BEFORE THE
BOARD OF PHARMACY
DEPARTMENT OF CONSUMER AFFAIRS
STATE OF CALIFORNIA

In the Matter of the Cease and Desist Order Issued Against:

Edge Pharma LLC, Respondent

Nonresident Outsourcing Facility, License No. NSF 132

Agency Case No. CI 2021 92606

DECISION
AFTER HEARING TO CONTEST CEASE AND DESIST ORDER

This matter was heard by Seung W. Oh, President of the California State Board of Pharmacy (Board), in Sacramento, California, on August 24, 2021; the parties participated from various locations via videoconference. The matter was heard pursuant to Business and Professions Code section 4129.4, subdivision (c).

Kristina Jarvis and Katelyn Docherty, Deputy Attorneys General, represented Anne Sodergren, Complainant, Executive Officer of the Board. Joseph R. LaMagna and Scott Kiepen, Hooper, Lundy & Bookman, P.C., represented Edge Pharma, LLC (Edge Pharma).

Oral and documentary evidence was received at the hearing. The matter was submitted for decision on August 24, 2021.

FACTUAL FINDINGS

1. On August 6, 2021, Complainant issued the Cease and Desist Order (Order) in her official capacity. The Order compelled Edge Pharma to "immediately cease and desist compounding sterile drug products or nonsterile drug products for shipment into California." The Order is valid for 30 days from August 6, 2021, through September 5, 2021, unless an interim suspension order is issued before that time.

2. Respondent Edge Pharma timely contested the Order on Thursday, August 19, 2021.

3. The first sentence of the Order cites the text of Business and Professions Code section 4129.4, subdivision (a), and says,

> [W]henever the board has a reasonable belief, based on information obtained during an inspection or investigation, that an outsourcing facility compounding sterile drug products or nonsterile drug products poses an immediate threat to the public health or safety, the executive officer of the board may issue an order to the outsourcing facility to immediately cease and desist compounding sterile drug products or nonsterile drug products.

The Order cites Business and Professions Code section 4129.2, subdivision (b), which requires a nonresident outsourcing facility to compound all sterile products and nonsterile products to be distributed or used in this state in compliance … with federal good manufacturing practices (CGMPs) applicable to outsourcing facilities.

The Order further specifies nine provisions of the Code of Federal Regulations, Part 211, titled "Current Good Manufacturing Practice [CGMP] For Finished Pharmaceuticals," that were violated. Those nine provisions, with a description of how they were violated, form the basis for the belief that Edge Pharma poses an immediate threat to the public health or safety.

Jonathan Fujimoto, PharmD, California State Board of Pharmacy Inspector

4. Jonathan Fujimoto, PharmD., is a California licensed pharmacist and an Inspector for the Board who testified at the hearing. Dr. Fujimoto has been licensed as a pharmacist since at least 2010 and is licensed in several states. He earned certification as a Sterile Compounding Pharmacist by the Board of Pharmacy Specialties.[1] Prior to his 2020 employment by the Board, he worked in the fields of sterile compounding and outsourcing for five years. In that five-year period, he acted as the pharmacy director of an outsourcing facility. He was also employed by an FDA-registered ISO[2] certified analytical laboratory, where he acted as a subject matter expert in a variety of areas related to compounding and outsourcing.

5. Dr. Fujimoto testified about the existence of two documents issued by the federal Food and Drug Administration (FDA) identified as Guidance for Industry that are relevant to this proceeding. They are FDA's "Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the [Food Drug and

[1] This organization is not a part of the California State Board of Pharmacy, but is an independent organization.
[2] In outsourcing and compounding fields, "ISO" refers to the International Organization for Standardization.

Cosmetics] Act" (Draft Guidance, dated January 2020, Revision 2; hereafter, CGMP Outsourcing Guidance) and "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice" (Sept. 2004; hereafter, "Aseptic CGMP Guidance" Such documents represent the standard of practice in the industry for outsourcing facilities.

6. Dr. Fujimoto conducted an onsite inspection of Edge Pharma's licensed premises in Colchester, Vermont, on August 3, 4, and 5, 2021. The inspection was conducted as part of its annual renewal. Dr. Fujimoto took photos during his inspection. He did not go inside the cleanrooms themselves, but he did look through see-through partitions to make some of his observations. He prepared an Inspection Report and a Written Notice, both dated August 5, 2021, at the conclusion of his inspection. On the same date, Dr. Fujimoto provided copies of both documents to, and reviewed both with, Edge Pharma managerial staff, COO/pharmacist Tyler Wingood and Quality Assurance Director/Quality representative Kurt Radke; both individuals acknowledged receipt by their signatures on them.

Dr. Fujimoto's testimony was reliable and consistent with the contents of Inspection Report and Written Notice. His testimony was detailed and included specific examples.

William Chatoff, Managing Director, Edge Pharma

7. William Chatoff is the Managing Director for Edge Pharma. He was first licensed as a pharmacist in 1991; he is licensed in Vermont, as well as five or six other states. He is currently the Chairperson of the Vermont Board of Pharmacy. For the first part of his career, he founded nuclear pharmacy practices around the United States; he was a nuclear pharmacist for 14 years. He has worked in compounding since he was in school, and he got into outsourcing after leaving nuclear pharmacy. He has been working in outsourcing since December 2013, since that type of licensing came into existence by federal law in November 2013.

Edge Pharma is licensed in, and ships to, 48 states other than California. Mr. Chatoff explained that Edge Pharma's training for its staff is thorough, and that he goes to sleep at night concerning himself with patient safety, wakes in the morning concerning himself with patient safety, and meets with his staff every morning about patient safety. He explained that for him and Edge Pharma, "it's all about" the safety of the product, and each piece of the puzzle lining up, having only patient safety in mind.

Edge Pharma is complying with the Order, although it has impacted its business. It has had no adverse issues reported to it from other states since the Order issued. Allergy products have been a significant portion of its business in California, particularly in the last five years or so.

