IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF ARKANSAS
WESTERN DIVISION

UNITED STATES OF AMERICA, Plaintiff, v. CANTRELL DRUG COMPANY, a corporation, and JAMES L. McCARLEY, JR., an individual, Defendants.	)	Civil Action No. 4:18-cv-159

PLAINTIFF'S BRIEF IN SUPPORT OF PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

I. INTRODUCTION

Plaintiff, the United States of America, seeks a preliminary injunction to protect the public from drugs purporting to be sterile that are at risk of microbiological contamination. Defendants distribute nationwide injectable drugs they manufacture under conditions that fall short of the minimal legal requirements necessary to ensure the safety and quality of such drugs. The majority of drugs manufactured by Cantrell Drug Company ("Cantrell"), a corporation, and James L. McCarley, Jr., an individual, (collectively, "Defendants") purport to be and are expected to be sterile. Yet, FDA's inspections revealed that Defendants' injectable drugs were being manufactured under insanitary conditions and using deficient manufacturing practices, which Defendants were made aware of on repeated occasions. Notwithstanding FDA's 2015 Warning Letter informing Defendants of their ongoing current good manufacturing practice

("CGMP") violations, and subsequent FDA efforts to get Defendants to cease manufacturing drugs until necessary remedial actions are fully implemented, Defendants continue to manufacture purportedly sterile drugs and distribute such drugs in interstate commerce. Pursuant to Federal Rule of Civil Procedure 65 and 21 U.S.C. § 332, the United States hereby respectfully moves this Court for an order of preliminary injunction against Defendants to restrain and enjoin them from violating the Federal Food, Drug, and Cosmetic Act ("the Act"). A preliminary injunction is warranted because: (1) Defendants have violated the law, and (2) there is a cognizable danger that Defendants will continue to do so unless the Court acts.

First, Defendants violate the law by introducing adulterated drugs into interstate commerce, and causing drugs to become adulterated while such drugs are held for sale after shipment of one or more of their components in interstate commerce. *See* 21 U.S.C. § 331(a), (k). Defendants' drugs are adulterated within the meaning of the Act because: (1) the drugs have been prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health; and (2) the methods used in, or the facilities or controls used for, the drugs' manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with CGMP. *See* 21 U.S.C. § 351(a)(2)(A), 351(a)(2)(B).

Second, Defendants' violations will continue absent a court order to enjoin their operations. Despite repeated inspections by FDA highlighting insanitary conditions and failures to comply with manufacturing practices required by law, Defendants have failed to successfully remedy their operations to the standard required by federal law. Not only have Defendants' attempts at corrective action been unsuccessful, but they have refused FDA's repeated requests

to temporarily cease operations until they become compliant with the drug safety provisions in the Act.

Defendants' serious violations of the Act, and the likelihood that violations will continue without court action, demonstrate that preliminary injunctive relief is necessary to protect the public. In support of this motion, Plaintiff submits a memorandum of law and the following documents: (1) declaration of Brooke Higgins, Compliance Officer and Senior Policy Advisor, Office of Manufacturing Quality, Center for Drug Evaluation and Research ("CDER"), United States Food and Drug Administration ("FDA" or "agency") ("Higgins Decl."); (2) declaration of Latorie Jones, Investigator, Office of Pharmaceutical Quality Operations ("OPQO"), Division 2, FDA ("Jones Decl."); (3) declaration of Lisa Whitt, Investigator, OPQO, Division 2, FDA ("Whitt Decl."); (4) declaration of Shelby Marler, Investigator, OPQO, Division 2, FDA ("Marler Decl."); (5) declaration of Monica Maxwell, Acting Program Division Director, OPQO, Division 2, FDA ("Maxwell Decl."); and (6) a proposed Order of Preliminary Injunction.

II. BACKGROUND

A. Defendants' Operations

Cantrell is a 503B compounding pharmacy that primarily manufactures and distributes finished injectable compounded drugs purporting to be sterile directly to hospitals and health care entities throughout the United States.[1] Jones Decl. ¶ 10; Whitt Decl. ¶ 9. James L. McCarley, Jr. is Cantrell's Chief Executive Officer and has co-owned the firm since January 1992. Jones Decl. ¶ 9. Mr. McCarley is the person most responsible for Cantrell's operations.

[1] Cantrell registered with FDA as a 503B "outsourcing facility" on December 16, 2013, and, thereafter, its operations were subject to the requirements of 21 U.S.C. § 353b. Cantrell continues to be subject to 21 U.S.C. § 353b, and most recently re-registered as an outsourcing facility on October 12, 2016. As an outsourcing facility, Cantrell's operations are subject to the Act's adulteration provisions regarding CGMP. 21 U.S.C. § 351(a)(2)(B).

Id. He retains financial and operational authority over the business, including the ability to prevent, detect, and correct violations. *Id.*

B. Defendants Have a History of Manufacturing Adulterated Drugs

Defendants have a history of manufacturing their drugs under conditions and practices that fall short of the minimum requirements to ensure product safety and quality. *See* Higgins Decl. ¶¶ 8, 60.

