DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

OT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Winderley Place, Suite 200 ..tland, FL 32751 (407) 475-4700 Fax:(407) 475-4768 Industry Information: www.fda.gov/oc/industry	04/10/2014 - 05/09/2014* FEI NUMBER 3007271263

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Vern. A. Allen, Owner/Pharmacist

FIRM NAME	STREET ADDRESS
Premier Pharmacy Labs Inc	8265 Commercial Way
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Weeki Wachee, FL 34613-4511	Drug Outsourcing Facility

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 I OBSERVED:

OBSERVATION 1

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

Specifically, [redacted] (b) (4) sterilization [redacted] (b) (4) for sterilization of drug products have not been validated. In addition there are no established [redacted] (b) (4) for the [redacted] (b) (4) you are currently [redacted] (b) (4) for drug products that are [redacted] (b) (4) sterilized, for example Testosterone, Lidocaine, and Bupivacaine.

OBSERVATION 2

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

Specifically,

A. Aseptic techniques observed during the compounding of sterile drug products
   1. Technicians were observed picking up materials (e.g., syringes and [redacted] (b) (4) from bins adjacent to the ISO 5 hood and not sanitizing the items prior to placing them into the ISO 5 hood while compounding sterile drug products.
   2. A technician was observed preparing at least [redacted] (b) x 2 mL vials to be used for the filling of Lidocaine 2% gel. [redacted] (b) left the empty vials open (uncapped) while [redacted] (b) left the ISO 7 room for a break.
   3. Specifically, no time dependency requirements have been established for the repackaging of commercial, sterile drug products (e.g., Avastin) into single unit dose containers (e.g., syringes). Firm personnel stated the [redacted] (b) (4) operations for repackaging Avastin into single unit dose syringes can take up [redacted] (b) (4)

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B. Media fills conducted by the firm within the ISO 7 room and under the ISO 5 hoods were found to be deficient in that they do not accurately simulate production processes and conditions that would best represent the most stressful/challenging conditions and optimize detection of any microbiological contamination. For example,
   1. The media fill procedure uses (b) (4) glass vials. This does not represent the worst possible case since larger vials (20-100 mL) are filled at the firm.
   2. The media fills do not demonstrate lengthy (b) (4) processes, such as the (b) (4) operations of repackaging Avastin into single unit dose syringes ((b) (4) or the filling of more than 6 vials. In addition, current media fills do not record the time it takes to conduct the media fill.
   3. There is no media fill simulation for filling syringes or single unit dose droppers.
   4. The media fill procedure states the fill is completed without interruption. This does not simulate production practices, since it was observed and personnel stated that compounding of sterile drug products can be interrupted (e.g., lunch break).

OBSERVATION 3

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

Specifically, gowning procedures have not been written, as well as gowning qualifications have not been conducted for your technicians and pharmacists that work in the ISO 7 room and under the ISO 5 hoods. Inconsistent and inadequate gowning practices were observed during this inspection, for example:

A. There is no demarcation of the dirty and clean side of the ante room. It was observed that personnel walked all over the room during their gowning.

B. There is no determined maximum number of employees allowed in the ante room. I observed 3 employees sharing the space with no personnel flow of foot traffic. I observed a pharmacist in street clothing touching a technician's sterile garments prior to entering the ISO 7 room.

C. Technicians and a pharmacist would open the sterile garment bags prior to washing their hands or wearing sterile gloves.

D. Adequately sized, sterile garments are not available for usage. I observed a pharmacist's gowning practices for which he ripped (b) (6) suit trying to put it on and bare skin was observed

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between (b) (6) sleeve and sterile gloves once gowning was complete.

E. Technicians wipe personal protection equipment (safety glasses) with non-sterile paper towels prior to entering the ISO 7 room.

F. Technicians vary in their practice of placing the gloves over or under their sterile garments.

OBSERVATION 4

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

Specifically,

A. Active microbial air monitoring is not performed in dynamic conditions. I observed and personnel stated that settling plates are placed in the ISO 7 room and under the ISO 5 hoods when personnel are not present or conducting the formulation and filling of sterile drug products.

B. Your current environmental monitoring program does not include non-viable particle monitoring under dynamic conditions.

C. Personnel monitoring, including fingertip sampling, of operators involved in sterile operations of sterile drug products in the IS0 5 hoods is not conducted at least daily.

OBSERVATION 5

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

Specifically,

A. In-house and contract laboratories' sterility testing for all of your finished sterile drug products produced at your firm, have not undergone microbiological method suitability testing. The method suitability testing is required to demonstrate the drug product test samples do not inhibit growth in sterility test media. Firm personnel could not provide me written procedures on how they conduct sterility testing in-house.