Outsourcing Facility Standards and Consumer Harm

8. Under federal law, an outsourcing facility is held to very high standards – CGMPs – which prevent consumer harm by maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard drug products. CGMPs are also applied in manufacturing finished drug products, although outsourcing facilities need not comply with all the same requirements as a manufacturer. (See 21 C.F.R. § 210.1; 21 U.S.C. § 355.) The minimum standards make it more likely that a drug a patient receives should not contain something that itself might harm the consumer (for example, bacteria), nor should the drug harm the consumer because it does not provide the intended benefit (for example, the strength is less than intended).

As indicated in FDA's Guidances for Industry, those creating sterile drugs should have a keen awareness of the public health implications of distributing a nonsterile product. Poor CGMP conditions at a facility can ultimately pose a life-threatening health risk to a patient. The FDA sets, and the facility should maintain, the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products. CGMP requirements for finished drug products are established in title 21, Code of Federal Regulations, parts 210 and 211. The primary focus of the CGMP Outsourcing Guidance "is on those aspects of part 211 that relate to sterility assurance of sterile drug products and the safety of both sterile and non-sterile compounded drug products more generally, including with respect to strength (e.g., subpotency, superpotency), and labeling or drug product mix-ups, because these aspects of outsourcing facility operations pose the highest risk to patient safety if not conducted properly." (CGMP Outsourcing Guidance, p. 3)

The CGMP Outsourcing Guidance (p. 5) also provides an overview of the facilities requirements:

> Part 211 sets out the requirements applicable to the design of facilities used in the manufacture, processing, packing, or holding of a drug product (see, e.g., § 211.42). The design of a facility should consider the products produced and must provide the necessary level of control to prevent mix-ups and contamination (§ 211.42).
>
> The production areas in which components, drug products, in-process materials, equipment, and containers or closures are prepared, held, or transferred must be designed to minimize the level of contaminants so as to prevent objectionable microorganisms in non-sterile drug products (see § 211.113(a)) and prevent microbiological contamination of drug products purporting to be sterile (see § 211.113(b)). Processing and controlled areas must be clean and sanitary (§ 211.56).

Order Violation No. 1

9. a. The Order alleges that Respondent failed to conduct USP <788/789> sub-visible particulate testing for release on applicable drug product(s), in violation of title 21, Code of Federal Regulations (CFR) section 211.160(b). CFR section 211.160 expresses "general requirements" for a facility's "Laboratory Controls." It states, in part,

> (b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:
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> (1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
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> (2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.
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> (3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.
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> (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

b. Dr. Fujimoto explained that, as indicated in the Inspection Report and/or Written Notice, during the inspection, he reviewed the batch release specifications. He identified that not all products currently being produced and distributed that should be tested pursuant to USP <788/789> were being tested. Dr. Fujimoto identified examples, including formula identification (FID) numbered 815, identified as an ophthalmic solution, and FID number 1416. He explained that the significance of the USP <788/789> testing is to identify subvisible particle, particles that cannot be seen by the naked eye to know there was a problem. A product might, for example, fail that test as a result of a bad product formulation, degraded substances, or undissolved substances.

c. Mr. Chatoff explained that Edge Pharma was conducting subvisible particle testing on intravenous product it produces, and it is now doing so on ophthalmic drops. He admitted that Respondent was not previously conducting subvisible particulate testing in accordance with USP <788/789> on ophthalmic drops, but he represented that the failure to comply with that provision represents "minimal risk." Mr. Chattoff stated that subvisible particle issues do not have anything to do with sterility, endotoxins, or anything else. He believes that any product from an outsourcing facility is safer than a product prepared by a doctor, a nurse, or a hospital. In its written argument, Respondent stated,

> [T]he risk to patients using ophthalmic products without subvisibility testing is extremely low. This issue was only for ophthalmic solutions. There were no allegations of stability, sterility, endotoxin, or other areas. At most the concern is that sterile, subvisible products might have been in a solution and dropped into the eye. If that occurred the eye would handle the issue as we all experience that daily, let alone something that is visible and the slight irritation that might create. There was no material health or safety risk. However, Edge has updated is practices, and the change has been made already.

d. FDA's CGMP Outsourcing Guidance provides that finished drug products be subject to release testing "to determine whether they meet final product specifications before their release for distribution." It explains that a facility's quality control unit to be responsible for "ensuring that the finished drug product is not released until this testing is conducted and the results confirm that the finished drug product meets specifications." It explains that the release procedure specifications are established for each drug product "to ensure the quality of the finished drug product." For drug products that are solutions purporting to be sterile, those includes subvisible particle testing. (CGMB Outsourcing Guidance, p. 25-26.)

e. Respondent failed to conduct subvisible particle testing on relevant products, including FID 815 and 1416, in accordance with USP <788/789>, before release of the finished drug product into the stream of commerce, in violation of CFR section 211.160(b). Failing to meet that requirement represents a risk to the quality of the finished drug product, which represents a risk to the public health or safety. This violation, when

considered in conjunction with other violations discussed elsewhere, poses an immediate threat to the public health and safety.

Order Violation No. 2

10. a. The Order alleges that Respondent failed to provide assurances that its aseptic processing areas meet ISO 5 conditions for the duration of the aseptic filling process, in violation of CFR section 211.113, subdivision (b), pertaining to control of microbiological contamination. That subdivision requires,

> Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

b. The standard of practice requires that outsourcing facilities produce sterile drugs only in ISO 5 or better air quality. In addition, the facility should be designed and operated with cascading air quality (e.g., by proper air classification and air pressurization) to protect the ISO 5 zone (or critical area). The facility layout, room separation, and process flow must be designed to prevent the influx of contamination from adjacent areas and rooms of lower air quality and to avoid any disruption of HEPA unidirectional flow. (CGMP Outsourcing Guidance, p.6)

The production of sterile drug products may be accomplished using an aseptic process or using terminal sterilization. Using terminal sterilization, products are filled and sealed under conditions designed to minimize risks, and then the product in its final container is subjected to a sterilization process such as heat or irradiation. In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together. Before aseptic assembly into a final product, the individual parts of the final product are generally subjected to various sterilization processes. For example, glass containers are subjected to dry heat; rubber closures are subjected to moist heat; and liquid dosage forms are subjected to filtration. Each process requires validation and control; each process could introduce an error that ultimately could lead to the distribution of a contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control. (Aseptic CGMP Guidance, pp. 2-3.)

