OBSERVATION 1

Your firm produces drug products intended for intrathecal use from non-sterile bulk active ingredients that are not controlled for endotoxin level. Therefore, you have no assurance that your final product is within allowable limits for bacterial endotoxins. Intrathecal (IT) drug products manufactured for use in pumps for pain management, such as various combinations of Baclofen, Clonidine, Dilaudid, Ketamine, Fentanyl, Morphine, Sufentanil, Methadone and Bupivacaine, are made with non-sterile bulk drug substances as starting materials e.g. (b)(6), (b)(7)(C) Hydromorphone/Fentanyl/Bupivacaine/Clonidine/Ketamine [hydro - (b)(4), fenta - (b)(4) bupi (b)(4), clonidine (b)(4), and keta - (b)(4)]. Your firm lacks a mechanism for endotoxin control.

OBSERVATION 2

The use of sporicidal agents in the cleanrooms and ISO classified areas are inadequate.

Specifically, your firm references cleaning agents (b)(4) used to maintain a state of microbial control in your classified areas, where you manufacture intrathecal drug products such as RX Hydromorphone/Bupivacaine/Clonidine (b)(4) manufactured 20 JUNE 2017. A review of your firm's cleaning and gowning procedures: SOP #4.01, Cleaning Procedure Rev. 01 and SOP 2.04 Washing and Garbing Rev. 01, revealed that your firm has no stipulation of established contact times for cleaning with a sporicidal agent such as (b)(4) or sanitizing agents such as (b)(4) listed in these SOPs, which your technicians are trained on and use as for guidance while cleaning. The manufacturer's instructions...
OBSERVATION 2 continued:

for use of (b) (4) stipulate effective contact times of: (b) (4) for bacterial spores, (b) (4) for bacteria and viruses, (b) (4) for fungi, and (b) (4) for TB. The manufacturer's instructions for use of (b) (4) on gloves stipulates a (b) (4) contact time for sanitization of gloves and hard surfaces. Contact times were not noted to be adhered to during the inspection.

OBSERVATION 3

ISO-5 classified areas were not certified under dynamic conditions. Specifically, uni-directional airflow was not verified under operational conditions.

Specifically, your firm has not executed smoke studies under normal, dynamic working conditions in your classified areas where you manufacture sterile intrathecal drug products such as RX (b) (6), (b) (7)(A) Hydromorphone/Bupivacaine/Clonidine (b) (4) manufactured 20 JUNE 2017.

OBSERVATION 4

The ISO classified areas have difficult to clean, particle-generating, or visibly dirty equipment of surfaces.

Specifically, the pass through between the ISO 8 (b) (4) where products are staged and transferred into the ISO 7 (b) (4) is made of wood with a laminated surface that demonstrates wear marks and unidentified stains. The doors sealing the pass through have a porous foam strip between the door and the frame which has obvious signs of particulate contamination and unidentified staining. Rust was also noted on the legs of the stainless steel preparation table located in the ISO 7 (b) (4).