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*PCAB Accredited
Compounding Pharmacy*

US FDA Detroit District Office (DET-DO)
ATIN: Detroit District Director, DET-DO
Art Czabaniuk, DET-DO
300 River Place, Suite 5900
Detroit, MI 48207

Re: Posting of FDA Form 483 Response

FEI: 3004587403

EI: 01/12/2016 – 01/29/2016

Dear Sir,

Please accept this letter as authorization to post on the US FDA Internet website Clark Professional Pharmacy's response to the FDA Form 483 Notice of Observations, dated 02/11/2016, as submitted to DET-DO, un-redacted but without attachments. We understand this response will be posted under the FDA Form 483 Notice of Observations for Clark Professional Pharmacy, issued on 01/29/2016 by Investigator Emily J Orban (DET-DO).

Thank you,

Nathaniel Worthing, PharmD
Pharmacist in Charge
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Hard copy send to:

US FDA, Detroit District Office
ATTN: Detroit District Director
300 River Place, Suite 5900
Detroit, MI 48207

February 11, 2016

US FDA Detroit District Office (DET-DO)
ATIN: Detroit District Director, DET-DO
Art Czabanuk, DET-DO
300 River Place, Suite 5900
Detroit, MI 48207

Re: Posting of FDA Form 483 Response

FEI: 3004587403, Clark Professional Pharmacy

EI: 01/12/2016 -01/29/2016

Dear Sir,

Clark Professional Pharmacy would like to thank the FDA for assessing our facility for deviations from cGMP and giving us an opportunity to exceed the current requirements of USP <797> Pharmaceutical Compounding – Sterile Preparations where possible. Our organization has a history of exceeding the minimum standards of USP <797> to improve patient safety where feasible. Our organization adheres stringently to the tenets of 503 A guidelines as set forth in the Guidance "Pharmacy Compounding of Human Drug Products" Under Section 503 A of the Federal Food, Drug, and Cosmetic Act as we understand it. We also understand that according to the same document that;

"FDA expects state boards of pharmacy to continue their oversight and regulation of the practice of pharmacy, including pharmacy compounding. FDA also intends to continue to cooperate with state authorities to address pharmacy activities that may be a violation of the FD&C Act, Including section 503A."

It was also our understanding that in the instance an organization adheres to 503 A guidelines that the State Board of Pharmacy would be given the cGMP derived observations to ensure that the organization was adherent to current USP <797> guidelines. Conversely, it is understood that the FDA expects the State Board of Pharmacy to notify the FDA if violations of 503 A were found.

Our organization looks forward to working with the FDA to ensure that any deviations from 503 A tenets that would require 503 B guidelines to take affect and adherence to cGMP are quickly addressed to the satisfaction of the FDA. As our organization feels it is a 503 A compliant facility and has met or exceeded all requirements of USP <797>, we look forward to working with both the FDA and Michigan State Board of Pharmacy in a partnership to ensure that USP <797> is met or exceeded at all times.

Sincerely,



Nathaniel Worthing, PharmD
Pharmacist in Charge
Owner



Inspection of Clark Professional Pharmacy

Response Date: 02/11/2016

OBSERVATION 1:

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

- 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 10 ml vials through a 0.22 micron filter. This process does not include for example, worst case lot size, vial sizes, syringes sizes, and equipment used in normal aseptic operation such as repeater pumps. For example, media fill simulation are not representative of:

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

Response to Observation 1.i

While our organization feels that USP <797> guidelines were met with our current media fill, our organization agrees to increase media fill qualifications for each operator to include the processes of filling multiple smaller vials while using a 0.22 micron filter to more accurately reflect current aseptic practice. In addition, a media fill test to include vial filling using the Baxa Pump representative of our current aseptic filling practices will also be performed.

It is our expectation that this will meet the more rigorous proposed standards of USP <797> currently under revision: "When performing these testing procedures, use the most difficult and challenging compounding procedures and processing conditions encountered by the person during a work shift (e.g., the most manipulations, most complex flow of materials, longest time to compound), replacing all the components used in the CSPs with microbial growth medium."

