DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
One Montvale Avenue Stoneham, MA 02180 (781)587-7500 Fax:(781)587-7556 ORAPHARM1_RESPONSES@fda.hhs.gov	9/20/2021-11/30/2021* FEI NUMBER 3010490167

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
William Marc Chatoff, Managing Director

FIRM NAME	STREET ADDRESS
Edge Pharma, LLC	856 Hercules Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Colchester, VT 05446-8014	503B 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

Buildings used in the manufacturing, processing, packing and holding of a drug product are not maintained in a good state of repair.

Specifically,

A. The firm does not properly maintain the ISO-5 biological safety cabinets (BSC) in the ISO-7 cleanroom (b) (4) to ensure clean and sanitary conditions for the production of hazardous drugs intended to be sterile. For example, on 9/23/2021, an unknown brownish rust like material was noted on surface coupling ports within the ISO-5 environment of BSCs # (b)(and # (b)(. The unknown brownish rust like material was approximately 2 feet from the center of the BSCs where production of drugs intended to be sterile occurs. Cleanroom (b) (4) is utilized to produce hazardous drug products intended to be sterile that have been distributed to customers. Since 4/16/2020, the firm has produced and released (b) (4) lots of hazardous drug products intended to be sterile in BSCs # (b)(and # (b)(for distribution to include Gemcitabine for intravesical irrigation, (b) (4) lot (b) (4). What appeared to be rust was also observed on surfaces throughout the cleanroom (b) (4) suite to include:

- On 9/22/2021, we noted what appeared to be rust on carts and on the exterior of the ISO-5 BSCs in cleanroom (b) (4).
- On 9/30/2021, we noted the clamps that hold the room (b) (4) to (b) (4) material (b) (4) down to the floor were noted to have an unknown brown like rust material on them.

B. The firm does not prevent the presence of vermin in the facility where drug products intended to be sterile are prepared, and throughout the facility. During the walk-through of the facility, several insects

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were observed within the firm's glue traps and on 9/27/2021, a live mosquito like flying insect was observed on the doorway that leads into the cleanroom suite (b) (4) where hazardous drug products intended to be sterile are produced. In addition, review of the firm's pest control records revealed numerous days between August to September of 2021 in which insects were observed in proximity of the firm's (b) (4), and (b) (4) cleanroom areas. Gaps and spaces measuring approximately 1 inch in width by ½ inch in height were noted on the bottom of the material (b) (4) from the firm's unclassified areas to the firm's non-hazardous ISO-7 cleanroom (b) (4) and on the bottom of the door to the firm's ISO-7 classified cleanroom (b) (4). Furthermore, review of the firm's deviation investigations revealed the following:

Deviation#	Date initiated	Description
DR-2021-084	5/20/2021	Live ant found on bin of final product near entrance to administrative office on manufacturing floor.
DR-2021-099	6/9/2021	Live ant found on gowning of personnel within ISO 7 cleanroom (b) (4)
DR-2021-109	6/15/2021	Live spider found on bin of final product within visual inspection area.

C. The is no formal mechanism to escalate and address facility issues noted in drug production cleanrooms. The following facility deficiencies were observed during the current inspection and also documented by the firm on cleaning forms which indicated that the affected areas had failed due to the observations, however, no investigation, evaluation, and/or remediation was initiated.

- Review of the firm's level (b) (4) classified area cleaning forms for Suite (b) (4) revealed the following:
  - On 9/2/2021, a member of the firm's personnel documented that ISO-7 classified cleanroom (b) (4) had failed due to chipped floors.
  - On 9/7/2021, the form was reviewed by a cleanroom manager; however, no investigation,

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risk assessment or remediation action was conducted.

- Missing caulking and a gap measuring approximately 1 inch in width by ¼ inch in height in the seal for the material (b) (4) that connects cleanroom (b) (4) to room (b) (4) were noted on 9/23/2021. The missing caulking was also noted in the firm's level (b) (4) classified area cleaning forms for Suite (b) (4) on 2/25/2021 and the firm indicated that the area had failed inspection. No immediate investigation or remediation action was initiated by the firm for the cleanroom failure.

D. On 9/28/2021, the following deficiencies were observed in the ISO controlled areas:

- Unsealed holes were noted on top of the (b) (4) refrigerator units that connect an unclassified area to the interior of the ISO-7 cleanroom (b) (4) (approx.6 feet from the ISO-5 production area).
- A greenish unknown fuzzy substance was noted in the tray where the refrigerator compressor was draining into, which was directly adjacent to the noted holes. The unit compressor also appeared to be leaking fluid.
- On 10/1/2021, (b) (4) bags of 0.9% sodium chloride for injection were noted in a wire rack directly below the noted holes in cleanroom (b) (4) formed by the (b) (4) refrigerator. The bags of saline were noted to be taken from the rack, wiped down with (b) (4) and passed into the firm's ISO-5 hoods for production operations of Vancomycin for IV injection lot (b) (4)). Vancomycin was observed being dosed directly into the noted (b) (4) bags of 0.9% sodium chloride for injection.

E. On 10/6/2021, a ceiling tile was noted to be stained with a brown discoloration directly under the firm's sterilization services area. The ceiling tile was directly adjacent to an air supply vent. The sterilization services area is where production glassware is processed to include being washed and sterilized. Other production materials are also sterilized and depyrogenated (if necessary) in the area. The processed materials are then transferred to cleanroom suites for use in drug production operations.

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F. On 10/6/2021, the air return duct above the cleanroom suite (b) (4) was noted to have what appeared to be unknown white crusty residue stains. The stains appeared to have originated from the air supply duct directly above it. Similar staining was also noted on the air supply duct within the suite (b) (4) plenum space on 10/13/2021.

