DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, CA 92612-2445 (949)608-2900 Fax:(949)608-4417	7/10/2023-8/25/2023*
	FEI NUMBER 3004378804

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Leslie (nmi) Nguyen, Director of Pharmacy

FIRM NAME	STREET ADDRESS
Central Admixture Pharmacy Services Inc	7935 Dunbrook Rd Ste C
CITY, STATE, ZIP CODE, COUNTRY San Diego, CA 92126-6322	TYPE ESTABLISHMENT INSPECTED 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 WE OBSERVED:

OBSERVATION 1

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically,

Your firm's Quality Unit failed to ensure drug product purported to be sterile produced at your facility meets established specifications for quality, strength, identity, and purity. Examples include, but are not limited to:

A. Your Quality Unit failed to reject drug product lots that did not meet batch yield specification after 100% Visual Inspection and Quality Unit AQL inspection as instructed in procedure, SOP-CAPS-4000688 Visual Inspection. For example:

1. Fentanyl 20 mcg/mL in NS in 250 mL bag, Lot (b) (4), Exp. 11Apr2023; Total batch yield failed to meet specification, 86.3% (specification (b) (4)) due to high number of particulate matter rejects (18 out of (b) (4)) during multiple rounds of 100% VI/AQL inspection; Despite not meeting batch yield requirement and the high number of particulate matter rejects, the lot was released by your Quality Unit.

2. Fentanyl 10 mcg/mL in NS in 250 mL bag, Lot (b) (4), Exp 17Apr2023; Total batch yield failed to meet specification, 88.8% (specification (b) (4)) due to high number of particulate matter rejects (16 out of (b) (4)) during multiple rounds of 100% VI/AQL inspection (specification (b) (4)). Despite not meeting batch yield requirement and the high number of

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particulate matter rejects, the lot was released by your Quality Unit.

3. Fentanyl 10 mcg/mL in NS in 250 mL bag, Lot (b) (4) Exp 19April2023; Total batch yield failed to meet specification, 83.9% (specification (b) (4)) due to high number of particulate matter rejects (23 out of (b) (4)) during 100% VI. Despite not meeting batch yield rejects requirement and the high number of particulate matter rejects, the lot was released by your Quality Unit.

The above product lots were produced using 250 mL bag container-closures, Lot (b) (4) from Manufacturer A. Please refer to **OBSERVATION 2**

B. Your Quality Unit failed to complete (b) (4) requalification for thirty-one (31) suppliers of critical API used for sterile compounding as instructed in procedure, SOP-CAPS-4000343 Supplier Qualification Process. As of July 18, 2023, eleven (11) requalifications were past due in 2018-2021; nine (9) requalifications were past due in 2022; and eleven (11) requalifications were past due in 2023. Your Quality Unit relies on assurances of quality, purity, and sterility reported on qualified supplier certificate of analyses to release critical materials for use in lieu of testing each lot of critical API and materials used for sterile compounding.

C. Your firm repeatedly failed to follow SOP-CAPS-4000693, titled Quality System procedure, Notification of Quality Event (NQE), v 11, dated 2023-05-31, section 6.1 which states, "Any employee aware of an issue that meets the above definition of Quality Event shall: ...Immediately upon observing or becoming aware of an event, inform the DOP [Director of Pharmacy] or Quality Manager [Director of Quality]... Complete the Notification of Quality Event Form and submit to Quality systems." There is no assurance that all incidents/deviations are documented for Quality Unit review throughout the subsequent production stages, including but not limited to aseptic processing in ISO 5, sterility testing, and visual inspection. During the inspection, we observed three different methods of communicating incident events and no NQE was ever initiated. For example, but not limited to:

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1. On July 18, 2023, we observed several emails sent to the Quality Director and the Director of Pharmacy, inquiring about the need to open an NQE for incidents that occurred during aseptic processing in ISO 5 hood and whether the batch should be released. For example, email dated June 16, 2023, the Quality Control Coordinator asked the Director of Quality "could you let me know if this incident...will require NQE initiation? (refer Lot: (b) (4))". Then the Director of Quality stated, "Since it was captured in real time and it was already resolved we don't need NQE". Hydromorphone 0.2mg/mL in NS 30mL syringe, lot (b) (4) processed on May 11, 2023, with the following comment in the EBR "RC2 cancelled, (b) (4) units not made due to sterility concerns with NS bag 1, 1 unit short due to short of solution."
2. On July 13, 2023, the quality technician responsible for Acceptable Quality Limit (AQL technician) noted on a laminated Pallet ID form and verbally communicated that there is a need for a discussion with the ISO 5 compounding technician due to a discrepancy between the Electronic Batch Record (EBR) and the Pallet ID form for active ingredient, Phenylephrine 100 mcg/mL in NS 10 mL syringe found during the review of the batch after compounding and visual inspection. There was a discrepancy where the Pallet ID indicated (b) (4) mL of wasted drug, while the Electronic Batch Record (EBR) indicated (b) (4) mL. The AQL technician communicated their need to discuss their findings to the compounding technician on the whiteboard in the visual inspection room. No NQE was initiated, and there is no assurance these findings on the whiteboard are addressed, documented, or reviewed by the quality unit prior to batch release.
3. On July 16, 2023, the microbiology technician communicated their need to discuss a missing negative control to another microbiology technician utilizing (b) (4) Chat. The discrepancy was discovered during the sterility review of the vials within the (b) (4) system. No NQE was initiated, and there is no assurance these findings communicated in (b) (4) are addressed, documented, or reviewed by the quality unit prior to batch release.

