determine trends. Negative trends will be discussed and evaluated on a case by case basis". Your firm's procedure fails to require the documentation of these reviews and your firm's final conclusions as result of the review.

E. The (b) (4) system has produced anomalous results for negative controls and no deviation or "Internal Findings Report" was created to investigate or trend the performance of this equipment. The following examples show products tested and passing on the same days:

- 15 August 2017 – Injectable Glycopyrrolate 0.2mg/mL (lot# 10744)
- 21 August 2017 – Succinylcholine Chloride 20 mg/mL (lot #10750)
- 20 February 2018 – Injectable Morphine 2mg/mL (lot #11487)

This instrument is used for testing all drug products produced at your facility for sterility prior to commercial distribution as stated by your Senior Quality Assurance Manager.

F. Between 30 August 2017 and 13 March 2018, your contract testing lab performed multiple assay re-testing of Injectable Norepinephrine Bitartrate as part of a stability study. Results returned between (b) (4) and (b) (4) percent of the labeled value (4mg in 250mL IV bag) at the (b) (4) and (b) (4) day time points. The documented specification is (b) (4) - (b) (4) %. This product is currently labeled with a 90-day BUD (Beyond Use Date). However, no investigation or IFR has been initiated to track and trend OOS results from your contract testing lab.

G. On 17 February 2018, your contractor completed a "Certified Test, Adjust, and Balance Report" that included adjustments to air velocities in ISO-7 Cleanrooms #(b) (4) . The adjustments were made both to HEPA air supply and (b) (4) . After these changes were made to your clean room air handling and room pressures, there was no air visualization (smoke study) performed on the ISO 7 rooms.

This is a repeat observation from the previous inspection in June 2017.

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OBSERVATION 2

Complaint procedures are deficient in that they do not include provisions that allow for the review to determine if the complaints represent serious and unexpected adverse drug experiences which are required to be reported to FDA.

Specifically, your written procedure P&P No. 1.100 (R8), "External Complaints and Corrective & Preventative Action," state that "[m]anagement will review complaints and determine if FDA needs to be informed," but do not provide that adverse events that are both serious and unexpected, as defined in FDA regulations at 21 CFR 310.305, will be reported to FDA.

Additionally, full documentation of complaints is not always maintained such as original communication from the complainant and photos or descriptions of returned units.

OBSERVATION 3

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

Specifically, on 12 March 2018 we observed an operator (b) (4) and filling Morphine Sulfate for injection batch #11585, whose (b) (4) glove had come off of the end of the gown sleeve while handling syringes inside the ISO-5 class hood. We also observed a technician cleaning the ISO 7 room #(b) (4) after production completed where the technician's glove had slipped off the end of the sterile gown sleeve.

Technicians wear a (b) (4) glove during gowning (b) (4) (b) (4) immediately prior to entering the ISO-7 or ISO-5 areas. The (b) (4) glove is (b) (4) (b) (4)

This is a repeat observation from the previous inspection in June 2017.

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OBSERVATION 4

Component testing is deficient in that each component is not tested for conformity with all appropriate written specifications for purity, strength, and quality.

Specifically, there are no written specifications for water used in topical non-sterile drug products such as topical LET (Lidocaine/Epinephrine/Tetracaine) gel to meet at least the USP purified water standard.

For example, you used a "(b) (4) water" purchased from (b) (4) that has no certificate of analysis to show conformance to at least USP purified water standards.

LET gel has been produced in over (b) (4) batches since 1 July 2017.

OBSERVATION 5

You compound drugs that are essentially a copy of one or more approved drugs within the meaning of sections 503B(a)(5) and 503B(d)(2).

Specifically, you compound drug products that:

(a) are identical or nearly identical to an approved drug that is not on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing; or

(b) are not identical or nearly identical to an approved drug, but contain a bulk drug substance that is also a component of an approved drug, and for which there is no change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded drug and the comparable approved drug.

Examples of compounded drug products that are essentially a copy of one or more approved drugs include:

- ePHEDrine Sulfate 50 mg/1 mL (50 mg/mL) Injection Solution
- Succinylcholine 100 mg/5 mL (20 mg/mL) Injection Solution
- Glycopyrrolate 1 mg/5 mL (0.2 mg/mL) Injection Solution
- Neostigmine Methylsulfate 5 mg/5 mL (1 mg/mL) Injection Solution

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OBSERVATION 6

The labels of your outsourcing facility's drug products do not include information required by section 503B(a)(10)(A).

Specifically, your drug product labels do not show the specific day the drug was compounded. Examples of drug product labels that include the month and year, but not the date of compounding include:

- Rocuronium bromide 50 mg/5 mL (10 mg/mL) Injection Solution
- ePHEDrine Sulfate 50 mg/1 mL (50 mg/mL) Injection Solution
- Succinylcholine 100 mg/5 mL (20 mg/mL) Injection Solution
- Glycopyrrolate 1 mg/5 mL (0.2 mg/mL) Injection Solution
- Morphine Sulfate 2 mg/1 mL (2 mg/mL) Injection Solution
- Neostigmine Methylsulfate 5 mg/5 mL (1 mg/mL) Injection Solution
- Morphine Sulfate 0.2 mg per 1 mL Oral Solution (0.2 mg/mL)

OBSERVATION 7

Your outsourcing facility has not submitted a report to FDA identifying a product compounded during the June 1, 2017, through November 30, 2017, reporting period as required by section 503B(b)(2)(A).

An example of a drug product that was compounded and not identified on your December 2017, report is Morphine Sulfate 2 mg/mL Injection Solution.

*DATES OF INSPECTION

3/09/2018(Fri), 3/12/2018(Mon), 3/13/2018(Tue), 3/14/2018(Wed), 3/15/2018(Thu), 3/16/2018(Fri), 3/19/2018(Mon), 3/20/2018(Tue), 3/21/2018(Wed), 3/22/2018(Thu)

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