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VIA Overnight Mail and Fax

November 7, 2016

Reynaldo R Rodriguez Jr
Acting District Director
U.S. Food and Drug Administration
Dallas District Office
4040 North Central Expressway, Suite 300
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(214)253-5222

RE: Guardian Pharmacy Services. WAIVER for Publication of Response to FDA Form 483 Issued on October 21, 2016; FEI No. 3012669715

Dear Mr. Rodriguez,

On behalf of Guardian Pharmacy Services (hereafter referred to as GPS), located in Dallas, Texas, I hereby authorize the United States Food and Drug Administration (FDA) to publicly disclose the information described below on FDA's website. I understand that the information that is disclosed may contain confidential commercial or financial information or trade secrets within the meaning of 18 U.S.C. §1905, 21 U.S.C. §3310), and 5 U.S.C. §552(b)(4) that is exempt from public disclosure under those statutory provisions and/or relevant FDA regulations. I agree to hold FDA harmless for any injury caused by FDA's sharing the information with the public.

Information to be disclosed: GPS' Response to FDA Form 483 issued October 21, 2016; FEI No. 3012669715. The waiver shall extend only to GPS' Response to the FDA Form 483 issued October 21, 2016, and not to any of the supporting or underlying documents implicated or involved in the FDA Form 483 issued October 21, 2016 such as Attachments and Exhibits.

Authorization is given to FDA to disclose the above-mentioned information which may include confidential commercial or financial or trade secret information. As indicated by my signature, I am authorized to provide this consent on behalf of GPS, and my full name, title, address, telephone number, and facsimile number is set out above for verification.

In the event there are any questions regarding the disclosure of such information, I hereby request pre-disclosure notification so that we can address any such questions prior to disclosure of the material. Thank you.

Very truly yours,

Jack R Munn, RPH
Owner

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Acting District Director
U.S. Food and Drug Administration
Dallas District Office
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RE: Response to Inspectional Observations Issued to Guardian Pharmacy Services (GPS) on October 21, 2016; FEI No. 3012669715

Dear Mr. Rodriguez,

GPS would like to take this opportunity to respond to the inspectional observations listed within Form 483 dated October 21, 2016; FEI No. 3012669715. During FDA's inspection, GPS engaged cooperatively and constructively with FDA as GPS would like to assure FDA that it is committed to providing patients with the highest quality compounded preparations and takes FDA's observations and its professional responsibilities very seriously.

GPS is a Texas licensed compounding pharmacy, which compounds medications in compliance with Texas law, USP Chapter 795 and USP Chapter 797 respectively, and in compliance with Section 503A of the Federal *Food, Drug, and Cosmetic Act* (hereafter referred to as Section 503A). For the past years, GPS has been providing the highest quality compounded medications to its patients for a multitude of conditions to fulfill their otherwise unmet medical needs.

As a Section 503A pharmacy compliant with Texas state law, we would like to note that many of the observations included within the Form 483 are based on current good manufacturing practices ("cGMP"). Section 503A specifically exempts 503A pharmacies compliant with state law from complying with Section 501(a)(2)(B) of the Federal *Food Drug and Cosmetic Act* , which requires compliance with cGMP. Therefore, GPS is not required to meet the cGMP regulations that are cited within the Form 483. FDA's guidance, published July 2, 2014 reiterated that drugs compounded in compliance with Section 503A will be exempt from certain sections of the *Food, Drug, and Cosmetic Act*, including cGMP requirements.[1] FDA further recognized this to be correct within the most recently released FDA inspections notice stating that FDA will not cite violations based on cGMP regulations for 503A pharmacies.[2]

GPS takes great satisfaction in compounding in compliance with Texas state pharmacy law as well as in compliance with Section 503A. As such, GPS is fully entitled to the exemption from cGMP set forth in Section 503A and objects to any observation in the Form 483, which inappropriately relies on cGMP regulations. While GPS is addressing all of FDA's inspectional

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[1] Final Guidance; Pharmacy Compounding of Human Drug Products under Section 503A of the Federal Food, Drug, and Cosmetic Act; Availability; 79 FR 37742 (Jul. 2, 2014).