D. Your Quality Unit failed to ensure comprehensive procedures for quality review of audit trails and electronic data review have been established to ensure completeness, consistency, and accuracy of

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all electronic data generated by your firm. For example, your firm lacks controls to ensure that the results of all tests performed on the (b) (4) Particulate Matter equipment are retained and reviewed by the quality unit to assure acceptance criteria have been met prior to product release. When results are generated by the (b) (4) the operator is presented an option to manually click either a "save" button (where the results will go into the history section of the testing), or a "Queue, and Clear" button (results are moved to the approved and verify section which there is no assurance the data is reviewed). The operator downloads results onto a portable USB drive which is taken to the warehouse where the results are printed to a hardcopy. The data on the USB drive is not retained and the USB drive is reused, only hardcopies of the results are printed and reviewed.
On Jul 26, 2023, we observed a microbiology technician test (b) (4) samples of (b) (4) lots of Fentanyl 2mcg/mL/ 0.125% Bupivacaine PF in 0.9% Sodium Chloride 250mL bags. Lot (b) (4) had (b) (4) samples, which were labeled as (b) (4) however, when running the test, the microbiology technician forgot to click the manual save button and three of the test results, (b) (4) were not recorded. The technician did not notice there were three files short when transferring the saved files to the portable USB drive until we counted the files and notified the technician.

There is no assurance that the printed hardcopy results are corroborated with the data stored on the (b) (4) machine, or that audit trails are reviewed to ensure your product has not undergone unauthorized retesting or manipulation. Furthermore, there is a lack of oversight by the QU to ensure the rightful access of operators to computerize systems. Please refer to **OBSERVATION 16**

E. Your Quality Unit failed to have procedures in place to maintain production and control records. Please refer to **OBSERVATION 7**

F. Your firm's QU failed to investigate and appropriately determine if batches can be released for distribution. For example, but not limited to, please refer to **OBSERVATION 2** and **OBSERVATION 10**

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OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy and 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,

A. Your Quality Unit failed to thoroughly investigate instances of microbiological contamination within critical ISO 5 areas during aseptic production of parenteral and injection drug products purported to be sterile.

1. According to Quality Unit reports from January 2022 to December 2022, your environmental monitoring recovered approximately 100 events of 1 CFU microbiological contamination from ISO 5 equipment surfaces and personnel gowning. For these approximately 100 events, you only conducted 13 documented investigations.
2. According to Quality Unit reports from January 2023 to May 26, 2023, your environmental monitoring recovered approximately 30 events of 1 CFU microbiological contamination from ISO 5 air, equipment surfaces and personnel gowning. For these approximately 30 events, you only conducted 8 documented investigations.

Microbial identification of objectionable organisms found in 1 CFU recoveries in ISO 5 included, but not limited to:

Submission Report Number	Microorganism ID	Recovery Location
R22-0245	*Staphylococcus aureus*	(b) (4)
R22-0277	*Paenibacillus glucanolyticus*	
R22-0914	*Alternaria alternata*	
R22-1309	*Chaetomium globosum*	
R23-0056	*Paenibacillus provencensis*	
R23-0056	*Candida parapsilosis*	
R23-0593	*Bacillus firmus*	

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B. Your Quality Unit failed to conduct a timely investigation for customer complaint of a "cloudy syringe" found in distributed epidural injection drug produced at your facility. On June 12, 2023, you received a customer product complaint regarding one (1) "cloudy syringe" found in product lot, Fentanyl 1.5 mcg/mL Bupivacaine 0.125% in 50 mL syringe, Lot (b) (4) Exp 26July2023. This product lot consisted of (b) (4) syringes shipped to (b) (4) . Product expiry permitted use for over thirty (30) days beyond date of customer complaint notification. Product complaint investigation, NQE-US32-230613-100, was initiated June 13, 2023. Although your investigation found the complaint "implied potentially critical implications", no corrective action was proposed, and the investigation was not closed until August 9, 2023, approximately sixty (60) days after receiving the complaint. Your procedure, SOP-CAPS-4000742 Customer Inquiry Handling and Reporting, states that customer product complaint investigations should close within (b) (4) days.

C. Your Quality Unit failed to thoroughly investigate to determine risk and product quality impact associated with particulate matter found in 250 mL bag container-closures used to produce parenteral finished drug products. On February 16, 2023, you initiated Supplier Compliance Audit, (b) (4) for rejection of approximately (b) (4) unused units from approximately (b) (4) total lot units of 250 mL bags, Lot (b) (4), due to particulate matter identified as cellulose, cotton fiber and inorganic material found in an empty 250 mL bags from Manufacturer A. At that time, your firm had produced approximately (b) (4) units of parenteral drug product using 250 mL bag container-closures from Lot (b) (4). As of July 21, 2023, SCAN 230125-015 remained open without investigation of risk related to released parenteral drug product produced in container-closures from Lot (b) (4), and without corrective action to ensure 250 mL bag container-closures from Manufacturer A do not contain particulate matter.

D. Identification of critical defects during your quality unit process check are not investigated to

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identify deficiencies in the 100% visual inspection process. From January 2021 to July 2023 a critical defect was identified during Quality Unit AQL check for approximately (b) (4) drug product lots. Your written procedure, SOP-CAPS-4000688 Visual Inspection, instructs a (b) (4) 100% visual inspection without investigation for drug product lots that have undergone 100% visual inspection, but failed quality unit AQL inspection for critical defects.