FDA has conducted three inspections of Defendants' facility, located at 7321 Cantrell Road, Little Rock, Arkansas, in 2013, 2016, and 2017. Maxwell Decl. ¶ 6. During each of these inspections, FDA investigators observed that Defendants were operating under insanitary conditions and in violation of CGMP requirements for drugs. *See* Jones Decl. ¶ 15-16; Whitt Decl. ¶ 6; Marler Decl. ¶ 7; Maxwell Decl. ¶¶ 7, 13, 18 and Exhs. 1, 7, 13; Higgins Decl. ¶¶ 8, 18-33, 40-57. At the conclusion of each inspection, FDA investigators provided a List of Inspectional Observations (Forms FDA-483) to Defendants and discussed the cited CGMP violations with Defendant McCarley and other individuals. *See* Jones Decl. ¶ 28; Marler Decl. ¶ 10.

FDA most recently inspected Cantrell's facility between June 12 and 29, 2017. Maxwell Decl. ¶ 18; Jones Decl. ¶ 5. This inspection was initiated to determine whether Defendants corrected the deficiencies observed and discussed with Defendant McCarley during the previous FDA inspection conducted in 2016. Jones Decl. ¶ 5. The 2017 inspection revealed that Defendants had not remedied many of their deficiencies, and FDA investigators observed that Defendants continued to operate under insanitary conditions and in violation of the CGMP requirements. *See id.* ¶ 6. For example, in 2017, after detecting bacteria on surfaces in the area used for aseptically processing an injectable drug, Cantrell released the drug for distribution.

Defendants have also failed to ensure the necessary air quality in areas used for aseptic processing.

After the most recent FDA inspection, Defendants voluntarily ceased manufacturing operations on July 20, 2017. Maxwell Decl. ¶ 19. Defendants then informed FDA on July 28, 2017, that they intended to resume compounding of sterile products without waiting for FDA's concurrence that their operations have been brought into compliance with the law. Maxwell Decl. ¶ 21 and Exh. 19. Then, despite FDA's repeated recommendations, Defendants notified FDA that they began distributing its compounded drugs to the public starting in September 2017. Maxwell Decl. ¶ 28 and Exh. 21. Indeed, on at least six (6) occasions, FDA advised Defendants to refrain from distributing their products because there was no assurance of product sterility. *Id.* ¶¶ 21, 23, 26, 27, 29 and Exh. 17, 19, 23, 24, 26.

Based on their history of non-compliance, Defendants' own judgment is insufficient for determining whether their drug processing operations are adequately controlled to resume production of drugs intended to be sterile. As recently as July 25, 2017, Defendants recalled all lots of non-expired drug products intended to be sterile that were compounded and distributed nationwide between February 16 and July 19, 2017, due to lack of sterility assurance. *See* Maxwell Decl. ¶ 19. Previously, on November 18, 2016, Defendants recalled 29 lots of drug products intended to be sterile due to lack of sterility assurance. *See id.* ¶ 14.

On November 7, 2017, Cantrell filed for Chapter 11 bankruptcy. This type of bankruptcy, sometimes called a "reorganization," allows the debtor to remain in control of its business operations. After exiting reorganization, Cantrell has stated that it plans to continue with a planned expansion into a second production facility.

B. Defendants' Purported Remediation Efforts are Insufficient to Ensure Sterility of Their Products

FDA has given Defendants sufficient opportunity to bring their operations into compliance. However, Defendants' repeated attempts at corrective action have been unsuccessful. For example, Defendants stated that they made corrections in response to FDA's inspection in 2016, but FDA investigators observed CGMP violations during a 2017 inspection that were the same as or similar to the previously-identified deficiencies. *See* Maxwell Decl. ¶ 18 and Exh. 13. Moreover, several of the 2016 inspectional observations were repeats of or similar to observations from the 2013 inspection. *See id.* ¶ 13 and Exh. 7. Following FDA's 2013 inspection, the agency issued a Warning Letter, dated January 21, 2015, to Defendants, informing them of the serious nature of their CGMP violations and putting them on notice that their products "may be produced in an environment that poses a significant contamination risk." *Id.* ¶ 9 and Exh. 3. In response to the 2013 inspection and Warning Letter, Defendants stated that they took corrective actions. *Id.* ¶ 10 and Exhs. 5-6. However, the serious and pervasive CGMP violations and insanitary conditions documented by FDA investigators during the 2016 and 2017 inspections provide ample evidence of the likelihood of recurring violations. *See* Higgins Decl. ¶¶ 8, 18-33, 39-57.

