DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1431 Harbor Bay Parkway Alameda, CA 94502-7070 (510) 337-6700 Fax:(510) 337-6702 Industry Information: www.fda.gov/oc/industry	03/11/2013 - 03/15/2013
	FEI NUMBER 3006306504

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Scot Silber, President/CEO

FIRM NAME	STREET ADDRESS
FVS Holdings, Inc. dba. Green Valley Drugs	1850 Whitney Mesa Dr Suite 180
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Henderson, NV 89014-2091	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:

QUALITY SYSTEM

OBSERVATION 1

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

Specifically, cleanroom technicians who engage in aseptic operations do not use sterile gloves, sterile lab coats, sterile masks, sterile hair nets, or sterile shoe covers. In addition, they do not wear eye protection. Furthermore, technecians with exposed skin around their face and neck were observed performing aseptic operations on multiple occassions.

MATERIALS SYSTEM

OBSERVATION 2

There was a failure to handle and store drug product containers at all times in a manner to prevent contamination.

Specifically, sterilized vials, which are ready for use in lots of finished sterile drug products, are stored uncovered on a shelf in the ISO Class 7 Cleanroom. The storage unit, which is located next to the door leading to the ISO Class 8 Anteroom, consists of five shelves, with the lowest shelf containing the sterilized vials being approximately one foot from the floor.

OBSERVATION 3

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without performing at least one specific identity test on each component and establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Specifically, components used in the production of sterile drug products, are not tested for conformance with appropriate

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specifications of purity, strength, and quality, including the total bioburden of non-sterile raw materials.

PRODUCTION SYSTEM

OBSERVATION 4

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

Specifically, on 3/11 & 12/2013, aseptic filling operations were observed for multiple sterile drug products, during which the following objectionable observations were noted:

- Technicians contacting the open neck of sterile vials with non-sterile gloves prior to filling with sterile product
- Technicians contacting the product contact surface of sterile stoppers with non-sterile gloves while hand stoppering vials of sterile drug product
- White dried residue clogging portions of the back grate of an ISO Class 5 Horizontal Laminar Air Flow Hood, used to conduct aseptic operations
- Technician's upper body entering the LAFH with bare skin exposed around their neck and face
- Sporadic movements within the LAFH, such as spraying hands with IPA and rubbing together or waving vigorously
- Multiple technicians working in a single LAFH concurrently, including performing bubble point testing adjacent to filling open vials with sterile drug product
- Multiple sterile products being processed at the same time under the same LAFH
- Technician seated immediately against the edge of the LAFH with forearms occasionally resting on the corner of the stainless steel table
- (b) used to sanitize equipment entering the LAFH, such as the metal crimp sealer used for capping sterile vials, did not always contact the entire surface of the equipment
- Beaker with an unidentified brown residue being used for mixing product prior to (b) sterilization
- Technicians entering the cleanroom from the anteroom without changing gloves prior to conducting aseptic operations
- Green residue around the base and faucet of the sink located in the ISO Class 8 Anteroom, which is adjacent to the cleanroom. The sink is used by the technicians to wash their hands prior to putting on gloves and to wash glassware.
- Gap in the drop ceiling next to the HEPA filter in the ISO Class 8 Anteroom
- Disassembly of (b) [redacted] syringes during filling of vials, including exposing the inner black seal, which contacts product, to the ceiling of the vertical LAFH
- Technician contacting the sterile syringe tip with non-sterile gloves
- Contacting of syringe cap with non-sterile gloves prior to placement of cap on syringe tip
- Technician reaching over uncapped vials containing sterile drug products during filling operations, thus restricting the movement of "first pass" air around the vials and allowing for potential contact of the vials with non-sterile garb

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OBSERVATION 5

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

Specifically,

a) Qualification studies have not been performed on the (b) (4) (b) (4) or the (b) (b) (4), which are used to sterilize drug products, stoppers, syringes, and utensils. For example, studies utilizing current maximum load patterns for each (b) (4) have not been conducted to demonstrate the equipment's ability to adequately sterilize product, containers, closures, or utensils.

Furthermore, the process of sterilizing suspensions and emulsions has not been validated, including an evaluation of each cycle's impact to drug product identity, potency, quality, purity and stability.

b) Qualification studies have not been performed on the (b) (4), which is used to sterilize glassware, including beakers used for mixing and vials. For example, studies utilizing current maximum load patterns for the (b) (4) have not been conducted to demonstrate the equipment's ability to adequately sterilize glassware.

c) The media fill test procedure does not closely simulate the most challenging or stressful conditions encountered in typical high-risk sterile production. For example, the current media fill test involves (b) (4) However, the typical process for a lot of sterile drug product involves dissolving up to four or five non-sterile components in (b) (4); (b) (4) into a sterile bulk container; transferring the sterile product into individual vials via a sterile syringe; and hand stoppering with sterile rubber stoppers using non-sterile gloves.