E. No assurance was provided that the Quality Unit is thoroughly reviewing, investigating, tracking, and trending discrepancies, to implement appropriate corrective and preventive actions to prevent their reoccurrence. For example, but not limited to:
The (b) (4) USP Liquid Particle Counter (Particulate matter (PM) testing) is used to test the finished product of 1 mL, 2 mL, 5 mL, 10 mL, 25 mL, 30 mL syringes and 50 mL, 100 mL bags. The Microbiology Supervisor stated that "(b) (4)
(b) (4)
(b) (4) and "No email record was found from (b) (4) with the suggestion of (b) (4) This suggestion must have taken place during an on-site visit or phone conversation." For example, during the review of the system data for March 3, 2023, we observed testing of seven different products from (b) (4) lots with (b) (4) (b) (4) added in between the test samples for the following:

Lot #	Product
(b) (4)	Succinylcholine study
	Fentanyl products
	Hydromorphone product
	Ephedrine products
	Midazolam product
	Succinylcholine product

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(b) (4)	Phenylephrine products

You did not create an NQE or conduct an investigation for the incident of the sample skipping incident on the (b) (4) USP Liquid Particle Counter, and the issue stayed in email correspondence.

F. In lot (b) (4), Fentanyl 10 mcg/mL in 0.9 Sodium Chloride mL in 3mL BD syringe, the automatic percent yield calculation in the Electronic Batch Record (EBR) of 95.7% indicated that the batch met the established yield specification of (b) (4) of theoretical yield, established in your Drug Master Formula. However, when the pharmacist responsible for checking the batch opted to perform a manual calculation, it resulted in 87.6% of theoretical yield, failing to meet the established specification. At the time of this observation, your firm had not initiated an NQE or formal investigation, rather the incident was communicated through email.

G. Between 2018 and 2022, there were more than 80 lots of drug products identified with particulate matter in solution. Your firm documented these findings in an NQE, as a known event that occurs occasionally. Your firm did not perform a thorough investigation and implement appropriate corrective and preventative actions, for example but not limited to:

1. NQE-US32-180328-037:
   "During PM inspection of NDC 71286-6009-1, 100MCG/ML, lot (b) (4) 1 unit rejected due to hair found in syringe under plunger." "This is a known event that occurs occasionally. This NQE has been opened for the purposes of tracking and trending."
2. NQE-US32-180612-092:
   "During PM inspection of ...Fentanyl Citrate in DSW 10 mcg/mL 250mL in 250 mL bag (b) (4) (b) (4) there was a total of 14 units found to have particulate matter in bags." "Particulate matter is a known defect that occurs occasionally...rejected units destroyed...no further action is required."
3. NQE-US32-191011-108

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"On Sep 27, 2019, during first AQL inspection...Midazolam in NS 1mg/mL in 100mL (b) (4) bags (b) (4) with quantity of (b) (4) units, 2 units were found with particulate matter out of (b) (4) sample size. Upon 100% inspection, 5 more units with particulate matter...and 1 more unit was later found." "This is a known issue that has been experienced frequently. An investigation is not being performed at this time. This issue will be monitored through trending."

4. NQE-US32-220513-066:
"On May 11, 2022, during first AQL inspection of NDC# 71286-2071-4 with the L/N: (b) (4) Fentanyl 10 mcg/mL in 0.9% Sodium Chloride 100 mL in 100 mL (b) (4) Bag, QA found one unit with particulate matter... Operation found an additional 3 units with particulate matter... second AQL inspection QA found one additional unit with particulate matter. "This is a known issue. An investigation is not being performed at this time. However, the issue will be monitored through trending."

Furthermore, in 2023, your firm continued to see particulate matter in solution. For example, lot (b) (4) (b) (4) which also failed batch yield specification of (b) (4) . You did not perform a thorough investigation and implement appropriate corrective and preventative actions prior to batch release.

5. NQE-US32-230131-018:
"On January 20, 2023, during production labeling a total of (b) (4) units were rejected due to particulate matter...on January 21, 2023, during AQL Fentanyl 10 mcg/mL in 0.9% Sodium Chloride in 250 mL bag...lot (b) (4) did not meet the specification for precent batch yield due to the excessive amount of rejections." Fentanyl lot (b) (4) did not meet the passing requirement...calculated batch yield (b) (4) %...This lot went through all the necessary steps of visual inspection...It is safe to say that there is no product impact from this event because lot (b) (4) (b) (4) passed all the necessary steps of visual inspection and ...will be dispositioned as OK to release."

Please refer to **OBSERVATION 1.**

OBSERVATION 3

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

Specifically,

A. Your ISO 5 aseptic operators failed to demonstrate adequate aseptic technique. For example:

1. On July 11, 2023, two (2) of your aseptic operators repeatedly dragged the underside of their gowning sleeves along the inside surface of the ISO 5 hood during aseptic production of injection drug products. The underside of aseptic operator sleeves also regularly touched ISO 7 surfaces, such as operator body gowning and plastic containers holding production materials. Your aseptic operators did not disinfect the underside of gowning sleeves when moving from ISO 7 to ISO 5. Underside of gowning sleeves were not sampled for personnel bioburden monitoring. Your procedure, SOP-CAPS-4000614 Gowning, instructs tucking gowning sleeves into gloves "to minimize excess material hanging from the forearm."
2. During observation of aseptic production on July 10, 11, 18, 21, 28, 2023, your aseptic operators failed to move slowly and deliberately within the ISO 5 laminar flow hoods during aseptic production and within the ISO 7 cleanroom suite. Your procedure, SOP-CAPS-4000175 Aseptic Technique, instructs (b) (4) movement in clean room areas.

