AseptiKits™
Revolutionizing Sterile Preparations

White Paper: Regulatory Compliance

USP Chapter <797> and PALA Technology Products

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It is understood that the Expert Committee that authored the U.S. Pharmacopeia Chapter 797 ("USP 797") standard based its content on technologies that were available at the time. The Committee also, wisely, included an alternative technology clause in the Introduction and Scope Section of <797> that "allows for the use of technologies not mentioned in the chapter as long as they are non-inferior to what is in the chapter and validated for the intended purpose."

Between February 20, 2020 and July 2, 2025, the FDA sent 78 Warning Letters to 503B pharmacies for failing to meet the USP 797 standards for prevention and contamination of sterile preparations. These involved discovery of insanitary conditions and operations. These letters speak to the extraordinary difficulties in meeting the USP 797 standard using the specified 797 procedures and equipment.

A new alternative technology named "PALA Technology" has been developed and utilized for making Autologous Blood Serum Tears (Serum Tears) for over six years without a single sterility issue. PALA Technology has been analyzed and certified for use for a broad band of applications for providing a consistent SAL (Sterility Assurance Level) of "at least 10^{-6}." The PALA Technology accomplishes 100% of this achievement without the use of highly regulated clean rooms, special garbing, detailed training. or expensive equipment.

The term "PALA" is an acronym that stands for "Portable Aseptic Level Assurance."

From the evidence, to follow, it should become clear that the information provided herein justifies the use of PALA Technology-based products for use as an "alternative technology." Each PALA based product meets the "non inferior" criteria and offers superior features that resolve each of the critical issues, cited hereafter facing regulators, pharmacists, and other clinicians today.

This is accomplished while still following the tenets of USP Chapter 797 and/or FDA requirements (e.g. "concerning beyond-use dates, the amount of time a single-dose or multiple-dose container may be used, while assuring the sterility of a clean room environment").

Contents

Introduction **5**

Executive Summary **8**

Sterile Preparation History 8

USP Chapter 797 Background 8

PALA Demonstration Video – Insert Video from Dr. Matthew S. Ward, MD 10

Joint Commission Inspections 10

FDA Findings and USP <797> Requirements 10

FDA Insanitary Findings and Warning Letters 11

FDA Warning Letter December 17, 2024 11

PALA Technology as a Non-Inferior Product Solution 15

Institution Evaluation Tool: PALA Technology and USP <797> Sterile Preparations **18**

PALA Technology and Clean Room Feature Comparison Chart 20

USP <797>/PALA Technology Evaluation Form 21

Detailed PALA Technology Description **31**

PALA Technology Product Patents **33**

PALA Technology Regulatory Overview and Schematic **34**

General Regulatory Schematic **36**

Insanitary Conditions in USP 797 Certified 503B Pharmacies **37**

Expanded Excerpts from the 15 FDA Warning Letters (Used to create insanitary summary) **46**

Certified Regulatory Consultant Reviews **66**

Joint Commission Inspections 67

USP 797 Overview / AseptiKits White Paper 74

Regulatory Compliance – PALA Technology Convenience Kits 74

Background 75

The Problems with Current USP Standards and cGMP 77

Significance and Roles Relative to Enforcement Discretion 79

Communications and Enforcement Discretion 81

What Is Enforcement Discretion? 82

Issues surrounding “Misuse of Vials” 83

Purpose of 503B Pharmacies 85

Summary and Conclusions 92

PALL Sterilizing-Grade Filter Specification 96

Areas of Critical Need 98

USP <797> Compliance Labels and PALA Products Sales Brochures 99

Summary and Conclusions 101

References 103

Appendix A: Fagron FDA Warning Letter (as cited in AseptiKits White Paper) 104

Appendix B: Propharma White Paper 113

Appendix C: Peak Consulting Letter 121

Appendix D: Links to FDA Warning Letters Cited Under the Heading: Sources of Insanitary Conditions in USP 797 Certified Facilities 124

Introduction

Between February 20, 2020 and July 2, 2025, the FDA sent 78 Warning Letters to 503B pharmacies for failing to meet the USP 797 standards for prevention and contamination of sterile preparations. Of note is an FDA quote addressing the sterility of preparations made within USP Chapter 797 certified clean rooms and a contamination violation:

> *"Please note, microbial contamination, when present, is not uniformly distributed within a batch; therefore, it may not be identified in a sterility test. Compounding facilities producing drug products intended to be sterile under insanitary conditions should not rely upon or cite a passing sterility test result as an indication of product sterility." (FDA, 2024 – See Appendix A).*

Note: Virtually all USP Chapter 797 clean rooms are or become "insanitary" at some point or on some level for many reasons. For example, numerous studies have demonstrated that pharmacists and pharmacy technicians tend to fall back into old habits over time where lapses in procedures can and do occur. The following excerpt is only one example which also highlights the deep concerns involved:

> *"Patient safety is in jeopardy due to a rise in the preparation of adulterated parenteral products with poor technique identified as a significant contributing factor. Pharmacy technicians perform an overwhelming majority of aseptic compounding practices; however, this group's progressive loss of aseptic technique knowledge has not been documented" (Davis and Ayars, 2021).*

Further, as shall be demonstrated in this analysis, it is difficult, if not impossible, to achieve the following (e.g.):

- Clean/sterilize product surfaces going through a pass-through window,
- Clean/sterilize equipment surfaces
- Remove contaminated particulate from clean rooms
- Consistently, thoroughly sanitize gloves
- Prevent users from breaking aseptic technique e.g. managing sleeves and other surfaces in a laminar flow hood
- Conduct adequate, regular cleaning

- Assure that compounders consistently follow the requirements of the Standard to maintain the sterility required for making "compounded sterile preparations" ("CSPs")
- Develop detailed and validated SOPs that assure corrections as contaminations occur

The more complicated a procedure, the more likely for errors to occur. Therefore, it is not surprising, but often alarming, that errors under USP 797 occur on a too frequent basis in these environments. These involve medication errors as well as CSP contaminations.

As a Summary Note: The above contends that NO pharmacy can claim "continuous uniformly distributed sterility" even when fully committing to follow USP 797.

As demonstrated by the volume of FDA Warning Letters and recalls due to contaminated products and the details of issues identified by the FDA (see "Insanitary Conditions in USP 797 Certified 503B Pharmacies" below and Links to FDA Warning Letters Cited Under the Heading: Sources of Insanitary Conditions in USP 797 Certified Facilities in Appendix D), the evidence makes clear the extreme difficulty of avoiding "insanitary conditions".

Note: This means that NO pharmacy can claim "uniformly distributed sterility" when following USP 797.

USP 797 contains similar verbiage as shown below:

> *"14.2.3 Sterility testing:*
>
> *Sterility testing (see 12.2 Sterility Testing) of a CSP can provide additional assurance of the absence of contamination,* ***although passing a sterility test does not guarantee that all units of a batch of CSPs are sterile because contamination may not be uniformly distributed throughout the batch.*** *A longer BUD is permitted if sterility testing results are within acceptable limits. The maximum batch size for all CSPs requiring sterility testing must be limited to 250 final yield units."*

Note: USP 797 requires that all preparations be held to a standard of "non contaminated" in order to "minimize harm, including death" (Introduction to USP Chapter 797) as made to be further clear in the quote below (bolding, underlining and italics added for emphasis):

"1.1 Scope

CSPS AFFECTED

The requirements in this chapter must be met to ensure the sterility of any CSP. ***Although the list below is not exhaustive, <u>the following must be sterile:</u>***

• Injections, including infusions

• Irrigations for internal body cavities (i.e., any space that does not normally communicate with the environment outside of the body such as the bladder cavity or peritoneal cavity). [NOTE—Irrigations for the mouth, rectal cavity, and sinus cavity are not required to be sterile.]" (USP 797 2022).

Note: Given the following FDA statement that passing a sampling sterility test cannot assure with 100% likelihood sterility of an entire preparation batch, the following FDA warning cited:

"Compounding facilities producing drug products intended to be sterile under insanitary conditions should not rely upon or cite a passing sterility test result as an indication of product sterility." (FDA, 2024 – See Appendix A)."

These events point to a need for improved "alternative technologies" that reliably meet or exceed USP 797 standards. PALA Technology-based products have been demonstrated to achieve this objective. PALA Technology provides sterile compounding opportunities for a wide range of products that include eye drop bottles, syringes, elastomeric pumps, and IV bags – including 3-in-1 TPN bags.

Executive Summary

USP Chapter 797 represents a sincere and professional effort by the Expert Committee to correct issues surrounding pharmacy sterile drug preparations. The tireless and detailed efforts by regulators including the FDA and state inspectors to assure compliance, where enforced, is also recognized as necessary and conducted in good faith.

That being said, the intensity, genius and firmness of support for USP 797 gives insight to the idiom that no strength of desire, merit of brilliance, depth of study nor weight of management can, through the control and authority of regulation, make perfect a widely used process that is inherently imperfect.

