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 Industry Information: www.fda.gov/oc/industry	10/15/2013 - 11/04/2013* FEI NUMBER 3004483441

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Michael W. Pierce, President

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

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

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

Specifically,

A) Your firm has not fully established the aseptic technique in written procedures for operators during aseptic filling operations in the ISO 5 hoods for Area 300 and Area 400. For example, there are no directions for operator movements, operator actions under the unidirectional airflow is not described and proper aseptic manipulation when working in vertical unidirectional airflow. For example, on 10/15/13 in Area 300, we observed operator (b) (6) touch the non-sterile objects including sharps container, calculator, pen and paper, and then manipulate the IV bag under the ISO 5 hood without sanitizing his gloved hands while aseptically filling Hydromorphone 0.4mg/ml in 0.9% Sodium Chloride 30 ml syringe, Lot number 131011@22. In addition, operator (b) (6) touched the non-sterile sharps container and then entered the ISO 5 hood TR #70343 where he attached a product syringe for filling downstream of the [redacted] (b) (4) without sterilizing his gloved hands.

B) Your firm utilizes a [redacted] (b) (4) germicidal cabinet to sanitize the reusable goggles worn by the operators working in the ISO 5 hoods in Area 300 and 400. According to SOP #4.230, rev. 0, Use of [redacted] (b) (4) [redacted] (b) (4) Germicidal Cabinet, the cabinet is equipped with a [redacted] (b) (4) " that delivers UV irradiation represented as "[redacted] (b) (4) ". Your firm has no data to demonstrate the cabinet is capable of producing sanitized goggles that are suitable for operators working in the ISO 5 hoods. In addition, your firm has no data to verify the intensity of the UV lamps has not degraded over time, which is necessary to achieve the purported sanitization process. On 10/15/13, we observed an operator aseptically filling Hydromorphone 0.4mg/ml in 0.9% Sodium Chloride 30 ml syringe, Lot number 131011@22 while wearing the reusable goggles.

C) Your procedure is to wipe the exterior surface of the [redacted] (b) (4) and wipe the exterior of the stainless steel trays (aluminum foil removed) immediately prior to entering the ISO 5 hood with sterile IPA and a nonsterile, nonwoven wipe. Your firm's packaging and handling of these containers does not ensure the entry into the ISO 5 hood does not introduce microbial contamination or particulates into the environment.

D) Your firms media fill studies do not represent actual aseptic filling operations. For example,

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1. SOP #7.170, rev. 4, dated 10/14/13, Media Fill Testing Using the [(b) (4)] Repeater Pump, provides for the media fills for bag to syringe and bag to vial aseptic filling.

   a. The media fill includes filling [(b) (4)]-10 ml syringes. However, a review of batch sizes indicates syringes are typically between [(b) (4)] fills, with a maximum batch size observed of [(b) (4)]. In addition, your firm fills syringes with volumes to include 1, 3, 5, 10, 30, 35 & 60 ml.

   b. The media fill includes [(b) (4)] vials (size not specified). However, a review of batch sizes indicates vials are typically between [(b) (4)] fills. In addition, your firm fills vials with volumes of 2, 5, 10, 30, 50 & 100 ml.

2. SOP #7.120, rev. 1, dated 10/14/13, Media Fill Testing for High Risk Level CSPs: Syringe to Syringe Transfer, provides for the media fills for syringe to syringe transfers. The media fill includes aseptically transferring media from one 30 ml syringe into a second 30 ml syringe. However, your firm routinely fills ~~1, 3, 5, 10,~~ 30, ~~35~~ & 60 ml syringes with a variety of volumes.

3. Your firm aseptically fills PCA vials (pre-sterilized), Deltec cassettes and IV bags (admixing). You have not conducted a media fill studies for any of these packaging configurations.

4. Your firm has not validated the sterilization process ([(b) (4)]) for vials and stoppers or loading patterns used for your drug products aseptically filled in your firm. Your firm [(b) (4)] stoppers at [(b) (4)] and vials are processed in the [(b) (4)] at [(b) (4)]

5. Your firm has not validated any cleaning processes including the ISO 5 hoods. The ISO 5 hoods are manually cleaned with non-sterile wipers that have been sprayed with [(b) (4)]). You have no data to demonstrate this process is effective to maintain the ISO 5 conditions.

E) An issue with smoke studies was removed.

OBSERVATION 2

Clothing of personnel engaged in the processing and packing of drug products is not appropriate for the duties they perform.

Specifically,

A) Your firm utilizes gowning materials for operators in the aseptic areas 300 and 400 that are not established as sterile and non-shedding. For example, on 10/15/13,we observed operators conducting aseptic processing of Hydromorphone 0.4mg/ml in 0.9% Sodium Chloride 30 ml syringe, Lot number 131011@22. The following

gowning materials were in use by the operators in the ISO 5 hoods that were non-sterile and not lint free:

- Polypropylene non-skid shoe covers
- Basic procedure face mask with shield
- Isolation face mask with earloops

In addition, we observed exposed skin on operators working in the ISO Class 5 hoods to include the nose and forehead.