B. On July 11, 2023, your aseptic operator performed incomplete disinfection for over 100 drug substance vials prior to (b) (4) in ISO 5 hood during aseptic production of Fentanyl 10 mcg/mL in NS, 250 mL bag, Exp. Oct 9, 2023. Specifically,

1. Vial caps were not disinfected during materials transfer from ISO 7 to ISO 5. In ISO 7 vial caps were covered by the operator's gloved hand when (b) (4) of vials were sprayed with disinfectant. In the ISO 5 hoods the operator did not disinfect vials caps prior to removing the caps from vials with disinfected gloves. After removing vials caps, the operator did not disinfect gloves before performing additional aseptic operations in the ISO 5. Your procedure, SOP-CAPS-4000720 Product and Material Introduction and Movement, instructs spraying each

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item (b) thoroughly, coating all surfaces with disinfectant, before placing into ISO 5 areas.

2. Puncture sites for vials were not uniformly coated when sprayed with disinfectant. The distribution of spray was inconsistent with some puncture sites left dry, some with droplets, and some with pooled disinfectant. The operator used (b) (4) to puncture all the vials, and then connected that same (b) (4) to the IV bag holding (b) (4) drug substance. Your procedure, SOP-CAPS-4000175 Aseptic Technique, states that after the removal of cap/cover "the exposed surface must be properly sanitized."

OBSERVATION 4

Procedures describing the handling of written and oral complaints related to drug products are not written or followed and deficiently written or followed.

Specifically,

Your firm failed to thoroughly investigate reported customer complaints that involved adverse patient drug experiences. From January 2021 to May 2023, you received seven (7) customer complaints related to adverse patient responses for nine (9) sterile drug product lots produced at your facility. Your investigations failed to classify these reports as adverse drug events and failed to determine if these events were serious or life-threatening. Customers reported adverse patient drug experiences for the following drug product lots:

- Apneic episode (cessation of breathing) in pediatric patient
  - Morphine 1 mg/mL in NS, 30 mL syringe, Lot (b) (4), Exp 22Dec2021
- Severe rise in blood pressure for stimulant injection drug
  - Ephedrine 50 mg/mL in NS, 10 mL syringe, (b) (4), Exp 19Dec2022
- Lack of effect for pain-relief epidural drug:
  - Fentanyl 2 mcg/mL Bupivacaine 0.125% in NS, 250 mL bag, Lot (b) (4) Exp

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9MAY2021

- Fentanyl 2 mcg/mL Bupivacaine 0.125% in NS, 250 mL bag, Lot (b) (4) Exp 04JAN2022
- Fentanyl 2 mcg/mL Bupivacaine 0.125% in NS, 250 mL bag, Lot (b) (4) Exp 11JAN2022

- Lack of effect for paralytic injection drug,
  - Succinylcholine 100 g/mL in 5 mL syringe, Lot (b) (4) Exp 15NOV2022
  - Succinylcholine 100 g/mL in 5 mL syringe, Lot (b) (4) Exp 16MAY2023
- Lack of effect for anesthesia injection drug
  - Rocuronium 10 mg/mL in 5 mL syringe, Lot (b) (4) Exp 19DEC2021
  - Rocuronium 10 mg/mL in 5 mL syringe, Lot (b) (4) Exp 29Dec2021

Your Quality Unit did not report these events to FDA within (b) (4) calendar days as instructed in your procedure, SOP-CAPS-4000235 CAPS 503B Adverse Drug Experiences Processing.

Your outsourcing facility has not submitted an adverse event report to FDA in accordance with the content and format requirements established through guidance or regulation under 21 CFR 310.305 as required by section 503B(b)(5).

OBSERVATION 5

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,

A. There is no assurance that personnel qualified for 100% visual inspection can identify all known critical and major defects found in your parenteral and injection drug products. There is no

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documented assurance that these defects are all represented in "positive" samples of your visual inspection standards used for inspector qualification.

B. Your Director of Pharmacy stated that it is common practice to fill finished product in 1 mL and 2 mL syringes an additional (b) (4) mL up to a total volume of (b) (4) and (b) (4) mL with (b) (4) respectively. This practice is not described in the Drug Master Files nor your written procedures and is not documented in the batch records. Furthermore, there is no record of the visual inspection (VI) technicians, and Acceptable Quality Limit (AQL) personnel conducting the (b) (4) mL and (b) (4) mL with (b) (4) checks on the syringes in their review. For example, on July 4, 2023, lot (b) (4) Fentanyl 10 mcg/mL in 0.9 Sodium Chloride mL in 3mL BD syringe was over filled to (b) (4) mL per syringe and not the common practice of (b) (4) mL, which resulted in (b) (4) units short of expected (b) (4) units planned for the batch. The batch record did not document the error or address the (b) (4) units that were short from the batch.

C. There is no assurance the weight of the IV bags of finished products is as labeled. Your firm does not perform quality checks, sampling or verification of the weight after it has been compounded. During aseptic compounding the IV bags are placed on a scale. The operator sets the Repeater Pump to fill the IV bags with a preset amount of solution. The Repeater Pump does not consistently dispense to the set volume. Consequently, the compounder must (b) (4) make adjustments by referencing the bag's weight on the scale. There is no secondary verification of the weight of each bag or other form of quality review to ensure weight accuracy on (b) (4) aseptic compounding processes (b) (4) (b) (4). Your firm has (b) (4) (b) (4) where you conduct a weigh check on IV bags during Visual Inspection for the compounding (b) (4) process.

D. On July 14, 2023, your Chemistry Supervisor, Director of Operations, and Deputy Director of Operations stated you routinely use the (b) (4) lot number for the (b) (4) stability study for a product

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under the same NDC number, even if a new lot was compounded at a different time to replace the original one. Please refer to **OBSERVATION 12.**

OBSERVATION 6

Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance.