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B. Personnel at your firm use test tubes filled with fluid thioglycollate medium (FTM) or tryptic soy broth (TSB) for performing microbiological sterility testing on all sterile drug products. A review of your firm's inadequate practices are found as follows:

1. Raw data of the documented sterility testing is recorded on an unprotected, Excel spreadsheet that is authored by front desk office staff. These employees have not been trained in microbiology methods or how to determine if growth has occurred in the test tubes. I could not verify who actually conducts the reading of the sterility test tubes, since the pharmacist keeps no record of (b) (6) readings. I also observed that the Excel spreadsheet data is not reviewed for accuracy by the pharmacist.
2. Personnel do not use suitable strains of indicator microorganisms when performing growth promotion testing on FTM and TSB sterility test media. A pharmacist stated that he goes outside and swabs a "dirty" area for the (b) (4) growth promotion testing.
3. I reviewed in-house sterility testing during the time period from 02/21/14 to 04/04/14 (6 weeks). According to the above mentioned Excel spreadsheet, a positive control (FTM and TSB) was not conducted or was documented as negative growth for 5 out of the 6 weeks for the FTM positive control and 6 out of the 6 weeks for TSB positive control.

C. You stated that you based your firm's sampling plan off of USP <71>, which states Lots of less than or equal to 100 units, sampling will consist of 10% of the Lot or 4 units, whichever is greater. For Lots greater than 100, but less than 500 units, sampling will consist of 10 units. Documentation was provided showing the sampling plan on your Post-Clearance Qualifications form. However, your firm did not always follow the sampling plan prior to distribution, for example:

- For Lot # MIT031414svhm (b) (4) vials, each containing 10 mL of Mitomycin 40mg/10mL), your firm tested (b) vials in-house for sterility and sent (b) vials to contract labs for endotoxin and sterility testing. However, your sampling plan and firm personnel stated (b) (4) samples should have been tested for sterility and endotoxin prior to release and distribution.

D. You could not provide scientific rationale for why only a portion of the samples are tested for endotoxins prior to products being released for distribution. You stated that (b) (4) of the samples pulled from each Lot would be tested in-house for sterility only, while the remaining samples (b) (4)) would be sent to a contract laboratory for sterility and endotoxin testing.

E. No documentation could be provided stating which testing (in-house and/or contract laboratory)

must be completed prior to releasing the product for distribution, for example:

- For Lot # AVA032614ijhm (b)(4) repackaged syringes, each containing 0.05mL of Avastin, 25mg/mL), your firm tested (b)(4) vials in-house for sterility and sent (b)(4) samples to a contract lab for endotoxin and sterility testing. Documentation and firm personnel stated that the Lot was released after receiving the contract lab data, while in-house sterility testing was only on incubation day 2 of 14 (FTM & TSB). Firm personnel further stated that Lots can be released based on contract laboratory data only and do not have to wait for the 14 day in-house sterility test results prior to distribution.

OBSERVATION 6

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically,

A. No dynamic airflow pattern studies (smoke studies) have been performed in the (b)(4) ISO 5 hoods inside your ISO 7 room where sterile drug products are formulated and filled.

B. There is not continuously or at least periodically monitoring of air pressure differentials during production from the ISO 7 areas and ante room to the surrounding non-classified pharmacy area. Technicians and pharmacists stated that they record a daily value from the one magnehelic pressure gauge in the morning that is located in a corner of the L-shaped ISO 7 room. In addition:
   1. A partitioned area in the ISO 7 room that contains ISO 5 hoods HLF70064 and HLF69994, does not contain a magnehelic pressure gauge to measure air pressure differentials.
   2. The ante room does not contain a magnehelic pressure gauge to measure air pressure differentials to the surrounding non-classified pharmacy area.

C. No calibration documentation could be provided for the only magnehelic pressure gauge that has been installed in the ISO 7 room, as referenced in Observation 6B above.

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OBSERVATION 7

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

Specifically, the suitability and efficacy of disinfecting agents and procedures have not been assessed to ensure potential contaminants are adequately removed from the surfaces in the classified areas. For example:

A. Routine cleaning procedures for the ISO 5 hoods do not include the use of a sporicidal cleaning agent at an established frequency.

B. [redacted] (b) (4) is one of the cleaning agents used on the floor, walls, and ceilings.

C. Bulk packages of sterile wipes are opened and used over a period of time, lasting more than a week.

OBSERVATION 8

There are no written standards or specifications, methods of testing, methods of cleaning, and methods of sterilization to remove pyrogenic properties.

Specifically,

A. The dry heat depyrogenation cycle has not been validated. This process is used for all glass vials and caps used in the filling of sterile drug products.