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OBSERVATION 6

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, since December 2012, the following potency out-of-specification (OOS) results have been obtained for lots of sterile drug products:

- Lidocaine HCl 1%, lot # 20130107-F: Result 191.3% (Specification: (b) (4))
- Methylcobalamin 1000 mcg/mL, lot # 20130104-G: Result 77.4% (Specification: (b) (4))
- Medroxyprogesterone Acetate 150 mg/mL Suspension, lot # 20121120-B: Result 126.60% (Specification: (b) (b))
- Methylprednisolone Acetate 40 mg/mL Preservative Free SDV, lot # 20130219: Result 114.4% (Specification: (b) - (b))

There is no documentation that an investigation was initiated into any of the above four OOS results to determine the root cause of the failure, impact to product, and preventative actions.

(REPEAT OBSERVATION)

LABORATORY CONTROL SYSTEM

OBSERVATION 7

Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Specifically, all lots of finished sterile drug product do not undergo sterility and/or endotoxin testing. For example, lots of single-dose vials less then (b) units are only tested for sterility and endotoxins on a (b) (4) basis. In addition, lots of multi-dose vials and lots of single-dose vials greater then (b) units are only tested for endotoxins on a (b) (4) basis.

Lidocaine HCl 1% lots 20130107-H, 20130107-G, 20130107-I, and 20130107-J, produced on 1/7/2013 and approved/released for distribution on 1/8/2013, did not undergo sterility or endotoxin testing. The (b) lots, each consisting of (b) single-dose vials, were labeled with 30 day expiry periods.

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OBSERVATION 8

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

Specifically, not all lots of sterile drug product are tested for potency prior to approval and release for distribution. Although certain lots of product are periodically analyzed for potency, there is no predetermined schedule stating the required frequency of testing.

OBSERVATION 9

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

Specifically, there is no written stability testing program in place to set appropriate expiration dates, continuously monitor the stability of batches on the market, and assess the on-going state of control of aseptic processing operations.

Of the ~258 different types of sterile drug products produced since December 2012, approximately eight have been sent to an outside laboratory for confirmation of current expiry periods. Of those approximately eight products with stability data, one product, Cyanocobalamin 400 mcg/mL, was found to not meet potency specifications when tested at 93 days on 1/16/2013. The result was 89.92%, whereas the specification is (b) (4) [redacted] No investigation was conducted into the root cause of the stability failure, or to determine corrective and preventative action. Cyanocobalamin 400 mcg/mL is currently labeled with a 90 day expiry period based on the suggestion stated in the product formula.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 10

The separate or defined areas and control systems necessary to prevent contamination or mix-ups are deficient.

Specifically, on 3/11/2013, raw materials for multiple lots of sterile drug products were observed in white plastic unlabeled weigh boats sitting on top of formula sheets on a counter in the ISO Class 8 Anteroom. The lots were being staged adjacent to one another, prior to entering the cleanroom for mixing in a Laminar Air Flow Hood (LAFH). Several of the raw materials were observed to be white powders of similar appearance.

Furthermore, three different drug products and one component, including Ascorbic Acid 500 mg/mL, Lidocaine HCl 1%, Nandrolane Decanoate 30 mg/mL, and Hydrogen Peroxide 3% solution, respectively, were observed in-process within the

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same ISO Class 5 LAFH in the cleanroom. Two of the products, along with the one component, were in the mixing stage, and one product was in the sterile (b) (4) stage. Formula sheets indicating each solution's identity were affixed to the top of the LAFH with clasps. None of the containers holding the products/component were labeled with the solution's name.

OBSERVATION 11

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

Specifically,

a) The air pressure differentials between the Cleanroom, Anteroom, and Pharmacy Area are not continuously monitored or alarmed during aseptic production of sterile drug products. On 3/12/2013, the door entering the anteroom from the pharmacy room and the door entering the cleanroom from the anteroom, were observed open at the same time on several occasions.

b) There is no monitoring of the environment within the ISO Class 5 laminar air flow hoods during aseptic processing operations, including air and surface sampling, on a routine basis.

c) The gloves of technicians performing aseptic manipulations are not monitored daily.

d) Smoke studies conducted during the (b) (4) certification of the LAFHs, are not performed under dynamic conditions. During typical production, up to (b) technicians are present in the cleanroom, with up to (b) people working within a single LAFH at a time.

OBSERVATION 12

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

Specifically, there is no written procedure describing the rotation of cleaning agents used to disinfect the ISO Class 5 Laminar Air Flow Hoods, ISO Class 7 Cleanroom, and ISO Class 8 Anteroom. In addition, there is no sporicidal agent currently being used in the cleaning of the previously mentioned areas. Furthermore, there has been no evaluation of the effectiveness (b) (4), which are used to clean the floors, counters, hoods, and/or walls in the cleanroom and/or anteroom.

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PACKAGING AND LABELING SYSTEM

OBSERVATION 13

Procedures designed to assure that correct labels are used for drug products are not followed.

Specifically, on 3/12/2013, two mislabeled vials of sterile product, Bupivacaine HCL MDV 0.5% Lot 20130212-E, 50ml and Dexamethasone Sodium Phosphate MDV 8mg/ml Lot 12112810000AE, 30ml, were observed in a non-refrigerated stock area located in the pharmacy room. The labels stated, "**Store at 2-8C**", however, the correct label for both products should have read, "**Store at 20-25C**".

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