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

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 6th & Kipling St. (P.O. Box 25087)<br>Denver, CO 80225-0087<br>(303) 236-3000 Fax:(303) 236-3100<br>Industry Information: www.fda.gov/oc/industry | 03/05/2013 - 03/15/2013*<br>FEI NUMBER<br>1000117234 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

**TO:** Mr. Jerry S. Gillick, R.Ph., President/Pharmacy Manager

| FIRM NAME | STREET ADDRESS |
|---|---|
| College Pharmacy Incorporated | 3505 Austin Bluffs Parkway<br>Suite 101 |
| **CITY, STATE, ZIP CODE, COUNTRY** | **TYPE ESTABLISHMENT INSPECTED** |
| Colorado Springs, CO 80918 | 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

Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to aseptic processing of drug products.

Specifically, the firm does not have documentation supporting the design and maintenance of the facility to ensure the high quality air required for the production of the sterile products.

1) The area designated as the clean room and identified by the firm as being classified with ISO 5 and ISO 6 areas has been modified structurally and is not supported by continuous monitoring data to be considered a classified area for sterile drug production. For example:

   a. The clean room HEPA recertification is performed (b) (4) (b) (4) [redacted]; however, the recertification does not include leak testing. The firm also has no documentation supporting that leak testing has ever been performed. In addition, each of the classified rooms (including the ISO 7 gowning room located immediately outside of the clean room) was recertified at static conditions only. No dynamic evaluations have ever been performed and no active or non-active particulate monitoring is routinely performed outside of the [redacted] (b)(4) review.

   b. The HEPA filter identified as #5 was observed to have been stained on the filter surface. This HEPA filter was located immediately above the ISO 5 workbench where a production employee was observed to be producing sterile product on 3/5/13. The production employees stated that the stain was due to drug product which had exploded due to excessive pressure applied when forcing non-sterile product through a sterilizing [redacted] (b). The product which had transferred to the HEPA filter surface was, in-part, non-sterile product. No investigation was performed to assure the continued proper function of this filter or the effects that it may have on further sterile processing. Additionally, the exact date of this occurrence could not be determined.

   c. There were a total of [redacted] (b) return vents for HEPA filtered air each of which were located below the workbench near HEPA #1 and #2. [redacted] (b) (4) vents were covered with [redacted] (b) (4) which were affixed to the wall leaving only one functioning return vent. The firm could not provide any documentation

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supporting that they have evaluated what affect this would have on air currents within the room or the effects on finished sterile product including the use of smoke study evaluation.

2) Pressure differentials are not monitored continuously between areas of (b) (4) air quality. For example, the firm's air quality (b) (4) from the ISO5 to ISO 6 areas of the clean room then to ISO 7 (gowning room) and finally to the ISO 8 (formula preparation area). The only pressure differential which is monitored is between the ISO 6 area of the clean room and the ISO 7 gowning area and is not reflective of the air quality during routine operations due to the following:

a. The pressure differential is not monitored continuously as the reading is recorded (b) (4)

b. When the door connecting the clean room and ISO 7 room is opened for any reason, the pressure reads 0.0 inches of water.

c. The firm does not have any monitoring parameters in place to determine how long or how often the doors between the classified areas can remain or be opened during normal operations prior to investigating the possible effects on finished product quality.

d. Although the pressure is not monitored between the ISO 7 and ISO 8 rooms, the firm has a (b) (4) pressure gauge on the outside of the ISO 7 room which read 0.0 inches of water on each day of the inspection. The firm's technician stated that the pressure between the rooms could not be maintained because there is a wall mounted heater conduit affixed to the wall of the ISO 8 room and extends into the ISO 7 gowning area. This area of the wall, hidden behind an ISO 8 work countertop, could not be properly sealed shut to maintain room pressures.

3) Environmental monitoring performed by the firm is not reflective of continued daily sterile operations. For example:

a. Personnel monitoring only occurs (b) (4) during employees' gowning re-qualification/media fill and only includes assessing the employees' finger tips. This is not reflective of the daily sterile operations or the batches of sterile product produced at the facility.

b. Viable and non-viable particulates are not monitored more frequently than during the (b) (4) re-qualification of the clean room and are performed only at static conditions. This is not reflective of the normal dynamic operations which occur during routine sterile drug production.

c. The firm performs surface and air microbial monitoring of the ISO 5 areas on a (b) (4) basis which is not reflective of the daily sterile operations. In addition, the firm's written procedure for Environmental Monitoring, SOP 8.020.1 does not delineate specific locations where the surface and air sampling should be taken from. The descriptions are recorded by the sampling employee as taken from the (b) (4) bench. Each of these benches has approximately (b) (4) of work space and there is no

way to determine if the employees were selecting from worst case locations.

d. Rolling carts are used to transport sterile and non-sterile processing materials from the ISO7 gowning area to the clean room. During environmental monitoring, the firm obtains a surface sample from the top surface of the cart, as described by sampling technicians, but neglects to test other portions of the cart, including the wheels, which make contact with the flooring of both rooms. This environmental monitoring practice is not documented in the Environmental Monitoring procedure, SOP 8.020.1.

e. I reviewed the 2011, 2012, and 2013 environmental monitoring results which documented environmental surface testing failures which were never investigated and the isolates were never identified. They included the following:

i. Two clean room cart failures (dated 6/25/12 and 7/09/12) each with one colony forming unit.

ii. Two ISO 5 work surface area failures (dated 5/2/11 and 4/9/12) each with one colony forming unit.