The standard of practice also requires that the Outsourcing Facility must establish environmental monitoring practices that are acceptable and qualified for the operations the facility performs. The CGMP Outsourcing Guidance provides minimum standards;

depending on the nature of the outsourcing facility's practice, additional safeguards might be required. (CGMP Outsourcing Guidance , p. 10)

Aseptic CGMP Guidance (p. 50) says, "It is essential to monitor the microbial air quality. Samples should be taken according to a comprehensive sampling plan that provides data representative of the entire filling operation. Continuous monitoring of particles can provide valuable data relative to the control of a blow-fill-seal operation."

c. Dr. Fujimoto explained that, as indicated in the Inspection Report and/or Written Notice, during the inspection, Edge Pharma failed to provide assurances that microbiological contamination was being appropriately measured because it used "settling plates" in the ISO 5 area, and failed to provide continuous non-viable monitoring. Despite this, Dr. Fujimoto recognized that, the necessary equipment was onsite and estimated to be fully implemented beginning in the fourth quarter of 2021. During his annual inspection (conducted virtually) of Respondent in 2020, this matter was flagged; Dr. Fujimoto would have expected completion within six months.

d. Mr. Chatoff stated said that 24-hour continuous monitoring for non-viable particles is required by California, and "not an FDA issue." He did not indicate if FDA had inspected the particular nature of type of finished drug products Edge Pharma was making to make that determination. He also testified that Edge Pharma does non-viable monitoring, but that it takes time to do the design. Respondent has "air-samplers" on the table next to and during the compounding, but they don't do that continuously. He believes there is zero risk, as a result of the other controls Edge Pharma was using. Respondent is working on installing the appropriate equipment, but it is taking longer than six months to do so, and a twelve-month timeframe is more reasonable.

e. Dr. Fujimoto was persuasive that Edge Pharma was required to provide continuous monitoring based on the type of sterile drug products being produced, in violation of CFR § 211.113, subdivision (b); it is not yet doing so. Since the monitoring is designed to identify contaminants, inadequate monitoring represents a risk to the public health and safety. This violation, when considered in conjunction with other violations, collectively poses an immediate threat to the public health and safety.

Order Violation No. 3

11. a. The Order alleges that Respondent failed to provide an environment free of infestation by rodents, birds, insects, and other vermin, in violation of CFR § 211.56, subdivision (c), regarding the facility's sanitation. That section provides,

> (a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation by rodents, birds, insects,

and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

(b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

(c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).

(d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

b. On two days during his inspection, as indicated in the Inspection Report and/or Written Notice, Dr. Fujimoto observed "copious amounts" of insects, at least one living, in multiple locations, near the floors but also near eye level, including outside of two of the facility's cleanrooms (close to cleanrooms 200/201 and immediately outside cleanroom 300). In one location he found three spiders in a web, at eye level. Most of the same insects were visible in both days' photos. As described by Dr. Fujimoto, the areas around the cleanrooms are considered controlled, not-classified, which areas also require protective apparel (booties, facility scrubs, hairnet, and/or gloves). He also observed insect traps where insects were lodged half-in and half-out, at both ends of the trap, as well as insect debris and insect excrement at the entrance of the trap. In addition, on two days, a day apart, the same, sizable piece of clear plastic trash is visible on the floor immediately outside a cleanroom. Dr. Fujimoto concluded the pest control procedures were inadequate.

Dr. Fujimoto evaluated some of Respondent's internal records for Corrective and Preventative Actions (CAPA), Deviations, and Out of Specifications (OOS). Those records included situations where an ant was found in cleanroom 202 (DR-2021-099) and one where an ant was found in a bin with FID 1456 (DR-2020-084 and CAPA 2020-004).

Dr. Fujimoto noticed that the emergency exit door at loading dock #1 was found only partially sealed. Visible light could be seen from the outside when viewing from the

controlled, not-classified, side of the door, meaning that outside air and contaminants could continuously come in.

Similarly, Dr. Fujimoto observed that, in cleanroom 103, the ceiling fire sprinkler had lost its protective cap that prevents ingress into the cleanroom from the unclassified area immediately above. Dr. Fujimoto saw a similar design in cleanroom 100, which had a covering such that a hole could not be seen, and the outer surfaces would be easily cleanable.

Respondent asked if Dr. Fujimoto observed that insects in the cleanroom, or that the insects outside the cleanroom had affected the conditions within the cleanroom. In response, Dr. Fujimoto had not entered the cleanroom, nor had he observed insects in the portion he could see. He had observed an adverse trend when he reviewed Respondent's quarterly environmental monitoring trending reports. He observed an adverse trend for the ISO 7 room 201 based on the recovery rate of microorganisms, a measurement indicating that more particulates were identified. He noted that the first quarter (Q1) recovery rate was 15%, Q3 was 10%, and Q4 was 24%. He also observed an adverse trend for non-viable particulates in room 201; in Q4, 36% of samples reached the alert limit. He explained that the insects could be a cause of the higher rate of microorganisms, but he was unable to make draw such a conclusion based on his inspection.

c. Mr. Chatoff testified that the photos taken were of the "worst" area of a 40,000 square foot facility that was very clean, and "every corner is clean." He also said that some of the photos were taken on a loading dock, not in the facility. Finally, he said there was a "zero risk of harm" from the insects that were present, and that there was zero risk of harm because of sterility. Mr. Chatoff also explained that Edge Pharma has a contract with a pest control company, Orkin, for regular service, and that company had, after the inspection, performed a reviews and prepared a report after the inspection and determined that, by its standards, there was no infestation. The pest control report was not admitted into evidence.