Since the June 2017 inspection, Defendants claim to have remediated many of the insanitary conditions observed. Indeed, Defendants have hired at least three different third-party consultants since July 2017 to manage their quality assurance operations and provide "final review" of their products. *See* Maxwell ¶ 28. Defendants' supplemental submissions to FDA do not demonstrate compliance with the law. While Defendants' failures run deep, the United States, as discussed below, highlights two areas — environmental monitoring and air quality at

Defendants' facility, which demonstrate Defendants' inability to manufacture sterile drugs in a way that demonstrates their sterility and safety.

III. Legal Standard

The Act empowers federal district courts to enjoin violations of 21 U.S.C. § 331. 21 U.S.C. § 332(a). Because the United States seeks an injunction authorized by statute, the injunction standard applicable to private litigants in equity does not apply. *United States v. City and County of San Francisco*, 310 U.S. 16, 31 (1940); *United States v. Pro-Ag, Inc.*, 796 F. Supp. 1219, 1231 (D. Minn. 1991), *aff'd*, 968 F.2d 681 (8th Cir. 1992). If a statute authorizes injunctive relief, as does the Act at 21 U.S.C. § 332(a), injunctive relief is appropriate if the statutory conditions are satisfied. *United States v. Articles of Drug*, 633 F. Supp. 316, 326 (D. Neb. 1986), *aff'd in relevant part*, 825 F.2d 1238, 1248 (8th Cir. 1987). It is not necessary for the government to demonstrate irreparable harm or the absence of an adequate remedy at law. *Id.* (citations omitted); *see also United States v. Diapulse Corp. of America*, 457 F.2d 25, 27-29 (2d Cir. 1972). The requirements of injunctive relief are satisfied when the government establishes that the defendant has violated the applicable statute and that there is some cognizable danger of recurrent violations. *United States v. W.T. Grant Co.*, 345 U.S. 629, 633 (1953); *United States v. Articles of Drug*, 633 F. Supp. at 327. Moreover, the government need only show that it would be likely to succeed, both as to violation and risk of recurrence. *City of New York v. Golden Feather Smoke Shop, Inc.*, 597 F.3d 115, 120-21 (2d Cir. 2010). Examining Defendants' past record of noncompliance is the best way to predict the likelihood of future violative conduct. *W.T. Grant Co.*, 345 U.S. at 632-33; *Diapulse Corp.*, 457 F.2d at 28-29; *see United States v. Laerdal*, 73 F.3d 852, 855 (9th Cir. 1995) (holding that even one past violation is sufficient to show likelihood of future violations). Injunctive relief is particularly appropriate

where, as here, despite repeated warnings, defendants have persisted in violating the statute. *United States v. Kasz Enterprises, Inc.*, 855 F. Supp. 534, 544, *amended on other grounds*, 862 F. Supp. 717 (D.R.I. 1994). Based on the extensive evidence collected during FDA inspections, the United States is highly likely to succeed in demonstrating that Defendants have violated, and are likely to continue violating, the Act by manufacturing and distributing adulterated drugs.[2]

IV. ARGUMENT

A. Defendants Have Violated the Act

1. Defendants' Drugs Are Adulterated Based on Insanitary Conditions

Defendants manufacture drugs within the meaning of the Act. Products that are intended "for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "to affect the structure or any function of the body" are drugs within the meaning of the Act. 21 U.S.C. § 321(g)(1)(B). Defendants manufacture and distribute products intended for administration to patients by doctors to treat diseases or affect the body's structure or function.

Defendants' drugs are adulterated within the meaning of the Act because they have been "prepared, packed, or held under insanitary conditions whereby [they] may have been

[2] A preliminary injunction would also be warranted under the standard that applies to private litigants in equity. Under that standard, the Court would consider whether: (1) there is a threat of irreparable harm; (2) the threat of irreparable harm outweighs potential injury to the other party; (3) the movant is likely to succeed on the merits; and (4) a preliminary injunction is in the public interest. *Dataphase v. C.L. Sys., Inc.*, 640 F.2d 109, 114 (8th Cir. 1981) (en banc). First, FDA has repeatedly observed insanitary conditions and violations of CGMP at Defendants' facility, creating a real risk that their products will become contaminated. Second, the risk of harm to patients readily outweighs any risk of harm to Defendants. Cantrell's injectable drugs have nationwide distribution. They are meant to be injected, and when insanitary conditions cause microbiological contamination of injectable drugs, patients who receive the contaminated drug products may be at risk. This risk to human health and life outweighs the risk to Defendants' business. Third, the government is likely to succeed on the merits. To obtain permanent injunctive relief here, the government need only demonstrate that Defendants have violated the Act and that there is "cognizable danger of recurrent violation." *W.T. Grant Co.*, 345 U.S. at 633; *see United States v. 22 Rectangular or Cylindrical Finished Devices*, 714 F. Supp. 1159, 1167 (D. Utah 1989). Given their history of recurrent violations, Defendants are likely to continue to violate the law without an injunction. Finally, there is compelling evidence that the public interest is best served by granting the preliminary injunction. Cantrell has had multiple opportunities to remedy its deficiencies; the risk to patients is too great to wait any longer for voluntary compliance. Even if this standard is applicable, the United States meets it here.

contaminated with filth, or whereby [they] may have been rendered injurious to health." 21 U.S.C. § 351(a)(2)(A). To establish adulteration under this provision, the government need not show actual contamination, "only conditions that may result in contamination." *Berger v. United States*, 200 F.2d 818, 821 (8th Cir. 1952) (foods case); *cf. United States v. 789 Cases, More or Less, of Latex Surgeons' Gloves*, 799 F. Supp. 1275, 1287 (D.P.R. 1992) ("*Latex Surgeons' Gloves*") (device case) (stating that the government need only show "a reasonable expectation that the articles *could* become contaminated with filth.") (emphasis in original).

