

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER

19701 Fairchild
Irvine, CA 92612
(949) 608-2900 Fax: (949) 608-4417
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

02/19/2013 - 02/25/2013*

FEI NUMBER

3006345305

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: John D. Musil, Pharm.D., Chief Executive Officer / Founder

FIRM NAME

Avella of Deer Valley, Inc.

STREET ADDRESS

23620 N 20th Dr Ste 12

CITY, STATE, ZIP CODE, COUNTRY

Phoenix, AZ 85085-0621

TYPE ESTABLISHMENT INSPECTED

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:

[Amendment issued to correct Title of "Report Issued to" and to include clarification to Observation 2.]

PRODUCTION SYSTEM

OBSERVATION 1

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically,

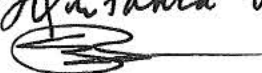
- a) During sterile drug production, technicians were observed wearing non-sterile gowning with exposed skin within the cleanroom environment. Per the firm's written procedure, SOP 03 S-32, "Personnel Hand Hygiene and Gowning for Cleanroom Entry", Revision 10-17-12, the firm's uniform components for entry into the cleanroom includes: shoe covers, head and facial hair covers, face mask donned to cover bridge of nose, a non-shedding lab coat or gown, and sterilized gloves. There is no provision for the areas of the face around the eyes and area around the neck. During the walkthrough of the facility on 02/19/13, operators were observed with exposed skin around the eyes and neck area in the cleanroom ISO 7 environment in which the ISO 5 Biosafety cabinets are located.
- b) The firm does employ the use of sterilized gloves in the ISO 5 environments. However, the sterile gloves are donned by the operator in the ante-room area (ISO 7) prior to entry into the cleanroom and subsequent ISO 5 environment. We observed an operator contact the outside of the sterile glove with bare hands while gowning. After cleanroom entry, the operator was observed wiping down the interior surfaces of the ISO 5 Biosafety cabinets with sterile (b)(4) wipes while wearing the sterilized gloves. Next the operator was observed wiping materials and components with sterile (b)(4) wipes and placing them into the ISO 5 Biosafety cabinet. The same operator then proceeded to conduct aseptic processing of drug products within the ISO 5 environment using the same gloves sprayed with sterile (b)(4) and air dried. There were no additional sterile gloves donned within the ISO 5 environment prior to contacting sterile materials for production. Furthermore, the operator's forearms which enter into the ISO 5 environment to perform aseptic operations are covered with non-sterile gowning which is not

AMENDMENT 2

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EMPLOYEE(S) SIGNATURE

Joey V. Quitania, Investigator
Sonia R. Peterson, Investigator

Joey V. Quitania 02/25/13


DATE ISSUED

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adequate to protect from contamination.

OBSERVATION 2

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

Specifically,

Environmental Monitoring of the firm's ISO 5 Hood environments and ISO 7 Cleanroom Environments used to produce sterile drug products ~~is inadequate and~~ does not represent actual production, for example:

- a) Lack of [routine] viable particulate air monitoring (ISO 5). There is no [routine] monitoring of the viable air particulates during aseptic processing of drug products in the ISO 5 environments. [There is (b) (4) viable air particulate monitoring conducted by an outside contractor that was explained to be under dynamic condition.] The firm employs the use of (b) (4). However, it was explained that this (b) (4) monitoring is conducted at static condition (b) (4) (b) (4).
- b) Lack of [routine] viable particulate air monitoring (ISO 7). There is no [routine] monitoring of the viable air particulates in the ISO 7 environments during active processing. [There is (b) (4) viable particulate monitoring conducted by an outside contractor.] The ISO 5 Biosafety cabinets and Laminar air flow hoods are located within ISO 7 cleanrooms. The firm employs the use of (b) (4). (b) (4) However, it was explained that this (b) (4) monitoring is conducted at static condition [condition] (b) (4).
- c) Lack of active non-viable particulate air monitoring (ISO 5). There is no monitoring of the non-viable air particulates during aseptic processing of drug products in the ISO 5 environments. Monitoring is only performed during certification by an outside contractor every (b) (4) at static condition.
- d) Lack of active non-viable particulate air monitoring (ISO 7). There is no monitoring of the non-viable air particulates during production of drug products in the ISO 7 environments. The ISO 5 Biosafety cabinets and Laminar air flow hoods are located within ISO 7 environments. Monitoring is only performed during certification by an outside contractor every (b) (4) at static condition.
- e) Lack of active monitoring of differential pressures. There is no monitoring of the cleanroom pressure differentials during aseptic processing of drug products. Differentials pressures of the ISO 7 Ante-room, ISO 7 Chemo room, and ISO 7 IV room are (b) (4) (b) (4) under static condition. There is no further monitoring of the cleanroom pressure differential gauges either manually or by electronic devices during production.