Respondent also offered its Environmental Monitoring Trend Report for Quarter 2 (April – June) of 2021 to show the lack of contamination. According to Mr. Chatoff, the report shows that Edge Pharma's cleanroom environment "was in an exceptional state of control, from personnel to machines." It shows that there is "zero risk of harm" from the insects that were seen in the facility, because the insects were not in the cleanroom, and they stay on the outside.

d. The areas outside a cleanroom must be maintained in a manner to avoid tracking in contaminants into the cleanroom. According to the CGMP Outsourcing Guidance, "[p]rocessing and controlled areas must be clean and sanitary ([CFR] § 211.56)." (p. 5.) As described by Dr. Fujimoto, the areas around the cleanrooms are considered controlled, not-

classified, which areas also require protective apparel. The protective apparel is to protect drug products from contamination. (CFR § 211.28(a).) The numerous insects on the walls and floors, in combination with the numerous visible insects partially captured in the traps, over multiple days, in the area, immediately indicates that the facilities procedures, or its execution of those procedures, were insufficient.

e. The facility did not create an environment free of infestation by rodents, birds, insects, and other vermin, in violation of CFR section 211.56; Dr. Fujimoto observed what he described as "copious amounts" of insects and insect-related debris, particularly in a controlled, not-classified, portion of an outsourcing facility, poses a risk of contamination. Respondent's representations that every corner of the facility was clean, and that the potential contamination does not pose a risk of harm to patients, or poses minimal risk, is unpersuasive and concerning. To the contrary, the numerous insects in various locations outside multiple cleanrooms, pose an immediate risk to the health and safety of consumers. It also allowed its facility, through a gap under the door and around a sprinkler in a cleanroom, to be more vulnerable to air and contaminants, including insects, from unregulated areas, which poses an immediate threat to the public health or safety for the same reason.

The piece of clear plastic trash that remained on the floor, in what appeared to be inches from the cleanroom door, for more than a day, is not violation as described in the cease and desist order; it is, however, a concerning reflection on the facility's diligence in cleaning.

Order Violation No. 4

12. a. The Order alleges that Respondent failed to adequately maintain and monitor pressure differentials in classified areas, as required by CFR section 211.46, subdivision (b), pertaining to a licensee's building and facilities' ventilation, air filtration, air heating and cooling. CFR section 211.46 provides, in part,

> (b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

b. Dr. Fujimoto explained his findings in the hearing and in the Inspection and/or Written Notice that the facility had failed to adequately monitor the pressure differentials. Although a continuous monitoring system was in place for pressure differentials, some gauges had differed significantly from the certifier's standards. Specifically, on May 26, 2021, Steris conducted a certification review of cleanrooms 200/201/202, which demonstrated that pressure differential between cleanrooms 201 and 202 did not have the required pressure differential of >0.02 inches of water column (WC) as required. The certifier observed the pressure to be 0.006 WC, significantly less than half of the standard.

A blockage in the air supply was remediated and the pressure was restored. Although the pressure was restored, a related pressure gauge, which measured the data to the building monitoring system (BMS) for that room, had inaccurately measured the pressure differential at 0.025 WC. Once the discrepancy was identified, Edge Pharma did not investigate the duration of the pressure loss event and whether commercial batches of drug products were potentially impacted. Additionally, even when the certifier left, Edge Pharma's pressure gauge failed to provide accurate data for evaluation (Edge Pharma's pressure gauge read 0.033 WC compared to the reference standard device's 0.021 WC). Dr. Fujimoto concluded that, based on the BMS continuous monitoring data he reviewed, the pressure differential was noncompliant from May 21, 2021, until the certifier intervened on May 26, 2021. Respondent's quality assurance officer told Dr. Fujimoto that he did not believe the incident required any investigation.

Dr. Fujimoto also observed in his written findings that, in cleanroom 202, the HEPA filter supplying workstation 1C was observed to have a red, dark stain and/or a particulate matter of an unknown content on it. Dr. Fujimoto's initial interview of the operators suggested that the stain had been there "a while."

c. Mr. Chatoff disagreed that Edge Pharma was out of compliance with respect to pressure differentials. The discolored HEPA filter was one of 20 HEPA filters in that room, not including those assigned to a particular workspace. Mr. Chatoff asserted there was "zero risk of harm" from Edge Pharma's products because it had environmental monitoring to prove the "complete picture" that products were sterile, pyrogen-free, viable and non-viable tested, and that personnel participated in fingertip testing and gowning requirements.

d. Outsourcing facilities should produce sterile drugs only in ISO 5 or better air quality. In addition, the facility should be designed and operated with cascading air quality (e.g., by proper air classification and air pressurization) to protect the ISO 5 zone (or critical area). The facility layout, room separation, and process flow must be designed to prevent the influx of contamination from adjacent areas and rooms of lower air quality and to avoid any disruption of HEPA unidirectional flow. (CGMP Outsourcing Guidance, p.6)

To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas. Pressure differentials between cleanrooms is to be monitored continuously throughout each shift and frequently recorded. All discrepancies should be documented and "deviations from established limits should be investigated." (Aseptic CGMP Guidance, p. 7)

FDA concluded that, as a scientific matter, a system for environmental monitoring must include the establishment of pressure differential limits (see CFR § 211.42), and control systems should include built-in alarms to detect excursions. An adequate control system

includes monitoring for pressure differentials, humidity, and temperature during production and taking prompt action to correct adverse conditions, which are necessary activities to prevent contamination during aseptic processing (see §§ 211.42, 211.46, 211.58). (CGMP Outsourcing Guidance, p. 9)

The CGMP Outsourcing Guidance also provides (p. 8),

> HEPA filters should be qualified to provide appropriate air quality and be periodically maintained and tested to ensure intended air quality. Discolored, dirty, or damaged HEPA filters should be repaired or replaced.

e. Respondent failed to adequately maintain and monitor pressure differentials in classified areas when it failed to accurately monitor the pressure in cleanroom 201 and 202 between May 21 and 26, 2021. Perhaps more concerning, however, is that Respondent failed to adequately maintain and monitor the pressure differentials when it failed to investigate not just the source of the deviation, but also the impact of the identified deviation on its processes in May 2021, and failed to ensure that the inaccurate gauges were corrected or replaced once a problem was identified. This was a violation of CFR section 211.46, subdivision (b). Under the circumstances, these violations, by themselves, pose an immediate threat to the public health and safety.