G. On 9/27/2021, what appeared to be a black mold was noted on the wall within the firm's warehouse. Components are transferred from the warehouse space into the main building for production operations. Additionally, items that are stored in the warehouse that are transferred to the main building are not cleaned with a sporicidal disinfectant until entering the ISO-8 areas of the cleanroom suites. Materials and components utilized to produce non-sterile drug products are not cleaned with a sporicidal disinfectant prior to production operations.

H. On 9/27/2021, the baseboard trim in the firm's component staging area where components are stored within the main facility was damaged and exposed drywall was noted. Components stored in the staging area are brought into the cleanroom suites to produce drugs intended to be sterile.

I. On 9/20/2021 and 9/27/2021, the floors just in front of the doors leading into the ISO-8 areas of the (b) (4) and (b) (4) cleanroom suites were noted to have an unknown blackish grime on the floor. Firm personnel and carts move over the areas with unknown blackish grime to enter the cleanroom suites for production of drugs intended to be sterile.

THIS IS A REPEAT OBSERVATION TO THE 2020 FDA INSPECTION.

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.

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Specifically,

A. The firm has failed to investigate numerous instances of sterility samples contaminated with objects such as particles, fibers, and filaments. The firm's SOP S-QMR-005 - Sterility Testing, states (b) (4) The firm has observed and documented various objects such as filaments, particles, and fibers in (b) (4) drug product sterility samples since April 2021. These objects were not documented on the day 0 reading of the sterility samples and instead during subsequent day readings (e.g., days 2, 4, 7, 14). The firm concluded that the objects were non-viable objects as they did not appear to change shape, size, or confirmation, however, as per the firm's sterility testing procedure the objects can be only be considered non-viable if no change is documented for the particle from the day 0 reading. The unknown objects were not subsequently sub-cultured and/or identified. The firm does not know the identity or source of the various objects observed in the noted sterility samples. Since April 2021, the firm distributed (b) (4) out of (b) (4) (approximately (b) (4)) lots of drug products intended to be sterile for which sterility samples were contaminated with a variety of particles, fibers, and filaments. Examples of commercially distributed drug product intended to be sterile with potentially compromised sterility include:

- Buffered Lidocaine HCl/Epinephrine solution (b) (4) lot (b) (4). The sterility samples were documented as clear (b) (4) and (b) (4) on day 0 of the sterility test. On day 2-4, a particle was documented in the (b) (4) media. On day 7 and 14 particles in both (b) (4) and (b) (4) were documented but this lot was designated as passing sterility testing and distributed (b) (4) times to health care professionals for patient use based on these sterility test results.

- EDTA 3% ((b) (4)) ophthalmic solution (b) (4)) lot (b) (4). The sterility samples from day 2-14 were documented containing "Fiber and Particles in (b) (4) & (b) (4)," but this lot was designated as passing sterility testing and distributed (b) (4) times to health care professionals for patient use based on these sterility test results.

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- (b) (4) Bevacizumab ophthalmic injection ((b) (4)) lot (b) (4) . The sterility samples for day 7 and 14 were documented containing "white particles in (b) (4)," but this lot was designated as passing sterility testing and distributed (b) (4) times to health care professional for patient use based on these sterility test results. Additionally, the firm received complaint CC-2021-035 which documents that the customer observed, "fibers of some sort" in this drug product that was intended to be sterile.

B. The firm failed to conduct investigations for multiple quality related customer complaints. Below are selected examples:

Complaint# and category	Date initiated	Date closed	Drug name	Description
CC-2020-016 minor	8/11/2020	8/17/2020	Mitomycin Ophthalmic Solution	Customer reported that they received leaking syringe
CC-2020-028 minor	11/12/2020	11/16/2020	Buffered Lidocaine/Epinephrine	Customer reported that they were experiencing more burning than usual
CC-2020-027 serious	11/11/2020	12/7/2020	Benzocaine/ Lidocaine/ Tetracaine	Customer reported a lack of effect
CC-2020-014 minor	8/7/2020	9/1/2020	Cantharidin	Customer reported that the product

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				appeared viscous and gel-like

C. The firm failed to conduct investigations into OOS results for drug products as exampled below:

- In March 2021, the firm documented subpotent OOS results for Gemcitabine lot (b) (4) ((b) (4), result 94%, specification (b) (4) via LIR-2021-042. The firm opened investigation INV-2021-009 for the OOS potency result to investigate for a possible production related root cause(s). As of 9/21/2021, firm management could not provide evidence that INV-2021-009 was conducted nor assessed if any subsequent production related root causes affected other distributed lots of Gemcitabine.

- In December 2020, the firm documented sub-visible OOS results for Cefuroxime lot (b) (4) via LIR-2020-249. The firm opened investigation INV-2020-070 for the OOS result to investigate for a possible production related root cause(s). As of 9/21/2021, firm management could not provide evidence that INV-2020-070 was conducted nor assessed if any subsequent production related root causes affected other distributed lots of Cefuroxime.

D. The firm failed to conduct adequate investigations and assess product impact as a result of microbiological environmental excursions. For example:

- The firm initiated Recall# 2020-004 in response to elevated bacterial counts for consecutive days (03/25/2020 and 03/26/2020) within the firm's Suite (b) (4) classified area. The firm identified the contaminating bacterium as *Bacillus altitudinis* and detected over 500 CFU on 03/25/2020 and over 700 CFU on 03/26/2020. They continued to detect the same bacterium at lower levels in Suite (b) (4) until the full sporicidal clean on 04/03/2020. The firm's recall investigation detailed that all allergy treatment sets made from 03/25/2020 to 04/06/2020 were recalled. The investigation also indicated that a review was conducted of the environmental monitoring data

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from 03/25/2020 to 04/02/2020 and that all products made from 03/27/2020 forward were approved by QA for release. The firm's recall investigation did not include an impact assessment and risk assessment for products other than allergy treatment sets. The firm produced (b) (4) batches of drug products intended to be sterile from 03/25/2020 to 04/03/2020 within Suite (b) (4). The firm released (b) (4) of these lots for patient use, despite the ongoing presence of the contaminating bacterium in ISO-7 classified cleanroom (b) (4) until the full sporicidal clean occurred on 04/03/2020.