Sterile Preparation History

A long list of sad events well exemplifies the serious patient risks when preparations do not meet high standards for sterility. Drug preparation errors are well known to seriously worsen patient health. Such issues include, but are not limited to, CSP contaminations that lead to patient infections and medication errors either of which can cause severe patient harm including death. Prevention of non-sterile events focus on clean room and laminar flow hood design, cleaning / maintenance, garbing, introduction of products into the clean room, following SOPs intended to improve user aseptic technique, require testing by sampling, and other scheduled testing often without dealing with primary issues as cited by the FDA Warning Letters provided hereafter.

Further, it is well known in medicine, that the more complicated a procedure, the greater the likelihood for errors to occur. Therefore, it is not surprising, but often alarming, that errors under USP 797 occur on a too frequent basis in these environments. These involve medication errors as well as CSP contaminations.

USP Chapter 797 Background

The Chapter 797 Standard is detailed and well written while being nearly impossible to fully achieve as demonstrated by the many recalls and FDA Warning Letters due to failures to meet requirements including contaminations due to “insanitary conditions.”

The primary objective of USP 797 is to maintain sterility. The Standard also suggests that, optimally all preparations that can be, should be terminally sterilized. It should be noted that virtually all existing forms of terminal sterilization tend to degrade, contaminate

or destroy pharmaceutical drugs (e.g. gamma, heat/steam, ethylene oxide gas aka ETO, and e-beam) making them ineffective or even harmful.

The Standard recognizes that .22-micron sterilization can be used, but cannot be regarded as a form of "terminal sterilization". The reason for such is obvious given that filter use, as described in the Standard, does not provide a closed system and contamination is still possible, i.e. there is always an operational gap between the filter use and other interactions at "critical sites" (as defined in the Standard) that could still result in contamination during the preparation. It should be noted that, with PALA Technology, a .22-micron filter is affixed to provide a sealed, closed system connection, thereby creating a sterile compartment making such filtering a final and complete sterility step.

PALA Technology Solution

These events, and others, discussed in detail below, point to a need for improved "alternative technologies" that reliably meet or exceed USP 797 standards as provided in the Introduction to USP Chapter797.

PALA Technology products are USP Chapter 797 compliant by offering an "alternative technology" that provide a "non-inferior and validated" product that "does not modify requirements outlined in [chapter 797] (e.g., extending beyond-use dates, the amount of time a single-dose or multiple-dose container may be used and compounding in alternative environments)." Importantly, the product offers a consistent and effective means of offering terminal sterilization for all drugs that are compatible with a .22-micron sterilizing grade filter.

PALA Technology provides sterile compounding opportunities for a wide range of products that include eye drop bottles, syringes, elastomeric pumps, and IV bags – including 3-in-1 TPN bags.

PALA Demonstration Video – Insert Video from Dr. Matthew S. Ward, MD

https://www.youtube.com/watch?v=AgcTwOSyQFo&t=1s

Syrikit Demo Video by
Dr. Matthew S. Ward, MD

Joint Commission Inspections

Joint Commission on Accreditation of Healthcare Organizations ("JCAHO") plays a significant regulatory role relative to sterile drug preparations during its accreditation process. JCAHO inspections tend to be thorough and involve virtually every clinical person and patient-related activity in each facility with a focus on patient and provider safety.

JCAHO focuses on three general areas related to sterile pharmaceutical drug preparations. These include:

- USP Chapter 797 compliance
- State boards of pharmacy rules and regulations
- Adherence to manufacturer instructions for use regarding medical devices

FDA Findings and USP <797> Requirements

As stated supra, the FDA, issued the following statement:

> *"Please note, microbial contamination, when present, is not uniformly distributed within a batch; therefore, it may not be identified in a sterility test. Compounding facilities producing drug products intended to be sterile under insanitary*

conditions should not rely upon or cite a passing sterility test result as an indication of product sterility." (FDA, 2024 – See Appendix A).

This finding stands in direct conflict with the USP 797 standard which states (underlining and italics added for emphasis):

"1.1 Scope

CSPS AFFECTED

The requirements in this chapter must be met to ensure the sterility of any CSP. Although the list below is not exhaustive, the following must be sterile:

- *Injections, including infusions*
- *Irrigations for internal body cavities (i.e., any space that does not normally communicate with the environment outside of the body such as the bladder cavity or peritoneal cavity). [NOTE—Irrigations for the mouth, rectal cavity, and sinus cavity are not required to be sterile.]" (USP 797 2022).*

FDA Insanitary Findings and Warning Letters

The FDA has a long list of Warning Letters relative to "insanitary conditions," discovered during inspections, the causes for such include observed failures involving a substantial list of companies that failed to meet these standards. At this writing, there were 78 such letters posted between May 20, 2020 and July 2, 2025. These may be broken down into three broad categories:

- User technique caused
- Inadequate or faulty testing
- Lack of regulatory compliance relative to defined SOPs and testing to assure sterility

FDA Warning Letter December 17, 2024

"Gowned personnel are the greatest source of microbial contamination in an aseptic process. Operators performing a media fill of less than their typical production volume and duration does not represent the worst-case challenge and

stressful condition as it does not take into regard operator fatigue." (FDA Warning Letter Right Value Drug Stores, LLC December 17, 2024)

Many of the lists of violations in each case citing insanitary conditions are often surprisingly long, identifying multiple violations. A broader summary is provided under the heading "Insanitary Conditions in USP 797 Certified 503B Pharmacies. For instructions on reading the full FDA Warning Letter documents see Appendix D (including sources, with named addresses referenced in Appendix D).

Several highlights relative to FDA inspector observations and samples of 15 of the cited warning letters are provided below (underlining and italics are added for emphasis):

*"Aseptic operators reaching into the ISO 5 laminar flow hood past their elbows during aseptic production. However, microbial contamination action limit for personnel monitoring of the elbows is **(b)(4)**. This practice may introduce contamination into the ISO 5 work area."*

"Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility."

"...lack of gowning qualification program at your facility for entry to Cleanroom... ensuring sterile gowning is donned without contamination"

"Any microbial contamination in the ISO 5 area is considered an insanitary condition and is a serious concern."

"Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination."

"The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated."

"Your firm failed to perform adequate routine environmental monitoring. Specifically, your cleanroom certification consists of nonviable airborne

particulate and viable airborne particulate sampling of locations surrounding your ***(b)(4)*** *filling line, but does not include sampling within the critical area where aseptic processing occurs."*

Note: Bacteria often travel on particulate and is therefore a major concern when compounding in a clean room and laminar flow hood while attempting to maintain sterility.

"Your firm failed to appropriately sterilize equipment located in the ISO 5 area."

"You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area."

"Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b))."

"Your firm failed to establish an adequate system for maintaining equipment used to control the aseptic conditions (21 CFR 211.42©(10)(vi))."

"Your firm failed to clean and sterilize and process, where indicated by the nature of the drug, container closures to remove pyrogenic properties to assure they are suitable for their intended use (21 CFR 211.94©)."

"Your firm failed to provide equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature when appropriate for the manufacture, processing, packing, or holding of a drug product (21 CFR 211.46(b))."

"Your firm produced drug products while construction was underway without adequate controls to prevent contamination of the product environment and products."

"Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192)."

"You did not perform adequate product evaluation and take appropriate corrective actions after mold was recovered on operator glove finger plate samples taken after aseptic operations within the ISO 5 area.

"An operator placing their upper left side of their body into the ISO 5 hood within the syringe filler. In addition, another operator was observed placing their sleeves, chest, and forehead under the ISO 5 hood."

"Your facility is designed and operated in a way that first air is either not provided or blocked within ISO 5 areas where critical in-process operations are performed. For example:

a. Lack of first pass air over unwrapped, open IV bags prior to filling.

b. Blocked first pass air for exposed sterile closures (ports and syringe plungers) during introduction and conveyance on IV bag filling lines."

"Your smoke studies demonstrated that the air in an ISO 5 classified zone was turbulent and non-laminar near areas where IV bag filling and sealing are performed. "

"You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area."

"Your firm does not maintain the sterility of inter seals and outer closures for IV bags during production. ***(b)(4)*** *IV bags and caps with ports are exposed to worse than ISO 5 quality air prior to and during assembly/capping."*

"The ISO-classified areas had visibly dirty equipment and difficult to clean surfaces. Specifically, chipped and missing paint, apparent rust, adhesive tape, and a build-up of residues were observed on and around ***(b)(4)*** *equipment in an area where parisons are cut and conveyed to the point of aseptic filling."*

"FDA investigators also noted CGMP violations at your facility, that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

Your firm failed to establish an adequate air supply ***(b)(4)*** *particulate air filters under positive pressure in the aseptic processing areas (21 CFR 211.42(c)(10)(iii)).*

Your firm failed to ensure container closure systems provide protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product (21 CFR 211.94(b)).

Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

Your firm failed to ensure that substances required for equipment operations, such as lubricants and coolants, do not come in contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements (211.65(b)).

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils 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 (21 CFR 211.67(a)).

Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b))."