[2] See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM510684.pdf

observations, its cooperation with FDA should not be interpreted as GPS' admission or agreement that it is required to comply with cGMP regulations, thereby leaving GPS exposed to repeat citations for failing to confirm with cGMP regulations.

As demonstrated in the following responses, GPS is thoroughly addressing each of the observations presented in the Form 483. In this same vein, GPS is evaluating its overall policies and procedures and will revise them as deemed necessary, to ensure compliance with FDA's expectations, in conjunction with those of the Texas Board of Pharmacy. Without conceding that any of the Observations are applicable, set forth below are FDA's Observations, followed by GPS' responses thereto.

We appreciate the opportunity to address the observations set forth in the Form 483, and if FDA has any questions regarding our responses or would like to discuss these responses further, we welcome a meeting with the District Office to continue this dialogue to resolve any outstanding issues regarding the observations noted in the Form 483.

GPS' RESPONSES TO FDA'S INSPECTION OBERSERVATIONS

Observation 1
Procedures designed to prevent microbial contamination of drug products purporting to be sterile do not include validation of Sterilization Process.

Specifically,

i. Media fills performed by your firm with each of the operators who work in the IS05 area do not closely simulate actual production conditions or cover worst case or most challenging conditions. The media fill your firm performs has the operator filling 5 ml of media in three (3) test syringes and three (3) test vials. I n routine production, your firm fills various size vials (2ml–10ml) as well as syringes and batch sizes up to 300 units.

For example, on 8/22/16, your firm produced and dispensed 400- 3cc syringes containing 1ml of Hyaluroniase 150U/ml Injectable preservative free (Lot# 50449:00) with a Beyond Use Date (BU D) of 11/10/2016.

ii. Your firm has not validated the sterilization process for any of the drug products that you prepare.

For example,

1. Your firm prepares Triamcinolone acetonide injectable and Medroxyprogesterone acetate suspension injectable and both are terminally sterilized using your autoclaves.

2. Your firm prepares Nandrolone deconate injectable, Estradiol valerate Injectable and Testosterone cypionate Injectable, which are all terminally sterilized using your dry heat oven.

Additionally

You do not consistently document the dry heat oven log for drug products which have been sterilized using the dry heat oven. The following drug products were not documented on the dry heat oven log:

i. Nandrolone Deconate in Oil 200mg/ml Injectable in 10 ml vials, Lot 49752:42, made on 7/11/16

ii. Nandrolone Deconate in Oil 200mg/ml Injectable in 10 ml vials, Lot

49141:00, made on 6/16/16

iii. Testosterone Cypionate in Sesame Oil 200mg/ml Injectable in 10ml vial, Lot 50379:00, made on 8/16/16

Written procedures for bubble point testing have not been established. Your firm uses 0.22 micron filters to filter sterilize drug products prepared from non-sterile drug substances in the ISO 5 laminar flow hood. Your firm conducts bubble point testing using a bubble point gauge.

On 9/23/16 I observed a sterility failure on Day 14of Lidocaine/Sodium Bicarbonate Injectable (Lot# 50699:00); batch size of 505 syringes (0.5ml in 3ml syringes). This was a drug product prepared from sterile drug substances, filter sterilized and dispensed for office use.

Response to Observation 1:

As a Section 503A compounding pharmacy, GPS is compliant with its regulatory requirements under the authority of the Texas Board of Pharmacy and operates in full compliance with Texas state law including USP <797> guidance.

A. A new method of media validation will be implemented within the next 6 months, and it will include the following:

Medium Risk- in addition to our standard protocol each operator will be required to fill the following:
100 syringes each with 0.5ml
10 x 2 cc vials,
5 x 10cc vials
1 x 30cc vial

In addition, GPS will review the SOP 9.110 Sterile Compounding Process Validation – Media Fill within 30 days and the next Media fill Tests Schedule for March 2017 will include the new procedure.