- On 9/4/2020, the firm obtained an action level environmental monitoring excursion from personnel monitoring post production for operator (b) (6) (result: *Microbacterium liquefaciens* - too numerous to count left sleeve, specification (b) (4) CFU). Operator (b) (6) was compounding succinylcholine chloride ((b) (4)) lot (b) (4) in ISO-5 hood (b) (4) on 9/4/2020 in cleanroom (b) (4). (b) (4) additional operators were compounding the same lot in the adjacent ISO-5 hoods (b) (4) and (b) (4). While the firm rejected the portion of the batch compounded by operator (b) (6), the firm's environmental monitoring excursion investigation (EEI-2020-127) failed to assess the risk and impact of the microbiological excursion on the remainder of the lot produced in adjacent ISO-5 classified areas, which was released for patient use. Further, the firm detected the same bacterium in a different area of ISO-7 classified cleanroom (b) (4) on the same day. Additionally, the firm detected the same bacterium on different drug production days (8/28/2020) as described in EEI-2020-111 in ISO-7 classified cleanroom (b) (4), however, the firm failed to assess the impact of these microbial excursions on other lots of drug products intended to be sterile which were made during this time period in ISO-7 classified cleanroom (b) (4).

E. The firm failed to adequately investigate and remediate adverse mold trends in production cleanrooms for drugs intended to be sterile. For example:

- In June 2020, the firm had numerous mold recoveries in cleanroom suites (b) (4) and (b) (4) where production of drug intended to be sterile occurs. The firm opened investigation INV-2020-045 to determine the root cause of the mold events and identified upon inspection, free standing water

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described as mostly rusty, above the (b) (4) suite plenum. Mold spores were also recovered from above both the suite (b) (4) and (b) (4) plenums. The firm attributed the water condensate ingress to inadequately insulated HVAC air supply ducts. The firm rejected (b) (4) lots of drug products intended to be sterile due to the mold excursions. The firm also opened CAPA-2020-026 in July 2020 to address the issues that caused the adverse mold trend in June 2020. While the affected ductwork has been re-insulated and the affected suite (b) (4) and (b) (4) areas disinfected via (b) (4) (b) (4), CAPA-2020-026 remains open and in draft format.

- In July of 2020, the firm contracted (b) (4) to perform a certification of Suites (b) (4) and (b) (4) following the water condensate ingress into the plenum spaces. Review of the report revealed that they only conducted a truncated certification to ensure that there were no breaches in the HEPA filters which included the following tests: (b) (4) and (b) (4). The firm failed to conduct a complete recertification of Suites (b) (4) and (b) (4) to ensure that the water leakage and subsequent remediation activities had no impact to the classification of the suites. The report detailed that the following certification tests were not conducted: Airflow Volume Profile, Air Changes Per Hour, Room Differential Pressures/Room Pressurization & Airflow Directional Smoke Pattern Tests, and Airborne Particle Count Survey. The firm continues to document an adverse mold trend in suite (b) (4) and has not identified the root cause.

- Since June 2021, the firm has had numerous surface and airborne viable mold recoveries in the hazardous drug production suite (b) (4) Mold recoveries include airborne viable action levels in cleanroom (b) (4) ISO-7 areas directly adjacent to ISO-5 biological safety cabinets utilized for the production of hazardous drugs intended to be sterile. A variety of mold species such as *Aspergillus shendaweii, Aspergillus versicolor, Aspergillus creber, Cladosporium cladocporioides* and *Irpex lacteus* have been recovered in airborne viable sample areas directly adjacent to the firm's ISO-5 production areas in ISO-7 cleanroom (b) (4) on the same day production operations took place, however, the firm's investigations have indicated that these recoveries are not product affecting. The firm has not identified the source(s) of the mold,

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however, has attributed deficient humidity control in the (b) (4) suite and inadequate disinfection practices for materials as contributing factors. The corrective action identified by the firm to help remediate the adverse mold trend, CAPA-2021-008 (opened 6-21-2021, evaluation of cleaning process), remains open as 10/1/2021. The firm has produced various drug products intended to be sterile in areas with multiple air-viable mold recoveries that occurred on the same day. For example, Gemcitabine lot (b) (4), Gemcitabine lot 0 (b) (4), and Ceftazidime lot (b) (4) were all produced in cleanroom (b) (4) on 9/1/2021. The firm documented air-viable mold recoveries from five different locations within the cleanroom directly adjacent to the ISO-5 BSCs utilized to produce the above lots. The above product lots were not placed on QA hold for the mold related excursions on 9/1/2021, and instead placed on QA hold for the conditions of cleanroom (b) (4) that were noted during the current inspection for Observation 1A.

F. The firm failed to conduct an adequate deviation investigations. For example, DR-2020-111 was initiated on 7/2/2020 for visual inspector (b) (6) conducting visual inspections between 6/14/2020 to 7/2/2020 while the inspector's (b) (4) had expired on 6/14/2020. The investigation documented that the inspector had conducted a visual inspection of (b) (4) lots of product during the aforementioned time frame. The firm's only corrective action was to reschedule the inspector's (b) (4), which was completed on 7/3/2020. The firm failed to re-examine the implicated lots with a qualified visual inspector or conduct a risk assessment for the implicated released lots.