4) The areas identified as the ISO 5 sections of the clean room were observed to have various areas with non smooth surfaces for cleaning. For example:

a. Embedded within the wall between the ISO 5 area of the clean room and the ISO 8 room was a pass through window which is no longer used and was observed to be duct taped shut from the ISO 8 room. The track by which the window used to slide open still remained exposed within the ISO 5 area.

b. The ISO 5 work bench area had a power outlet track along the wall which extended from the wall approximately 1 inch and surrounded the circumference of the ISO 5 areas of the room.

c. Within the ISO 5 areas of the clean room along the interior wall there was a piece of duct tape (measuring approximately 2 x 3 inches) affixed to the wall with no apparent function.

d. Resting on the surface of the ISO 5 area bench top was a radio which is an object which is not easily cleanable.

5) Materials and cleaning supplies for use in the ISO 5 areas of the clean room were not each identified as sterile. In addition, the clean room written procedure does not include the specific cleaning agents authorized for use. For example:

a. A production employee was observed to use sterile (b) (4) [redacted] and non-sterile (b) (4) [redacted] during cleaning operations for the surfaces of the area identified as the ISO 5 work bench. Neither of these agents were identified as authorized for use in the firm's written procedure including the order in which these

agents should have been used.

b. On 3/7/13, during cleaning operations of the clean room (as delineated in written procedure 11.100.1) we observed an employee using a tacky roll mop to remove lint from the ceiling (making direct contact with the surface of the HEPA filters) as part of the (b)(4) cleaning process. This tool was observed to be stored immediately next to the hand cleansing sink located in the ISO 7 gowning room area.

## OBSERVATION 2

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

Specifically, the firm's current sterility testing methods for prepared sterile drug products are not being completed in accordance to their written procedure SOP 11.050.2 in that their sample size does not match what is required by the procedure and is not sufficient to be representative of the batch of sterile product produced. In addition, their formula worksheets contain spaces for sample documentation, but do not specify how much sample should be tested by the sterile processing employee. There is also no documentation for how much sample was actually selected for testing. For example:

1) The Formula Worksheet for EDTA/Mag Sulfate PF 3 gm/1gm/20ml injectable involves the production of (b) x 100 ml vials of the preservative free sterile product. Although not specified on the sampling section of the form, 3 x 1 ml each was tested by the firm for sterility assurance. The sample size according to their procedure should have been (b) mls from each of (b) x 100 ml vials.

2) The Formula Worksheet for Phosphatidyl Choline I.V. Pres 5% Inj includes the production of (b) x 30 ml vials of the sterile injectable product. Although not specified on the sampling section of the form, 1 x 30 ml vials was sent for testing to a contract lab. The sample size according to the written procedure should have been a minimum of ( ml from each of ( vials.

3) The Formula Worksheet for Methylcobalamin PF 25 MG/ML Inj includes the production of (b) x 30 ml vials of preservative free sterile product. Although not specified on the sampling section of the form, 1 x 30 ml vials was tested by the firm for sterility assurance. The sample size according to their written procedure should have been a minimum of ( ml from each of ( separate vials.

Finally, the firm has failed to perform growth testing for any of the media which they purchase for conducting in house sterility testing. In addition, the Endosafe-PTS used by the firm to test produced sterile drug products for endotoxin has not been calibrated to assure the quality of the data produced by the equipment. The Endosafe-PTS was last calibrated in February 2011 despite the User's Guide recommendation of (b) calibration.

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## OBSERVATION 3

Each lot of a component liable to objectionable microbiological contamination is deficiently subjected to microbiological tests before use.

Specifically, the firm's Sterility Supervisor stated that they use approximately 99% non-sterile raw materials to produce sterile finished injectable products relying on their sterile (b) (4) methods to ensure product sterility. Proper use of sterile (b)(4) methods depends on their evaluation of the material which they are (b) (4) and they have not routinely challenged certificates of analysis provided by raw material suppliers prior to utilization in sterile production of their drug products. Additionally, the firm has never performed bioburden studies or have established limits for bioburden to ensure that the (b) (4) methods used for their finished products are adequate for their sterile processing operations.

