

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

DISTRICT ADDRESS AND PHONE NUMBER 300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax: (313) 393-8139	DATE(S) OF INSPECTION 1/12/2016-1/29/2016* FEI NUMBER 3004587403
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED  
Nathan J. Worthing , Pharmacist in Charge and Co-Owner

FIRM NAME Clark Professional Pharmacy, LLC	STREET ADDRESS 3280 Washtenaw Avenue
CITY, STATE, ZIP CODE, COUNTRY Ann Arbor, MI 48104	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:**

**OBSERVATION 1**

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

Specifically,

i. Adequate validation of aseptic processing operations, specifically, process simulations (media fills), have not been performed under representative worst case aseptic processing conditions to assure the sterility of drug products. Currently, *SOP Media Fill High Risk Compounding For Sterile Compounding Personnel*, requires use of three syringes for the filling of six 10ml vials through a 0.22 micron filter. This process does not include, for example, worst case lot sizes, vial sizes, syringe sizes, and equipment used in normal aseptic operations such as repeater pumps. For example, media fill simulations are not representative of:

- Methylcobalamin (PF) 0.3ml 25 mg/ml injectable lot 12232015@56, filled with a repeater pump, 3 ml syringes, lot size 300 syringes
- Bi-Mix Papaverine/Phentolamine 15mg – 0.5mg/ml injectable lot 01122016@32, vial size of 2ml, lot size of 25 vials

ii. Gloved hands are not always sanitized after touching items in the "ISO 7" prep room during formulation of drug products. For example, on 1/19/16, an operator working in the "ISO 7" prep room was observed to weigh several raw ingredients and walk back and forth while touching the plastic curtains that separate the prep side of the room from the glove box side of the room without sanitizing hands frequently.

iii. No documentation was provided to support that the Tuttnauer Table-Top Autoclave, used to terminally sterilize Methylcobalamin (PF) Stock 25mg/ml injectable, has been adequately validated for its intended use.

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iv. The bioburden of non-sterile drug components is not evaluated, and bioburden limits have not been established, for non-sterile bulk formulated products to ensure the sterilizing process is adequate to remove the microbiological load. For example, non-sterile drug components used in the processing of Bi-Mix Papaverine/Phentolamine 15mg – 0.5mg/ml injectable lot 01122016@32.

**OBSERVATION 2**

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

Specifically,

Gowning of operators performing aseptic operations in the "ISO 5" glove box is inadequate in that protective gowns and face masks worn during aseptic processing are not sterile. For example, gowning worn as observed during the aseptic processing of Bi-Mix Papaverine/Phentolamine 15mg – 0.5mg/ml injectable lot 01122016@32.

**OBSERVATION 3**

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

Specifically,

i. Non-sterile disposable wipes are used to wipe the "ISO 5" glove box with sterile 70% isopropyl alcohol. For example, such wipes were used for cleaning the "ISO 5" glove box prior to the aseptic processing of Enoxaparin lot 01112016@77on 1/12/2016.

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ii. Not all sanitizers and cleaning agents used in the classified areas are sterile. For example, CaviCide, Hydrogen Peroxide 7.5%, PeridoxRTU, and Barrier Cleaner are all used in the "ISO 5" glove box and are not purported to be sterile.

**OBSERVATION 4**

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

Specifically,

- i. Environmental monitoring is not performed at least daily during drug production in the critical areas to evaluate the quality of the aseptic processing environment and assess whether aseptic conditions are maintained.
  - a. Non-viable particulate monitoring is performed in the aseptic processing areas once every six months
  - b. Viable air monitoring is performed in the aseptic processing areas once every six months
  - c. Viable surface monitoring is performed in the aseptic processing areas once per week
- ii. No data was provided to support that the incubators used to incubate environmental monitoring surface and fingertip samples are qualified for their intended use. Prior to 1/15/16, the temperatures of the incubators were checked once daily and no documentation was provided to support calibration of the unit's temperature probe or the external temperature probe that was rotated between the two incubators.
- iii. Incubator with model #12-140AE has a set range of 35-40C for incubation of TSA plates, however, the TSA media supplier recommends incubation at the range of 20-35C. On 1/13/16, this incubator was observed to have a temperature of 36.9C. Incubator with model #10-140AE has a set range of 30-35C for incubation of Sabouraud Dextrose plates, however, the Sabouraud Dextrose media supplier recommends incubation at the range of 25-35C for 1-7 days. No justification was provided to support incubating Sabouraud Dextrose plates at the higher end of the temperature range.

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**OBSERVATION 5**

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

The monitoring frequency of pressure differentials between the aseptic processing areas and surrounding areas of lower air quality is not justified. Currently, such pressure differentials are checked and documented by operators once at the start of each day.

**OBSERVATION 6**

Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

Specifically,

Adequate container closure integrity testing has not been performed for any sterile product container closure systems. Specifically, vials are filled through insertion of a needle through the rubber vial closure, and data was not provided to support that this closure will prevent the ingress of microbial contamination post puncture. For example, the container closure system used to package Bi-Mix Papaverine/Phentolamine 15mg-0.5mg per ml injectable lot 01122016@32.

**OBSERVATION 7**

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

Specifically,

i. Beyond use dates assigned to sterile drug products are not supported by sterility testing over the labeled shelf life in representative container closure systems, for example:

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- Methylcobalamin (PF) Stock 25mg/ml injectable lot 12172015@8, beyond use date of 90 days refrigerated
- Methylcobalamin (PF) 0.3ml 25mg/ml injectable lot 12232015@56, beyond use date of 45 days frozen
- Bi-Mix Papaverine/Phentolamine 15mg-0.5mg per ml injectable lot 01122016@32, beyond use date of 45 days frozen

ii. For drug products containing a preservative, testing has not been performed to support that the preservative system retains antimicrobial effectiveness over the labeled shelf life of the drug product. For example, Bi-Mix Papaverine/Phentolamine 15mg-0.5mg per ml injectable lot 01122016@32.

**OBSERVATION 8**

Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements.

Specifically,

Aseptically filled sterile injectable drug products are released and distributed without finished product testing for sterility and endotoxins. For example, Bi-Mix Papaverine/Phentolamine 15 mg/0.5mg per ml injectable lot 01122016@32 was made on 1/19/16 and shipped on 1/20/16 and 1/26/16. This lot was not sent for finished product testing.

**\*DATES OF INSPECTION**

1/12/2016(Tue), 1/13/2016(Wed), 1/14/2016(Thu), 1/19/2016(Tue), 1/22/2016(Fri), 1/29/2016(Fri)

1/29/2016

Emily J Orban

Emily J Orban  
Investigator  
Signed by: Emily J. Orban -S

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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 judgment, 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."