G. The firm failed to conduct adequate investigations into OOS results for drug products as exampled below:

- The firm failed to thoroughly investigate and holistically evaluate endotoxin testing failures for drug products intended to be sterile. Out of the 364 laboratory investigation initiated since April 2020, 167 of these investigations involved the endotoxin testing. The firm has not performed adequate investigations to determine and correct the root cause(s) of these failures. For example, the firm has had multiple endotoxin OOS failures for the

drug product intended to be sterile (b) (4) – lidocaine HCl/bupivacaine HCl/hyaluronidase for retrobulbar injection. After obtaining OOS endotoxin results, the firm released the affected product for distribution and patient use based on passing re-testing results without a definitive root cause identified as exampled below:

LIR Number	Date initiated	(b) (4) Lot#	OOS Value (Specification < (b) (4) /mL)	Probable Root Cause from LIR Investigation
LIR-2021-158	9/1/2021	(b) (4)	0.343 EU/mL	Test interference by a biologic product
LIR-2021-091	5/18/2021	(b) (4)	1.20 EU/mL	Test sample contamination
LIR-2021-008	1/6/2021	(b) (4)	0.259 EU/mL	External sample contamination

- In June 2020, super potent OOS stability results were reported by your contract lab for non-sterile Promethazine HCl Transdermal lot (b) (4) . The OOS timepoint was (b) (4) (result: 110.6%, specification (b) (4) BUD of product 134 days). At that time, the lab investigation found no lab error, however you did not open an investigation to determine possible production related root causes and assess product impact until March 2021, which currently remains ongoing as of the current inspection. Promethazine HCl Transdermal lot (b) (4) was distributed to customers in 3/2020.

H. The firm failed to conduct adequate investigations into the following customer complaints:

Complaint#	Date initiated	Date closed	Drug name	Complaint Description	Noted Investigation Deficiency
CC-2021-003	1/27/2021	3/9/2021	Epinephrine Shugarcaine	Higher incidence of prolonged	Retain samples were not tested to

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				double vision	rule out all potential root causes
CC-2020-033	12/8/2020	3/11/2021	Lidocaine/Bupivacaine Hyaluronidase Injection	One syringe was unlabeled	Retain samples were not examined
CC-2021-022	4/29/2021	5/17/2021	Epinephrine/ Lidocaine Ophthalmic Injection	Patient complained about lack of numbing effect	Retain samples or complainant sample not examined

THIS IS A REPEAT OBSERVATION TO THE 2017, 2018 and 2020 FDA INSPECTIONS.

OBSERVATION 3

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

Specifically,

A. The firm's disinfectant efficacy studies that were conducted in September and December of 2020 respectively by (b) (4) and (b) (4) were inadequate. The (b) (4) study only evaluated the effectiveness of (b) (4) on stainless steel, while the study for (b) (4) was only evaluated on stainless steel and plastic. The study conducted by (b) (4) only evaluated the effectiveness of (b) (4) and (b) (4) on stainless steel and plastic. The efficacy studies failed to evaluate the effectiveness of the firm's cleaning agents on all of the surfaces within the classified spaces including (b) (4) painted surfaces (walls, ceilings, and exterior of

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biosafety cabinets and refrigerators), (b) (4) (floors), glass (windows and doors), (b) (4) (shielding above ISO-5 classified area tables), and (b) (4) (paper siding of materials).

B. The following discrepancies were observed with the firm's established contact time for the sporicidal agent – (b) (4) :

- The firm's disinfectant efficacy study conducted by (b) (4) evaluated a (b) (4) contact time for stainless steel only.
- The firm's procedure: Cleaning Classified Areas (S-CMP-003) mandates that personnel allow for a (b) (4) contact time.
- The (b) (4) label recommendations stated that a contact time of at least (b) (4) be maintained.
- On 10/21/2021, firm personnel were observed wiping down components with (b) (4) within Room (b) (4) (ISO-8) for transfer into cleanroom (b) (4) (ISO-7). The plastic bins and (b) (4) packaging for the (b) (4) syringes were wiped down and only allowed a contact time of approximately (b) (4).

A review of the firm's microbial excursions from March 2020 to September 2021 revealed that the firm has had approximately 179 recoveries of spore-forming microorganisms from surface samples, airborne viable samples and personnel monitoring samples. Additionally, the firm has had numerous action level environmental excursions from spore forming microorganisms, as detected during personnel monitoring after ISO-5 aseptic operations, that had direct product impact to include (b) (4) in which mold was recovered from an operator's fingertips after production of Vancomycin for IV injection ((b) (4)) lot (b) (4). Furthermore, the firm initiated Recall 2020-004 in response to elevated microbial counts from 03/25/2020 to 03/26/2020. The recall investigation determined the root cause to be improper wiping of plastic bins with (b) (4) and the elevated microorganisms were identified as *Bacillus altitudinis*, which is a spore-forming microorganism.

C. The firm has failed to conduct studies for the cleaning of all glassware that is utilized in manufacturing activities. The firm utilizes (b) (4) automatic glasswashers and (b) (4) glasswasher. The firm has no data to support that the glasswashers and cleaning agents are effective in removing all residues from the glassware. The firm has indicated that none of the glassware is dedicated and that they can be utilized in the manufacturing

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of both hazardous and non-hazardous drug products. The firm also indicated that the (b) (4) glasswashers are utilized for products intended to be sterile; however, there is no dedicated glasswasher which is utilized for the washing of hazardous drug glassware. Furthermore, pink residue was noted on the interior bottom of the firm's (b) (4) glasswasher ((b) (4)).

D. The firm does not ensure ISO-5 workstations utilized for drug production of products intended to be sterile are clean and free of residue. On 9/22/2021, during observation of aseptic production activities, a white unknown residue was noted on the table within the ISO-5 hood (b) (4) in cleanroom (b) (4) where operators were producing Vancomycin for IV injection. The unknown white residue was directly adjacent to the tubing utilized for dosing.