## OBSERVATION 4

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

Specifically,

1) Personnel qualification for sterile processing is delineated in the firm's written procedure, SOP 11.010.2, which includes (b) (4) media fills. On 3/7/13, during the inspection I observed the media fill process and noted the following:

   a. The firm uses (b) (4) in performing the media fill which is produced by the their production employee using (b) (4); however, the (b)(4) is never challenged prior to use to ensure that it is capable of growing aerobic bacteria.

   b. In accordance with SOP11.010.2, and the associated written procedure titled "Media Fill Test for Aseptic Technique 3% Solution Liq", the maximum number of manipulations within the clean room environment during media fill qualification is (b) This is not reflective of the maximum batch size which may potentially be produced by an employee which may total (b) manipulations.

2) The firm has not evaluated the container closure systems used to produce sterile product which undergoes further lyophilization to assure that the sterile work in process is properly protected when the partially stoppered vials are transferred from the ISO 5 clean room bench surface to the lyophilization chambers which are maintained in the ISO 7 gowning room.

3) The (b) sterilization methods used by the firm have not been properly validated to assure the quality of sterile product produced at the facility. For example, the firm uses (b) (4) testing to evaluate (b) integrity for each

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batch of sterile product produced; however, the ranges for an acceptable (b) integrity tests range from (b) (4) psi (pounds per square inch) for each of the (b) (4) (b) (4) used during production. In addition:

a. The firm has failed to establish a minimum (b) (4) psi required to test the integrity for the (b) (4) and (b) (4) (b) sets;

b. The firm has not properly challenged these (b) (4), based on product or raw material bioburden knowledge or other scientific means (including challenge organisms) to assure that their methods are capable of consistently produce sterile product. In addition, the sterility testing conducted by the firm at their facility or contract labs may not be sufficient to detect microbial contamination potentially due to (b) failure because they fail to follow their own written procedures for finished product sterility testing sample size which was may not be reflective of the batch (see Observation #2).

c. The employees document that the minimum (b) (4) has been reached during routine operations for (b) integrity testing by signing the batch record; however, they do not document what the actual pressure was which resulted in the passing exam.

4) On 3/5/13, I observed the production employee producing Selenium preservative free 40 mcg/ml injectable products ((b)(4) x 2 ml vials and (b) x 10 ml vials). During this production, I observed the following pertaining to aseptic production practices:

a. When the production employee donned her sterile gloves within the clean room area designated as ISO5, she had touched the palm of her ungloved right hand with the sterile glove surface of her left hand.

b. The employee was observed to break the ISO 5 air flow to the tops of the 2 ml vials with her right gloved hand. This occurred immediately after the tops of the vials had already been sterilized using an (b)(4).

c. After observing the employee sterilizing the 2 ml vials, she was observed to break the ISO 5 air flow to the tops of the 2 ml vials with her left gloved hand while entering and filling each vial using the (b) (4).

## OBSERVATION 5

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

Specifically, the firm does not have a stability testing program in place for the more than 5,000 different products produced at their facility, including sterile injectable products. They also do not have a formal change control process to assist in delineating when more recent stability tests have to be conducted and their Sterility Supervisor has stated that product stability testing (including assay) is only performed on product (b) (4) after they have established a beyond use date (BUD). For example:

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1) Their firm had changed the (b) [redacted] type for use for EDTA/Mag Sulfate on 5/20/2011 and since this time, they haven't generated any current data supporting a 180 day BUD despite the five stability failures that preceded (including failures in 2005, 2006, 2007, and 2008). Their Sterility Supervisor has stated that the firm had dispensed EDTA/Mag Sulfate from these failed batches as they do not always perform analytical testing for potency prior to distribution.

Additionally, the firm does not perform routine ongoing stability testing to ensure that current data continues to support beyond use dates. For example:

2) Methylcob 25 mg/ml preservative free stability testing in support of a 120 day refrigerated stability has not been re-evaluated since April of 2010.

Finally, although sterility testing is performed for each batch of product produced, the firm does not have a ongoing sterility testing program as part of their stability testing to support the current BUD for preservative and preservative free products produced at their facility. Products are (b) (4) [redacted] selected by the Senior Sterility Production Personnel for evaluation. This practice is not delineated in a written procedure and the firm could not explain how certain products are selected and others are not. For example:

3) Methylcob PF was last placed on extended sterility testing in May of 2010 and has not been re-evaluated since that time.

## OBSERVATION 6

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

Specifically, the firm does not have a written established program and does not conduct routine analytical evaluation of the products produced at their facility for identification or potency of each batch of product produced prior to dispensing to end users.

*** DATES OF INSPECTION:**
03/05/2013(Tue), 03/07/2013(Thu), 03/14/2013(Thu), 03/15/2013(Fri)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."