PALA Technology as a Non-Inferior Product Solution

PALA Technology Products ("PALA") offer a solution to all the above cited issues. PALA has been described as a "clean room in a bag" and each bagged kit (using medical grade header bags) meets FDA requirements as a "convenience kit." All components are manufactured and assembled in clean rooms in conditions that are consistent with FDA approved medical devices. All Class 2 product components come from already FDA approved devices. Everything inside each medical grade header bag has been sterilized

using common medical device sterilization procedures by well-known sterilization processing companies (e.g. Steris and Sterigenics). All fluids entering the bag are sterilized via a .22-micron sterilizing grade filter having an SAL of "at least 10^{-6}. (Note: HEPA filters used in Class 5 clean rooms, including those used in laminar flow hoods generally have a pore size of .3-microns). All vessels inside PALA Header bags are filled, capped, and sealed prior to opening the PALA bag thereby assuring safety when making each sterile preparation without a clean room or laminar flow hood.

PALA Technology products are simple and easy to use following conventional technique (prior to USP 797), thereby addressing concerns about complicated procedures where the likelihood of errors is arguably high under 797 processes.

As a result, PALA Technology offers an FDA cleared product with inherent safeguards that guarantee and assure sterility that meet or exceed USP 797 standards and objectives.

As provided, under USP 797 PALA Technology products offer an "alternative technology" that resulted in a "non-inferior and validated" product that "does not modify requirements outlined in [chapter 797] (e.g., extending beyond-use dates, the amount of time a single-dose or multiple-dose container may be used and compounding in alternative environments)."

Note: The clean room, sterile environment inside a medical grade header bag is an improved environment compared to a contemporary certified 797 clean room and laminar flow hood. PALA Technology Kits are manufactured in an FDA registered clean room and then sterilized. This exceeds the 797 clean room environment as a closed and validated sterile environment as is intended and required under Chapter 797.

Improvements to the 797 standard include, but are not limited to the following:

1.) Closed system sterile processing
2.) User technique independent – no direct human contact with "critical sites" during compounding i.e. touch contamination is eliminated
3.) All injected non sterile fluids are sterilized via the .22-micron filter to "an SAL of at least 10^{-6}" (Propharma report)
4.) .22-micron sterility is superior to HEPA filtration (HEPA filters are rated as .3-microns)
5.) Sterility is achieved via use of an FDA cleared medical device and not as a user-dependent relative to aseptic technique procedure

6.) All preparations that can pass through a .22-micron filter are terminally sterilized (filter is integral to the PALA Header Bag) to an SAL of 10^{-6}
7.) All vessels are capped and sealed from the outside of the header bag prior to opening
8.) Simplified procedure – results, in principle, in fewer errors (contamination and medication errors) by reducing a long document and resulting SOPS, required for USP 797 to a single sheet of Instructions for Use ("IFU")
9.) Simple to understand and easy to meet USP sterility requirements
10.) FDA cleared product, including testing verification and validation assures the sterility assurance level and results of FDA approved and FDA cleared medical devices
11.) A post preparation filter bubble test assures that the integrity of the filter has not been compromised
12.) No critical sites, as defined in 797, are exposed during drug preparation.

Institution Evaluation Tool: PALA Technology and USP <797> Sterile Preparations

Scope:

USP <797> states:

> *"The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (USP <797> Section 1)."*

This document evaluates the use of PALA technology kits in a USP <797> sterile compounding facility.

PALA Technology: Convenience kits with PALA technology are designed with the following principles:

A header bag is filled with terminally sterilized drug containers (e.g. syringes, vials, elastomeric pumps, eye dropper bottles, etc.). Caps or other suitable closure devices are also included inside each kit. These containers will be filled and capped before the header bag is opened, thus maintaining sterility.

1. The sterilized header bag features an integrated sterilizing-grade 0.22-micron filter. All drug passing through the filter and into the drug containers is sterilized via this filter. Sterile processing is verified by testing the filter using a bubble test at the conclusion of the filling process.

2. Other devices inside the header bag are provided to facilitate the filling and capping process.

Discussion: USP <797> states, "*The requirements in this chapter must be met to ensure the sterility of any CSP*" (USP<797> Section 1.1.1), acknowledging that any human error or mechanical deviation may lead to adulterated product. US FDA further concludes that post-process sterility testing is insufficient to determine sterility, saying: *microbial contamination, when present, is not uniformly distributed within a batch; therefore, it may not be identified in a sterility test. Compounding facilities producing drug products intended to be sterile under insanitary conditions should not rely upon or cite a passing*

sterility test result as an indication of product sterility. (Fagron WL # 698861, see also USP <797> section 14.2.3).

The challenge is self-evident. Clean rooms and laminar flow hoods are not sterile environments, despite best efforts to sanitize them. Human errors, mechanical failures and biological ingress will occur resulting in the distribution of adulterated drug. In summary: USP <797> is insufficient as evidenced by FDA warning letters.

In comparison, PALA technology offers clinicians primary engineering controls (PECs) that are sterile, single use, portable, intuitive, simple-to-use closed systems that maintain a sterile compounding environment, prevent touch contamination and sterilize drugs as they enter each drug container.

PALA Technology and Clean Room Feature Comparison Chart

Facilities and Engineering Controls	Clean Room	PALA Technology
Environment	Not a closed system, positive pressure	Closed system, sterile environment inside the header bag.
Air filtration	HEPA Filter (0.30 microns)	Integrated 0.22-micron air filter in the header bag.
Positive air flow	Required with verification testing	Not required. PALA is a terminally sterilized, closed system.
Anteroom	Required	Not required. PALA is a terminally sterilized, closed system.
Clean room sanitization	Required	Not required. PALA is a terminally sterilized, closed system.
Gloving and garbing	Required	Required only for personnel safety
Sterilization of drug	Optional	Integrated engineering control
Airflow/smoke testing	Required	Not required. PALA is a terminally sterilized, closed system.
Sanitization of items entering the clean room	Required	Required only for bag contents
Pass-through box	Required	Not required. PALA is a terminally sterilized, closed system. Drug passes through a sterilizing grade 0.22 micron filter as it enters the kit.
Number of process steps	Numerous with many opportunities for contamination	Few steps and simplified workflow (one page instructions for use).
Validation steps	Testing: numerous and complicated.	Simple training and validation of sterile process.
Beyond Use Date Testing	Required	Required

USP <797>/PALA Technology Evaluation Form

The following is an evaluation form to determine the suitability of using PALA technology kits (e.g. Vitrala™, Syrikit™, PALA YourTears™, etc.) for sterile compounding in a facility without a clean room or laminar flow hood.

Firm Name and Address	Evaluation Date

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
2. Personnel Training and Evaluation	Training and Evaluation Required	Training and Evaluation Required	☐ Inferior ☐ Non-inferior ☐ Superior
2.1 Demonstrating Knowledge and Competency of Core Skills	Training and Evaluation Required	Training and Evaluation Required	☐ Inferior ☐ Non-inferior ☐ Superior
2.2 Demonstrating Competency in Garbing and Hand Hygiene	Training and Evaluation Required	Training and Evaluation Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior
2.3 Competency Testing in Aseptic Manipulation	Training and Evaluation Required	Training and Evaluation Required. Sterility is maintained by the PALA technology kit (User technique independent)	☐ Inferior ☐ Non-inferior ☐ Superior

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
3. Personal Hygiene and Garbing	Training and Evaluation Required	Training and Evaluation Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior
3.1 Personnel Preparation	Training and Evaluation Required	Training and Evaluation Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior
3.2 Hand Hygiene	Training and Evaluation Required	Training and Evaluation Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior
3.3 Garbing Requirements	Training and Evaluation Required	No special garbing required. Training and Evaluation Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior
4. Facilities and Engineering Controls	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
4.1 Protection from Airborne Contaminants	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
4.1.1 Air quality standards	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
4.1.2 Design requirements to maintain air quality	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
4.2 Facility Design and Environmental Controls	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
4.2.1 Types of SECs and design	Required	Not Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior
4.2.2 The CSP compounding environment	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
4.2.3 Types of PECs and placement	Required	Not Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior
4.2.4 Air exchange requirements	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
4.2.5 Establishing and maintaining pressure differentials	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
4.2.6 Facilities preparing Category 2 or Category 3 CSPs from nonsterile starting components	Required	Not Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior
4.3 Creating Areas to Achieve Easily Cleanable Conditions	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
4.4 Water Sources	Required	Required.	☐ Inferior ☐ Non-inferior ☐ Superior

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
4.5 Placement and Movement of Materials	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
5. Certification and Recertification	Required	Validation testing and certification from the manufacturer.	☐ Inferior ☐ Non-inferior ☐ Superior
5.1 Total Airborne Particle Sampling	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
6. Microbial Air and Surface Monitoring	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
6.1 General Monitoring Requirements	Required	Not Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
6.2 Monitoring Air Quality for Viable Airborne Particles	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
6.3 Monitoring Surfaces for Viable Particles	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
6.3.1 Surface sampling—timing and locations	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
6.3.2 Surface sampling procedures	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
6.3.3 Surface sampling data evaluation and action levels	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
7. Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA	Required	Cleanliness recommended in the workspace.	☐ Inferior ☐ Non-inferior ☐ Superior
7.2 Procedures for Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA in the PEC	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior
8. Introducing Items into the SEC and PEC	Required	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
9. Equipment, Supplies and Components	Required	Not Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior
10. Sterilization and Dehydrogenation	Process dependent	Not Required. Sterility is maintained by the PALA technology kit.	☐ Inferior ☐ Non-inferior ☐ Superior