THIS IS A REPEAT OBSERVATION TO THE 2018 AND 2020 FDA INSPECTION.

OBSERVATION 4

Test procedures relative to appropriate laboratory testing for sterility are not written and followed.

Specifically,

The firm's sterility testing program is inadequate as noted below:

A. The firm conducted the sterility method suitability for the Vancomycin for IV injection product ((b) (4)) in 2020, however, the suitability study did not pass for growth of *B. subtilis* and *S. aureus*. Despite the noted issue, the firm never went back and repeated the sterility method suitability experiments or reassessed the method. Since the previous inspection, the firm has produced and released (b) (4) lots of the Vancomycin bag product intended to be sterile ((b) (4)) without an appropriately verified sterility method. Additionally, other products have failed sterility method suitability testing (b) (4) – dexamethasone phosphate for otic injection, (b) (4) – vancomycin for IV injection, (b) (4) – vancomycin for IV injection) and have been produced, quality unit released, and distributed to customers based on data from un-verified sterility methods.

B. The firm had no evidence as of 10/19/2021 that sterility suitability studies for drug products have

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been reviewed and approved by the firm's quality unit to ensure sterility tests are appropriate. Sterility suitability studies noted during the current inspection without quality unit review and approval include for product (b) (4) – vancomycin for IV injection, (b) (4) – vancomycin for intraocular injection, (b) (4) – mitomycin for ophthalmic irrigation, (b) (4) – mitomycin for ophthalmic irrigation, (b) (4) – mitomycin for intravesical irrigation and 1(b) (4) – gemcitabine for intravesical irrigation.

C. The firm does not perform appropriate controls for sterility testing.

- The firm does not perform growth promotion testing on (b) (4) and (b) (4) media lots utilized for sterility testing of drug products to ensure that the media is suitable for use. For example, the firm utilized (b) (4) and (b) (4) media lots (b) (4) and (b) (4) respectively, for the sterility test of buffered Lidocaine HCl/Epinephrine solution ((b) (4)) lot (b) (4) . The firm never conducted growth promotion testing on the above media lots prior to use.
- The firm does not perform negative controls to determine that the media is sterile and to assist with any subsequent investigations, as necessary. For example, the sterility testing results for buffered Lidocaine HCl/Epinephrine solution ((b) (4)) lot (b) (4) document the presence of, "particles in both (b) (4) and (b) (4),". The firm did not perform a negative control and therefore could not determine whether the media was the source of this sample contamination.

THIS IS A REPEAT OBSERVATION TO THE 2018 AND 2020 FDA INSPECTION.

OBSERVATION 5

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

Specifically,

A. The firm's media fill program is inadequate for the following reasons:

- The firm does not perform media fills in the ISO-7 classified cleanroom (b) (4) where they prepare hazardous drug products intended to be sterile, and rely on the media fill studies performed in cleanroom (b) (4) to demonstrate that the ISO-5 areas in cleanroom (b) (4) are capable of ensuring the sterility of drug products prepared in these areas. They have no documented justification that the media fill simulation studies conducted in room (b) (4) represent worst case scenarios and are appropriate for cleanroom (b) (4). The cleanroom designs and ISO-5 areas are different between cleanrooms (b) (4) and (b) (4). Hazardous drugs intended to be sterile have been produced in cleanroom (b) (4) to include Gemcitabine for intravesical irrigation ((b) (4)) lot (b) (4), which has been distributed to customers.

- The firm does not conduct nor document common interventions that can occur during manufacturing such as (b) (4) drug products due to failed sterilizing (b) (4) or adjustment of production equipment (e.g., due to pinched tubing during (b) (4) filling).

- Since the previous inspection, approximately 31% ((b) (4)) of media fill studies demonstrated contamination, in that they were contaminated with a variety of particles, fibers, and filaments. For example, the firm documented objects in the media fill studies conducted on 02/10/21(Syringe to Syringe (b) (4), filament documented) and 06/24/21 (Pump to (b) (4), fiber documented). The firm does not know the identity or source of the objects and the Quality Control Unit reviewed and approved these media fill studies as passing.

- The firm does not have a process to ensure that the number of media fill units made, the number of media fill units incubated, and number of media fill units read for microbiological growth are tracked and reconciled. The firm also does not have a mechanism in place to evaluate and investigate any discrepancies noted for reconciliation during media fill studies.

B. The firm's mechanism for the evaluation and remediation of viable microbiological environmental monitoring trends is inadequate and not followed. Per the firm's Evaluation and Remediation of Viable

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William Marc Chatoff, Managing Director	
FIRM NAME Edge Pharma, LLC	STREET ADDRESS 856 Hercules Dr
CITY, STATE, ZIP CODE, COUNTRY Colchester, VT 05446-8014	TYPE ESTABLISHMENT INSPECTED 503B Outsourcing Facility

Environmental Monitoring Trends procedure – S-QMR-015, when a cleanroom has mold counts for (b) (4) consecutive evaluation intervals, the room will be considered under probation. For (b) (4) intervals, an assessment is to be made to determine if the area is to be quarantined and taken out of service. The firm had three consecutive air viable mold recoveries for sampling site (b) (4) in the ISO-8 room (b) (4) on **7/6/2021, 7/14/2021, and** ~~7/1/2021,~~ 7/22/2021, ~~and 7/27/2021~~ and two consecutive air viable mold recoveries for sampling site (b) (4) in the ISO-7 cleanroom (b) (4) on 9/1/2021, and 9/9/2021. No area evaluations were performed as required per procedure.