13. Respondent's HEPA filter should have been repaired or replaced because it was discolored, and had been that way for a while; this was a violation of CFR section 211.46, subdivision (b). That said, this violation will not be considered as a basis for the cease and desist order because the allegation was only that the pressure differentials were not appropriately maintained and monitored. Its poor condition does, however, reflect on the nature and gravity of the risk to the public in so far as it demonstrates Respondent's diligence with environmental practices, and Respondent's credibility in its representation about the cleanliness of the facility.

Order Violation No. 5

14. a. The Order alleges that Respondent failed to conduct testing utilizing stability indicating methods, in violation of CFR section 211.166(a)(3), pertaining to stability testing. That section provides, in part,

> (a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:
>
> …

(3) Reliable, meaningful, and specific test methods;

…

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

b. Dr. Fujimoto explained his findings in the Inspection Report and/or Written Notice that Edge Pharma failed to conduct testing utilizing stability indicating test methods. He found that many active pharmaceutical ingredients (APIs) were not fully validated as previously stated in 2020 inspection report. He also noted that a progress report was provided, but that 36 assays, representing 36 products, are currently still under development and/or review.

c. Mr. Chatoff stated that Edge Pharma has had a plan to add this additional protection for the last 12 months and it will soon be done. Edge Pharma is putting the plan in place for each and every product. Edge Pharma has "stability" and "stability data" for each product, although not "stability indicating" methods. Stability indicating has come out in the last three years, it was primarily a manufacturing standard. Outsourcing processes are usually only used for a 30, 60, or 90-day product; stability indicating only becomes significant when a product will need to last for six months or more. Mr. Chatoff said there was "zero risk" to the consumer because Edge Pharma has stability, endotoxin, sterility, subvisible particle testing, and this is just an "added level" on the CGMP side.

d. According to FDA, a stability program must be established to assess the stability characteristics of finished drug products, and the results of stability testing must be used to determine appropriate storage conditions and expiration dates (CFR § 211.166). Stability testing is used to ensure that a drug product will retain its quality (e.g., strength) and remain sterile, if applicable, through the labeled expiration date. (CGMP Outsourcing Guidance, p. 26)

e. Dr. Fujimoto's finding is credited that Edge Pharma had 36 studies under development or review for finished drug products, and it therefore lacked satisfactory

stability indicating test methods for those drug products, in violation of CFR section 211.166(a)(3). Given that a stability testing program is required to determine the stability of the appropriate storage conditions and expiration dates, its absence for certain drug products, poses a risk to the public health and safety. This violation, when considered in conjunction with other violations, poses an immediate threat to the public health and safety.

Order Violation No. 6

15. a. The Order alleges that Respondent failed to perform and provide a robust disinfectant procedure and qualification program, in violation of CFR section 211.42(c)(10), pertaining to the design and construction features of the facility's buildings. That section provides, in part,

> (a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.
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> …
>
> (c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures:
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> …
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> (10) Aseptic processing, which includes as appropriate:
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> (i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;
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> (ii) Temperature and humidity controls;
>
> (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;
>
> (iv) A system for monitoring environmental conditions;
>
> (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;

(vi) A system for maintaining any equipment used to control the aseptic conditions.

b. Dr. Fujimoto explained during his testimony, and in the Inspection Report and/or Written Notice, that Respondent failed to perform and provide a robust disinfectant procedure and qualification program by failing to perform cleaning validation. The facility had conducted testing for a disinfectant qualification program, but the items and or substrates tested were not sufficiently robust to meaningfully measure the effect of the disinfectant on all surfaces to which it was to be used. For example, one product was only tested on stainless steel, but stainless steel is one of the easiest surfaces to clean, so testing on it is not the same as testing on more porous or flexible surfaces, such as plastics or epoxies.

Further, Edge Pharma lacked a validation study showing that its procedures for handwashing glassware, utensils and other items would effectively remove previous ingredients (from prior batches) from the items. Dr. Fujimoto explained that Respondent created a lot of creams, which contain a lot of oil, and the handwashing must be demonstrated to adequately remove the oil from the items.

c. Mr. Chatoff said his facility was clean, that Respondent had no sterility issues, and that it posed "zero risk of harm" to the health or safety of the public. He says this because he has an enormous amount of data reflecting that there is no viable bacteria, fungus, or mold growing in the cleanrooms.

d. FDA's CGMP Outsourcing Guidance supports Dr. Fujimoto's conclusions. "To prevent contamination or mix-ups during the course of operations," CFR section 211.42 requires separate or defined areas or other similar control systems for a facility's operations, and procedures for cleaning and disinfecting. (CGMP Outsourcing Guidance, p. 7-8, citing CFR §§ 211.42, 211.56, 272 211.67.)

Equipment surfaces that come in contact with drug products, containers, or closures must be cleaned at appropriate intervals to prevent contamination. The suitability and efficacy of the cleaning agents and cleaning methods should be evaluated, and the cleaning agent's compatibility with applicable work surfaces should be assessed. For multiuse facilities and nondedicated equipment, changeover and cleaning procedures for equipment and utensils must be established and followed to prevent contamination, including cross-contamination between products (see §§ 211.42, 211.67). (CGMP Outsourcing Guidance, p. 7-8)

e. Respondent failed to perform and provide a robust disinfectant procedure and qualification program when it failed to validate the effectiveness of its cleaning processes, in violation of CFR section 211.42(c)(10). It failed to make sure that the cleaning and disinfectant being used would be effective on all the surfaces to which it was applied, and it

failed to demonstrate that its procedures for handwashing would remove all contaminants. Under the circumstances, this violation, by itself, poses an immediate threat to the public health and safety.

Order Violation No. 7

16. a. The Order alleges that Respondent failed to adequately validate equipment prior to use and maintain equipment in a validated state, in violation of CFR section 211.67(b), pertaining to equipment cleaning and maintenance. That section provides,

> (a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
>
> (b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:
>
> (1) Assignment of responsibility for cleaning and maintaining equipment;
>
> (2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
>
> (3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;
>
> (4) Removal or obliteration of previous batch identification;
>
> (5) Protection of clean equipment from contamination prior to use;
>
> (6) Inspection of equipment for cleanliness immediately before use.
>
> (c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§211.180 and 211.182.

b. Dr. Fujimoto explained his concerns during his testimony, in his Inspection Report, and in the Written Notice. He identified that Respondent had failed to adequately maintain

and validate equipment when it used processes and operated equipment without having validated such equipment. He viewed some of respondent's systems, and identified unvalidated and/or partially validated equipment, including final product storage refrigeration, dishwashers, glassware washing, cleaner / disinfectant in-use times.