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
10.1 Depyrogenation	Process dependent	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
10.2 Sterilization by Filtration	Process dependent	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
10.3 Sterilization by Steam Heat	Process dependent	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
10.4 Sterilization by Dry Heat	Process dependent	Sterile closed environment maintains sterility (SAL 10-6) equal to or better than an ISO Class 5 cleanroom environment.	☐ Inferior ☐ Non-inferior ☐ Superior
11. Master Formulation and compounding records	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
12. Release Inspections and Testing	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior
12.2 Sterility Testing	Required as per BUD specification and sample testing	Terminally sterilized. Testing required as per BUD specification and institutional protocols.	☐ Inferior ☐ Non-inferior ☐ Superior
12.3 Bacterial Endotoxins Testing	Required as per BUD specification and sample testing	Terminally sterilized. Testing required as per BUD specification and institutional protocols.	☐ Inferior ☐ Non-inferior ☐ Superior
13. Labeling	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior
14. Establishing Beyond-Use Dates	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior
15. Use of Conventionally Manufactured Products as Components	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior
16. Use of CSPs as Components	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior
17. SOPs	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior
18 Quality Assurance and Quality Control	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior

USP <797> Section	Preparation in a USP <797> Clean room	Sterile Preparation with PALA Technology	PALA Technology Determination (check one box per row).
19. CSP Handling, Storage, Packaging, Shipping and Transport	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior
20. Documentation	Required	Required	☐ Inferior ☐ Non-inferior ☐ Superior
21. Compounding Allergenic Extracts	Required	Required Note: Some large molecules allergenic extracts may not be compatible with a sterilizing-grade filter.	☐ Inferior ☐ Non-inferior ☐ Superior

Evaluated By	
Title	
Date	
Signature	

Detailed PALA Technology Description

PALA Technology Kits feature single use, closed-system products using a medical grade header bag and integral 0.22-micron sterilizing grade filter.

PALA Technology products are sterilized in the manufacturing process to an SAL of 10^{-6} via ETO sterilization under strict and controlled conditions.

These products enable clinicians to prepare sterile solutions without a clean room or laminar flow hood. These are commonly referred to as "a clean room in a bag."

Perhaps an apt comparison of PALA Technology Kits to cGMP and USP Chapter 797 Standards is to indicate two major differences:

1. PALA Technology Kits are FDA cleared medical devices designed to provide sterile compounding in a closed system using a "new technology" without a clean room or laminar flow hood. These Kits are shown to be "non inferior," reliable and USP Chapter 797 compliant (Propharma, 2024).
2. USP Chapter 797 Standards describe a lengthy process involving a clean room/laminar flow hood, and pass-through window operations, SOPs, extensive training, frequent testing, certification, and inspections to reasonably achieve consistent sterile preparations. As shown supra, these processes sometimes, and without warning, often break down resulting in large drug and medical device recalls that cause major supply chain interruptions while placing patients at risk for serious infections and harm, including death.

PALA Technology Kits provide features that set it apart from current cGMP and USP Chapter 797 described processes as shown in Table 2 below:

Table 2: Features and Benefits

Features	Benefits
Each kit is a sterile, single use, FDA cleared Convenience Kit.	**Built-in safeguard:** Kit contents begin sterile and remain sterile through filling, capping and sealing.
Fluids passing through the integral 0.22-micron filter are sterilized to an SAL of "at least 10^{-6}" inside a closed system.	**Built-in safeguard:** Sets a higher standard by terminally sterilizing each preparation
Drug containers are filled inside a sterile environment equal to or better than an ISO Class 5 clean room and laminar flow hood.	**Built-in safeguard:** Avoids touch and other harmful microbial contaminations. Provides user technique independent sterility - equal to or better than USP <797> standards.
All preparations are capped and sealed before opening the header bag	**Built-in safeguard:** Assures a finished sterile preparation
Post-fill bubble test	**Built-in safeguard:** Verifies filter integrity.
Designed for conventional user technique	Intuitive use
Ergonomic design	Easy-to-use
Optimal dosing from a variety of source containers	Lowers drug and device costs, maximizes drug utilization
Supports drug and device supply chains	Reduces the probability of recalls and supply chain interruptions.
Portable use without a clean room and laminar flow hood	Drug compounding anytime, anywhere including natural disaster conditions.
Complies with FDA regulations, USP, CDC standards, state boards of pharmacy and Joint Commission.	Meets or exceeds regulatory requirements for sterile preparations
Reduces processing steps	Simplifies drug preparation – known to reduce preparation errors
510(k) approved components	Meets FDA regulatory requirements as a Convenience Kit.

PALA Technology Product Patents

The importance of patents goes beyond protecting intellectual property. Requirements to get a patent boil down to three things. Any patentable invention must be:

1.) New
2.) Novel and non-obvious
3.) Useful

In patent law, "usefulness," or utility, is a core requirement for an invention to be patentable. It means the invention must have a practical, real-world application and serve a purpose. This ensures that patents are granted for inventions that offer genuine value and are not merely theoretical or speculative ideas.

Inventions must also be “reduced to practice.” In patent law, "reduced to practice" signifies that an invention has been developed to the point where it is either physically built and tested (actual reduction to practice) or described in sufficient detail in a patent application to enable someone skilled in the art to make and use it (constructive reduction to practice).

New patented technologies are critical to improving healthcare. These patents prove that the PALA Technology products are useful by meeting critical healthcare needs by assuring consistent sterility of compounded, re-packaged and other sterile drug preparations.

To date, AseptiKits owns seven granted patents plus eight filed applications (commonly referred to as “patent pending”).

A list of granted patent numbers references and patent application numbers is shown below:

PALA Technology Protected by Patents	U.S. Patent Applications
US 10,555,872	US 17/803,552
US 10,940,087	US 18/831,587
US 10,800,556	US 18/445305
US 11,312,605	US 18/08305
US 12,121,693	US 18/831,101
US 12,064,394	US 18/831,353
US 12,350,235	US 18/831,400
	US 18/831,587

PALA Technology Regulatory Overview and Schematic

This document is intended to address common regulatory questions. The following outline provides a brief overview of PALA Technology products. The term "PALA" is an acronym for Portable Aseptic Level Assurance. PALA Technology products provide means for assured sterile preparations without a clean room or laminar flow hood. These products are USP 797 compliant and FDA cleared.

The schematic that follows is intended to illustrate a general description of regulatory responsibilities relative to the U.S. Pharmacopeia Chapter 797 Standard ("USP 797"), State Boards of Pharmacy (these vary from state to state) and the FDA.

Beyond Use Dating ("BUD") can be established through testing to assure sterility and drug stability over time. It is up to each facility to conduct such testing as appropriate based on industry standards.

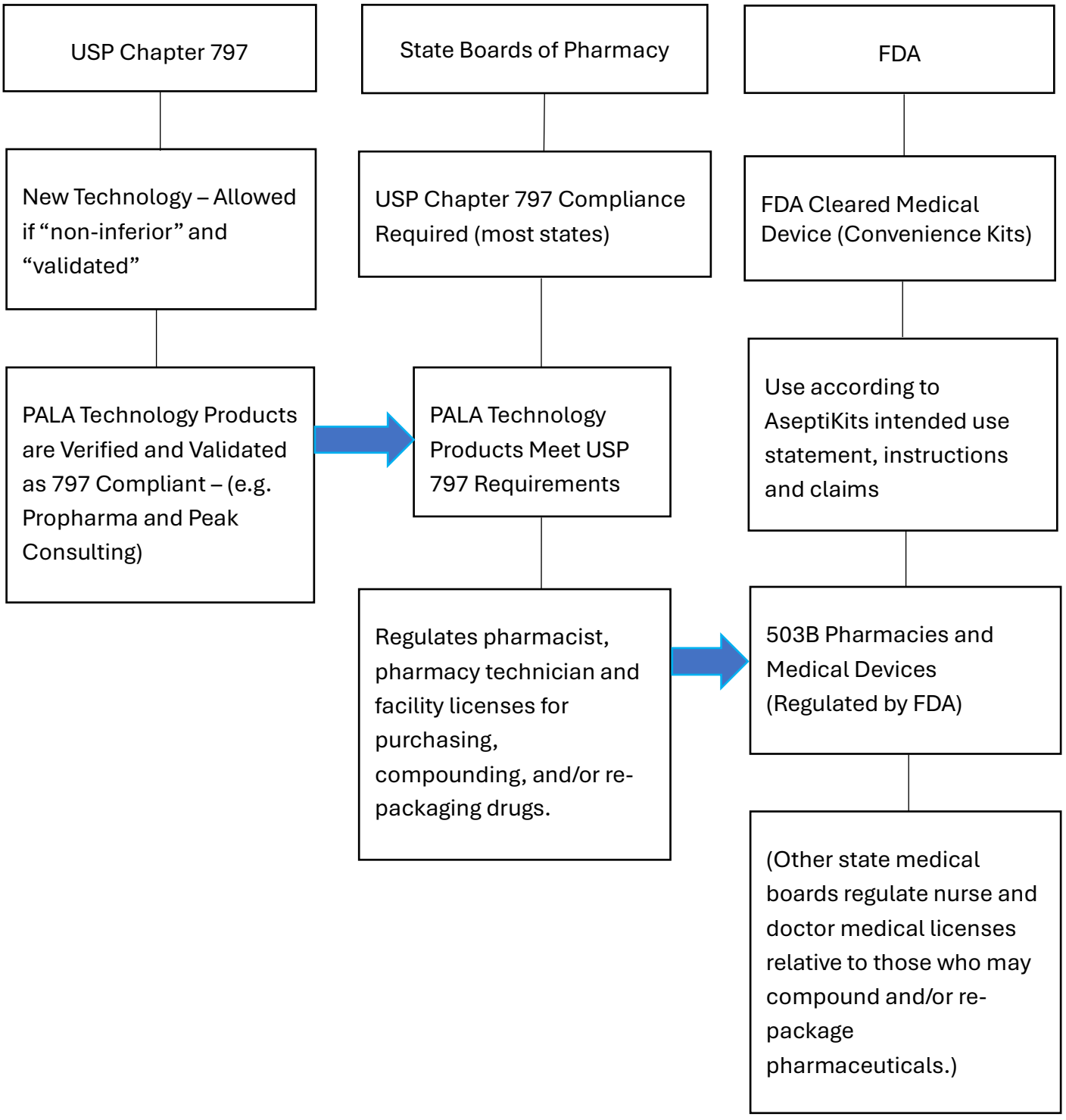
Brief PALA Technology Specification:

1. PALA Technology utilizes a sealable plastic, medical grade, header bag (the PALA Bag). The PALA bag is preferably a "Medical Grade Header Bag" which is permissive to filtered air influx which is used to permit tenting the bag for easier in-bag component access and displacement. The PALA bag is fitted with a filter assembly by which all matter entering the bag is filtered to the sterile state. Bag contents including vessels to be filled and tools for filling and capping are displaced into The bag before the bag is closed and sealed; after which the bag and contents are sterilized as a final step in kit manufacture. Thus, all fluids entering the bag are sterilized to a Sterility Assurance Level ("SAL") "of at least 10^{-6}," the industry standard for medical devices and pharmaceutical injectables via an integral .22-micron sterilizing-grade filter.
2. All filling, capping and sealing is accomplished from the exterior of the closed PALA bag making the process user-technique-independent. No critical sites are exposed during this process.
3. Once all receiving vessels (e.g. syringes, eye drop bottles, vials, IV bags, elastomeric balls) are capped and sealed, the bag may be opened, filled products accessed and labeled per institutional protocol.

4. A filter bubble test is accomplished to assure the integrity of the .22-micron filter as described in the product Instructions for Use (“IFU”).
5. The IFU also provides an Intended Use Statement in addition to product use instructions.

For additional information see the AseptiKits website at: https://www.aseptikits.com/ or contact AseptiKits by email at sales@aseptikits.com .

General Regulatory Schematic



Insanitary Conditions in USP 797 Certified 503B Pharmacies

AseptiKits found 78 entries for FDA Warning Letters related to “insanitary conditions” between February 20, 2020 and July 2, 2025. The following samples are provided as examples from 15 of those letters only and do not comprise the scope of all violations in each letter or overall.

The companies involved in these Warning Letters were identified as having long histories of honorable performance in their respective fields. This document is not intended to vilify any company or person, but rather to identify issues in meeting conditions established under USP 797 and the difficulties involved in achieving compliance. Copies of the entire Warning Letters can be found by following the link and search instructions found in Appendix D.

As becomes evident, the difficulties in achieving and maintaining the USP 797 standards are difficult at best, while vulnerabilities to sterile preparation contaminations persist.

It is important to note that virtually all medical device companies experience identified corrective action and/or suggestions for improvement from well trained and knowledgeable FDA agents. These agents are tasked with assuring patient safety and regulatory compliance involving a complicated process having high objectives (consistently sterile preparations). These tend to be instructive in nature intended to improve and ensure compliance with all regulatory requirements. FDA Warning Letters tend to provide insight into more serious issues, in this case, insanitary conditions involved in the production of sterile preparations under USP 797 standards that can lead to serious patient infections.

The specific FDA statement below is particularly important when considering issues surrounding personnel operating within a 797 certified facility and likelihood of contaminations:

FDA Warning Letter Right Value Drug Stores, LLC, December 17, 2024

> *“Gowned personnel are the greatest source of microbial contamination in an aseptic process. Operators performing a media fill of less than their typical production volume and duration does not represent the worst-case challenge and*

stressful condition as it does not take into regard operator fatigue." (FDA Warning Letter Right Value Drug Stores, LLC December 17, 2024)

The following FDA Warning Letter statements are instructive relative to sources of contaminations within 503B certified USP 797 compliant facilities. These were selected as exemplary and not all-inclusive relative to issues that are occurring in all such facilities nationwide as a whole or pertaining to specific Warning Letters. **These, in no way, are intended to embarrass or harm companies who received the letters or highlight them in a way that demeans their efforts to comply with USP 797 or FDA regulations.**

Note: No attempt, at this point was made to identify issues found by state boards of pharmacy relative to sterile 503A preparations on a state-by-state basis. However, it is reasonable to conclude that similar findings are likely.

Excela Pharma Sciences, LLC July 2, 2025

"Your firm failed to conduct laboratory testing to determine whether each batch of drug product purporting to be sterile conforms to such requirements (21 CFR 211.167(a))."

FDA Warning Letter to Staska Pharmaceuticals, May 5, 2025

*"Aseptic operators reaching into the ISO 5 laminar flow hood past their elbows during aseptic production. However, microbial contamination action limit for personnel monitoring of the elbows is **(b)(4)**. This practice may introduce contamination into the ISO 5 work area."*

"Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility."

FDA Warning Letter OSRX April 23, 2025

"address a lack of gowning qualification program at your facility for entry to Cleanroom... ensuring sterile gowning is donned without contamination"

"Any microbial contamination in the ISO 5 area is considered an insanitary condition and is a serious concern."

"Your investigations did not include environmental trending reports for each personnel performing work inside the ISO 5 classified area when microorganisms were recovered inside the ISO 5BSC from active viable air sampling plates." (FDA Warning Letter OSRX April 23, 2025)

"This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products" (Exela Pharma Sciences, LLC 2025)

Tailstorm Health Inc. dba Medivant Health, April 8, 2025

"Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination."

"The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated."

Empower Clinic Services, LLC dba Empower Pharmacy, April 2, 2025

*Your firm failed to perform adequate routine environmental monitoring. Specifically, your cleanroom certification consists of nonviable airborne particulate and viable airborne particulate sampling of locations surrounding your **(b)(4)** filling line, but does not include sampling within the critical area where aseptic processing occurs.*

Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility.

Your firm failed to appropriately sterilize equipment located in the ISO 5 area.

You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Your firm failed to establish an adequate system for maintaining equipment used to control the aseptic conditions (21 CFR 211.42©(10)(vi)).

Fagron, December 19, 2024

You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

Your firm produced drug products while construction was underway without adequate controls to prevent contamination of the product environment and products.

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

2. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).

3. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Right Value Drug Stores, LLC, December 17, 2024

Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

3. Your firm failed to clean and sterilize and process, where indicated by the nature of the drug, container closures to remove pyrogenic properties to assure they are suitable for their intended use (21 CFR 211.94©).

4. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

5. Your firm failed to provide equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature when appropriate for the manufacture, processing, packing, or holding of a drug product (21 CFR 211.46(b)).

QuVa Pharma Inc., January 26, 2024

You did not perform adequate product evaluation and take appropriate corrective actions after mold was recovered on operator glove finger plate samples taken after aseptic operations within the ISO 5 area.

An operator placing their upper left side of their body into the ISO 5 hood within the syringe filler. In addition, another operator was observed placing their sleeves, chest, and forehead under the ISO 5 hood.

Carolina Infusion, May 22, 2023

Your firm produced drug products with materials that had not been verified to assure that they did not contribute endotoxin contamination that may be objectionable given the product's intended use.

2. Your facility design allowed the influx of poor-quality air into a higher classified area.

3. Your firm used non-pharmaceutical grade components in the formulation of non-sterile drug products.

4. Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility.

5. Your ISO-5 classified areas were not certified under dynamic conditions.

Imprimis, May 26, 2023

One of your ISO 5 classified aseptic processing areas contained HEPA filters that were stained.

2. Your facility is designed and operated in a way that may permit the influx of lesser quality air into a higher quality air area.

3. Your cleanroom contained fiber-like particles hanging from the ceiling as well as ceiling tiles with peeling caulking.

4. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination.

5. An operator placed their gloved hands outside the ISO 5 work area to retrieve supplies without sanitizing their gloved hands before re-entry into the ISO 5 hood.