C. The firm does not follow the Environmental Monitoring and Utilities Excursion Investigations (EEI) procedure – S-QMR-010, and corresponding environmental monitoring specifications. For example, per the firm's environmental monitoring specifications for ISO-8 areas, (b) (4) mold recoveries are to be escalated from alert to action and require an investigation. On two separate occasions (May-June 2021 & September 2021), the firm had three consecutive alert level air-viable mold recoveries from sampling site (b) (4) in room (b) (4). The firm never escalated the (b) (4) alert level excursions to action and investigated.

D. The firm does not adequately assess mold recoveries from ISO-7 personnel monitoring. Operators obtain ISO-7 personnel monitoring when leaving the cleanroom drug production area after production operations and include aseptic production operators, support staff, and supervisors, all of which can enter the ISO-5 areas as direct production personnel and/or in support roles (e.g., passing materials into the ISO-5 hood). The firm has documented 6 separate instances of mold recoveries on personnel during ISO-7 personnel monitoring since the previous inspection that have not been adequately assessed or evaluated for potential product impact. The recoveries have included mold recoveries from operator fingertip and sleeve samples.

E. Sterile wipes that are utilized in the firm's ISO-7 cleanroom (b) (4) are not protected from potential contamination. For example, on 10/22/2021, an operator was noted to place a stack of sterile wipes directly on an analytical balance enclosure. The wipes were not contained in any packaging and placed adjacent to a calculator, pen and on top of a batch record. Additionally, an unknown white crusty residue

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was noted directly adjacent to the wipes. A firm operator was also observed talking into a walkie talkie and then placed the walkie talkie down on the wipes. The operator then utilized the wipes, after spraying with (b) (4), to wipe down materials that were then transferred into the ISO-5 hood during production of lot Phenylephrine HCl for IV injection ((b) (4)) lot (b) (4).

THIS IS A REPEAT OBSERVATION TO THE 2020 FDA INSPECTION.

OBSERVATION 6

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

Specifically,

The firm's smoke studies, performed by the third party contractor (b) (4) in November 2020 for cleanroom suites (b) (4), and (b) (4), do not demonstrate that HEPA-filtered air supplied to critical areas is sufficient to maintain unidirectional airflow during aseptic processing operations. For example:

- The dynamic smoke studies for the firm's ISO-5 BSCs in the hazardous production cleanroom (b) (4) failed to include the transfer and staging of materials (e.g., devices, tubing, materials) into and out of the hood.

- Airflow patterns inside the ISO-5 production processing areas are turbulent and not unidirectional. During dynamic smoke study evaluation of the ISO-5 hood (b) (4) in cleanroom (b) (4), turbulence was observed at approximately 10:09 minutes in video Suite (b) (4) (b) (4). The turbulence appears to be directly over the production materials. The firm's smoke study assessment report does not discuss the noted turbulence.

- Airflow patterns within the ISO-7 area of the cleanroom circulate upward and back towards the ISO-5 production areas as demonstrated in smoke study evaluation of the ISO-5 hoods in

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cleanroom (b) (4) in videos:
- Suite (b) (4) at approximately 00:44 minutes
- Suite (b) (4) at approximately 00:13 minutes
- Suite (b) (4) at approximately 00:13 minutes
- Suite (b) (4) at approximately 00:09 minutes

The firm's smoke study assessment report does not discuss the noted events.

- For the production of the Vancomycin for IV injection product ((b) (4)), firm operators were observed to utilize (b) (4) adjacent hoods in cleanroom (b) (4) for Vancomycin lot (b) (4) on 10/1/2021. Aseptic operators were observed to reach through the adjacent hoods to transfer saline bags for production. The firm's smoke studies for cleanroom (b) (4) fail to include this process and it is unclear if unidirectional airflow is maintained in the space between hoods during material transfer.

- Smoke study evaluation of the ISO-5 hoods in cleanroom (b) (4) demonstrate that airflow appears to transfer between adjacent ISO-5 aseptic workstations. Examples include video Suite (b) (4) at approximately 6:47minutes (between hoods (b) (4) and (b) (4)), 8:35 minutes (between hoods (b) (4) and (b) (4)) and 16:36 minutes (between hoods (b) (4) and (b) (4)). The firm's assessment of the smoke studies failed to include a holistic evaluation for possible hood to hood contamination.

- Smoke study evaluation of the air return vents in cleanroom (b) (4) demonstrate that airflow appears to move from underneath the table and back up through perforation holes and into the ISO-5 classified areas. This phenomenon can be seen for ISO-5 workstations (b) (4), (b) (4), (b) (4), (b) (4), and (b) (4), however, no assessment has been conducted to determine the potential impact of the noted airflow on aseptic operations.

- The firm has changed the non-viable particulate environmental monitoring probes utilized in cleanroom (b) (4). The new probes are now located (b) (4) where

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production activities take place vs. the previously used non-viable particulate monitors were placed (b) (4). The firm's smoke studies failed to include the above noted change to ensure unidirectional airflow is maintained in the direct production area.

The **firm's** smoke study assessment reports (b) (4) -do not address the deficiencies described above. Further, the firm's Quality Control Unit did not review these reports in a timely manner. All studies were completed in November 2020, but the reports for cleanroom Suite (b) (4) was not reviewed until August 2021, and the report for cleanroom Suite (b) (4) was not reviewed until 10/27/2021, during the current FDA inspection.

THIS IS A REPEAT OBSERVATION TO THE 2018 AND 2020 FDA INSPECTIONS.

OBSERVATION 7

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable to facilitate cleaning, maintenance, and proper operations.