Even more specifically, a refrigeration unit (Frig-030) was holding product intended for commercial distribution without being qualified or validated. Another unit, Frig-002, which stored final product at the time of investigation, was not fully validated. After subfreezing temperatures had been observed in refrigeration unit (Frig-030), Respondent's investigation (EE1-2021-010) failed to document potentially impacted batches, products, or materials. There was limited and insufficient data to support that other drug products did not experience a freeze thaw cycle. The investigation failed to identify that Frig-030 was holding product intended for commercial distribution without being validated. Raw data from the temperature probe was requested, but complete records could not be provided.

Dr. Fujimoto explained that Respondent had failed to fully validate, or failed to define load patterns for, several dishwasher units, which are used for glassware and/or utensils. Specifically, washers WAS-001, WAS-003, WAS-004 were not fully validated.

c. Mr. Chatoff explained that the majority of Edge Pharma's "tier 1" equipment is validated. The facility has a Corrective and Preventative Action and a master validation equipment plan, which explain exactly where each remaining item is in the validation process. For the last 12 months, Edge Pharma has been "going to the straight CGMP" standards.

d. FDA Guidance says that an outsourcing facility's equipment (mechanical, electronic, or automated) must be qualified as capable of performing its intended functions or operations before first use, and procedures for routine calibration and maintenance must be established and followed. Equipment needs to be designed to facilitate operations, cleaning, and maintenance. (CGMP Outsourcing Guidance, p. 12.)

It also provides that, once the problem was identified, as part of its quality assurance process, it should have "fully investigated" what occurred to make effective corrective actions, including changes necessary to prevent recurrence. (CGMP Outsourcing Guidance, p. 5; see 211.22(a).)

e. Respondent failed to validate or qualify, and maintain its equipment in a state to determine it was capable of performing its intended functions, in violation of CFR section 211.67(b), when it did not qualify or validate the functioning of two refrigerators, and when it failed to validate and define load patterns for several dishwashers. Unexpected temperature conditions in the refrigeration unit during storage may adversely affect the drug products; the absence of a validated use for the dishwashers pose a risk of cross

contamination. Under either circumstance, there is an unacceptable risk to consumers. Under the circumstances, this violation, without any other, poses an immediate threat to the public health and safety.

Order Violation No. 8

17. a. The Order alleges that Respondent failed to properly assign beyond use dates and that the beyond use dates exceeded the allowance of the law, in violation of CFR section 211.22(c), pertaining to the responsibilities of the facility's quality control unit. That section provides, in part,

> (a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.
>
> …
>
> (c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

FDA defines the beyond-use date (BUD) as the date beyond which a compounded drug product should not be used. A BUD notifies the user of the period during which a compounded drug product's required quality characteristics (e.g., sterility, strength, purity, freedom from particulate matter) can be ensured. (CGMP Outsourcing Guidance, p. 34.)

b. Dr. Fujimoto explained during his testimony, as indicated in the Inspection Report and Written Notice, that Respondent had failed to properly assign BUDs and assigned BUDs beyond the dates permitted by law.

Dr. Fujimoto explained that the BUDs for allergen extract sets have inappropriate BUDs applied. A BUD of up to one (1) year can be applied for very dilute sets. As an example, Rx# 959762 had a dilution of 1:1,000,000 being readied for production and distribution. The related product package inserts of the source materials state: *Storage and Handling Maintain at 2 to 8°C (36 to 46°F) during storage and use. Dilutions of concentrated extracts that result in a glycerin content of less than 50% can reduce extract stability. Extract dilutions at 1:100 volume to volume* ***should be kept no longer than a month, and more***

dilute solutions no more than a week. Other allergen sets reviewed show both highly dilute and dilutions where glycerin content was less than 50%.

c. Mr. Chatoff strongly disagreed with the conclusion that the BUDs were improper; he believed that Respondent's finished drug products were safe. He referenced an FDA Guidance about allergy treatment sets that permitted the BUD, but he did not identify it by number nor did he provide it. Mr. Chatoff testified that he has asked the manufacturer to modify its labeled instructions, but modified label instructions had not yet been approved. He also argued there was no risk of harm based on the other controls in place and lack of prior harm.

d. Dr. Fujimoto's testimony was persuasive that Respondent's BUDs for allergen extract sets had inappropriate dates that exceeded the appropriate time frames, in violation of CFR section 211.22(c). If Respondent inaccurately assigned a BUD that was beyond the permitted date, FDA's definition can be inverted: after the BUD, "a compounded drug product's required quality characteristics (e.g., sterility, strength, purity, freedom from particulate matter)" **cannot** "be ensured." As a result, an inaccurate BUD creates risk to the public health and safety. This violation, when considered in conjunction with other violations, collectively poses an immediate threat to the public health and safety.

Order Violation No. 9

18. a. The Order alleges that Respondent failed to validate shipping methods and provide assurances of cold chain for products requiring refrigerated or frozen storage conditions, in violation of CFR section 211.22(c), pertaining to the responsibilities of the facility's quality control unit (quoted in number 8 above).

b. Dr. Fujimoto explained that, as indicated in the Inspection Report and/or Written Notice, during the inspection, shipping validations and procedures were inadequate. Packaging and validation reports did not adequately demonstrate that the products produced and shipped by Edge Pharma maintain cold chain during transit for all products and configurations. For example, a 25L payload box was tested with a max load 108 vials of lO mL (1080 mL max load preconditioned). Respondent distributed IV bags of up to 500 mL (FID 1458) in unit size. Dr. Fujimoto concluded that the actual distribution likely exceeds the validated maximum load tested. Additionally, he was concerned that frozen products (FID 1003) were being shipped without a validated pack out. Dr. Fujimoto felt a vial that was supposed to be refrigerated, but which felt room temperature to his touch; Respondent's staff believed that the product could be left out for eight hours, when the related materials only specified four hours. The public safety issues and risk are product specific, but as a general matter, increased time and temperature allow microorganisms to grow and/or allow product degradation to occur, and potency could be reduced.

c. Mr. Chatoff stated that, even where there were deviations from CGMPs, those deviations posed no risk to the health and safety of consumers. He also testified that no products had been identified as lacking in sterility. That argument is addressed below.

d. Validated storage and shipping conditions for drug products ensure prevents possible contamination or deterioration of the finished drug product (e.g., cracked vials, leaks in bags, overheating), in violation of CFR section 211.22(c). Failure to use validated shipping methods, under the circumstances, this violation, by itself poses an immediate threat to public health and safety.