6. Your firm did not disinfect materials during transfer from the ISO 7 cleanroom into the ISO 5 hood.

Pharmedica, April 28, 2023

Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. Your firm also failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas (21 CFR 211.113(b) & 211.42(c)(10)).

You manufactured a multi-dose, preservative-free, over-the-counter (OTC) ophthalmic drug product for the product owner, Purely Soothing, without adequate

facility design, controls, and procedures to ensure sterility of containers/closures and finished ophthalmic drug product. If ophthalmic drugs are not sterile, they pose an unacceptable risk to patients including infection and potential for vision loss.

Furthermore, it is essential that multi-dose ophthalmic drug products contain one or more suitable substances that will preserve a product and minimize the hazard of injury resulting from incidental contamination during use.

During the inspection, you informed us that you were unaware that ophthalmic drug products are required to be sterile, and acknowledged that your facility is not designed and equipped to handle or manufacture sterile drug products, even though your drug products are intended for use as "eye drops."

Sagent, July 27, 2022

Your facility is designed and operated in a way that first air is either not provided or blocked within ISO 5 areas where critical in-process operations are performed. For example:

Lack of first pass air over unwrapped, open IV bags prior to filling

Blocked first pass air for exposed sterile closures (ports and syringe plungers) during introduction and conveyance on IV bag filling lines.

2. Your smoke studies demonstrated that the air in an ISO 5 classified zone was turbulent and non-laminar near areas where IV bag filling and sealing are performed.

3. You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

4. Your firm does not maintain the sterility of inter seals and outer closures for IV bags during production. ***(b)(4)*** *IV bags and caps with ports are exposed to worse than ISO 5 quality air prior to and during assembly/capping.*

5. The ISO-classified areas had visibly dirty equipment and difficult to clean surfaces. Specifically, chipped and missing paint, apparent rust, adhesive tape,

*and a build-up of residues were observed on and around **(b)(4)** equipment in an area where parisons are cut and conveyed to the point of aseptic filling.*

*6. Sterilized equipment and utensils wrapped **(b)(4)** and **(b)(4)** were stored in your "transition area," an unclassified area, without an established hold time to ensure that these items remain sterile.*

FDA investigators also noted CGMP violations at your facility, that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

*1. Your firm failed to establish an adequate air supply **(b)(4)** particulate air filters under positive pressure in the aseptic processing areas (21 CFR 211.42(c)(10)(iii)).*

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42©(10)(iv)).

3. Your firm failed to ensure container closure systems provide protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product (21 CFR 211.94(b)).

4. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

5. Your firm failed to ensure that substances required for equipment operations, such as lubricants and coolants, do not come in contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements (211.65(b)).

6. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

7. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils 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 (21 CFR 211.67(a)).

8. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Expanded Excerpts from the 15 FDA Warning Letters (Used to create insanitary summary)

Example 1: Excela Pharma Sciences, LLC July 2, 2025

Adulterated Drug Products

The FDA investigators noted CGMP violations at your outsourcing facility, that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act. The violations include, for example:

1. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

2. Your firm failed to conduct laboratory testing to determine whether each batch of drug product purporting to be sterile conforms to such requirements (21 CFR 211.167(a)).

3. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

4. Laboratory records are deficient in that they do not include the initials and signature of the second person reviewing the record for accuracy (21 CFR 211.194(a)(8)).

5. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

6. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions (21 CFR 211.25(a)).

7. Your firm failed to establish acceptance criteria for the sampling and testing conducted by the quality control unit that are adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release (21 CFR 211.165(d)).

Example 2: ProRx, LLC, March 4, 2025

1. Your firm's operator was observed filling drug product intended to be sterile in a manner that directly blocked first pass air over uncapped filled vials.

2. Your firm's Pharmacist in Charge (PIC) was observed rapidly prodding a pile of sterilized rubber caps with forceps, in an attempt to dislodge them, inside of the ISO 5 Biosafety Cabinet (BSC), near uncapped filled vials of drug product intended to be sterile. This practice, moving quickly in a critical area, may disrupt airflow and increases the risk of bringing lesser quality air into the ISO 5 area.

3. An operator exposed their bare hands within the ISO 5 work area while donning gloves in preparation for aseptic production.

4. Your firm's PIC put on gowning apparel in a way that may cause the gowning apparel to become contaminated. Specifically, your firm's PIC was observed bending down on the floor, on their hands and knees, inside of the ISO 7 Anteroom. Your firm's PIC then only sprayed their gloves with ***(b)(4)*** *and proceeded to produce drug products intended to be sterile.*

Your firm's PIC put on gowning apparel in a way that may cause the gowning apparel to become contaminated. Specifically, your firm's PIC was observed bending down on the floor, on their hands and knees, inside of the ISO 7 Anteroom. Your firm's PIC then only sprayed their gloves with ***(b)(4)*** *and proceeded to produce drug products intended to be sterile.*

Your firm's ISO 5 BSC is powered off when not in use and during the cleaning and disinfection process prior to aseptic drug production. There is no assurance that contamination is not introduced when the BSC is powered off as it may allow for the influx of lesser quality air into a higher quality air area.

Your firm used non-sterile wipes within the ISO 5 aseptic processing area.

7. Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility.

8. Your firm has never performed environmental monitoring in the ISO 5 area.

9. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination.

10. A flying insect was observed on the walls and ceilings of the ISO 7 Anteroom and on the door inside of the ISO 7 Buffer Room, approximately 10 feet from the ISO 5 BSC used for sterile drug processing.

FDA investigators also noted CGMP violations at your facility, that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42©(10)(iv)).

3. Your firm failed to establish an adequate quality unit and the responsibilities and procedures applicable to the quality control unit are not in writing and fully followed (21 CFR 211.22(a) and 211.22(d)).

4. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

5. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

6. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42©(10)(v)).

7. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).

8. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

9. Your firm failed to establish an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

Example 3: FDA Warning Letter to Staska Pharmaceuticals, May 5, 2025

C. Violations of the FDCA

Adulterated Drug Products

The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator noted:

1. Aseptic operators reaching into the ISO 5 laminar flow hood past their elbows during aseptic production. However, microbial contamination action limit for personnel monitoring of the elbows is ***(b)(4)****. This practice may introduce contamination into the ISO 5 work area.*

2. Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility.

3. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your

products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination.

The FDA investigator also noted CGMP violations at your facility, that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

3. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions (21 CFR 211.25(a)).

4. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42©(10)(iv)).

5. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils 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 (21 CFR 211.67(a)).

6. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Example 4: OSRX April 23, ,2025

The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may

have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator observed:

1. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 classified critical area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination. Specifically, you did not include ***(b)(4)*** *operators working inside the ISO 5* ***(b)(4)*** *Biosafety Cabinet (BSC) simultaneously to perform check weighing, filling, and capping activities, as per your production activities.*

2. You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

The FDA investigator also noted CGMP violations at your facility, that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

3. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42©(10)(iv)).

4. Your firm failed to establish and follow adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product (21 CFR 211.110(a)).

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the

preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a revised draft guidance, Current Good Manufacturing Practice — Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. *This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.*

Under section 301(a) of the FDCA [21 U.S.C. § 331(a)], the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, it is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

Example 5: Tailstorm Health Inc. dba Medivant Health, April 8, 2025

The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator observed that:

1. You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

2. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination.

The FDA investigator also noted CGMP violations at your facility, that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42©(10)(iv)).

Example 6: Empower Clinic Services, LLC dba Empower Pharmacy, April 2, 2025

The FDA investigators noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators observed that:

1. Your firm failed to perform adequate routine environmental monitoring. Specifically, your cleanroom certification consists of nonviable airborne particulate and viable airborne particulate sampling of locations surrounding your ***(b)(4)*** *filling line, but does not include sampling within the critical area where aseptic processing occurs.*

2. Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility.

3. Your firm failed to appropriately sterilize equipment located in the ISO 5 area. Specifically, your firm did not sterilize the stopper sorting bowl, supply hopper, and insertion station that come into contact with stoppers used in the production of injectable drug products.

Under section 301(a) of the FDCA [21 U.S.C. § 331(a)], the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, it is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

Example 7: Empower Clinic Services, LLC dba Empower Pharma, April 2, 2025

Adulterated Drug Products

FDA investigators noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators observed:

1. You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

2. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination.

FDA investigators also noted CGMP violations at your facility, that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

3. Your firm failed to establish an adequate system for maintaining equipment used to control the aseptic conditions (21 CFR 211.42©(10)(vi)).

4. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42©(10)(iv)).

5. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a revised draft guidance, Current Good Manufacturing Practice — Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. *This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated*.

Under section 301(a) of the FDCA [21 U.S.C. § 331(a)], the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, it is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

Example 8: ProRx LLC, March 4, 2025

Violations of the FDCA

Adulterated Drug Products

FDA investigators noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators observed that:

1. Your firm's operator was observed filling drug product intended to be sterile in a manner that directly blocked first pass air over uncapped filled vials.

