DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
250 Marquette Avenue, Suite 600 Minneapolis, MN 55401 (612) 334-4100 Fax:(612) 334-4134 Industry Information: www.fda.gov/oc/industry	12/03/2013 - 12/13/2013* FEI NUMBER 3010538416

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Monica M. Zatarski PharmD, RPh, Compounding Pharmacist, Owner and President

FIRM NAME	STREET ADDRESS
Brookfield Prescription Center Inc. dba MD Custom Rx	19035 W. Capitol Dr Suite 105
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Brookfield, WI 53045	Sterile Drug Producer

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, written, and followed.

Specifically,

1. SOP 9.110 Sterile Compounding Process Validation (Media Fills) procedure is inadequate in that it does not reflect actual practices which occur during processing.
   a. The media fill failed to simulate actual compounding activities.
      i. (b)(6) media fill, dated 8/20/13, demonstrated she was qualified to manually fill (b)(4) vials at 10 mL. In practice, management stated they manually fill vials when the batch size is (b)(4) A technician could manually fill up to (b)(4) vials. On 12/10/13 (b)(6) manually filled (b)(4) vials at 3.5 mL each.
      ii. Media fills are not performed using the (b)(4). On 10/29/13 (b)(6) filled (b)(4) vials of Glycopyrrolate (MDV) 0.2 mg/mL injection using the (b)(4).
      iii. The number and type of interventions was not included during media fills.

2. The (b)(4) used to sterilize product are not validated.
   a. SOP 3.1112 (b)(4) procedure states in the Validation section, *"***To ensure every load throughout the day has met the sterilization parameters, a (b)(4), which has been cleared by the FDA as equivalent in performance" to a biological indicator, shall be used in each load**At least (b)(4) a (b)(4) should be run in the sterilizer***".*
   b. SOP 3.111 (b)(4) procedure states in the Validation section, *"***To ensure every load throughout the day has met the sterilization parameters, a (b)(4), which has been cleared by the FDA as equivalent in performance" to a biological indicator, shall be used in each load**At least (b)(4) a (b)(4) should be run in the sterilizer***".*

   The use of (b)(4) and the (b)(4) do not replace the need to validate the (b)(4). Examples of (b)(4) products are as follows: Procaine HCl (PF) 2% Injectable, EDTA Calcium Disodium (PF) 300 mg/mL injection, Edetate Disodium (PF) Ophthalmic 1.7 injectable, Nicardipine (PF-SDV) 2.5 mg/mL injectable, Scopolamine Ophthalmic 0.25% solution and Magnesium Chloride 500 mg/mL Hexahydrate (PF) 500 mg/mL injectable.

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3. Smoke studies are not conducted in the ISO 5 hoods.

4. The ISO 5 hoods have not been certified under dynamic conditions.

5. Your firm does not have any procedures in place to ensure that non-penicillin beta-lactam drugs (cephalasporins) have not been exposed to cross-contamination with penicillin or vice versa. The firm stated they will compound anything except cytotoxins. The firm has compounded a non-sterile penicillin powder in the past ([redacted] times a year). This activity is performed in a hood in the general laboratory. They have also used cefazolin to compound ophthalmic drops in 2010 and in 2011. The ophthalmic drops would be compounded in the ISO 5 area.

6. Bacterial retention and compatibility studies have not been conducted on the [redacted] (b) (4) used to [redacted] (b) (4) compounded products.

7. The firm does not wipe down all equipment/components with 70% sterile alcohol prior to exposing them to the ISO 5 hood. The technician uses non-sterile wipes on the equipment/components they do wipe down. The use of non-sterile wipes with [redacted] is also used to wipe down equipment/components during the transfer from ISO 8 to ISO 7 areas.

8. The firm uses depyrogenated glassware during the compounding of [redacted] (b) (4) product. The firm does not sterilize the glassware.

OBSERVATION 2

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

1. SOP 6.201 Potency Testing of Compounded Preparations states, *"***If a sample fails a potency test:**Determine if a recall procedure is necessary on any dispensed Compounded Preparation and recall (pursuant to SOP) any dispensed preparations**Review the Formula Worksheet to determine steps that can be taken to improve the potency of the Compounded Preparation**Document the Out of Specification (OOS) result and make appropriate changes to the Formula Worksheet **Repeat the Process Verification procedure as outlined in Section 2***".*

   a. The firm was notified of the OOS for the Glycopyrrotate injection on Nov. 12, 2013. As of 12/3/13, the firm had yet to initiate a formal OOS investigation.

   b. Four OOS investigations have been documented since January 2013. None of these investigations determined whether a recall was necessary or whether the OOS affected additional product already distributed.