Specifically,

A. The design of the firm's cleanroom air delivery systems to production cleanrooms for drugs intended to be sterile is inadequate. Cleanroom suites (b) (4) (ISO-8 ante room (b) (4), ISO-7 gowning room (b) (4), and ISO-7 cleanroom (b) (4)) and (b) (4) (ISO-8 ante room (b) (4), ISO-7 gowning room (b) (4), and ISO-7 cleanroom (b) (4)) utilize common open plenum spaces that supply air to ceiling mounted HEPA filter fan units. The following deficiencies were noted for the common open plenum space above suite (b) (4):

- -The common plenum space for suite (b) (4), where air is mixed with recirculated air from the cleanroom, has exposed building materials such as wood, electrical conduit, and metal bracing beams.
- -The air returns that recirculate air from the cleanroom areas back up to the open plenum space are (b) (4). (b) (4) contain electrical conduit lines and metal framing material. Additionally, cleanroom items that appeared to be wipes and

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(b) (4) were observed in the (b) (4) during the current inspection.

The firm has had numerous air-viable mold recoveries in cleanroom suites (b) (4) and (b) (4) in 2020 and 2021 (see Observation **2E** ~~3B~~). The 2020 adverse mold trend was attributed to water ingress into the common plenum spaces due to inadequately insulated HVAC air supply ducts. The definitive root cause(s) of the 2021 adverse mold trend in suite (b) (4) remain to be determined. The firm has failed to holistically evaluate the adequacy of their cleanroom design in regard to air return and air delivery systems to ensure drugs intended to be sterile are produced under acceptable environmental conditions.

B. The firm's HVAC system that supplies air to the firm's hazardous drug production suite (b) (4) is inadequate. The HVAC system is unable to maintain room humidity within required specifications (b) (4) %RH) . In August 2021 alone, there were six humidity excursions in room (b) (4) and ten humidity excursions in room (b) (4). The firm has attributed the HVAC system failures to the HVAC system not being able to maintain humidity specifications due to ambient facility and outdoor weather conditions. The firm's current (b) (4) cleanroom suite pressure differential cascade design is such that room (b) (4) is under positive pressure and rooms (b) (4) and (b) (4) are under negative pressure environments and thus any adverse environmental/facility trends in room (b) (4) can impact upon room (b) (4) and cleanroom (b) (4). The firm has attempted to install (b) (4) dehumidifying units in the unclassified spaces of the facility in an attempt to resolve the issue. The firm has known about the HVAC/humidity issue since 2018 when the qualification report for suite (b) (4) noted the HVAC deficiencies. The firm has also implicated the numerous humidity excursions in suite (b) (4) to the 2021 adverse mold trends seen in the suite.

C. The firm's facility is inadequate to prevent the influx of lesser quality air into a higher quality air area in cleanroom suite (b) (4). For example:

- Smoke studies were performed at the (b) (4) between room (b) (4) where gowning occurs and cleanroom (b) (4) where preparation of non-hazardous drug products intended to be sterile occurs. These smoke studies demonstrate that air does not flow from cleanroom (b) (4) into

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cleanroom(b) (4), but instead flows in a general upward direction toward the ceiling.

- The firm does not have a reliable continuous monitoring system for pressure differential readings between the ISO-7 production cleanroom(b) (4) and gowning room(b) (4). In May 2021 during recertification activities, the firm's third party contractor documented an as left pressure differential reading between cleanroom(b) (4) and room(b) (4) as (b) (4) using the contractor's reference standard, while the firm's building monitoring system indicated a pressure differential of 0.033 water columns (W.C.). The firm opened investigation INV-2021-047 into the discrepancy and could not determine an exact cause for the issue and resolution of the problem is still ongoing. The firm has installed a temporary pressure differential monitor between cleanroom(b) (4) and room(b) (4) and per CAPA-2021-011 is to record the pressure differential readings every (b) (4), however, the firm is not following the interim temporary pressure differential monitor control. On 10/21/2021, it was noted that cleanroom operators acknowledged that no monitoring form had been completed for that day and the firm had not recorded any differential pressure monitoring results using the interim temporary monitor since 10/7/2021. After the observation was noted to the firm and monitoring was resumed, the pressure differential monitoring results that have been recorded have shown OOS results for the differential pressure between cleanroom(b) (4) and gowning room(b) (4). For example, on 10/27/2021, the differential pressure readings from 10:00 am to 4:00 pm were 0.014, 0.013, 0.015 and 0.013 W.C. (specification (b) (4))

OBSERVATION 8

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

Specifically,

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A. The firm has no timeframe requirements/expectations within respective quality procedures for the timely execution of quality related tasks and functions to include LIRs, deviations, evaluating customer complaints and conducting investigations.

The below are examples of investigations that have been opened by the firm and remain open as of the current inspection without adequate justification:

Report ID	Date Opened	Classification	Status	Comments/ Description	Days open as of 9/20/2021
INV-2020-063	11/5/2020	No Classification Documented	In Progress	True OOS 1459 lot (b) (4). LIR-2020-165.	319
INV-2020-070	12/30/2020	Serious	Open	True OOS for sub-vis particles in (b) (4), lot# (b) (4)	264
INV-2021-009	3/9/2021	Non-Serious	Open	True potency OOS, (b) (4), (b) (4). Gemcitabine 1g/50ml	195

B. The firm does not review and approve endotoxin test validation assessments in a timely manner. For example, the firm conducted endotoxin validation experiments for the intended to be sterile product (b) (4) – lidocaine HCl/bupivacaine HCl/hyaluronidase for (b) (4) injection in 2019. The firm's quality unit documented the review and approval of the validation documentation over two years later and during the current inspection on 10/27/2021.