B. As a Section 503A compounding pharmacy, GPS is fully compliant with its regulatory requirements under the authority of the Texas Board of Pharmacy and operates in full compliance with Texas state law including USP<797>by ensuring that each autoclave cycle includes a biological indicator, which is tested and monitored for decontamination and using temperature sensing devices. However, due to our continued commitment to patient safety, the following will be implemented:

1. A sample of each of the products that are steam sterilized via the Autoclave including Triamcinolone and Medroxyprogesterone products will be further sent out for third party testing after sterilizations to ensure that the process of autoclaving is valid for each product.
Target Date of Completion: 90 Days

2. A sample from each of the products that are subject to Dry Heat Sterilization including Nandrolone, Estradiol and Testoterone Injections will not be sent out for third party testing to ensure that the process of dry heat sterilizing is valid for each product.

Target Date of Completion: 90 Days

3. A monthly audit will be done to ensure that all products that are terminally sterilized are documented on either the Autoclave logs or the Dry Heat oven logs.

Target Date of Implementation: December 1st 2016

C. Written Standard Operating Procedures (SOP 4.210 Use and Maintenance of the Millex/Sterivex Integrity Tester) will be completed, reviewed and implemented within 30 days.

Target Date of Completion: 30 days

Observation 2
Each batch of drugs purporting to be sterile is not laboratory tested to determine conformance to such requirements:

Specifically, your firm does not conduct finished product testing for sterility on any of your terminally sterilized drug products. All of your terminally sterilized drug products are prepared from non-sterile bulk drug substances. Your firm has prepared and dispensed 15 lots terminally sterilized injectable drug products from 6/1/2016 to 9/9/2016.

Response to Observation 2:

The SOP 9.121 Finished Product Testing has been amended to ensure that all terminally sterilized products made in batches of 25 units or more for individual single-dose packages or in multiple dose vials for administration to multiple patients are tested for sterility.

Observation 3
Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room to produce aseptic

Specifically,

D. Non-sterile disinfectants are routinely used by your employees during cleaning of aseptic processing areas, including the critical ISO 5 work area and ISO 7 areas including the clean room and ante room. Also, your firm does not utilize a sporicidal agent in the ISO 5 area. On 9/13/16, I observed the firm technicians disinfect the ISO 5 laminar flow hoods and ISO 7 clean room and ante room. The disinfectant used was non sterile disinfectant TexWipe TexQ, a quarternary ammonium disinfectant. The firm utilizes sterile 70% isopropyl alcohol as well as the following non sterile disinfectants on a rotational basis:

1. TexWipe TexQ Disinfectant (Quarternary Ammonium Disinfectant) (non-sterile)

2. TewWipe BruClean TbC Disinfectant Cleaner (Alternative to Bleach) (non-sterile)

3. Hydrogen peroxide 3% USP (non-sterile)

Additionally, your firm has failed to utilize a sporicidal agent in your rotational schedule of disinfectants.

E. Your firm uses non-sterile wipes (CleanPro polycellulose, low particle, highly absorbent wipes) when disinfecting the ISO 5 laminar flow hood and the ISO 5 chemical hood where drug products are prepared.

Response to Observation 3:

D. As a Section 503A compounding pharmacy, GPS is fully compliant with its regulatory requirements under the authority of the Texas Board of Pharmacy and operates in full compliance with Texas state law including USP<797>. USP<797> Appendix states,

"Cleaning and disinfecting shall occur before compounding is performed. Items shall be removed from all areas to be cleaned, and surfaces shall be cleaned by removing loose material residue from spills e.g. water soluble residues are removed with Sterile water (for injection or Irrigation) and low shedding wipes. This shall be followed by wiping with a residue free disinfecting agent, such as Sterile 70% IPA, which is allowed to dry before compounding begins"

While USP <797> Appendix II provides information on what disinfectants *CAN* be used for cleaning and disinfecting the aseptic areas, there is no stipulation that such disinfectants be sterile. We currently ensure that all disinfectant cleaning is followed by sterile 70% Isopropyl alcohol on all work surfaces (e.g. counter and Primary Engineering Controls) as recommended by the ASHP best practices and USP<797> Appendix II given that there is no regulatory mandate.