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- f) Insufficient frequency of personnel monitoring. Sampling of personnel gloves post shift of aseptic processing of drug products in the ISO 5 environment is conducted on a (b) (4) basis. In addition, personnel monitoring of operator's fingertips is conducted (b) (4) and repeated every (b) (4) for each operator. However, sampling of the operator's gloves or arms is not conducted after every lot of aseptically processed drug products in the ISO 5 environment.
- g) Insufficient frequency of environmental monitoring of the ISO 5 Environment, surfaces. Environmental sampling is collected (b) (4). However, the locations are rotated and not every ISO 5 surface used for aseptic processing of drug products is sampled. Furthermore, there is no environmental monitoring surface sampling for the aseptic processing of each lot of drug production.
- h) Insufficient frequency of environmental monitoring of the ISO 7 cleanrooms (surfaces, floors, walls, ceilings). Environmental sampling is collected (b) (4) and the sampling locations are rotated (b) (4).

OBSERVATION 3

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

Specifically,

- a) The firm prepares some components in-house via (b) (4) sterilization utilizing the (b) (4) (b) (4) located in the ISO 7 Ante room. Operators are trained to the use of the equipment verbally through on-the-job training. However, there is no written SOP outlining the use and maintenance of the equipment. The firm sterilizes vials used in the processing of aseptically processed drug product with this equipment.

The firm processes Biological Indicators through the (b) (4) on a (b) (4) basis. However, for routine runs, there is no (b) (4) monitoring. The equipment does not display or record (b) (4) exhibited during each cycle. Furthermore, there is no chart or data recording made for each run.

- b) The (b) (4) water system located in the ISO 8 Prep room supplies water to the firm's (b) (4) (b) (4). There is no written SOP outlining the use and maintenance of the water system. The water system is maintained (b) (4) by an outside contractor. In addition, the firm does not perform conduct any sampling and testing of the water quality produced by the (b) (4) (b) (4) water system.

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OBSERVATION 4

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

Specifically,

- a) Media fills conducted by the firm within the ISO 5 Environments on a (b) (4) frequency are inadequate in that the firm does not record the results of the positive control to indicate the media was able to support growth. In addition, the media fill record does not include sufficient detail to establish that the conditions mimic those that occur during routine production, (such as number of individuals in the room, equipment placement, doors opening and closing, etc). The total time to completion of the media fill is not recorded. Furthermore, there is no documentation made of which ISO 5 Environment or room was used to conduct each media fill.
- b) In April 2012, certification conducted by an outside contractor for the firm's ISO 5 and ISO 7 environments used to aseptically process drug products yielded out of specification results in the firm's IV Cleanroom in (3) three locations for non-viable particulate air. The following results were reported:

Sampling Location ISO 7	5.0µ per m ³ - Result (Specification (b) (4) 5.0µ per m ³)
IV Room Sample 5	4,250 particulates
IV Room Sample 6	3,536 particulates
IV Room Sample 7	3,286 particulates

There was no re-sampling of the locations performed. Although these locations exceeded the specification at the static condition, the room was still certified.

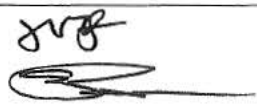
- c) Certification conducted by an outside contractor for the firm's ISO 5 environments used to aseptically process drug products includes performing smoke studies to demonstrate the air flow within the Biosafety Cabinet or Air Flow Hood. There is no recording made of the smoke study to confirm that the airflow is smooth, laminar, and without turbulence. It was explained that during certification, there is no firm representative involved to view the air flow smoke patterns. The smoke studies are conducted at static conditions.

OBSERVATION 5

Individual equipment logs do not show time, date, product, and lot number of each batch processed.

Specifically,

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The firm does not maintain a use log for each of the (b) (4) ISO 5 units used to produce sterile drug products. The ISO 5 units (Biosafety Cabinets and Laminar Air Flow hoods) located within the firm's Chemo room and IV room are not dedicated. There is no documentation to show what products were produced within the units and the equipment is not recorded on the individual product formulation sheets.