Most of Defendants' drugs are aseptically processed, which involves filling the drugs, which have been rendered sterile, into their final containers in a manner that maintains sterility. *See* Higgins Decl. ¶ 12. Because the products are not sterilized in their final containers, it is expected that containers are filled and sealed in an environment that is free of microorganisms. *Id.* Processes must be tightly controlled so that they do not introduce the risk of contamination during operations. *Id.* ¶ 11. Any discrepancies and failures in environmental conditions or production processes must be investigated and addressed to assure the quality of distributed and future products, and prevent ongoing deviations. *See id.* ¶¶ 34-38, 40, 51, 55.

Defendants' aseptic processing areas are not sufficiently controlled to protect drugs that are intended to be sterile against contamination during processing. *See id.* ¶ 18, 25-26, 31. Cantrell's own records of microbial contamination in ISO 5[3] or adjacent areas during aseptic production, and the lack of adequate product evaluation and remedial action, demonstrate that

[3] A cleanroom is a room in which the concentration of airborne particles is controlled and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room. Higgins Decl. ¶ 15. Cleanrooms are classified under the International Standards Organization ("ISO") standard, which defines a cleanroom environment based on the concentration of total particulates per volume of air. Id. An ISO 5 area requires a higher air quality and represents a clean environment for the most critical processing steps, i.e., where sterile product is exposed to the air. Other areas, such as ISO 6, ISO 7, and ISO 8, have somewhat less-stringent requirements, because sterile product in these areas should be at lower risk of contamination. Id.

drugs processed in those areas have been prepared, packed, or held under insanitary conditions. *Id.* ¶¶ 19-26. FDA investigators also observed microbial growth on environmental monitoring plates from Cantrell's ISO classified areas that Cantrell employees had also examined and recorded as having no growth. *See id.* Additionally, Cantrell is unable to control and manage its own air handling system. For example, positive air pressure differentials are not maintained to ensure proper air flow from areas of higher quality air to adjacent areas with lower quality air, and in some instances, the pressure has reversed, which can contaminate the cleanroom and place drug products processed in those rooms at risk for contamination. *Id.* ¶ 27.

All of Defendants' drug products intended to be sterile are at risk of contamination because there is no assurance that: (a) processing operations are sufficiently controlled to protect such drugs from contamination; and (b) any failures in environmental conditions and processing operations are appropriately investigated and adequately addressed to assure the quality of products already on the market and prevent recurrence of substandard operations during drug manufacturing. *See id.* ¶ 8.

Microbiological contamination of drug products intended to be sterile presents a significant public health risk. In 2012, injectable drug products produced under insanitary conditions by another compounding facility caused a fungal meningitis outbreak that spanned several states and resulted in more than 60 deaths and 750 cases of infection.[4] *See id.* ¶ 10. While this case is factually distinct, the example illustrates the nexus between the regulations and the health and safety of patients.

[4] *See* Centers for Disease Control and Prevention, "Multistate Outbreak of Fungal Meningitis and Other Infections – Case Count," available at https://www.cdc.gov/hai/outbreaks/meningitis-map-large.html.

Defendants' drugs are adulterated within the meaning of the Act because the insanitary conditions that FDA investigators observed during the inspections at Cantrell create a reasonable possibility that drugs manufactured and distributed by Defendants may be contaminated. *See id*. ¶¶ 26, 33.

a. Defendants Fail to Respond to Environmental Monitoring Results

During the 2017 inspection, FDA investigators documented that Defendants failed to establish and follow appropriate written procedures to prevent microbiological contamination of drug products intended to be sterile, as required by 21 C.F.R. § 211.113(b). *See* Jones Decl. ¶ 18. According to Defendants' own environmental monitoring records, they recovered several types of microorganisms in their cleanrooms – in the air and on the surfaces used for sterile processing of drugs, as well as on personnel engaged in manufacturing. *Id.* On twelve (12) separate occasions between January and May 2017, Cantrell's environmental and personnel monitoring in its ISO 5 areas detected microbes in excess of their "action limit" (i.e., a level of contamination high enough to trigger a remedial response such as an investigation and corrective action). *Id*. Cantrell failed to conduct follow-up investigations to determine the root cause or examine the impact to products intended to be sterile and therefore disregarded the potential adverse impact of this microbial contamination on patients. *Id.* ¶ 24. For example, on May 12, 2017, after detecting *Staphylococcus epidermidis* on surfaces in the ISO 5 area used for aseptically processing Sodium Bicarbonate 8.4% Injection Solution (50 mL) Syringe (Lot 10204), Defendants released the product for distribution. *Id.* ¶ 19. FDA investigators also noted that Defendants' environmental monitoring records recorded no microbial growth (measured in colony forming units ("CFUs")) on environmental and personnel monitoring plates when, on the

same day, FDA investigators observed a range of one (1) to twenty-six (26) CFUs on the very same plates. *Id*. ¶ 20.