Time Line: Each operator will perform new media fill process at their next regularly scheduled validation and every six months as instructed per USP <797>.

- ii. Gloved hands are not always sanitized after touching items in the "ISO 7" prep room during formulation of drug products. For example, on 1/19/2016, 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.

Response to Observation 1.ii

We agree that practice of more frequent hand sanitizing with sterile 70% isopropyl alcohol is required. The operator observed has been retrained in the process of hand sanitation. In addition, all other sterile operators have been retrained to reinforce hand sanitizing more frequently with sterile 70% isopropyl alcohol, allowing it to have its effect and dry.

Time Line: Each operator has been retrained in this process and will be revalidated every six months with a competency assessment every six months per USP <797>.

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

Response to Observation 1.iii

The Tuttnauer Table-Top Autoclave currently in use has been calibrated and certified by the manufacture's third party contracted medical equipment company on an annual basis according to manufacturer's specifications. Continuous temperature, pressure, and time monitoring has been validated by the manufacture's third party contractor. Products terminally sterilized using the autoclave, have been exposed to temperature, pressure, and times that are consistent with USP <797> guidelines. In addition, each autoclave cycle is validated with an in-house biological indicator and a third party biological indicator. Terminally sterilized sterile products are also sent to an FDA registered third party lab to validate proper sterilization process. According to manufacture specifications and current USP <797> guidelines, temperature mapping is not required for this unit. The operation of the unit is validated per USP <797> guidelines via use of both the continuous monitoring log printed during operation of the unit and the use of Biological Indicators in each cycle.

- 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-0.5 mg/ml injectable lot 01122016@32

Response to Observation 1.iv

Bioburden limits for Papaverine and Phentolamine non-sterile components have not been established by the USP or the manufacturer of the API's. Since we are a compliant 503A pharmacy, USP <797> does not dictate that such test are required for patient specific prescriptions.

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

Response to Observation 2:

Sterile gowns are not a current requirement of USP <797> for 503a compliant pharmacies. In fact, the proposed revision of USP <797> does not require sterile gowns or coveralls when using RABS devices or LFS. However, the organization agrees that sterile gowns are important to reduce the overall bioburden to the ISO certified rooms. New sterile garbing has been obtained and updated garbing SOP's and operator training has taken place. The face mask being used is

appropriate for its intended use according to the manufacture specifications and meets USP <797> and USP <800> guidelines. The proposed USP <797> does not require face masks when using RABS devices but our organization feels that the face mask being used is a best practice for 503 A compliant facilities.

Time line: Evidence of current compliance with the use of sterile gowns was provided to investigator at time of inspection.

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 01122016@77 on 1/12/2016

Response to Observation 3.i.

The use of sterile wipes in an ISO 5 environment is currently not a requirement of USP <797> or the manufacture of the glove box. Our organization does agree that the use of sterile wipes in the ISO 5 environment represents best practice procedures for cleaning. Sterile wipes are now used in the ISO 5 glove box environment.

Time line: Evidence of current compliance with the use of sterile wipes was provided to investigator at time of inspection.

- 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.

Response to Observation 3.ii.

Cleaning agents used in our facility are part of a comprehensive chemical rotation to reduce bacterial and spore counts in ISO classified areas. The chemicals used in the ISO 5 glove box are in compliance with manufacture guidelines and meet EPA guidelines for their intended use. All cleaning chemicals that are used in the ISO 5 glove box are allowed to dwell for the appropriate amount of time for effectiveness. After appropriate contact time is achieved, the remaining chemicals are removed with a sterile lint free wipe. Chemical residue is then wiped and removed with *sterile* 70% isopropyl alcohol. For best practice procedures, Clark Professional Pharmacy will update the use of cleaning chemicals used in the ISO 5 environment to include the use of *sterile* sporicidal agents and *sterile* detergents to adhere to future compliance with USP <800> guidelines.