C. The firm's quality unit (Quality Control and Quality Assurance) has failed to draft, issue, review or

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approve stability reports per the firm's procedures: S-QAC-022 Stability Testing Program and Requirements and S-QAC-042 Stability Data Trending and Reports. Below are selected examples in which the firm failed to conduct reports for completed stability studies:

Product name	Lot number	Start date	Final timepoint
Buffered Lidocaine HCl/Epinephrine	(b) (4)	(b) (4)	(b) (4)
Promethazine HCl	(b) (4)	(b) (4)	(b) (4)
Mitomycin Irrigation	(b) (4)	(b) (4)	(b) (4)

OBSERVATION 9

Routine calibration, inspection and checking of automatic and mechanical equipment is not performed according to a written program designed to assure proper performance.

Specifically,

The firm has failed to complete qualification of all critical temperature controlling units including: refrigerators ((b) (4) total), walk-in coolers (b) (4), freezers (b) (4), incubators (b) (4), and (b) (4). Temperature mapping for the units was completed in September of 2020; however, the data has yet to be compiled into a report for review by the firm's Quality Unit. The Performance Qualification (PQ) for two of the (b) (4) was completed during the inspection (10/01/2021). The firm has continued to utilize the aforementioned unqualified equipment for storage of temperature sensitive raw materials and finished drug products (refrigeration units) as well as for (b) (4) since the previous inspection in March of 2020. In addition, the qualification of the (b) (4) Glassware Washer ID# (b) (4) was last conducted on 06/29/2016. The firm has not evaluated the need for a re-qualification of the glasswasher since its initial qualification in 2016. Furthermore, the (b) (4) glasswasher (ID# (b) (4)), which is utilized for the cleaning of glassware for manufacturing

activities, has never been qualified.

THIS IS A REPEAT OBSERVATION TO THE 2020 FDA INSPECTION.

OBSERVATION 10

The written stability testing program is not followed.

Specifically,

Review of the firm's deviation investigations revealed approximately 6 instances in 2020 and 10 instances in 2021 in which stability samples were either not pulled or tested within an appropriate time frame or in which a stability testing time point was missed. Below are selected examples:

Deviation#	Date opened	Description
DR-2020-053	4/4/2020	The test for pH at the (b) (4) timepoint was not completed.
DR-2020-144	7/24/2020	The test for sterility was conducted late for (b) (4).
DR-2021-070	5/5/2021	The tests for appearance, pH and potency were missed for timepoint (b) (4) and conducted late for T=104

STABILITY PROGRAM DEFICIENCIES WERE ALSO NOTED DURING THE 2018 AND 2020 FDA INSPECTIONS.

OBSERVATION 11

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

Specifically,

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The firm does not have validated potency stability indicating methods to support the beyond use date (BUD) assignments for drug products. The firm has not validated stability indicating potency methods for 15 drug products to include (b) (4) - buffered lidocaine HCl/epinephrine solution intended to be sterile for infiltration and nerve block injection.

OBSERVATION 12

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically,
Complete records of all GMP data are not maintained. For example, partially completed GMP documents to include a Compounding Instructions for Allergy Treatment Sets Form F-CMP-010.I, (b) (4) Pipette Verification From F-QCH-013.B, Out-of-Specification or Reportable Viable Growth Form F-QMR-020.A, and Visual Inspection of Incoming Final Devices Form F-IRS-005.B were located in the firm's shred bins. The firm's procedure, S-GEN-005 – Good Documentation Practices (GDP) Procedure, prohibits this practice.

THIS IS A REPEAT OBSERVATION TO THE 2020 FDA INSPECTION.

OBSERVATION 13

The labels of your outsourcing facility's drug products are deficient.

Specifically, the labels of your outsourcing facility's drug products do not include information required by section 503B(a)(10)(A).

The following information is not found on some of your drug product labels:

- The statement "This is a compounded drug"

AMENDMENT 1

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	Sean R Marcsisin, Investigator Erik W Koester, Investigator	X Erik W Koester Investigator Signed By: Erik W. Koester -S Date Signed: 12-01-2021 11:37:59	12/1/2021

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
One Montvale Avenue Stoneham, MA 02180 (781)587-7500 Fax:(781)587-7556 ORAPHARM1_RESPONSES@fda.hhs.gov	9/20/2021-11/30/2021* FEI NUMBER 3010490167

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
William Marc Chatoff, Managing Director	
FIRM NAME Edge Pharma, LLC	STREET ADDRESS 856 Hercules Dr
CITY, STATE, ZIP CODE, COUNTRY Colchester, VT 05446-8014	TYPE ESTABLISHMENT INSPECTED 503B Outsourcing Facility

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

The following drug products were identified as missing the aforementioned information:

- Let Topical Gel
- Lidocaine HCL 1%
- Metacholine Chloride 1mg/mL
- Lidocaine/Epinephrine 1%/1:100,000
- Lidocaine/Epinephrine 3%/1:400,000
- Phenylephrine 1mg/10mL

DEFICIENCIES REGARDING LABELING INFORMATION REQUIRED BY SECTION 503B(A)(10)(A) WERE ALSO NOTED DURING THE 2018 AND 2020 FDA INSPECTIONS.

***DATES OF INSPECTION**

9/20/2021(Mon), 9/21/2021(Tue), 9/22/2021(Wed), 9/23/2021(Thu), 9/24/2021(Fri), 9/27/2021(Mon), 9/28/2021(Tue), 9/29/2021(Wed), 9/30/2021(Thu), 10/01/2021(Fri), 10/06/2021(Wed), 10/13/2021(Wed), 10/21/2021(Thu), 10/28/2021(Thu), 11/30/2021(Tue)

X Sean R Marcsisin
Investigator
Signed By: Sean R. Marcsisin -S
Date Signed: 12-01-2021 11:38:44

AMENDMENT 1

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Sean R Marcsisin, Investigator Erik W Koester, Investigator	X Erik W Koester Investigator Signed By: Erik W. Koester -S Date Signed: 12-01-2021 11 37 59	12/1/2021

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."