Appendix II *does not require* the use of a sporicidal disinfectant in the cleaning rotation. Regarding the use of sporicidal agents, USP Chapter <1072> states that

"It is prudent to augment the daily use of bactericidal disinfectant with weekly (or monthly) use of sporicidal agent"

Therefore, as of October 17, 2016 a sporicidal agent (Tex-Cide TX 690) has been added to the rotational schedule of disinfectants

E. GPS is compliant with its regulatory requirements under the authority of the USP<797>which states

"All cleaning materials such as wipers, sponges and mops shall be non shedding, preferably composed of synthetic fibers and dedicated to use in the buffer or Clean area, ante Area and segregated compounding areas shall not be removed from these except for disposal"

USP<797> Appendix I, Section Cleaning and Disinfecting the Compounding Area

However, as GPS is committed to continued quality improvements, we will take this under advisement and will consider the incorporation of sterile wipes in the aseptic area and while operating in an ISO5 environment.

Target date of Completion: 30 days

Observation 4
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions

Specifically, Your environmental and personnel monitoring program is deficient in that your firm does not conduct air or surface sampling for viable or non-viable, particles during the aseptic operation of every batch or at least once per production day in which drug product(s), intended to be sterile are aseptically processed in your ISO 5 hood. Personnel monitoring of the operator's gloves has not been performed post aseptic processing of every batch or prior to exiting the Clean room. According to your Standard Operating Procedures (SOP), entitled Environmental Monitoring of the Clean Room Facility, Version 1.0, dated 04/12/16 and Pharmacist-In-Charge (PIC):

1. Personnel touch plates are conducted every two (2) weeks upon completion of sterile compounding and prior to cleaning
2. Surface sampling in the ISO 5 area are performed every two (2) weeks upon completion of sterile compounding and prior to cleaning
3. Viable and non viable air sampling are performed every 3 months during the clean room certification by third party vendor

During the previous six (6) month review of your environmental monitoring program, the personnel touch plate was performed on the following dates:

April	May	June	July	August	September
2016.	2016	2016	2016	2016	2016
4/1	513	6/24	7/4	8/8	9/2
4/29	5/27		7/19		9/16
					9/29

Additionally, the firm has not conducted monitoring every two weeks according to their SOP and there is no documented investigation, testing, document review or root cause identified for this deficiency.

From 6/1/16 through 9/12/16 you have prepared approximately 478 sterile drug products from non- sterile bulk and have prepared sterile drug products approximately 74 total days.
Response to Observation 4:

As a Section 503A compounding pharmacy, GPS is fully compliant with its regulatory

requirements under the authority of the Texas Board of Pharmacy and operates in full compliance with Texas state law including USP<797>. Per USP <797> Air and surface sampling shall be conducted every 6 months.

"Environmental Sampling shall occur as part of a comprehensive quality management program and shall occur minimally under the following conditions:

- *As part of the commissioning and certification of new facilities and equipment*
- *Following any service of facilities and equipment*
- *As part of the recertification of facilities and equipment (i.e every 6 months)"*

USP <797> Page 34 Section Viable and Non Viable Environmental Sampling (ES) Testing

"Surface sampling shall be performed in all ISO classified areas on a periodic basis"
USP<797> Page 47 Section: Surface Cleaning and disinfection sampling and assessment"

GPS has exceeded this request by ensuring the air sampling is done by a third party contractor every 3 months as indicated within the records. Surface sampling is additionally done at least monthly.

USP<797> Appendix I States:

"Air Sampling shall be performed at least semi –annually (i.e. every 6 months), as part of the re-certification of facilities and equipment for area where primary engineering controls are located"

Neither Section 503A nor USP <797> requires that the daily Personnel Monitoring of the operators gloves occur post aseptic processing of each batch.

