DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6th & Kipling St. (P.O. Box 25087) Denver, CO 80225-0087 (303)236-3000 Fax:(303)236-3100	6/16/2025-6/27/2025* FEI NUMBER 3030548360

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Robert J. Kilgore, Chief Executive Officer

FIRM NAME	STREET ADDRESS
BSO, LLC	741 Corporate Cir Ste A-H
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Golden, CO 80401-5602	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 did not include adequate validation of the sterilization process.

Specifically,

Your firm failed to establish and document adequate validation of the (b) (4) sterilization process used for Estradiol Pellets (6 mg, 10 mg, 12.5 mg, 15 mg, 18 mg, 20 mg, 25 mg, 37.5 mg, 50mg).

a. You implemented a new container-closure system for Estradiol Pellets, but your sterilization validation (BSO.ST.002.1R) did not include a method suitability study or calculation of a recovery factor (RF) to assess the efficiency of microbial recovery from the new configuration. Additionally, your firm has changed to a new bioburden test method (b) (4) since the original validation, which can significantly affect recovery efficiency.

   You provided method suitability data from (b) (4) and (b) (4) Estradiol pellets packaged in (b) (4) vials produced from your Lakewood, CO facility. You also provided method suitability data for (b) (4) vials. These studies did not demonstrate that the results are reproducible under defined conditions and reflect products in its current final container-closure system.

b. Your 2024 validation study (BSO.ST.002.1P) lacks documentation supporting the (b) (4) for Estradiol pellets in its current final container-closure

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system.

The 2015 Terminal Sterilization Validation Study (PQ.002.01VR) conducted potency testing on (b) (4) -sterilization Estradiol pellets packaged in (b) (4) vials. Separately, you provided an additional 2024 Potency/Sterilization Study that used Estradiol pellets in (b) (4) (b) (4) vials produced from your Lakewood, CO facility. However, these studies do not reflect the current packaged final configuration, which consists of Estradiol packaged in clear glass vials produced at your Golden, CO facility.

Qualification activities are expected to utilize product manufactured with the same components, container-closure system, and process intended for routine production. Estradiol Pellets are currently packaged in clear glass vials, which represents a change in the container-closure system. The product in its final configuration should be subjected to the (b) (4) to assess possible effects on potency, degradation, and performance.

OBSERVATION 2

Your firm failed to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess.

Specifically,

SOP 12, *Visual inspection of Pellets (BSO Lakewood & Golden),* Version 26.0, Effective Date 03/19/2025, does not have defined criteria for operator re-qualification outside of (b) (4) retraining, particularly in cases where re-qualification may be warranted due to performance issues, process deviations, or procedural changes. As a result, operators may remain in a qualified status despite demonstrating issues performing critical operations, without any reassessment of their competency. For example:

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i. On 04/02/2025, during the 100% visual inspection of Estradiol 12.5 mg pellets Lot # (b) (4), Operator (b) (6), (b) (7) found a total of thirty-five (35) defects, including nineteen (19) "Black Speck" (Scrap code: BS), and twelve (12) "Contaminant in vial" (Scrap Code: CVL).

- oThe BPR states, for a Batch size of (b) (4), sample size is (b) (4) pellets, reject allowed is (b) (4) The batch failed the AQL sampling, in which four (4) pellets were rejected, consisting of two (2) Black Speck defects, and two (2) "Stearic Acid" pellets found by QA. Your firm decided to perform a second 100% visual inspection of the batch.
- oOn 4/3/2025, a second 100% inspection of the same batch was conducted by Operator (b) (6), (b) (7), an additional sixty-seven (67) defective pellets were identified, including defects of the same type (thirty-six (36) "Black Speck" and twenty-two (22) "Contaminant in vial" defects that should have been detected during the first inspection. Final Batch yield was (b) (4) pellets and the batch was released.

ii. On 04/02/2025, during the 100% visual inspection of Estradiol 10 mg pellets Lot # (b) (4) Operator (b) (6), (b) (7)(C) found a total of twenty-five (25) defects, including five (5) "Contaminant in vial" (Scrap code: CVL), seven (7) "Black Speck" (Scrap code: BS) and 11 "Chipping/Cracking/Fracturing" (Scrap Code: CHP).