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 particle 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

Response to Observation 4.i.

As a compliant 503a pharmacy, environmental monitoring is in compliance with current USP <797> guidelines. Current USP guidelines require monitoring of surface, air and fingertips every 6 months. Our facility meets and or exceeds current USP guidelines as a best practice.

- 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.

Response to Observation 4.ii.

Continuous temperature monitoring with calibrated and certified temperature probes is now in place.

Time line: Evidence of current compliance was provided to investigator at time of inspection.

- 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 1/13/2016, 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.

Response to Observation 4.iii.

Incubator model #12-140AE will be adjusted to a lower temperature and monitored with a calibrated temperature probe to verify the lower temperature setting. Incubator model #10-140AE will be replaced with an incubator that can achieve the lower temperature range more consistently and monitored with a calibrated temperature probe.

Time line: Clark Professional Pharmacy ordered a replacement incubator and new SOP's will be implemented as part of placing new equipment in service.

OBSERVATION 5

Aseptic processing areas are deficient regarding systems for maintain 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 area checked and documented by operators once at the start of each day.

Response to Observation 5

Clark Professional Pharmacy is in the process of obtaining proposals for the installation of automated monitoring devices for pressure differential from two vendors. The automated monitoring system will be able to alert the operator in the event of a loss of pressure in the ISO certified rooms.

Time line: Installation of automated monitoring pressure devices will be installed prior to or at the time of our next ISO recertification.

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-0.5 mg per ml injectable lot 01122016@32.

Response to Observation 6:

Clark Professional Pharmacy is in the process of performing sterility/endotoxin over time studies of our closure system. According to FDA guidance, sterility over time studies can be used in lieu of a container closure system studies.

Time line: We are currently in the process of performing sterility/endotoxin over time studies and will continue such studies over the next six months.

OBSERVATION 7

There is not written testing program designed to assess the stability characteristics of drug products.

Specifically,

- i. Beyond use dates to sterile drug products are not supported by sterility testing over the labeled shelf life in representative container closure systems, for example:
 - Methylcobalamin (PF) Stock 25mg/ml injectable 12172015@8, beyond use date of 90 days
 - Methylcobalamin (PF) 0.3 ml 25 mg/l injectable lot 12232015@56, beyond use date of 45 days frozen
 - Bi-Mix Papaverine/Phentolamine 15mg-0.5 mg per ml injectable lot 01122016@32, beyond use date of 45 days frozen

Response to Observation 7.i

Clark Professional Pharmacy is currently in the process of testing the above products for stability over the stated beyond use date. The method used will be forced degradation over the intended storage time parameter and storage conditions performed by a qualified third party testing service.

Time line: Clark Professional Pharmacy intends to complete the necessary stability studies within the next six months.

- 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.

Response to Observation 7.ii.

Clark Professional Pharmacy agrees to validate the use of the preservative agent used in the Papaverine/Phentolamine injectable. We have contracted with a third party qualified lab to perform bracketed preservative validation studies on low and high dose preparations containing Alprostadil, Papaverine, and Phentolamine combinations. The studies will be performed in accordance with USP <51> guidelines.

Time line: Clark Professional Pharmacy intends to initiate the necessary studies within the next 4 weeks. We expect completion of the studies within a minimum of 90 days and maximum of 180 days.

OBSERVATION 8

Each batch of drug product purporting to be sterile and pyrogens 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 15mg/0.5 mg per ml injectable lot 01122016@32 was made on 1/19/2016 and shipped on 1/20/2016 and 1/26/2016. This lot was not sent for finished product testing.

Response to Observation 8

Since Clark Professional Pharmacy is a compliant 503A pharmacy, USP <797> does not dictate that such test are required for patient specific prescriptions prior to dispensing, provided the beyond use date does not exceed 45 days frozen solid or 3 days refrigerated. The Bi-Mix compound observed was dated in accordance with USP <797> guidelines. Evidence of proper dating was provided to investigator at time of inspection.