These observations appear to rely on cGMP standards, which do not apply to 503A pharmacies. However, GPS has made the following changes to its processes:

1. The Environmental Monitoring of the Clean Room SOP 3.030 has been amended to state that Personnel Touch Plate monitoring will be done **at least once a month** upon completion of compounding a prior to cleaning.
2. The Environmental Monitoring of the Clean Room SOP 3.030 has been amended to state Surface Sampling in the ISO Class 5 area will be done **at least once a month** upon completion of compounding a prior to cleaning.
3. Our Records show that as of September 2015 Viable and non viable air sampling have been conducted every 3 months.

These changes to process are still above the recommended frequency of every 6 months per USP <797>.

Observation 5
There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed

Specifically,

a. On 05/27/16, a surface sample collected from the top shelf of the Glove cart located in the ISO 7 clean room had 9 colony forming units (CFUs). The firm's action limit for ISO 7 is 5 CFUs/plate.
b. On 5/16/16, a surface sample collected at the sink located in the ISO 8 ante room had over 100 CFUs. The firm's action limit for ISO 8 is 20 CFUs/plate.

Additionally, the firm's SOP 3.030, Environmental Monitoring of the Clean Room Facility, version 1.0 states in section 9.10.3: "if an excursion occurs above an action level, the Pharmacist-In-Charge or Quality Control Officer must be notified and an investigation and correction action should occur." No investigation or corrective actions were documented for these excursions.

c. Your firm does not consistently document that bubble point testing has been conducted on drug products. Your firm produced and dispensed the following drug products and failed to document on your Quality Control Data Sheet, that bubble point testing was conducted.
    1. Hyaluronidase 1 50U/ml Injectable Preservative Free in 3cc syringes, Lot 50449:00, made on 8/19/16

    2. Mitomycin 40mg/60ml solution Injectable in a 60ml syringe, Lot 50592:00, made on 8/30/16

    3. Morphine 1mg/ml Injectable, Lot 49488: 14, made on 6/23/16

There was no documented investigation or corrective actions were documented for these excursions.

d. On 05/03/16, Doxycycline 200mg stock solution (Lot 48541) was prepared and did not pass the endotoxin testing. No documented investigation or corrective actions were documented for this excursion. Furthermore, your SOP 8.010, Sterilization and Depyrogenation, version 1.0 fails to address necessary steps to take in case of an endotoxin failure.

Response to Observation 5:

A. SOP 3.030 Environmental Monitoring of the Clean Room Facility has been amended to ensure that all EM Data sheets are reviewed and signed off by the Pharmacist In Charge or the Quality Control Manager prior to being filed away to ensure that any discrepancies are documented. This will be implemented as of December 1st 2016

B. Within 30 days, the pharmacy staff will be retrained and section 9.10.3 will be reinforced to ensure that any excursions above the action level are escalated to the Pharmacist in Charge or Quality Control officer as stated in the SOP.

C. Immediately effective, The Quality Control Data Sheet shall be completed before a product is released for dispensing. The staff shall be retrained on the completion of the Quality Control Data Sheet within the next 30 days. A bubble point result shall

accompany all products that are filter sterilized per the SOP on good documentation. If one is not available the checking pharmacist SHALL document why and indicate if further action is required. As of December 1st 2016. An audit will be conducted monthly of a sampling of 5% of the total lots made the previous month have Quality Control Data Sheets are completed.

With Immediate effect SOP 9.123 Endotoxin Testing of Sterile Compounded Products has been edited to ensure that the Pharmacist in Charge or Quality Control Manager has been notified of any failures. The products should be quarantined pending an investigation or further testing. As of December 1st 2016 the Pharmacist in Charge or the Quality Control Manager shall conduct a monthly audit to ensure any failures are documented and investigated

Observation 6
Equipment used in the manufacture, processing, packaging or holding of drug products is not of appropriate design to facilitate operations for its cleaning and maintenance.

Specifically,

Your Nuaire laminar flow hood, (Model 301-630, Serial Number 4246) has a stainless steel table supported by particle board which is difficult to clean and disinfect.

Response to Observation 6

Within 6 months the Nuaire Laminar flow hood (Model 301-630, Serial Number 4246) shall be modified to ensure compliance.

Target Date of completion 180 Days

Observation 7
The building lacks adequate space for the orderly placement of equipment and materials to prevent mix-ups between drug products and to prevent contamination.