OBSERVATION 6

Batch production and control records do not include the specific identification of each batch of component used for each batch of drug product produced.

Specifically,

For example, Compound Log Worksheets did not include lot information for the following items used in production of sterile products:

- a) (b) (4) vials used in the production of Progesterone 12-20121201@119 which are sterilized in your (b) (4)
- b) Components used in production and packaging of sterile products including:
 - i. Bupivacaine HCL/Lidocaine HCL/Hyaluronidase (Peribulbar) 0.36/1%/2.5U/ML (Injectable)
 - ii. Povidone Iodine 5% (Ophthalmic)

QUALITY SYSTEM

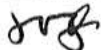

OBSERVATION 7

Written records are not always made of investigations into unexplained discrepancies.

Specifically,

- a) The firm manually reads and records the pressure differentials of the cleanroom suite (b) (4) (b) (4) Pressure differential excursions of low pressure observed in February 2011, August 2011, September 2011, October 2011, November 2011, December 2011, January 2012, February 2012, and February 2013 did not appear to be investigated. These excursions occurred in the firm's ante-room (ISO 7). Specification = (b) (4) H₂O; results recorded were low at (b) (4) H₂O. There was no investigation conducted in response to these out of specification results. Furthermore, there are some notes recorded on the forms referencing service calls of repair to

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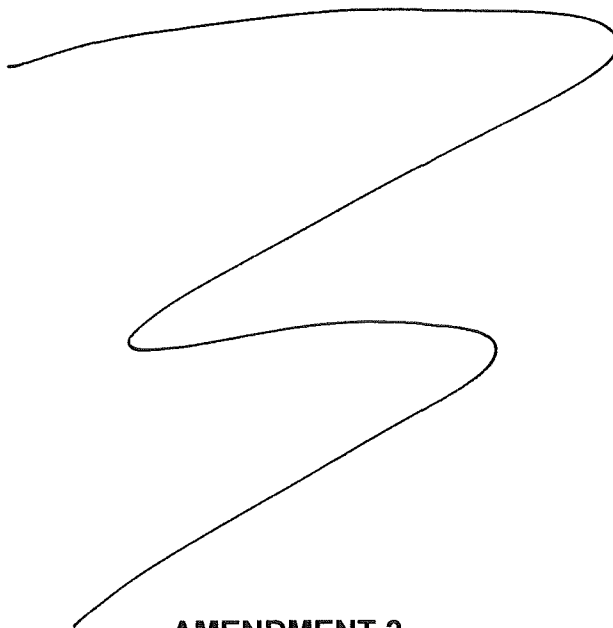
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the air handling units. There is no current review by the Quality department of the air handling equipment maintenance records or on-demand repair records.

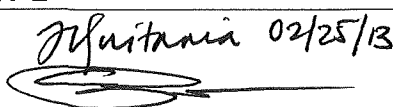
- b) During the walkthrough on 02/19/13, we observed an instance where the operator's glove tore exposing bare skin during aseptic processing within the ISO 5 environment of Hood 4 during the mixing of Bupivacaine HCl/ Cyclopentolate/ Flurbiprofen/ Gentamicin/ Phenylephrine/ Tropicamide Ophthalmic, Lot# 12-20131802@21. The glove tore during the mixing operation and the operator immediately exited the cleanroom to change gloves, then re-entered the cleanroom to continue the aseptic processing operation in Hood 4. In the presence of the firm's Quality Assurance manager, Pharmacist, and firm management, there was no action initiated by the operator or those present to assess product impact for the lot. After the operator's glove tore, bare skin was potentially exposed within the ISO 5 environment during the mixing step of this product. When asked whether or not the incident would be documented within the batch sheet, the firm's Quality Assurance manager indicated that it is not a requirement. There was no investigation initiated at that time. Furthermore, the firm's SOP 03 S-32, "Personnel Hand Hygiene and Gowning for Cleanroom Entry", Revision 10-17-12 does not provide any instruction to contact management or assess to product impact in the event of a glove integrity breach during aseptic processing of drug products. The operator re-entered the cleanroom after changing gloves and completed the operation.

*** DATES OF INSPECTION:**

02/19/2013(Tue), 02/20/2013(Wed), 02/22/2013(Fri), 02/25/2013(Mon)



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