b. Defendants Fail to Maintain Necessary Air Quality

Defendants have repeatedly failed to ensure air quality in aseptic processing areas by maintaining positive airflow and pressure differentials from areas of higher air quality (e.g., ISO 5 cleanrooms) to areas of lower air quality (e.g., anterooms adjacent to cleanrooms), which is necessary to prevent microbial contamination of sterile drug products during processing. Higgins Decl. ¶ 27. This recurring problem was observed recently in 2017, as well as in 2016, when Cantrell's third-party cleanroom certification found that the air pressure between the company's ISO 8 anterooms and ISO 7 buffer room did not meet the minimum pressure differential, as well as when FDA investigators reviewed multiple pressure differential gauges that read below the number necessary to prevent lower air quality from entering higher air quality spaces. *See* Jones Decl. ¶ 21; Higgins Decl. ¶ 44. Following the 2016 inspection, Cantrell committed to perform "enhanced monitoring and notification of critical differential pressures." Higgins Decl. ¶ 44. However, based on the 2017 inspection, Cantrell's corrective action was either ineffective or the company failed to meet its commitments.

Following the 2017 inspection, Cantrell stated it had conducted a comprehensive review and investigation of data from an internal system that was designed to monitor environmental conditions, including temperature and humidity, in controlled environments. Higgins Decl. ¶ 29. Specifically, Cantrell claimed that there were separate pressure sensors (secondary probes) to ensure backup for the primary pressure sensors in each cleanroom, and that per the company's investigation, "all backup probes maintained positive pressure readings…at the time of all excursions recorded in the [FDA] 483." *Id*. ¶ 28. However, Cantrell neither provided

justification as to why the data obtained from the backup probes could be used in place of the data from the primary probes, nor did Cantrell provide all the actual data from the backup probes. *Id*. Cantrell further explained that the primary probes may have been affected by "power surges, electrical fluctuations, an outside noise source or other electrical signal issues," without explaining why such disturbances would not affect the secondary probes. *Id*. FDA raised concerns about the backup probes in an October 6, 2017, letter to Cantrell. In response, Defendants contradicted their original statements, stating that there was no backup probe but only one probe. Given these inconsistent statements, Defendants' ability to understand what they are doing to ensure air pressure differentials are maintained across rooms is greatly in doubt. Further, despite FDA's repeatedly noted concerns, Cantrell has not investigated the possible root causes of pressure differential excursions and impact on drugs intended to be sterile.

Based on this and other evidence, Defendants continue to manufacture drugs under insanitary conditions.

2. Defendants' Drugs are Adulterated Based on Failure to Comply with CGMP as Required by Federal Law

In addition to the insanitary conditions at their facility, Defendants' CGMP violations also render their drugs adulterated. Drug manufacturers are responsible for establishing and implementing processes and procedures to ensure that the drugs they produce are free from contamination. *See* Higgins Decl. ¶¶ 9-12. The Act deems a drug to be adulterated if the "methods used in, or the facilities or controls used for, its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with [CGMP] to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to

possess." 21 U.S.C. § 351(a)(2)(B). FDA has promulgated regulations establishing minimum CGMP requirements applicable to drugs. *See* 21 C.F.R. Parts 210 and 211.

The CGMP regulations are designed to protect the public against exposure to substandard, ineffective, contaminated, or otherwise unsafe drugs. *See Latex Surgeons' Gloves*, 799 F. Supp. at 1285 (involving a parallel device adulteration provision). These regulations are preventive and focus on the conditions and methods by which drugs are produced. *See id*. The underlying principle behind CGMP is that quality is to be built into the finished product, which is achieved by controlling the manufacturing process at every step, and that quality cannot be "tested into" a finished product. *Id*. (citing CGMP Regulations, 43 Fed. Reg. 31,509 (1978)). Consumers generally cannot judge the quality of a drug by looking at it, and patients, physicians, and pharmacists must expect that a drug is safe, effective, and of high quality when they ingest, inject, or dispense it. *See id.* at 1285-86. Adequate and consistent control of manufacturing operations is necessary to prevent contamination, product failures, and other errors.