B. The steam sterilization autoclave cycles have not been validated. This process is used for rubber stoppers and laboratory glassware used in the filling of sterile drug products.

C. Glass vials, caps, rubber stoppers, and beakers sterilized and depyrogenated in-house, are not identified in a way that would allow a trace back to the autoclave or depyrogenation load/batch.

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OBSERVATION 9

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

Specifically, you could not provide valid analytical and sterility data to support the 90-day expiration date assigned to repackaged syringes of preservative free Avastin (bevacizumab) drawn from single-use vials. Information provided is not specific to your firm's operations and does not address sterility issues. The single-use, commercially available Avastin vials are punctured multiple times to fill the individual syringes that are then distributed. I observed repackaged syringes of Avastin, available for distribution, in your firm's refrigerator as being prepared in February, March and April of 2014.

OBSERVATION 10

Routine calibration of mechanical and electronic equipment is not performed according to a written program designed to assure proper performance.

Specifically, firm personnel stated they do not have a written calibration program and could not provide calibration documentation for the following equipment:

A. The dry heat (depyrogenation) oven has not been mapped during calibration.

B. (b) (4) used to (b) (4) (b) (4) and components have not been (b) (4) during calibration.

OBSERVATION 11

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, you do not perform tests to determine the preservative content in your sterile drug products prior to distribution, for example Cyanocobalamin, Lot # CYA041814svhm.

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OBSERVATION 12

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

Specifically, [redacted] (b) (4) has been used to prepare Mitomycin for injectable sterile drug products in the same ISO 5 hood (#12749RW) where other non-potent drugs are prepared.

In addition, there are no environmental controls such as negative pressure, closed system vial transfer devices, or a ventilation system to contain the cytotoxic materials from contaminating other sterile drug products in the ISO 7 room.

OBSERVATION 13

Batch production and control records are not prepared for each batch of drug product produced and do not include complete information relating to the production and control of each batch.

Specifically for the practice of filling multiple single dose syringes from one commercially available, sterile, single-use vial of Avastin (bevacizumab); you failed to prepare batch production and control records with complete information relating to the production and control of each batch of drug product for 3 out of the last [redacted] (b) Lots (AVA040814svhm, AVA040914ijhm, and AVA041814svhm) filled and distributed by your firm. For example, your firm did not document and could not provide the number of syringes filled per batch. Technicians stated that they do not complete these batch records at the time of filling.

In addition, your batch records do not always match the quantity that was distributed. For example, the batch record for Lot AVA032614ijhm documents the filling of [redacted] (b) (4) syringes (0.05mL) from an unknown number of commercially available, sterile, single-use vials (4mL) of Avastin, 25mg/mL (Lot [redacted] (b) (4)) on 03/26/14. However distribution documents state your firm has shipped approximately [redacted] (b) (4) syringes of Lot AVA032614ijhm and no documentation could be provided to explain this discrepancy.

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OBSERVATION 14

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, thorough investigations were not conducted for complaints received by your firm. For example:

A. Two complaints were received (12/9/13 & 12/12/13) for repackaged Avastin syringes. Documentation states that when the physicians tried to squeeze the syringe, no solution could be administered or the needle would actually pop off of the syringe. Your documented response to the complaint was that the refrigerator was too cold, however no scientific data or root cause analysis could be provided to support this claim. No documentation could be provided that the compounding records were reviewed or that other related Lots prepared during this time period where reviewed.

B. One complaint was received (07/19/13) for Multi Trace 4 concentrate PF (Lot # E050113schm). Documentation states that particles were observed in the 1 mL vials at the hospital pharmacy. Your documented response to the complaint was that the evaporation of a droplet in or around the needle left a small particle of electrolyte. This syringe and needle was then reused to access other vials, thus introducing the particles into the vials. You could not provide any documentation that reusing syringes is a practice of the hospital, nor could you provide any scientific data or root cause analysis to support this claim. No documentation could be provided that the compounding record was reviewed or that other related Lots prepared during this time period were reviewed.

OBSERVATION 15

The labels of your outsourcing facility's drug products do not contain the following information required by section 503B(a)(10) of the Act:

A. A list of active and inactive ingredients, identified by established name and the quantity or proportion of each ingredient.

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B. The statement "This is a compounded drug."

C. Information to facilitate adverse event reporting (www.fda.gov/medwatch and 1-800-FDA-1088).

D. Products designated for "office use" do not contain directions for use, which includes the drug product's dosage form and route of administration.

*** DATES OF INSPECTION:**
04/10/2014(Thu), 04/11/2014(Fri), 04/14/2014(Mon), 04/15/2014(Tue), 04/17/2014(Thu), 04/21/2014(Mon), 04/23/2014(Wed), 04/29/2014(Tue), 05/09/2014(Fri)

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