2. Your firm's Pharmacist in Charge (PIC) was observed rapidly prodding a pile of sterilized rubber caps with forceps, in an attempt to dislodge them, inside of the ISO 5 Biosafety Cabinet (BSC), near uncapped filled vials of drug product intended to be sterile. This practice, moving quickly in a critical area, may disrupt airflow and increases the risk of bringing lesser quality air into the ISO 5 area.

3. An operator exposed their bare hands within the ISO 5 work area while donning gloves in preparation for aseptic production.

4. Your firm's PIC put on gowning apparel in a way that may cause the gowning apparel to become contaminated. Specifically, your firm's PIC was observed bending down on the floor, on their hands and knees, inside of the ISO 7 Anteroom. Your firm's PIC then only sprayed their gloves with ***(b)(4)*** *and proceeded to produce drug products intended to be sterile.*

5. Your firm's ISO 5 BSC is powered off when not in use and during the cleaning and disinfection process prior to aseptic drug production. There is no assurance that contamination is not introduced when the BSC is powered off as it may allow for the influx of lesser quality air into a higher quality air area.

6. Your firm used non-sterile wipes within the ISO 5 aseptic processing area.

7. Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility.

8. Your firm has never performed environmental monitoring in the ISO 5 area.

9. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination.

10. A flying insect was observed on the walls and ceilings of the ISO 7 Anteroom and on the door inside of the ISO 7 Buffer Room, approximately 10 feet from the ISO 5 BSC used for sterile drug processing.

FDA investigators also noted CGMP violations at your facility, that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42©(10)(iv)).

3. Your firm failed to establish an adequate quality unit and the responsibilities and procedures applicable to the quality control unit are not in writing and fully followed (21 CFR 211.22(a) and 211.22(d)).

4. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

5. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

6. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42©(10)(v)).

7. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).

8. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

9. Your firm failed to establish an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

10. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and 211.84(d)(2)).

Example 9: Fagron Compounding Services, LLC, December 19, 2024

The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator observed that.

1. You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

2. Your firm produced drug products while construction was underway without adequate controls to prevent contamination of the product environment and products.

The FDA investigator also noted CGMP violations at your facility, that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

2. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).

3. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a revised draft guidance, Current Good Manufacturing Practice — Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. *This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.*

Under section 301(a) of the FDCA [21 U.S.C. § 331(a)], the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, it is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

Example 10: Right Value Drug Stores, LLC, December 17, 2024

Adulterated Drug Products

FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator observed:

1. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination. Specifically, your smoke studies demonstrated disruption in unidirectional airflow in your BSC hood 19-00133.

2. Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically

produce drug products within your facility. Specifically, your firm's media fill vial quantity per technician fails to reflect the most challenging conditions.

FDA investigator also noted CGMP violations at your facility, that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

3. Your firm failed to clean and sterilize and process, where indicated by the nature of the drug, container closures to remove pyrogenic properties to assure they are suitable for their intended use (21 CFR 211.94©).

4. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

5. Your firm failed to provide equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature when appropriate for the manufacture, processing, packing, or holding of a drug product (21 CFR 211.46(b)).

Example 11: QuVa Pharma Inc., January 26, 2024

FDA investigators noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators observed:

You did not perform adequate product evaluation and take appropriate corrective actions after mold was recovered on operator glove finger plate samples taken after aseptic operations within the ISO 5 area.

An operator placing their upper left side of their body into the ISO 5 hood within the syringe filler. In addition, another operator was observed placing their sleeves, chest, and forehead under the ISO 5 hood.

Example 12: Carolina Infusion, May 22, 2023

Adulterated Drug Products

The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator observed the following:

1. Your firm produced drug products with materials that had not been verified to assure that they did not contribute endotoxin contamination that may be objectionable given the product's intended use.

2. Your facility design allowed the influx of poor-quality air into a higher classified area.

3. Your firm used non-pharmaceutical grade components in the formulation of non-sterile drug products.

4. Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility.

5. Your ISO-5 classified areas were not certified under dynamic conditions.

Example 13: Imprimis Rx, May 26, 2023

Adulterated Drug Products

The FDA investigators noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators observed that:

1. One of your ISO 5 classified aseptic processing areas contained HEPA filters that were stained.

2. Your facility is designed and operated in a way that may permit the influx of lesser quality air into a higher quality air area.

3. Your cleanroom contained fiber-like particles hanging from the ceiling as well as ceiling tiles with peeling caulking.

4. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination.

5. An operator placed their gloved hands outside the ISO 5 work area to retrieve supplies without sanitizing their gloved hands before re-entry into the ISO 5 hood.

6. Your firm did not disinfect materials during transfer from the ISO 7 cleanroom into the ISO 5 hood.

Example 14: Pharmedica USA, LLC, April 28, 2023

CGMP Violations

During our inspection, our investigators observed specific violations including, but not limited to, the following.

Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. Your firm also failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas (21 CFR 211.113(b) & 211.42(c)(10)).

You manufactured a multi-dose, preservative-free, over-the-counter (OTC) ophthalmic drug product for the product owner, Purely Soothing, without adequate facility design, controls, and procedures to ensure sterility of containers/closures and finished ophthalmic drug product. If ophthalmic drugs are not sterile, they

pose an unacceptable risk to patients including infection and potential for vision loss.

Furthermore, it is essential that multi-dose ophthalmic drug products contain one or more suitable substances that will preserve a product and minimize the hazard of injury resulting from incidental contamination during use.

During the inspection, you informed us that you were unaware that ophthalmic drug products are required to be sterile, and acknowledged that your facility is not designed and equipped to handle or manufacture sterile drug products, even though your drug products are intended for use as "eye drops."

To help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, see FDA's guidance document Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice at https://www.fda.gov/media/71026/download.

Example 15: Sagent Pharmaceuticals, Inc., July 27, 2022

Adulterated Drug Products

FDA investigators noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators observed that:

1. Your facility is designed and operated in a way that first air is either not provided or blocked within ISO 5 areas where critical in-process operations are performed. For example:
a. Lack of first pass air over unwrapped, open IV bags prior to filling.
b. Blocked first pass air for exposed sterile closures (ports and syringe plungers) during introduction and conveyance on IV bag filling lines.

2. Your smoke studies demonstrated that the air in an ISO 5 classified zone was turbulent and non-laminar near areas where IV bag filling and sealing are performed.

3. You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

4. Your firm does not maintain the sterility of inter seals and outer closures for IV bags during production. ***(b)(4)*** *IV bags and caps with ports are exposed to worse than ISO 5 quality air prior to and during assembly/capping.*

5. The ISO-classified areas had visibly dirty equipment and difficult to clean surfaces. Specifically, chipped and missing paint, apparent rust, adhesive tape, and a build-up of residues were observed on and around ***(b)(4)*** *equipment in an area where parisons are cut and conveyed to the point of aseptic filling.*

6. Sterilized equipment and utensils wrapped ***(b)(4)*** *and* ***(b)(4)*** *were stored in your "transition area," an unclassified area, without an established hold time to ensure that these items remain sterile.*

FDA investigators also noted CGMP violations at your facility, that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to establish an adequate air supply ***(b)(4)*** *particulate air filters under positive pressure in the aseptic processing areas (21 CFR 211.42(c)(10)(iii)).*

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42©(10)(iv)).

3. Your firm failed to ensure container closure systems provide protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product (21 CFR 211.94(b)).

4. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

5. Your firm failed to ensure that substances required for equipment operations, such as lubricants and coolants, do not come in contact with components, drug product containers, closures, in-process materials, or drug products so as to alter

the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements (211.65(b)).

6. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

7. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils 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 (21 CFR 211.67(a)).

8. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Certified Regulatory Consultant Reviews

Conclusions from two certified regulatory consultant groups that evaluated PALA Technology products are provided below. Copies of the complete documents are available in appendices B and C.

propharma

"4. CONCLUSION

The ALAdrop and PALA 12 Convenience Kits are a technology that allows the user to have the equivalent of a desktop aseptic processing area. Clinicians transfer the collected autologous serum samples to the kit using the provided syringe. The sample passes through either one or two filters that are attached to the bag and is collected within the ophthalmic dropper bottles. Caps are placed on the bottles and secured in place using the provided ratchet. Once all bottles are filled, capped, and tightly closed, the bag is then opened (breaking the seal of the sterile environment) for retrieval of the bottles.

The ALAdrop and PALA 12 Convenience Kits are not a pharmaceutical drug product, yet the overall validation process follows some of the same principles of drug product sterility assurance (i.e., validation of sterilization process, validation of the sterilizing filter). ETO sterilization of the kit has been demonstrated to provide a sterile closed bag system for the processing of autologous serum eye drops, without impact to the form or function of the kit (Rane et al. 2023-attachment 2).

Furthermore, the sterile environment within the bag is maintained via use of the connected 0.22-micron filter. The use of a 0.22-micron sterilizing grade filter within a closed system achieves preparations having a sterility assurance level (SAL) of at least 10^{-6}, which is the equivalent to a moist heat terminal sterilization cycle using an autoclave.

Given the above, these closed systems comply with USP <797> for the compounding of sterile preparations" (Propharma, 2024).

