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.

Specifically,

A. Your firm rejected two lots of Betamethasone Sodium Phosphate PF 6mg/mL following low potency assay (Lot 120314MB (5mL) at 89.7%, Lot 110314MA (3mL) at 89.01%, specification (b) (4)), respectively. Your corrective action was to (b) (4) from (b) (4) and to (b) (4); However, your firm has still not evaluated the effect this change has on potency loss and degradation on product quality, including an evaluation of impurities and the establishment of scientifically justified impurity limits.

These inadequacies have not fully been addressed since the last inspection and your firm continues to manufacture, (b) (4) and release these products. This is a repeat observation from the 2015 FDA-483.

B. Additionally, your firm has not evaluated the impact of (b) (4) on Methylprednisolone Acetate and Triamcinolone Acetonide Suspension for Injection.

1. Since the last inspection your firm has also had two lots of Triamcinolone Acetonide 40mg/mL Suspension for Injection fail potency testing: Lot 012116MB at 119.7%/115.4%, specification (b) (4) and Lot 072616EB at 121.3%. This product is manufactured with a (b) (4) to (b) (4).

The investigation again failed to evaluate the impact of (b) (4).
2. Since the last inspection Lot 070815EA Methylprednisolone Acetate 40mg/mL suspension for Injection also failed potency specifications at 110.49%, specification (b) (4) has currently been (b) (4) the impact of which has not been further assessed.

C. Your firm lacks rationale for not investigating lots manufactured before and after lots your firm rejected. For example, between July and October 2016, your firm rejected five lots due to presence of low CFU of objectionable microorganisms in (b) (4) air samples and the investigations lack rationale for not further evaluating lots manufactured prior and after the microbial detections.

This is a repeat citation from the 2015 FDA-483.

OBSERVATION 2
Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically, your firm references cleaning agents (b) (4) used to maintain a state of microbial control in your classified areas, where you manufacture Betamethasone Sodium Phosphate, Methylprednisolone Acetate and Triamcinolone Acetonide for Injection. These cleaning agents are not used in the manner intended by the manufacturer. A review of the Firm’s cleaning procedures: SOP #4.01, Cleaning of the Clean Room and Ante Room, effective 2/28/2017, SOP #4.02, (b) (4) Cleaning of the Clean Room With Sporicidal Agent, effective date 8/13/2015, SOP #4.03, Cleaning of (b) (4) in Clean Room, effective date 4/12/16, and SOP #4.04 (b) (4) Cleaning Tasks, effective date 1/17/17,
revealed that your firm has no stipulation of established contact times for cleaning with a Sporicidal agent. The firm uses (b) (4) as sporicidal agents. The manufacturer's instructions for (b) (4)

There are also no contact times listed in the SOPs for the use of (b) (4) cleaning agents or sterile (b) (4)

OBSERVATION 3
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.

Specifically,
A. Your firm added a (b) (4) to the ISO5 LFH in an effort to provide a cleanable barrier over the previously exposed light bulbs; however you failed to execute a subsequent dynamic smoke study to demonstrate the (b) (4) addition does not interrupt the laminar flow of clean, first pass air.
B. On 07APR2017, your technicians were noted to carry an open (b) (4) of Betamethasone Sodium Phosphate for Injection through the ISO-8 anteroom to the ISO-7 cleanroom is located for further processing, without (b) (4) with sterile (b) (4) for further processing. This same practice was noted on 12APR2017 during the manufacture of Triamcinolone Acetonide Suspension for Injection. This routine practice is inadequate to prevent microbial contamination.

OBSERVATION 4
Written production and process control procedures are not followed in the execution of production and process control functions.
Specifically, your firm has failed to demonstrate a state of control in the manufacture of Betamethasone Sodium Phosphate, Methylprednisolone Acetate, and Triamcinolone Acetate, and continues to release lots without adequate rational when investigations referenced in Observation 1A related to super- and sub-potent product are incomplete.