- oThe note on the BPR, states that the Batch size is (b) (4), sample size is (b) (4) and the reject allowed is (b) (4) The batch failed the AQL sampling, in which one (1) pellet was rejected with "Contaminant in vial" defect found by QA. Your firm decided to perform a second 100% visual inspection of the batch.
- oOn 4/3/2025, a second 100% inspection of the same batch was conducted by Operator (b) (6), (b) (7)(C) An additional eighteen (18) defective pellets were identified, including defects of the same type (five (5) "Contaminant in vial" (Scrap code: CVL), eight (8) "Black Speck" (Scrap code: BS), and 4 "Chipping/Cracking/Fracturing" (Scrap Code: CHP) defects that should have been detected during the first inspection. This batch was ultimately rejected.

iii. On 04/28/2025, during the 100% visual inspection of Estradiol 10 mg pellets Lot # (b) (4), Operator (b) (6), (b) (7) found a total of 128 defects, including sixty-one (61) "Black Speck" (Scrap code:

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BS) and twenty-two (22) "Stearic Acid" (Scrap Code: SA), and forty (40) "Contaminant in vial" (Scrap Code: CVL).

- oThe BPR states, for a Batch size of (b) (4), sample size is (b) (4) pellets, reject allowed is (b) (4) The batch failed the AQL sampling, in which four (4) pellets were rejected, including three (3) "Fibers and Specs in Vials" were found by QA. Your firm decided to perform a second 100% visual inspection of the batch.
- oOn 4/29/2025, a second 100% inspection of the same batch was conducted by Operator (b) (6), (b) (7)(C) an additional 67 defective pellets were identified, including defects of the same type (thirty (30) "Black Speck" and thirty-four (34) "Contaminant in vial" defects that should have been detected during the first inspection. Final Batch yield was (b) (4) pellets and the batch was released.

Your firm has an open investigation into the root cause of the "Black Speck" and continues to release batches for distribution without determining the source of the defect. You release product without a full understanding of the original failures. There was no assessment of the performance of the personnel who conducted the initial inspection.

If visual defects are not reliably detected, potentially defective units could be released, which is especially critical for implantable hormone products like estradiol pellets.

OBSERVATION 3

The written stability program for drug products does not include specific test methods.

Specifically,

a. **Lack of Photostability Studies for Light-Sensitive Product:** Your firm manufactures Estradiol pellets, which are light-sensitive product, yet the product is packaged and released in clear, non-light-resistant containers. Stability Study BSO.SS.001, Estradiol Pellet Stability Study- Day (b) (4) Report, signed 03/24/2025, does not contain any data to demonstrate that the packaging protects

the drug from photodegradation. No photostability studies have been performed on the drug product in its container-closure system to demonstrate its protection from light, and no justification has been provided for the omission.

b. **Absence of Dissolution Testing in Stability Study**: Estradiol Pellet Stability Study Day (b) (4) Report, BSO.SS.001, does not include dissolution testing, to evaluate the maintenance of extended-release performance over the product's shelf life. Dissolution testing is a critical quality attribute for pellets and the lack of performance testing during stability undermines the assurance of continued dosage reliability.

c. **Omission of Impurities and Degradants Testing:** Estradiol Pellet Stability Study Day (b) (4) Report, BSO.SS.001, does not include does not include testing to detect and quantify impurities and degradants, such as related substances and known degradation products. The omission of impurities testing prevents the evaluation of changes in the product's purity over time.

Stability study is applicable to Estradiol Pellets (6 mg, 10 mg, 12.5 mg, 15 mg, 18 mg, 20 mg, 25 mg, 37.5 mg, 50mg).