In a CGMP-based case, the government need not introduce evidence that a product is actually defective in some way; instead, the government establishes its case by showing a deviation from CGMP in the manufacturing process. *See United States v. Regenerative Scis.*, LLC, 878 F. Supp. 2d 248, 259 (D.D.C. 2012), *aff'd*, 741 F.3d 1314 (D.C. Cir. 2014) (quoting *John D. Copanos and Sons, Inc. v. FDA*, 854 F.2d 510, 514 (D.C. Cir. 1988) ("Drugs produced in violation of these CGMP regulations are deemed to be adulterated without the agency having to show that they are actually contaminated.")); *see also United States v. Western Serum Co.*, 498 F. Supp. 863, 867 (D. Ariz. 1980), *aff'd*, 666 F.2d 335 (9th Cir. 1982); *United States v. Lit Drug Co.*, 333 F. Supp. 990, 998 (D.N.J. 1971); *U.S. v. Bel-Mar Labs. Inc.*, 284 F. Supp. 875, 881 (E.D.N.Y. 1968).

a. Defendants Fail to Adhere to CGMP Regulations

During FDA's 2017 inspection, investigators observed serious CGMP deficiencies. For example, FDA investigators documented that Defendants fail to establish adequate control systems necessary to prevent contamination during aseptic processing, including an air supply filtered through high-efficiency particulate air (HEPA) filters under positive pressure, as required by 21 C.F.R. § 211.42(c)(10)(iii). *See* Jones Decl. ¶ 21. Agency investigators also observed positive pressure differentials between Cantrell's cleanrooms and anterooms demonstrating a loss of pressure on numerous occasions, yet Cantrell released finished drug products intended to be sterile that were processed from those cleanrooms. *Id.* Additionally, FDA investigators observed gaps around the HEPA filters and cracks in the ISO 5 hoods within the ISO 7 cleanrooms. *Id.* ¶ 22.

FDA investigators also documented Defendants' failure to establish a system for cleaning and disinfecting the processing area and equipment to ensure aseptic conditions, as required by 21 C.F.R. § 211.42(c)(10)(v). *See id*. ¶ 25. For example, Defendants' operators were observed placing their heads and upper body inside the ISO 5 hoods that are used to process sterile drug products. *Id.* ¶ 23.

In addition, FDA investigators documented Defendants' failure to thoroughly review and investigate unexplained discrepancies and batch failures, whether or not the batch has already been distributed, as required by 21 C.F.R. § 211.192. *See id*. ¶ 27. For example, Defendants did not conduct adequate investigations regarding microbial contamination in aseptic processing areas (on surfaces, in the air, and on personnel), as well as regarding spore-forming bacteria detected in ISO 5 areas, ISO 7 areas, and on operator gloves. *See id*. ¶ 25. Defendants' third party cleanroom certification company determined that eight ISO 5 hoods used to manufacture

purportedly sterile drug products had HEPA filter leaks during re-certification in November 2016, but Cantrell did not investigate the leaks to determine their impact on manufactured drug products intended to be sterile. *Id*. ¶ 24. Additionally, Cantrell did not investigate instances in which its finished product samples tested with an internal sterility testing system resulted in inconclusive test results for sterility. *Id.* ¶ 27.

FDA investigators also observed Defendants' failure to establish and follow written procedures for cleaning and maintaining equipment used to manufacture, process, pack, or hold drug products, as required by 21 C.F.R. § 211.67(b). For example, Defendants lack an approved written procedure for performing "terminal cleans" (i.e., an extensive cleaning process with repeat cleaning to remove high levels of microbial contamination due to activities, such as repair/maintenance in a cleanroom or observed microbial contamination in an ISO 5 hood during environmental monitoring), and had no documentation of having conducted a terminal clean for environmental excursions recorded in the company's own environmental monitoring monthly summaries. *Id.* ¶ 25.

FDA investigators have also repeatedly observed that Defendants fail to maintain a quality control unit that can carry out responsibilities required by law, including approving or rejecting all procedures or specifications that have an impact on the identity, strength, quality, and purity of the drug products. *See* Higgins Decl. ¶¶ 55-57. Following findings during the 2016 inspection that Cantrell's quality control unit had failed to execute its responsibilities for evaluating manufacturing and testing records, Cantrell stated that it had reorganized the quality assurance department and committed to revamp the investigation process to include root cause analysis for all excursions. *See* Higgins Decl. ¶ 50. However, during the 2017 inspection, FDA investigators documented continued deficiencies associated with quality oversight related to

cleaning, environmental monitoring, testing, and production records. *Id*. ¶ 56. To date, Cantrell has not demonstrated that it has a quality control unit capable of meeting the requirements of the law. Cantrell's December 31, 2017 submission includes an evaluation summarizing the competencies of Cantrell's Quality Assurance, Quality Control, and Operations units and responsibilities. Notably, the evaluation identifies areas where Cantrell has "the requisite knowledge and experience to execute acceptably, but lacks sufficient quantity of personnel with the requisite capability" and "is missing personnel with the requisite knowledge and experience to execute acceptably." *Id*. ¶ 59. The evaluation also does not include all relevant responsibilities for quality assurance, quality control, and operations personnel. Based on its representations to FDA, Cantrell fails to maintain a quality control unit capable of overseeing Defendants' operations.