Specifically,

Your firm prepares a hazardous cytotoxic drug product, Mitomycin in 1ml syringes, in the positive pressure ISO7 clean room along with other non hazardous products. Your firm has prepared and dispensed 16 lots (25units or less each) of this product since June 2016.

Response to Observation 7:

As a Section 503A compounding pharmacy, GPS is fully compliant with its regulatory requirements under the authority of the Texas Board of Pharmacy and operates in full compliance with Texas state law including USP<797> which states,

> *In facilities that prepare a low volume of Hazardous Drugs, the use of two tiers of containment (e.g. a CSTD within a BSC or CACI that is located in a non negative pressure room) is acceptable.* USP<797> Page 20 Section: Hazardous drugs as CSPS

Given the low volume of Mitomycin drug production as well as use of the Chemo-Bloc CSTD in the BSC

USP <800>, which goes in effect in July 1st 2018, requires that hazardous substances be compounded in a negative pressure room. The pharmacy will ensure that it is compliant with USP 800 at least 30 days before it goes into effect.

Observation 8

Procedures describing the handling or written and Oral complaints related to drug products are deficiently written.

Specifically, Your complaint investigations are not followed as described in your SOP Number 5.030, Complaint/Grievances and Adverse Reactions, version 2.0, effective date: 05/01/2013, under section 9.7, which states "The PIC, or designee, should identify and document the specific facts involving the complaint." Your firm's PIC stated the firm has not documented complaints in the complaint log.

Additionally, the firm's sterile supervisor stated the firm has received approximately six (6) customer complaints involving the elastomeric eclipse pump between January 2016 and May 2016. There is no documented investigation, testing, document review or root cause identified for this deficiency.

Furthermore, your complaint procedures do not include directions for defining an adverse event and the actions that the firm needs to take regarding the following complaints filed with Halyard Health, the manufacturer of the elastomeric pump utilized by your firm.

In addition to not defining adverse events, you are not reporting them to the Food and Drug Administration and your firm failed to report these defective product issues.

Furthermore, an adverse event was reported by the consumer to the FDA on 05/27/16, regarding drug product, Ceftriaxone 2 gram in 50ml of 0.9% NaCl (Lot # 48058:42), prepared by your firm in an eclipse pump 50/50. This adverse event was known by your firm.

Response to Observation 8:

All customer complaints shall be documented. In addition, a staff pharmacist shall conduct a meeting weekly to review complaints from the previous week and ensure that the complaints are documented.

There is not a mandatory federal requirement for Section 503A pharmacies to report adverse events to the FDA. Pharmaceutical Manufacturers and most recently 503B Outsourcing Facilities are required to report adverse events.

U.S. Code 21 Section 310.305 requires that manufacturers, packers, and distributors of marketed prescription drugs that are not the subject of an approved new drug application or an abbreviated new drug application to report to FDA all adverse events through the Medwatch program.[3] In addition., Section 503B(b)(5) added this requirement for Sect6ion 503B Outsourcing Facilities

[3] 21CFR310.305

and this requirement was reiterated in the most recently released Final Guidance, *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, stating that all outsourcing facilities "must submit adverse event reports to FDA 'in accordance with the content and format requirements established through guidance ore regulation under section 310.305 of title 21, Code of Federal Regulations (or any successor regulations)."[4]
5

However, in order to provide the best care to patients, BPS' Standard Operating Procedure 5.030 Compliant Handling has been edited to include a definition of an Adverse Event and all adverse events will be investigated and documented

*DATES OF INSPECTION

9/12/20 I 6(Mon), 9/13/2016(Tue), 9/14/20 I 6(Wed), 9/I 5/2016(Thu), 9/I 6/2016(Fri), 9/19/2016(Mon), 9/21/2016(Wed), 9/23/20 I6(Fri), 9/28/2016(Wed), 10/03/2016(Mon), 10/07/2016(Fri), 10/11/2016(Tue), 10/12/2016(Wed), 10/21/2016(Fri)

[4] Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance for Industry, October 2015.