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OOS #/ Date/ Product/Lot #	OOS	Significance
Mar 2013 #1 3/15/13 Prostagladin E-1 (Alprostadil)* 03142013@21	Supra-potent measuring 12.98mg/mL (129.76%)	Prostagladin E-1 Dilution 500 mcg/mL, lot 03132013@18 and Prostaglandin E-1 100 mcg/mL, lot 03132013@19 were both used to produce the supra-potent lot. Both are made by (b) [redacted] (b) (4) of Prostagladin E-1 Dilution 500 mcg/mL, lot 03132013@18 was produced. (b) (4) of this solution was used to make Prostaglandin E-1 100 mcg/mL, lot 03132013@19. (The remaining (b) (4) would be used to make additional lots of Prostaglandin E-1 100 mcg/mL) (b)c of Prostaglandin E-1 100 mcg/mL, lot 03132013@19 was used to make Prostagladin E-1 (Alprostadil), lot 03142013@21. (The remaining (b)c would be used to make additional lots of Prostaglandin E-1 (Alprostadil). Neither of the dilution lots were tested for potency and it is unknown whether either of these concentrations were supra-potent. Although lot 03142013@21 was not shipped, the firm did not investigate if any additional lots of Alprostadil made with the dilution solutions were affected.
Mar 2013 #2 3/20/13 Estriol capsules 03132013@36	Supra-potent measuring 1.39mg (110.82%)	Testing was for training purposes to validate the technique of [redacted]. Was a requalification for [redacted] Product was already distributed when OOS results were obtained. No evaluation was made on other product made by [redacted]
May 2013 #1 5/15/13 Progesterone 100mg suppositories 05062013@58	Sub-potent measuring 88.41%	Testing was for training purposes to validate the technique of [redacted]. Product was already distributed when OOS results were obtained. No evaluation was made as to recalling the product.
June 2013 #1 6/24/13 Biest 50:50 0.5mg/mL cream 06112013@30	Supra-potent TOP 94.54% (0.24 mg/mL) MIDDLE 142.43% (0.36 mg/mL) BOTTOM 130.4% (0.33mg/mL)	Testing was for training purposes to validate the technique of [redacted] Product was already distributed when OOS results were obtained. No evaluation was made into recalling the product.

2. There was a failure to investigate the pressure differential out-of-specification of 0.019 between the ANTE and Buffer rooms on 8/5/13, (specification is not (b) (4) than (b) (4)).

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OBSERVATION 3

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

Specifically,

1. SOP 6.201 Potency Testing of Compounded Preparations states in the [redacted] (b) (4) procedure, *"***Every* [redacted] (b) (4) *time the preparation is made it should be communicated with the Quality Control Officer who will determine if it warrants sending to an approved third party testing facility for potency testing (dependent on how much testing has already been performed for this preparation and those similar to it). The date and initial record can then be reset to zero after this* [redacted] (b) (4) *recording***".* This "reset" takes place regardless of whether the potency was tested or not. Management stated for a first time preparations, if the master formula is from a reference book (i.e. handbook for ophthalmology), the firm would follow SOP 6.201 and would evaluate the need to test for potency after the [redacted] (b) (4) batch. This is significant as product could not be tested for potency for an extended period of time.

2. Your firm has failed to document the 100% visual inspection conducted per SOP 4.202 Quarantine and Release Specifications procedure. This procedure requires all compounded preparations to be quarantined until the preparation and its formula worksheet have been checked and verified for accuracy by the pharmacist. This includes, *"***Visually inspecting the finished preparation including the fill amount to ensure that it appears as expected**Visually inspecting the container-closure integrity**Examining all labeling to ensure the information matches the compounding and formulation record requirements***".*

3. There is no documentation of the evaluation of the sterility and potency results upon receipt.

4. No endotoxin testing was performed on Iohexol Sterile 300 mg/mL solution, lot 11/12/2013@5, prepared on 11/12/2013.

OBSERVATION 4

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

Specifically,

1. Preservative effectiveness studies have not been completed for the following products: Epinephrine Solution (MDV) 1mg/mL Injection, Glycopyrrolate (MDV) 0.2mg/mL Injection, Hdroxyprogesterone (MDV) 250mg/mL Injection, Magnesium Sulfate (MDV) 500mg/mL (4meq/mL) Injection, Magnesium Sulfate (MDV) 2mg/mL Injection, Papaverine (MDV) 30mg/cc Injection, Succinylcholine (MDV) Injection, and Trace Elements Concentrate 5 (MDV) Injection.