b. Defendants Have Not Adequately Remediated CGMP Deficiencies

Supplemental submissions sent by Cantrell to FDA after the 2017 inspection have not established remediation of significant CGMP violations. For instance, FDA continues to have significant concerns with the ability of Cantrell's personnel to accurately record environmental monitoring data and initiate appropriate responses to prevent the recurrence of improper recording as observed during the 2017 inspection. As part of routine environmental monitoring, 503B compounding pharmacies such as Cantrell must take samples from various surfaces and then incubate the samples to test if colonies of microorganisms grow. While the firm's Standard Operating Procedure requires personnel to document the number of colonies per plate and generate a report and investigation if the number exceeds the action limit, Cantrell has not yet proven that it can properly implement its own policy.

During the 2017 inspection, FDA investigators observed that Defendants' environmental monitoring records recorded no microbial growth (measured in colony forming units ("CFUs")) on environmental and personnel monitoring plates when, on the same day, FDA investigators observed a range of one (1) to twenty-six (26) CFUs on the very same plates. Jones Decl. ¶ 20. Defendants have not provided an explanation as to why its environmental monitoring technicians were improperly recording data (as noted in both the 2016 and 2017 inspections). This was a serious failure by Cantrell, especially after FDA put the company on notice following the 2016 inspection.

Cantrell has also repeatedly failed to adequately address issues with its HEPA filters. HEPA filters are positioned above the work area in the workstations, or "hoods," where technicians process sterile drugs. Gaps around the filters can allow air and particulate contaminants, which can act as a vehicle for microorganisms, to enter into the cleanroom. Higgins Decl. ¶ 31. In both 2016 and 2017, FDA investigators observed ¼ to ½ inch gaps between the filters and the adjacent ceiling tiles, and discussed these findings with Defendants. Jones Decl. ¶ 22. Although Cantrell committed to FDA that it would seal the openings after the 2016 inspection, the 2017 inspection revealed that any corrective actions either were not implemented universally throughout Cantrell's cleanrooms or were ineffective. After the 2017 inspection once again brought the gaps to Defendants' attention, Cantrell responded on July 28 that the gaps around the HEPA filters had been repaired with caulk, and included photographs of the areas. Higgins Decl. ¶ 31. The company did not, however, perform a leak test to determine whether it sufficiently fixed the gaps around the HEPA filters; photographs alone cannot convey the most critical information about the supposed repair. *Id*. Relatedly, Cantrell's 2016 routine re-qualification activities found leaks from HEPA filters in seven (7) hoods used for aseptic

processing. Despite their knowledge of the leaks, Defendants did not conduct an investigation to determine the impact of these leaks on drug products until *after* these failures were brought to the company's attention once again during the 2017 FDA inspection. *Id.* ¶ 45.

Defendants simply do not observe the foundations of sterile drug manufacturing operations and, as a result, are unable to establish and maintain the conditions, practices, processes, procedures, and controls that are necessary for processing drugs intended to be sterile. *See, e.g.*, Higgins ¶¶ 8, 25, 31, 40-41, 43-46, 47-49, 52, 54, 56-60. Because Defendants have failed to comply with CGMP requirements, they cannot provide even a minimum level of assurance that the drugs they manufacture meet the requirements of the Act and the expectations of doctors and patients that Defendants' drugs are sterile. For these and other reasons, Defendants' drugs are adulterated under 21 U.S.C. § 351(a)(2)(B).

3. Defendants Introduce Adulterated Drugs Into Interstate Commerce

Defendants violate 21 U.S.C. § 331(a) by introducing into interstate commerce drugs that are adulterated due to insanitary conditions and a failure to comply with CGMP requirements. Defendants distribute most of their drugs directly to hospitals and other health care entities throughout the United States, including North Carolina, Pennsylvania, Colorado, and Virginia.

4. Defendants Cause Drugs to be Adulterated While Such Drugs Are Held for Sale After Shipment of One or More of Their Components in Interstate Commerce

Defendants violate 21 U.S.C. § 331(k) by causing drugs to become adulterated due to insanitary conditions and a failure to comply with CGMP requirements, while such drugs are held for sale after shipment of one or more of their components in interstate commerce. Defendants manufacture drugs at Cantrell using components that were shipped in interstate commerce, including components from New York and Illinois.