B) Supervisors are permitted to reuse sterile gowning (frocks) upon reentry to the ISO 7 area during the same day. On 10/15/13 in Area 400, we observed a used frock hanging in the ante room (ISO 8) that appeared to be used. Management stated the frocks are reused during the shift and disposed of at the end of the shift.

OBSERVATION 3

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

Specifically, in Area 300 and Area 400 environmental conditions are monitored. Your firm aseptically fills drug products [redacted] (b) (4) and conducts operations in [redacted] (b) (4) shifts per day. Your firm's procedures for monitoring the ISO 5 hoods and ISO 7 and 8 processing and support rooms are not suitable to ensure the quality of air that complies with USP ~~71~~ 1116. For example:

1. personnel monitoring conducted on a [redacted] (b) (4) basis
2. non-viable particulate monitoring conducted every [redacted] (b) (4)
3. airborne viable particle testing conducted [redacted] (b) (4)
4. settling plates conducted [redacted] (b) (4)
5. surface viable particle testing conducted [redacted] (b) (4)
6. room and hood active air sampling conducted on a [redacted] (b) (4) basis

OBSERVATION 4

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

Specifically, your firm cleans the ISO 5 hoods used for aseptic processing with nonwoven wipers and [redacted] (b) (4) [redacted]. There is no data or other information to demonstrate that these wipers are sterile or non-shedding. On 10/15/13, we observed the wipers being stored outside of the protective covering in the ISO 7 area and were observed to be sprayed with [redacted] (b) (4) and then used to prepare (wipe) materials (syringes, equipment, packages) immediately prior to entry into the ISO 5 hoods while Hydromorphone 0.4mg/ml in 0.9% Sodium Chloride 30 ml syringe, Lot number 131011@22 was being aseptically filled.

AMENDMENT 1

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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, your firm utilizes the automated equipment [redacted] (b) (4) for sterility at release for most aseptically filled drug products. You conducted a method validation of your sterility testing procedure and compared against the USP 71 sterility test method for products tested for release according to this methodology. However, your validation reports indicated variability in the quantitative [redacted] (b) (4) results for spiked samples. The validations also do not demonstrate the ability to detect a single viable microbial cell in a product sample. For example, your [redacted] (b) (4) test method validation report for Heparin Sodium 2500 USP Units added to 0.45% Sodium Chloride, approved 11/13/12, does not demonstrate the ability to routinely recover a similar amount of CFUs present in the test sample which is inoculated with [redacted] (b) (4). The [redacted] (b) (4) include a theoretical microbe concentration of 30 CFU; however the test results ranged from 9 to 21 CFU detected by the [redacted] (b) (4). Further, there is no data to demonstrate that the [redacted] (b) (4) can detect a single CFU during the testing of this formulation, which is the established limit for sterility failure.

OBSERVATION 6

There is no written testing program designed to assess the stability characteristics of drug products.

Specifically, your firm's stability studies do not include placing all products on a stability program and not all stability programs include testing for sterility, which is necessary to ensure quality, strength and purity for the entire shelf life (Beyond Use Date, BUD). For example,

A) Your firm produces approximately 900 unique formulas of sterile drug products packed in vials, syringes, bags and cassettes. According to your Pharmacist-In-Charge, approximately [redacted] (b) (4) of those formulations include a non-sterile API. All products you aseptically fill, and with the exception of one, are preservative free and are almost all stored at ambient temperatures. All drug products are [redacted] (b) (4) during aseptic filling. You have completed 74 stability studies in support of your BUD that included sterility that covers 21 formulations in a variety of packaging (bags, syringes, vials, cassettes). The following are examples of products reviewed that lack sterility data for stability:

- Aminophylline 25/mg/ml, BUD 90 days
- Fentanyl citrate and bupivacaine hydrochloride 2mcg/ml and 0.125% in 100 ml IV bags, BUD ~~180~~ 90 days

B) Your firm produces twelve drug products that are listed on the drug shortage list for which the BUD is determined

exclusively by literature review. The following examples are current shortage products with BUDs that are not supported by any stability studies:

- Heparin Sodium 10 USP units in 0.9% Sodium Chloride preserved with Benzyl Alcohol, BUD 180 days
- Nitroglycerine 400 mcg/ml in 5% Dextrose, BUD 70 days
- Epinephrine HCL 0.1 mg/ml injection solution, BUD 90 days

OBSERVATION 7

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

Specifically, your firm does not conduct an adequate investigation of complaints in that you did not extend your investigation into other lots that have been compound. For example:

1) Complaint number 2013-33 was received 02/11/13 for lot number 201301122@1, Magnesium Sulfate 50%. The complaint reported 1 vial with "black floater". The investigation consisted of reviewing the batch records and inspecting the retention sample. The proposed preventative action was documented as continuing to follow vial/stopper washing and sterilization protocols and to continue vial inspection processes. There is no documented investigation of other lots compounded.

2) An example of a complaint for orange flecks in product was removed.