2. Your firm does not have documentation to justify the Beyond Use Date (BUD) of injectable products up to 90 days.

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Potency data is available where noted. Sterility testing was not performed at the end of the BUD.

Product Name	Preservative Used	BUD Date	Firm's Justification
Epinephrine Solution (MDV) 1mg/mL Injection	(b) (4)	30 days @ room temp.	BUD was based on having the compound using the same active ingredient as a commercial product. Firm's BUD dating is more conservative than commercial product
Glycopyrrolate (MDV) 0.2mg/mL Injection		30 days @ room temp.	BUD was based on having the compound using the same active ingredient as a commercial product. Firm's BUD dating is more conservative than commercial product
Hdroxyprogesterone (MDV) 250mg/mL Injection		90 days @ room temp.	BUD was based on having the compound using the same active ingredient as a commercial product. Limited potency data available @ Day 7: 100.04% (250.10mg/mL) Day 91: 98.70% (46.75mg/mL)
Magnesium Sulfate (MDV) 500mg/mL (4meq/mL) Injection		45 days @ frozen	BUD based on USP <797>
Magnesium Sulfate (MDV) 2mg/mL Injection		45 days @ frozen	BUD based on USP <797>
Papaverine (MDV) 30mg/cc Injection		90 day @ room temp. 28 days after first injection	BUD was based on having the compound using the same active ingredient as a commercial product. Limited potency data available @ Day 6: 104.18% (31.26mg/mL) Day 30: 103.46% (31.04mg/mL) Day 62: 103.95% (31.18mg/mL) Day 90: 101.17% (30.35mg/mL)
Succinylcholine (MDV) Injection		90 days refrigerated	BUD was based on having the compound using the same active ingredient as a commercial product. BUD was based on published documentation. Limited potency data available @ Day 7: 100.97% (20.19mg/mL) Day 32: 103.20% (20.64mg/mL) Day 60: 97.56% (19.51mg/mL) Day 90: 95.99% (19.20mg/mL)

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Product Name	Preservative Used	BUD Date	Firm's Justification
Trace Elements Concentrate 5 (MDV) Injection	(b) (4)	90 days @ room temp.	BUD was based on having the compound using the same active ingredient as a commercial product. Firm's BUD dating is more conservative than commercial product

OBSERVATION 5

Procedures describing the handling of written and oral complaints related to drug products are deficiently written or followed.

Specifically, SOP 5.030 Complaint Handling procedure states, *"***The Pharmacist-in charge, or designee, shall evaluate each complaint and, if necessary, commission an investigation***"*. No formal investigations were initiated into the following customer complaints. All of the examples listed below reached the patient:

1. 5/03/13 Rx filled under the wrong physician name
2. 6/24/13 Correct drug, did not add acidophilus (written to add on Rx)
3. 7/03/13 Sig written 1 po qam, 2 po qnoon; filled 2 po qam and 2 po qnoon
4. 7/19/13 Wrong strength written in sig (should have been 0.25 mg, was written as 0.25 g)
5. 11/15/13 Product was dispensed in non-light resistant packaging

OBSERVATION 6

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

Specifically,

1. Your firm has not conducted disinfectant effectiveness studies to demonstrate that disinfectants used in the ISO 5 and ISO 7 areas can sufficiently reduce bioburden. Currently, your firm utilizes the following disinfectants:
   a. (b) (4)
   b. (b) (4)
2. Your firm is not using the cleaning agent according to labeled directions. The firm currently wipes on the cleaning agent followed by spraying down with either (b) (4). The label on the cleaning agent requires having the solution soak for (b) (4) followed by rinsing with water. Currently, your firm utilizes the following cleaning agents:
   a. (b) (4)
   b. (b) (4)
3. On 12/4/13 we observed the ISO 5 and ISO 7 areas being cleaned. We observed the technician cleaning the work surface of the hood in a back to front motion. The technician did not use a clean surface of the cloth for each swipe during hood cleaning.

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OBSERVATION 7

Written production and process control procedures are not documented at the time of performance.

Specifically, the formula master sheet is placed into a plastic sheath which is wiped down with (b) (4) and brought into the ISO 7 room. All documentation is written on the plastic sheath with dry erase marker. When the batch is completed the record is removed from the room. The information on the plastic sheath is transferred to the formula master and the plastic sheath is wiped clean. This practice could lead to incorrect data being transferred to the master sheet or data being inadvertently lost.

*** DATES OF INSPECTION:**
12/03/2013(Tue), 12/04/2013(Wed), 12/05/2013(Thu), 12/09/2013(Mon), 12/10/2013(Tue), 12/13/2013(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."