Discussion

Immediate threat to the public health or safety

19. Respondent argued that, even if it violated CGMPs as alleged, there was no immediate threat to the public health or safety.

Mr. Chatoff stated that, even where there were deviations from CGMPs, those deviations posed no risk to the health and safety of consumers. He also testified that no products had been identified as lacking in sterility. He testified that Respondent has robust training, and robust media fill training and testing, and environmental controls. Although he was able to speak to the big picture topics, his testimony lacked specificity and detail. His dismissal of many cleaning-related standards as posing "zero" risk to consumers is concerning.

Respondent's Environmental Monitoring Trend Report for Quarter 2 of 2021 indicates that, during that quarter, 205 product lots were tested for sterility, none failed the sterility testing. Of 337 product lots tested for potency, 2 lots were "truly outside of specification (OOS) limits following a laboratory investigation report (LIR)." With regard to stability, the report indicates that, "In accordance with the stability program in place at Edge Pharma, each product is subject to a series of tests depending on the timepoint being tested." Only one had a failing result; it was "a pH out-of-specification result for Formula ID 1348 (beyond use date of 90 days) at timepoint 120 days."

Respondent's Quarter 2 Trend Report indicates that each tested product was found to be sterile, but the data set is limited in time and volume. In addition, the other results (for potency and stability) seem to offer qualified and/or incomplete conclusions. Even if each of the other test categories could be read in Respondent's favor, the results cannot be read to conclude that no products Respondent makes pose an immediate threat to the health and safety of the public, or that CGMP minimum standards to make a finished drug product were met.

The recommendations in the CGMP Outsourcing Guidance are consistent with the principles of good manufacturing practice, which hold that quality is best assured by implementing appropriate controls throughout the manufacturing process, with end-product testing providing additional assurance. This guidance also provides a risk-based approach to CGMP requirements. Accordingly, this guidance focuses on control of raw materials, facility design and maintenance, production techniques and controls, and personnel practices as the most critical aspects of ensuring quality for all drug products. Other CGMP requirements, such as testing samples of the finished drug product before batch release and the collection of reserve samples, provide additional assurance of drug quality and are described with respect to higher risk (sterile) outsourcing facility operations. (CGMP Outsourcing Guidance p.2)

Mr. Chatoff repeatedly testified, and Respondent argued, that any drug product created in Respondent's facility is better and safer than a drug product created in a physician's office. This rationale, however, confuses the standard to be applied. Drugs compounded or created in some physician's offices may indeed pose a greater risk to the patient, but that is not the measure by which an outsourcing facility is judged. In this context, the witness's comparison created the impression that the facility may be setting its standards well below that expected of an outsourcing facility.

As noted above, consumer harm may come from multiple means, including from a lack of sterility (for example, a patient might suffer a viral or bacterial infection), but also from other lacks in quality, strength or integrity (for example, the drug does not provide the intended effect on the patient). Those risks create an immediate threat to the health and safety of consumers. While it is fortunate that we have no current information about consumer harm, the focus here is prevention, especially because of the potentially dire consequences. An absence of evidence of actual harm does not mean there is no threat of the harm. Respondent's failure to follow the CGMP provisions described above, individually and collectively, posed an immediate threat to the public health and safety. The Board need not wait until harm occurs to act.

Other Arguments

20. Respondent argues that the Complainant is trying to effectively revoke Respondent's license without any concern for public safety, and without complying with due process, and to create a record that will undermine Respondent's ability to operate in California.

Respondent argues there has "never been and will never be a legitimate public safety concern." To the contrary, by itself, the "copious amounts" of insects and insect debris observed, in close proximity to the cleanroom, along with other indications that Respondent's cleaning practices are less than diligent, is cause for immediate and significant concern for public health and safety. Respondent also alleges that the action

based on the current inspection is somehow disingenuous because some of the same issues were noted last year. The 2020 inspection was, however, conducted remotely; a remote inspection does not allow the same type of observation that an Inspector can make in person.

If Respondent's argument about process is because another proceeding is pending, a cease and desist order cannot issue, that argument lacks merit. As noted above, the Board, through its Executive Officer, appears to have a reasonable belief, based on the inspection, to issue an order to cease compounding products for California for 30 days. The proceedings are not mutually exclusive; public protection permits such actions in such a highly regulated field, where errors can be fatal.

Any arguments not addressed here are considered without merit.

LEGAL CONCLUSIONS

1. The Complainant has the burden of proof for establishing cause for issuing a cease and desist order. Because the license at issue is issued to a facility, and not a particular individual, the standard of proof is the preponderance of the evidence. (*Imports Performance v. Dep't of Consumer Affairs, Bureau of Auto. Repair*, 201 Cal. App. 4th 911, 916, 135 Cal. Rptr. 3d 402, 406 (2011), *as modified* (Dec. 7, 2011).) For practical purposes, however, the standard is irrelevant because each factual finding above is found by clear and convincing evidence.

2. As provided in section 4001.1 of the Business and Professions Code,

> Protection of the public shall be the highest priority for the California State Board of Pharmacy in exercising its licensing, regulatory, and disciplinary functions. Whenever the protection of the public is inconsistent with other interests sought to be promoted, the protection of the public shall be paramount.