OBSERVATION 4

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,

Your firm manufactures Estradiol Pellets (6 mg, 10 mg, 12.5 mg, 15 mg, 18 mg, 20 mg, 25 mg, 37.5 mg, 50mg) intended for subcutaneous implantation, designed to release drug over a prolonged period. However, you do not perform dissolution testing as part of batch release. This omission of dissolution testing could potentially lead to the distribution of subpotent drug products, as well as potential dose dumping, inconsistent release rates, and incomplete drug release.

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OBSERVATION 5

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically,

The (b) (4) (BSO-016), used in the production of Estradiol granulate at the firm, has not been qualified with respect to its ability to remove residual solvents. Estradiol granulate contains (b) (4) as a granulating solvent. The equipment qualification study (BSO.EQ.016.1R (b) (4)) for this (b) (4) was performed using (b) (4) and (b) (4) and did not evaluate performance using (b) (4).

No study was provided to demonstrate equivalency between the qualification materials and the actual product formulation. No data were provided to demonstrate that the (b) (4) is capable of consistently and safely removing (b) (4) under the parameters used during routine production. Your firm provided residual solvent test data and (b) (4) qualification results from a different facility under the same corporate ownership (BSO.ST.009.1); however, no on site residual solvent testing was performed at this location to demonstrate that the equipment, as installed and operated, can achieve the validated performance. In the absence of such data, there is no assurance that the (b) (4) performs as intended for the (b) (4) of estradiol granulate containing (b) (4) or that residual solvent levels meet acceptable safety limits.

OBSERVATION 6

The master production and control records are deficient in that they do not include complete manufacturing and control instructions, specifications, special notations and precautions to be followed.

Specifically,

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a. **Inadequate (b) (4) Documentation and Control:** The Estradiol Granulate Production- Batch Production Record (Form 45-09E) does not record the (b) (4) parameters set point applied during the (b) (4) step and that it was maintained throughout the entire run of (b) (4). Section 8.6.8 of SOP 45, (b) (4) *Granulation (BSO- Lakewood & Golden)*, Version 22, Effective Date 03/27/2025, states "*Ensure that* (b) (4) *has reached an operating temperature of* (b) (4) *C, then place* (b) (4) *in the* (b) (4). There is no mention of verification of the (b) (4) setting before use. During qualification of the (b) (4) (b) (4) (BSO.EQ.016.1R), the (b) (4) had an operating setting of (b) (4) mbar and a set point of (b) (4) mbar.

On 06/18/2025, during the granulation Estradiol 15 mg Pellets, Lot # (b) (4), I observed an alarm on the (b) (4) noting the (b) (4) rise to 567 mbar. The Technician noted on the batch record the event and that the (b) (4) "maintained temperature the whole time". The technician did not note the duration of the alarm and when the (b) (4) returned to the set point. Towards the end of the run, the (b) (4) showed an alert and the technician noted on the batch record that the temperature and (b) (4) was in range. I observed the operator turn the (b) (4) alert off while the alert was in progress. Alarms and Alerts on the (b) (4) during production are not reviewed as part of batch release.

b. On 06/19/2025, I observed Technician (b) (6), (b) (7) use Estradiol granulate to set up the Pellet Press to complete weight adjustments on the press to ensure pellets are within range before actual production. These pre-production pellets were then placed into scrap. This process is not documented in the Master Batch Production Records. There are no procedures or instructions in the batch record authorizing the use of estradiol granulate when setting up the Pellet Press, and no limit on the amount of estradiol granulate has been determined. The Director of Operations agreed that the operator was following the current practice.

c. **Undocumented Use of Stearic Acid as Lubricant:** Section SOP 70, (b) (4) *Pellet Press (BSO – Lakewood & Golden),* Version 7.0, Effective Date 01/13/2025, states "*Repeat steps* (b) (4)

using stearic acid every (b) (4) *pellets pressed (or as needed) to lubricate the* (b) (4) ." On 06/19/2025 during production of Estradiol Pellet Lot # (b) (4) , I observed technicians perform the pressing of stearic acid and disposing of them in the trash bin next to the Pellet Press. The Master Batch Production Record does not record the pressing of stearic acid as a lubricant after every (b) (4) pellets and the disposal of the stearic acid pellets.

d. **Incomplete Equipment Documentation:** Form 45-09E, MMR Title: Estradiol Granulate Production Rev. 4.0, Effective Date 05/12/2025, does not record the Equipment ID on the Master Batch Production Record for the use of the (b) (4) and the (b) (4) .