B. There Is a Cognizable Danger that Defendants Will Continue to Violate the FDCA

Defendants have openly resumed sterile processing and shipment of their drugs despite FDA's repeated recommendations that they temporarily cease operations in light of evidence of continued insanitary conditions and CGMP violations, and the lack of assurance that Defendants' products are actually sterile. Past behavior is the best indicator of future violations. *See United States v. Articles of Drug*, 633 F. Supp. at 327 (internal citations omitted). In this case, FDA investigators have repeatedly documented deficiencies in Defendants' environmental monitoring and aseptic processing practices. In response, Defendants have revised their standard operating procedures and attempted corrective actions, but Defendants' own records reveal continuing microbial contamination in aseptic processing areas and an overall failure to adequately investigate and take appropriate corrective actions to remediate problems pertaining to their aseptic processing practices. *See* Higgins Decl. ¶¶ 8, 18-25, 27, 30, 56. For example, FDA investigators reviewed environmental monitoring plates and corresponding records maintained and found results that were not appropriately identified and documented. *See id*. ¶¶ 8, 18-20, 23, 41. FDA investigators have also repeatedly noted deficiencies with the air supply in Defendants' cleanroom, yet Defendants continued to manufacture and distribute injectable products purporting to be sterile, but lacking assurance of actually being sterile. *See id*. ¶¶ 18, 44, 52(a).

Since 2013, FDA's inspections have also documented that Defendants fail to ensure that their personnel engaged in manufacturing, processing, packing, or holding drug products intended to be sterile are properly trained. *See* Higgins Decl. ¶ 53. For example, since 2013, Defendants claimed to have instituted an extensive and subsequently enhanced training of compounding personnel to ensure that all cleanroom technicians know the procedures and are capable of following them; however, based on the repeated deficiencies relating to aseptic

practices and environmental monitoring observed during the 2017 inspection, the training is inadequate. *Id*. ¶ 54.

Moreover, Defendants have resumed drug processing and, despite repeat recommendations from FDA about not distributing their drugs due to lack of sterility assurance, Defendants informed FDA that they resumed shipment of finished drug products on September 22, 2017, for drug products manufactured beginning on August 22, 2017. *See* Maxwell Decl. ¶¶ 21-23, 26, and Exhs. 21-22, 26. Prior to that, FDA communicated to Defendants during a teleconference on July 18, 2017, and subsequently by email, that the agency expected notification before Defendants resumed sterile compounding. On July 28, just one week after Defendants conducted a recall of all of their sterile products within expiry and temporarily ceased production at their facility, Defendant McCarley informed FDA by email that the company would resume production mere hours later, and would begin releasing that product on August 2. Later, in a letter dated October 12, Cantrell told FDA that it has dispositioned product produced between July 19 and August 21 to be rejected, as it "agree[d] that the requisite production and environmental controls had not been in place or remediated to an acceptable extent with proper documented verification." Exh. 12. Notwithstanding Defendants' decision not to release these specific drugs, Defendants continue to manufacture and distribute drugs in violation of federal law. Defendants' decisions demonstrate that they will continue to violate the law and expose patients to risk without this Court's intervention.

C. The Requested Preliminary Injunction is Tailored to Restrain Defendants' Violations

The preliminary injunctive relief the United States requests is tailored to restrain Defendants' continuing violations of the law. The proposed order of preliminary injunction enjoins Defendants from manufacturing, processing, packing, labeling, holding, and/or

distributing any drugs manufactured from their facility unless and until specific remedial actions are taken to achieve compliance with the law. The proposed order of preliminary injunction requires Defendants to temporarily cease their current operations, which is necessary given their ongoing violations. The proposed order also requires Defendants to recall and destroy all non-expired drugs manufactured, held, and/or distributed by them, which is appropriate in light of the scope of Defendants' unlawful distribution. Finally, the Order also provides Defendants with a pathway to resume operations, once they can demonstrate that they are in compliance with the law.

V. CONFERENCE WITH DEFENSE COUNSEL

Prior to filing this Motion for Preliminary Injunction, undersigned counsel for the United States conferred with Defendants' attorney, S. Graham Catlett, but the parties were unable to come to an agreement. Mr. Catlett stated on February 27, 2018 that his clients opposed the United States Motion for Preliminary Injunction.

VI. CONCLUSION

Because Defendants' ongoing violations are a threat to public health, the United States seeks a preliminary injunction that prohibits Defendants from manufacturing and distributing drugs until they bring their operations into compliance with the law and implement corrective actions to ensure that compliance is maintained. Preliminary injunctive relief is appropriate because Defendants have violated, and are likely to continue to violate, the Act.

FDA has repeatedly warned Defendants that they produce drugs under insanitary conditions and in violation of CGMP requirements. Despite their efforts, Defendants have not demonstrated that they have remediated those conditions. In light of these factors, a preliminary injunction is necessary to protect the public health while Defendants undertake appropriate

corrective actions to come into compliance with the Act. Unless enjoined by the Court, Defendants will continue to violate the law and expose patients to the risks associated with drugs intended to be sterile that are manufactured under conditions that provide no assurance of product sterility. Patients and health care practitioners who rely on Defendants' products expect and deserve better. The United States respectfully requests that the Court enter the proposed preliminary injunction.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that I have mailed and served the document or paper to the following participants in the manner indicated by the participant's name:

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