Specifically,

A. On July 18, 2023, your visual inspection operator failed to inspect sets of drug-filled finished product syringes for the minimum required time in front of the (b) (4) during 100% visual inspection of drug product, Phenylephrine 100 mcg/mL in 10 mL syringes, Lot (b) (4) Exp. 15Oct2023. Your operator was observed inspecting sets of drug-filled syringes for approximately (b) (4) (b) (4) in front of each background for at least (b) (4) sets of (b) (4) syringes. Your procedure, SOP-CAPS-4000688 Visual Inspection, states that drug-filled finished product syringes must be inspected for at least (b) (4) in (b) (4)

B. Your procedure, Compounding Process for (b) (4) (b) (4) , SOP-CAPS-400604, v. 11, effective 2022-09-14 states in section "7.7.16. and 7.7.17 to (b) (4)

On July 15, 2023, the compounder technician did not cap the (b) (4) port during aseptic processing of Hydromorphone in 0.9% sodium chloride (10mg/50mL), Lot (b) (4) prior to filling (b) (4) units of 3mL syringes. They deemed the (b) (4) port contaminated and were not able to use the port to mix the product. The compounding technician then deviated from the established production

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process procedure during the mixing step by using an (b) (4) at the injection site to mix for (b) (4) The size of the tube (b) (4) and (b) (4) set port have an opening of approximately (b) (4) which is significantly larger than the (b) (4) for fluid to flow through during the mixing process. There was no assurance provided that the drug products evenly mixed in the large (b) (4) (b) (4) using the (b) (4) at the injection site instead of using a larger (b) (4) at the (b) (4) set port. Based on the email sent by your senior pharmacist, the "order proceeded as usual."

OBSERVATION 7

Batch production and control records do not include complete information relating to the production and control of each batch.

Specifically,

A. Your Quality Unit failed to have procedures in place to maintain production and control records. Your firm uses laminated plastic sheets (i.e., Pallet IDs) with ink markers to record batch production information, including but not limited to, lot numbers, product name, hood number, and notes from production staff. These sheets are used partially in parallel with your electronic batch record. The ink could be smeared or erased. Furthermore, you do not have a system in place to maintain these Pallet IDs. You used to shred them after products were distributed but ended this practice in May 2023.

B. Large quantities of paper documents from production and testing in the record storage room were not reviewed, scanned, or saved into the appropriate batch records. For example, a box labelled "Potency Test Results, (b) (4) May 16, 2023 to Jun 22, 2023" included five binders of:

1. Potency Test Results (b) (4) (May 16, 2023 to May 24, 2023)
2. Potency Test Results (May 24, 2023 to May 30, 2023)

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3. Potency Test Results (b) (4) (May 30, 2023 to Jun 06, 2023)
4. Potency Test Results (b) (4) (Jun 06, 2023 to Jun 14, 2023)
5. Potency Test Results (b) (4) (Jun 15, 2023 to Jun 22, 2023).

Only a portion of these documents were selected and included into your official batch records.

OBSERVATION 8

Established sampling plans are not documented at the time of performance.

Specifically,

A. Sample preparations are not documented at the time of preparation. On July 14, 2023, we observed the Chemistry laboratory technician load previously prepared samples into the HPLC equipment for testing. Despite working for the past 6 hours on the sample preparation for (b) (4) vials containing samples and standards for sample set (b) (4) he Chemistry laboratory technician did not record this activity on FRM-CAPS-4000246 form, titled "FRM Quality, Potency Analysis by HPLC Form", ver. 7, effective 2023-07-11, which has section for completing during the sample preparation to include (b) (4) ". The Chemistry laboratory technician stated that they usually fill out the form later.

Furthermore, the Chemistry laboratory technician stated that they can print the form, write in the form number and have the QU sign the logbook and form, indicating that it was issued by the QU. We observed a blank FRM-CAPS-4000246 form that the Chemistry laboratory technician stated was for documenting results of sample set (b) (4) The form indicated that it was printed by a chemistry laboratory technician on the edge of the form. However, we observed the "Potency Form Logbook" did not have any entry indicating QU issued the form. There is no quality control over the access to retrieve and print the form.

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B. Visual inspection (VI) and labeling activities are not documented at the time of performance. The firm only documents the time the batch starts VI and at the end of labeling in the Line Clearance logbook.
On July 13, 2023, we observed Fentanyl 10mcg/mL 100mL bags, lot (b) (4) with four different technicians' initials conducting the VI and labeling of (b) (4) over two different work shifts without specifying which technician conducted the activity. Furthermore, we observed over 20 units of finished product of lot (b) (4) left unlabeled with no indication as to whether the units have been visually inspected. In addition, per SOP-CAPS-4000688 Visual Inspection, operators are instructed to take (b) (4) breaks; however, there is no traceability for the visual inspection rest time of the technicians since your firm does not document time and operator specific times to include when a technician starts visual inspection, takes a lunch break, takes a (b) (4) visual inspection break, leaves the shift or starts the shift.

OBSERVATION 9

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that drug product containers, closures and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

A. Container closure integrity testing (CCIT) has not been performed for each formulation and container closure system marketed by your firm. Your Container Closure Integrity Validation of CAPS' Anticipatory Compounding Products Summary Report (Document # V0347) indicated this validation was conducted (b) (4) with media in 2013, not with actual drug product. Additionally, the CCI Study of (b) (4) (b) (4) with (b) (4) Tamper Evident Caps Summary Report (Document # V0743) indicated you used not only the media instead of drug product, but also a tamper evident syringe cap manufactured by (b) (4) was used instead of the actual (b) (4) tamper evident cap (b) (4)

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(b) (4) you use in production due to a shortage in 2018. This 2018 study has not been repeated since then with the actual container closure system. Your firm has not established CCIT procedures to ensure your package integrity is adequate to maintain product critical quality attributes within physicochemical label-claim specifications and to ensure product sterility until time of use.