3) Complaint number 2013-98 was received 05/31/13 for lot number 20130115@15, Potassium Phosphates. The complaint reported "black particles" in 2 vials. The investigation included reviewing batch records and sterility testing conducted on the returned vials. The proposed corrective actions was informing all compounding pharmacists that a light source would be installed, SOP for visual inspection to be completed and documenting training of visual personnel. There is no documented investigation of other lots compounded.

4) Complaint number 2013-131 was reported 08/16/13 for lot number 130711@12, Sodium Phosphates. The complaint reported 2 vials with "black floating specks". The investigation included a review of batch records. The proposed preventative action was additional training of technicians responsible for visual inspection and vial/stopper washing. In addition, better lighting would be installed and curtains to block out ambient light were on order. There is no documented investigation of other lots compounded.

5) Complaint number 2013-138 was received 08/22/13 for lot number 130430@3, Potassium Phosphates. The complaint was for "floater" in one vial. The investigation included re-scanning the product to determine

sterility and conduct a microcrystal test for aluminum using diluted sulfuric acid and cesium sulfate. The particulate did not react in solution. The proposed preventative action included implementing additional inspection stations with better lighting for visual inspection to minimize particles. There is no documented investigation of other lots compounded.

Your procedure, P&P No. 1.100(R4), External Complaints and Corrective & Preventative Action dated 09/28/2012, states a review of other compounded products prepared during the same time frame the original product was prepared will be conducted.

OBSERVATION 8

Drug product containers and closures were not clean to assure that they are suitable for their intended use.

Specifically, your firm's procedures for preparing vials and stoppers do not ensure they are free of particulates and do not contaminate the ISO 5 hood at the time of use. For example,

A) Vials and stoppers are received non-sterile and prepared according to SOP #4.010, rev. 5, Vial and Stopper Washing and Sterilization. The preparation occurs in an unclassified room in Area 400.

B) The washed vials and stoppers are transferred from Area 400 to Area 300 via a closed cart that does not seal, which is rolled outdoors and down a short section of parking lot, and into an unclassified area designated for entering all materials for the Area 300 from the warehouse (located in Area 400).

C) Your firm's preparation and storage of vials and stoppers, which occurs in Area 300, does not ensure they remain sterile and free of particulates post-sterilization/depyrogenation until the time of use. Post sterilization/dypyrogenation, stoppers and vials are stored in the ISO 7 clean room on a shelf for up to [redacted] (b) (4) prior to use. The stoppers remain in the [redacted] (b) (4) without any secondary protective layer and vials remain in the stainless steel trays with aluminum foil over the open end.

OBSERVATION 9

Approved drug product containers and closures are not retested or reexamined as appropriate for identity, strength, quality and purity after exposure to conditions that might have an adverse effect with subsequent approval or rejection by the quality control unit.

Specifically, your firm [redacted] (b) (4) stoppers and [redacted] (b) (4) sterilizes vials that are used in the production of sterile drug

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products. You store vials in the metal container used during sterilizaiton in the ISO 7 room. You store stoppers in the [redacted] (b) (4) in the ISO 7 room. Your hold time in storage for the stoppers and vials is up to [redacted] (b) (4). Your firm has no data to establish the [redacted] (b) (4) hold time. In addition, you have not validated your sterilization process.

OBSERVATION 10

The identity of each component of a drug product is not verified by conducting at least one test to verify the identity, using specific identity tests if they exist.

Specifically, your firm receives non-sterile active pharmaceutical ingredients (API) with a certificate of analysis (COA) that are used in compounding sterile drug products. You do not conduct identity testing on most lots of API received. In addition, your firm has not established any specifications for API, excipients, containers, closures and processing supplies [redacted] (b) (4)). While you do test drug products prior to release, you do not routinely conduct independent testing of API supplier COAs to verify the authenticity of the data, which is necessary to ensure the quality, safety, and purity of drug substances prior to use in compounding.

OBSERVATION 11

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations.

Specifically, in your firm's Area 400 where sterile drugs are staged, compounded and filled, the ante room adjacent to the ISO 7 room lacks a sink for personnel to use for hand washing prior to garbing. The sink personnel use to wash their hands before entering the ISO 7 room is located in an un-classified room that is adjacent to an ISO 8 room. On 10/15/13, we observed aseptic processing personnel wash their hands in the un-classified room; then pass through the ISO 8 room; and then enter the ante room to don gowning materials and enter the ISO 7 room where the ISO 5 hoods are located.

OBSERVATION 12

Employees are not given training in the particular operations they perform as part of their function.

Specifically, operators who perform visual examinations of vials of finished drug product for release are not given adequate training. No technician or supervisor has been qualified to detect defective vials through the examination of challenge units.

*** DATES OF INSPECTION:**
10/15/2013(Tue), 10/16/2013(Wed), 10/17/2013(Thu), 10/18/2013(Fri), 10/21/2013(Mon), 10/22/2013(Tue), 10/28/2013(Mon), 10/29/2013(Tue), 11/04/2013(Mon)

AMENDMENT 1

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Elizabeth D. Connell, Investigator EDC Torrance J. Slayton, Investigator TS	11/04/2013

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