Pharmacy Law also requires that public protection must take priority over rehabilitation and, where evidence of rehabilitation and public protection are in conflict, public protection shall take precedence. (Bus. & Prof. Code, § 4313.)

3. Business and Professions Code section 4129.4 authorizes the Executive Officer to issue of a cease and desist order to an outsourcer for 30 days, prescribes the contents of the order, and the method to appeal to the president and the court. It provides,

> (a) Whenever the board has a reasonable belief, based on information obtained during an inspection or investigation by the board, that an

outsourcing facility compounding sterile drug products or nonsterile drug products poses an immediate threat to the public health or safety, the executive officer of the board may issue an order to the outsourcing facility to immediately cease and desist compounding sterile drug products or nonsterile drug products. The cease and desist order shall remain in effect for no more than 30 days or the date of a hearing seeking an interim suspension order, whichever is earlier.

(b) Whenever the board issues a cease and desist order pursuant to subdivision (a), the board shall immediately issue a notice to the owner setting forth the acts or omissions with which the owner is charged, specifying the pertinent code section or sections and any regulations.

(c) The cease and desist order shall state that the owner, within 15 days of receipt of the notice, may request a hearing before the president of the board to contest the cease and desist order. Consideration of the owner's contest of the cease and desist order shall comply with the requirements of Section 11425.10 of the Government Code. The hearing shall be held no later than five days after the date the request of the owner is received by the board. The president shall render a written decision within five days after the hearing. In the absence of the president of the board, the vice president of the board may conduct the hearing permitted by this subdivision. Review of the decision may be sought by the owner or person in possession or control of the outsourcing facility pursuant to Section 1094.5 of the Code of Civil Procedure.

(d) Failure to comply with a cease and desist order issued pursuant to this section shall be unprofessional conduct.

4. As indicated in Factual Findings 1-3 and 8-18, the written Order contained the code sections considered violated and a brief description of the facts; the facts from the inspection were further specified in the Inspection Report and Written Notice given to the Respondent the day before. The Order provided appropriate notice.

5. Pursuant to Business and Professions Code section 4129.4, and Factual Findings 6 and 9-19, Complainant had a reasonable belief, based on information obtained during an inspection or investigation by the Board, that Respondent Edge Pharma's practices posed an immediate threat to the public health or safety, and therefore had cause to issue a Cease and Desist Order to Respondent.

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ORDER

For the reasons set forth above, the Cease and Desist Order is upheld.

It is so ORDERED on this 28th day of August, 2021.

BOARD OF PHARMACY
DEPARTMENT OF CONSUMER AFFAIRS
STATE OF CALIFORNIA

By 

Seung W. Oh, PharmD.
Board President

California State Board of Pharmacy
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BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY
DEPARTMENT OF CONSUMER AFFAIRS
GOVERNOR EDMUND G. BROWN JR.

ORDER TO CEASE AND DESIST

Date: August 6, 2021

Permit No.: NSF 132

Name as shown on Permit: EDGE PHARMA LLC

Address: 856 HERCULES DR. COLCHESTER, VT 05446

California Business and Professions Code Section 4129.4 provides that whenever the board has a reasonable belief, based on information obtained during an inspection or investigation, that an outsourcing facility compounding sterile drug products or nonsterile drug products poses an immediate threat to the public health or safety, the executive officer of the board may issue an order to the outsourcing facility to immediately cease and desist compounding sterile drug products or nonsterile drug products.

California Business and Professions Code Section 4129.2 (b) requires a nonresident outsourcing facility to compound all sterile products and nonsterile products to be distributed or used in this state in compliance with regulations of the board and with federal current good manufacturing practices (cGMPs) applicable to outsourcing facilities.

Edge Pharma LLC, a non-resident outsourcing facility compounded products to be distributed into California without complying with regulations of the board and with cGMPs applicable to outsourcing facilities, including but not limited to:

1. 21 CFR 211.160(b) – Failure to conduct USP<789/789> sub-visible particulate testing for release on applicable drug product(s).
2. 21 CFR 211.113(b) – Failure to provide assurances aseptic processing areas meet ISO-5 conditions for the duration of the aseptic filling process.
3. 21 CFR 211.56(c) – Failure to provide an environment free of infestation by rodents, birds, insects, and other vermin.
4. 21 CFR 211.46(b) – Failure to adequately maintain and monitor pressure differentials in classified areas.
5. 21 CFR 211.166(a)(3) – Failure to conduct testing utilizing stability indicating methods.
6. 21 CFR 211.42(c)(10) – Failure to perform and provide a robust disinfectant procedure and qualification program.
7. 21 CFR 211.67(b) – Failure to adequately validate equipment prior to use and maintain equipment in a validated state.
8. 21 CFR 211.22(c) – Failure to properly assign beyond use dates. Beyond use dates exceeded the allowance of the law.

9. 21 CFR 211.22(c) – Failure to validate shipping methods and provide assurances of cold chain for products requiring refrigerated or frozen storage conditions.

Edge Pharma LLC has failed to remedy these areas of non-compliance, despite having adequate opportunities to do so.

On the basis of the foregoing, the Board, through its Executive Officer, has a reasonable belief that drug preparations by Edge Pharma LLC pose an immediate threat to the public health and safety in California, and therefore **ORDERS**:

Edge Pharma LLC shall immediately **CEASE AND DESIST** compounding sterile drug products or nonsterile drug products for shipment into California. This cease and desist order shall remain in effect for 30 days or until the date of a hearing seeking an interim suspension order, whichever is earlier.

Pursuant to Business and Professions Code section 4129.4(c), within 15 days of the receipt of this notice Edge Pharma LLC may request a hearing before the president of the board to contest the cease and desist order. Such hearing shall comply with the requirements of Section 11425.10 of the Government Code.

California State Board of Pharmacy

By: Anne Sodergren

Signed: Sodergren, Anne@DCA Digitally signed by Sodergren, Anne@DCA Date: 2021.08.06 09:27:37 -07'00'

Date: 8/6/2021

Title: Executive Officer

I hereby acknowledge receipt of the above cease and desist order and notice.

By: KURT RADKE

Signed: [signature]

Date: 08-06-2021

Title: QA DIRECTOR