B. Your firm failed to provide scientific evidence that endotoxin specification for products intended for epidural administration is adequate. Specifically,

The endotoxin limits required by your firm for the IV and epidural products are the same, for example, NMT (b) (4) EU/mg of Fentanyl and NMT (b) (4) EU/mg of Bupivacaine. However, according to USP Chapter <85> the endotoxin limit for intrathecal products is 0.2 EU/kg, and the limit for parenteral products is 5 EU/kg. The endotoxin limit that is applied for intrathecal products should also be applied for epidural products. Some examples of your product release specifications for both epidural and IV products are listed below. This is not an exhaustive list.

Product Name	Lot#	Endotoxin Limits	Label for Product Use
Fentanyl 2 mcg/mL / 0.125% Bupivacaine PF in 0.9% Sodium Chloride 100 mL in 100 mL ICU Medical Bag	All	(b) (4)	Epidural Use Only.
Fentanyl 2 mcg/mL / 0.125% Bupivacaine PF in 0.9% Sodium Chloride 100 mL in 100 mL ICU Medical Bag	(b) (4)		Epidural Use Only.
Fentanyl 1.5 mcg/mL / 0.125% Bupivacaine PF in NS 50 mL SY			Epidural Use Only.
Fentanyl 1.5 mcg/mL / 0.125% Bupivacaine PF in NS 50 mL SY			Epidural Use Only.
Fentanyl 2 mcg/mL / 0.0625% Bup PF in NS 250 mL			Epidural Use Only.
Fentanyl 50 mcg/mL 100 mL			For IV Use Only.
Fentanyl 20 mcg/mL in NS 250 mL			For IV Use Only.
Fentanyl 10 mcg/mL in NS 250 mL			For IV Use Only.

OBSERVATION 10

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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,

A. Your epidural drug product Fentanyl 1.5 mcg/mL /Bupivacaine PF 0.125%, 50 mL Syringe, Lot (b) (4) (b) (4) was compounded on May 30, 2023. Audit trail review of the UPLC system (b) (4) revealed the Bupivacaine potency results obtained on June 2, 2023, from three vials (three sample preparations) from this lot with each vial injected twice, were as follows:

Vial#	Injection time	Potency (%)
1/3	11:43	0.134
1/3	11:49	0.135
2/3	11:56	0.134
2/3	12:02	0.133
3/3	12:09	0.132
3/3	12:15	0.132

The result of 0.135% was outside your established specification of (b) (4) This OOS vial was reinjected twice on a different UPLC system (b) (4) on 6/5/2023 with passing results. Your Chemistry Supervisor reported the averaged result of 0.133% from 6/2/2023 on 6/5/2023 in the electronic batch record. This lot of (b) (4) units was released on 6/7/2023 without any documentation in the batch record or investigation of this OOS result and re-injections. This product has a 90-day BUD.

B. Succinylcholine 200 mg/10 mL Syringe Lot (b) (4) was made on May 30, 2023 ~~and~~ tested on May

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31, 2023, with one of four OOS potency result of 22.4 mg/mL (specification (b) (4) mg/mL). Your firm stamped "Data not Used" with a note of "Poor Injections" for this OOS potency result in the UPLC chromatogram printouts. This set of vials were re-injected on the same day and had one more OOS result of 22.2 mg/mL, which was also stamped "Data not Used" with a note of "Poor Injections." The original sample was subsequently reprepared and retested on June 2, 2023,with all four potency testing results within the specification. This lot was released on June 6, 2023 without any documentation in the batch record or investigation of these OOS results, re-injection, and retesting. This product has a 90-day BUD.

C. Repeat injections of failed results during testing on the (b) (4) USP Liquid Particle Counter, are documented into a logbook, titled, "Particulate Matter Invalid Results Logbook", issued on March 30, 2023. Since the logbook has been implemented, repeat testing was documented on April 7, 2023, April 24, 2023, and July 3, 2023, for about (b) (4) ots of finished drug products. For example, in NQE US 32-230413-063 dated April 13, 2023, opened in response to the April 7, 2023, testing of Hydromorphone 1mg/mL in 0.9% Sodium Chloride, Fentanyl 10 mcg/mL in 0.9% Sodium Chloride, Fentanyl 1.5 mg/mL/ 0.125% Bupivacaine PF in 0.9% Sodium Chloride, Morphine 1 mg/mL in 0.9% Sodium Chloride, Hydromorphone 0.2 mg/mL in 0.9% Sodium Chloride, and Fentanyl 50 mcg/mL lots, (b) (4) (b) (4) Of the (b) (4) lots tested for particulate matter, 31 lots failed. You then conducted duplicate testing on the 31 lots, and of those, 9 lots failed the duplicate testing. You subsequently tested those 9 lots with triplicate testing, and all 9 lots passed. Stating "all samples passed testing." Furthermore, there is no assurance of documentation, review, and investigation into repeated testing since the Quality unit does not review the raw data from the system or conduct system audit review.

OBSERVATION 11

The accuracy, sensitivity, specificity and reproducibility of test methods have not been established and documented.

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Specifically,
Specifically,

Your firm's Quality Unit failed to perform a method transfer of your sterility test method used for release of drug products. Your firm utilizes the (b) (4) Microbial Detection System for sterility testing. The associated test method was developed and validated at the CAPS Technical Services Laboratory located in Irvine, CA. Your firm failed to conduct a method transfer ensuring the (b) (4) Microbial Detection System sterility method test method is suitable for release of your sterile drug products.

OBSERVATION 12

Results of stability testing are not used in determining appropriate storage conditions and expiration dates.