In the absence of this information, the record does not provide adequate traceability or assurance that all critical materials and process parameters were used and controlled as required.

OBSERVATION 7

Written production and process control procedures are not followed in the execution of production and process control functions.

Specifically,

Section 7.1.3.1 of SOP 58, *In-Process, Weight, and Hardness Sampling for Pellets (BSO- Lakewood & Golden),* Version 25, Effective Date 02/07/2025, states "*Regardless of weighing method, documentation will occur on* (b) (4) *pellets pressed...*". The following deviations from this procedure were observed on 06/19/2025, during the production of Estradiol 15 mg Pellets, Lot # (b) (4) :

a. **Incorrect Sampling Frequency:** Technicians conducted in-process checks every 25 pellets instead of every (b) (4) pellets as specified in the SOP and Estradiol Pellet Manufacture Batch Production Record- Form 46-12E.

b. **Incomplete Documentation:** Midway through the production of the batch, Technicians stopped

documenting the results of in-process checks, once all available spaces in the Batch Production Record where occupied.

OBSERVATION 8

Written procedures are not followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

On 6/17/2025, I observed the (b) (4) cleaning process for ISO 8 Inspection Room, where Estradiol pellets are weighed, vialed, and capped, and noted the following deviations:

a. **Improper Floor Cleaning Technique:** During floor cleaning with sporicidal agent, Technician (b) (6), (b) (7)(C) did not follow the method outlined in Section 8.2.2 of WI 163.01, *Cleanroom Cleaning Techniques (BSO-Golden),* Version 2.0, Effective Date 01/06/2025, which requires (b) (4) from (b) (4) and (b) (4). Section 8.2.9.2 of SOP 163, *Cleaning/Sanitation of Facility/Cleanroom (BSO-Golden),* Version 6.0, Effective Date 05/21/2025, states "*Enter and clean at location* (b) (4) *to avoid waling on clean surfaces*." Instead, the technician stepped on wet floor surfaces immediately after (b) (4) and placed chairs and tables directly on top of treated areas without allowing for the required contact (dwell) time.

b. **Incorrect Spray Pattern Application:** Technician (b) (6), (b) also failed to follow the required (b) (4) (b) (4) pattern described in Section 8.2.3 of SOP 165, (b) (4) *Surface Unit &* (b) (4) *Unit (BSO-Golden),* Version 2.0, Effective Date 09/02/2024. Instead, Technician (b) (6), (b) (b) (4) top-to-bottom, which can result in missed surface overlap. Additionally, the (b) (4) solution was not applied in a consistent manner, and hard-to-reach locations such as the area between the sliding door and wall were missed.

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c. **Incomplete Surface Treatment:** Section 8.4 of SOP 163 states *"Ensure every reachable surface is wiped down with* (b) (4) *and wipes."* I observed several surface locations were not treated with sporicidal agent, including the back ledge of two (2) workstations in the cleanroom and the area underneath the balances.

d. **Personal Protective Equipment (PPE)**: I observed Technician (b) (6), (b) removed PPE goggles three (3) times while actively wiping down surfaces with sterile (b) (4), which is contrary to WI 163.01, which states "*All personnel are required to wear area-specific Personal Protective Equipment (PPE) … Full cleanroom attire is required for performing cleanroom cleaning*". Technician (b) (6), (b) did not re-sanitize their hands or the goggles before returning to their cleaning operations.

***DATES OF INSPECTION**

6/16/2025(Mon), 6/17/2025(Tue), 6/18/2025(Wed), 6/19/2025(Thu), 6/20/2025(Fri), 6/23/2025(Mon), 6/24/2025(Tue), 6/25/2025(Wed), 6/26/2025(Thu), 6/27/2025(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 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."