Specifically,

A. Your (b) (4) stability program does not include sterility or endotoxin testing at the endpoint. Your firm only tests sterility and endotoxin at Time 0 per your SOP-CAPS-4000617 Establishing Stability Guideline for 503B Compounding section 6.2.5 L and SOP-CAPS-4000804 Procedure Annual Stability Testing - 503B Section 5.2.5. Furthermore, your Container Closure Integrity (CCI) Studies were inadequate; Please refer to **OBSERVATION 9.**

B. Fentanyl 2 mcg/mL and 0.125% Bupivacaine PF in NS 100 mL, NDC No. 71286-2082-1, lot# (b) (4) was used for your (b) (4) stability study in 2022. This (b) (4) stability lot was compounded on 8/23/2022. From the (b) (4) potency test, an unknown peak was observed in the two tested samples. The Chemistry Supervisor reported this lab finding in an email to your management on 10/10/2022. NQE-US32-221026-163 was generated for this event on 10/26/2022. The OOS was confirmed. However, you closed this NQE on November 7, 2022, with no root cause

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identified. Without any supporting evidence, you stated in the NQE, "The discrepancy has no impact on lots compounded for commercial use. The lot used for the stability study was destroyed." After this lot was destroyed, a new stability lot was compounded on October 25, 2022; however, under the same lot number of (b) (4) Based on the information kept inside the lab binder (Book No. 0119), testing results of this new lot confirmed the previous finding of this unknown peak at (b) (4) (b) (4)) and at (b) (4) for all four injections at each time point. You did not create a new NQE or update NQE-US32-221026-163 with these findings or conduct any risk analysis for the marked products. A January 11, 2023 email ,-among your management stated, "T0 unknown peak is not observed for (b) (4) stability study". However, these summarized calculations based on your data indicated the ratio of the unknown peak to one of the APIs, Fentanyl, increased from (b) (4) at (b) (4) to (b) (4) at (b) (4)

Date of Injection	Peak ID	UPLC Area Vial 1/2	UPLC Area Vial 1/2	UPLC Area Vial 2/2	UPLC Area Vial 2/2	UPLC Area Avg.	Ratio of Unknown to Fentanyl
10/7/2022	Unknown	(b) (4)					
	Fentanyl						
1/23/2023	Unknown						
	Fentanyl						

Additionally, the "Analysis/Discussion" inside the lab binder (Book No. 0119, page 112) revealed the "unknown" peak has been known since the original BUD study performed on June 29, 2015. An email dated January 11, 2023 among your CAPS Corporate Regional and San Diego site Quality management also demonstrated your awareness by stating "Original BUD shows an unknown peak at T0 around same RT (retention time) but very small (b) (4) area count) when BUD reaches (b) (4) the unknown peak has an area count of (b) (4) ... The unknown peak was not addressed in the

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stability report."

OBSERVATION 13

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

Specifically,

A. Your aseptic operators disinfect ISO 5 surfaces prior to environmental monitoring sample collection. This practice can yield false-negative results. For example:

1. On July 18, 2023, your aseptic operator applied disinfectant to the ISO 5 repeater pump and weigh scale prior to surface sampling while spraying disinfectant onto their gloves and a sterile wipe within the ISO 5 hood. Your aseptic operator proceeded to collect three samples from the repeater pump lid and touch pad, and weigh scale after the surfaces had been sprayed with disinfectant.
2. On July 28, 2023, your aseptic operator applied disinfectant to the ISO 5 hood surface and repeater pump prior to surface sampling while spraying disinfectant onto a sterile wipe within the ISO 5 hood. Your aseptic operator proceeded to collect two samples from the hood surface and repeater pump touch pad after the surfaces had been sprayed with disinfectant.

B. Your quality personnel in the cleanroom perform their own personnel bioburden sampling. This practice contradicts your procedure, SOP-CAPS-5000582, Environmental Monitoring - 503B, which states quality personnel must be sampled by another qualified person. For example, on July 28, 2023, your quality technician collected their own glove fingertip samples after preparing sterility test samples within the ISO 5 hood.

C. Environmental monitoring of ISO 5 equipment does not include disinfectant spray bottles stored within the hoods. Disinfectant spray bottles, which may be stored in the hood for up to (b) (4) days, are handled by multiple aseptic operators. Your procedure, SOP-CAPS-5000582, Environmental Monitoring - 503B, instructs monitoring of equipment stored in the ISO 5 hood, including pumps,

shakers, scales, and balances.

D. Environmental monitoring of cleanroom personnel does not reflect activities and associated bioburden within your cleanroom. Your procedure, SOP-CAPS-4000582 Environmental Monitoring – 503B, instructs monitoring, including glove fingertips, for technicians, pharmacists, and quality personnel working in the clean room, but your monitoring for pharmacists and supervising technicians is not representative of their activities within the cleanroom, which can include opening doors between rooms, handling the telephone, touching tablet screens, and moving containers holding materials. For example, on July 18, 2023, after performing activities described above the glove fingertips of your Supervising Technician were sampled after disinfection and performance of "aseptic manipulations" in an ISO 5 hood. These manipulations consisted of moving three items from one side of the hood to the other side.

OBSERVATION 14

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

Specifically,

A. Brown substance was observed inside your grey reusable spray bottles filled with the (b) (4) solution. On July 11, 2023, we observed grey reusable spray bottles used for the (b) (4) disinfectant process conducted in the HEPA room/ Wipe down room. This process is carried out on products and components intended for aseptic processing within the ISO 5 hoods, prior to being transferred to classified areas. On July 16, 2023, after the Warehouse Controlled Space (WSC) clerk made a new batch of (b) (4) solution and filled grey reusable spray bottles labeled (b) (4) we observed brown liquid coming out of two of three (b) (4) bottles intended for used to clean equipment and surfaces in the ISO 7 areas (where the ISO 5 hood is located) and ISO 8 areas of the facility. The clerk stated that the brown substance happens frequently when the solution sits in the

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bottle after few days and they "just ask for a new bottle." There is no incident report or Notification of Quality Event (NQE) for this production deviation and there has been no investigation to identify the root cause and prevent reoccurrence. Additionally, there is no scientific justification for the number of times the (b) (4) solution grey reusable spray bottles can be reused.

B. On July 16, 2023, we observed the mops used to clean the walls and floors ISO 7 and 8 areas had brown residue covering both sides of the mop head where you attach a disposable pad.

C. On July 11, 2023, your aseptic operator performed incomplete disinfection of ISO 5 hood surfaces prior to aseptic production of pain relief drug product, Fentanyl 10 mcg/mL in 1 mL syringe, Lot (b) (4) (b) (4) Exp. Oct 9, 2023. The operator failed to wipe all surfaces within the ISO 5 hood after spraying disinfectant.

OBSERVATION 15

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically, on July 16, 2023, we observed the following during the (b) (4) cleaning:

A. Rust on the stainless-steel pole that held the monitor to record production activities next to ISO 5 Hood (b) (4) in the ISO 7 cleanroom.

B. One panel of the HEPA filter not fitting completely, with visible gaps around the frame in the ceiling of the ISO 7 cleanroom, a few feet away from the ISO 5 hoods where aseptic processing was occurring.

C. Small cracks on one of the bolts on the edge of ISO 5 Hood (b) (4).

AMENDMENT 1

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Jolanna A Norton, Investigator Rachel C Stanton, Investigator Doan N Singh, FDA Center Employee Xiaohui Shen, FDA Center Employee	X Jolanna A Norton Investigator Signed By: Jolanna A. Norton -S Date Signed: 09-25-2023 23:24:13	8/25/2023

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, CA 92612-2445 (949)608-2900 Fax:(949)608-4417	7/10/2023-8/25/2023* FEI NUMBER 3004378804

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Leslie (nmi) Nguyen, Director of Pharmacy

FIRM NAME	STREET ADDRESS
Central Admixture Pharmacy Services Inc	7935 Dunbrook Rd Ste C
CITY, STATE, ZIP CODE, COUNTRY San Diego, CA 92126-6322	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility

OBSERVATION 16

Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition.

Specifically,

A. On July 11, 2023, during the walk-through we observed broken wooden pallets used to store drug product components in the receiving warehouse and finished products in the packaging/shipping warehouse. The drug products components stored on the wooden pallets are used in aseptic processing. Additionally, on July 17, 2023, we observed broken wooden pallets over open boxes of container closures used in aseptic processing.

B. On July 11, 2023, we observed that the HEPA/Wipe down area technician only shakes the fabric mop head over a trash bin to "clean" it before and after use as the method for cleaning the mop. The floor mop had visible chunks of debris attached to the fabric mop head.

C. On July 13, 2023, we observed that the room for visual inspection and labeling of the finished drug products appeared not in a good state of repair. For example, insulation materials were exposed at multiple places in the ceiling. Rusty pipes, peeling paints and several small/mid-size holes on the wall, and water stains on the wood frame of the sunroof were observed.

D. On July 10, 2023, and August 16, 2023, we observed layered dust on an air vent that exhausts into warehouse storage area where materials used in aseptic production are stored. On August 16, 2023, we observed eight (8) empty 100 ml bag container-closures, Lot (b) (4) , Exp 2025-10-01, on an open shelf exposed to air from the vent.

OBSERVATION 17

AMENDMENT 1

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, CA 92612-2445 (949)608-2900 Fax:(949)608-4417	7/10/2023-8/25/2023*
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Leslie (nmi) Nguyen, Director of Pharmacy	
FIRM NAME Central Admixture Pharmacy Services Inc	STREET ADDRESS 7935 Dunbrook Rd Ste C
CITY, STATE, ZIP CODE, COUNTRY San Diego, CA 92126-6322	TYPE ESTABLISHMENT INSPECTED Outsourcing Facility

Input to and output from the computer, related systems of formulas and records or data are not checked for accuracy.

Specifically,

On Jul 26, 2023, we observed a Microbiology technician use another technician's sign in for the (b) (4) Particulate Matter system to test 13 samples of Fentanyl 2mcg/mL/ 0.125% Bupivacaine PF in 0.9% Sodium Chloride 250mL bags, lots (b) (4) and (b) (4) When asked why this technician was using another person's sign in, they stated "I was on vacation and was locked out."
Appropriate controls are not established to assure that changes to CGMP records can only be made by authorized personnel.

***DATES OF INSPECTION**

7/10/2023(Mon), 7/11/2023(Tue), 7/12/2023(Wed), 7/13/2023(Thu), 7/14/2023(Fri), 7/16/2023(Sun), 7/17/2023(Mon), 7/18/2023(Tue), 7/19/2023(Wed), 7/20/2023(Thu), 7/21/2023(Fri), 7/24/2023(Mon), 7/25/2023(Tue), 7/26/2023(Wed), 7/27/2023(Thu), 7/28/2023(Fri), 8/16/2023(Wed), 8/17/2023(Thu), 8/18/2023(Fri), 8/25/2023(Fri)

X Rachel C Stanton
Investigator
Signed By: Rachel C. Stanton -S
Date Signed: 08-25-2023 23:24:53

AMENDMENT 1

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Jolanna A Norton, Investigator Rachel C Stanton, Investigator Doan N Singh, FDA Center Employee Xiaohui Shen, FDA Center Employee	X Jolanna A Norton Investigator Signed By: Jolanna A. Norton -S Date Signed: 08-25-2023 23:24:13	8/25/2023

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."