Joint Commission Inspections

Joint Commission on Accreditation of Healthcare Organizations (“JCAHO”) plays a significant regulatory role relative to sterile drug preparations during its accreditation process. JCAHO inspections tend to be thorough and involve virtually every clinical person and patient-related activity in each facility with a focus on patient and provider safety.

JCAHO focuses on three general areas related to sterile pharmaceutical drug preparations. These include:

- USP Chapter 797 compliance
- State boards of pharmacy rules and regulations
- Adherence to manufacturer instructions for use regarding medical devices

Regarding who can compound and repackage sterile medications, Joint Commission and USP are clear on this matter as stated below:

“Medication - Sterile Compounding - Supervision of Compounding Activities

The United States Pharmacopeia (USP) 797 refers to a 'designated person' (“DP”) as the individual to 'supervise all compounding activities'. Does The Joint Commission require this individual to be a pharmacist?

No. The Designated Person (DP) referenced in the USP 797 chapter is responsible for development of standard operating procedures, training, maintaining an appropriate physical environment and ensuring compliance with the chapter. The Joint Commission will survey to the USP 797 requirement for the DP, which the organization has deemed qualified through education, training, and competency to serve in this role” (Joint Commission 2023).”

The following embodies the clear objectives of Joint Commission surrounding drug compounding and re-packaging in locations where a pharmacist is running an operation in the areas stated supra:

“The Joint Commission's requirements for drug repackaging and compounding, particularly for sterile preparations, are based on USP General Chapter <797> and related standards. These standards emphasize the need for proper training, environmental controls, and quality control procedures to ensure patient safety.”

Areas of JCAHO foci include:

“1. Personnel and Training:

Compounding staff must demonstrate competency through media fill testing, gloved fingertip sampling, and written didactic testing.

Evaluation of hand washing and proper donning of personal protective equipment (PPE) is also required.

2. Environmental Controls:

Compounding should occur in an ISO Class 5 or higher environment.

Primary Engineering Controls (PECs), such as laminar airflow workbenches, are crucial for maintaining a sterile environment.

Facilities must adhere to air quality standards, including positive pressure in clean rooms and anterooms, and negative pressure for hazardous drug handling.

3. Compounding Process:

Low-risk compounding involves simple transfers of sterile ingredients using aseptic technique.

Medium-risk compounding utilizes aseptic technique for multiple transfers or multiple doses for multiple patients.

The process must be in accordance with a licensed practitioner's prescription or medication order.

Master formulas for non-sterile compounding must include specific information like ingredient names and quantities, stability data, and mixing instructions.

4. Quality Control and Beyond-Use Dates (BUDs):

Beyond-use dates must be assigned to compounded preparations, considering factors like sterility, stability, and storage conditions.

Quality control procedures are essential to ensure the accuracy and reliability of the compounded product.

5. Medication Security:

Medications must be stored securely to prevent tampering, theft, or diversion, in accordance with laws and regulations.

Two patient identifiers should be used when administering medications.

6. Compliance and Certification:

Organizations can pursue Medication Compounding Certification from The Joint Commission, which focuses on personnel, product, and environment standards.

This certification helps demonstrate a commitment to quality and safety in medication compounding practices.

Compounding practices must also comply with state and federal laws and regulations.

By adhering to these requirements, healthcare organizations can minimize risks associated with medication compounding and ensure patient safety, according to the Joint Commission" (Joint Commission, 2023).

Meeting requirements of state pharmacy boards is also important relative to Joint Commission inspections. A summary of State pharmacy board rules/regulations by state can be found using the internet link below:

chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.jointcommission.org/-/media/tjc/documents/accred-and-cert/cah/feb_2017_state_compounding_regulations.pdf

Who can be a designated person to repackage sterile medications under Joint Commission guidelines?

"The Joint Commission, when surveying for United States Pharmacopeia (USP) Chapter <797> (Sterile Compounding) compliance, requires that an organization designate one or more individuals as a "Designated Person(s)" (DP) responsible and accountable for the oversight of sterile compounding activities, including the development of standard operating procedures, training, maintaining an appropriate physical environment, and ensuring compliance with the chapter, according to The Joint Commission.

While a pharmacist is generally responsible for supervising all compounding, packaging, and dispensing of drugs and biologicals, the DP is not explicitly required to be a pharmacist.

Instead, the organization determines who is qualified to serve in this role based on their education, training, and demonstrated competency in sterile compounding practices.

Therefore, depending on the organizational structure and the qualifications of the individuals involved, a designated person could be:

A pharmacist [or]

A pharmacy technician with specialized training and demonstrated competency in sterile compounding [or]

Other qualified healthcare professionals with relevant education, training, and experience in sterile compounding and adherence to USP <797> requirements.

Important considerations:

State and Federal laws and regulations: All compounding, packaging, and dispensing must comply with applicable state and federal laws and regulations.

Competency Assessment: The organization must formally evaluate the competency of individuals performing repackaging activities.

Training and Documentation: The designated person(s) is responsible for developing and implementing training programs for staff involved in sterile compounding and maintaining records of their qualifications and training.

In essence, the Joint Commission emphasizes the organization's responsibility to ensure that anyone designated to oversee and perform sterile medication repackaging or compounding has the necessary qualifications, training, and demonstrated competency to safely and compliantly handle these sensitive processes. Among the top 5 issues for which Joint Commission cited hospitals was the following:

“In the infection control area, hospitals also struggled with reducing the risk of infections associated with medical equipment, devices and supplies.” (Hrickiewicz, 2018).”

Considering the findings provided in this document e.g. citations in the FDA Warning Letters relative to insanitary conditions (see information under the heading titled Insanitary Conditions

in USP 797 Certified 503B Pharmacies and Appendix D), healthcare facilities managers will need better alternative technologies to address infection control issues associated with drug re-packaging and compounding.

The following statements summarize what Joint Commission is looking for during inspections relative to drug storage practices (Lambert, 2022):

"1. Labeling requirements

Medications or solutions transferred to a different container must be immediately labeled.

Labels need to include essential information like the medication name, strength, amount, diluent details, and expiration date/time.

Labels must be verified verbally and visually by two qualified individuals, especially if administration is done by someone other than the preparer.

Unlabeled medications or solutions should be discarded immediately.

2. Sterile preparation and environmental controls

Repackaging typically occurs in controlled environments, often within a pharmacy.

Nurses generally focus on safe medication administration rather than extensive repackaging.

Practices that increase the risk of errors, such as preparing large batches of syringes in advance, are discouraged.

3. Storage and security

Medications must be stored securely to prevent issues like theft or diversion.

This includes securing controlled substances and following proper handling and disposal procedures.

Nurses should adhere to established policies for medication control from storage to administration and disposal.

Special attention should be given to multi-dose vials, hazardous, and refrigerated medications regarding labeling and expiration dates.

In summary: While TJC standards don't outright ban nurse repackaging, they require it to be done in a controlled environment with strict adherence to labeling, storage, and sterile preparation guidelines. Nurse responsibilities primarily revolve around safe medication administration, with extensive repackaging typically managed by pharmacy staff or designated personnel. “

As discussed supra, given identified contamination risks that occur in USP Chapter 797 certified clean room environments, there is an indicated need for alternative technologies that offer improved engineering controls results in consistently sterile preparations. These needs are well evidenced based on FDA Warning Letters issued between February 20, 2020 and July 2, 2025 to 503B pharmacies for failing to meet the USP 797 standards for prevention and contaminations of sterile preparations as described supra.

All the issues related to such contaminations are resolved using PALA Technology products as stated in the USP Chapter 797 standard.

“Conclusion:

The only enforcement agency related to the use and marketing of the Convenience Kits is the FDA. AseptiKits has complied with and demonstrated the safe and effective use of their Convenience Kits, and are legally registered with the FDA, and actively maintain their cGMP Quality Management System documentation in accordance with 21 CFR 820 and ISO 13485:2016. The USP and State Pharmacy Boards have no legal jurisdiction or enforcement capability or responsibility over the marketing and use of products that have demonstrated compliance with their standards. It is for the reasons outlined herein, that the AseptiKits Convenience Kits can legally and lawfully, in compliance with USP <797> and the FDA regulations and guidance documents, stated previously, be marketed for its intended purpose.”

USP 797 Overview / AseptiKits White Paper

The following document was written to address questions and issues concerning USP 797 while providing comparisons indicating compliance between USP 797 and PALA Technology products. Importantly, comparative tables not only show that the technology is "non inferior" but rather exceeds the standard in a variety of areas.

This document further illustrates the level of analysis, evaluation and thought put into the creation of the PALA Technology to ensure compliance with the USP 797 standard and FDA regulations. A copy of the full document with references is provided below:

Regulatory Compliance – PALA Technology Convenience Kits

Confidential

Matt S. Ward, M.D.
Gale H. Thorne, Ph.D., P.A.
Gale H. Thorne Jr., MBA Healthcare Management

"First, 'do no [preventable] harm' is the most fundamental principle of any health care service. No one should be harmed in health care; however, there is compelling evidence of a huge burden of avoidable patient harm globally across the developed and developing health care systems. This has major human, moral, ethical, and financial implications (World Health Organization, 2023)."

The U.S. Pharmacopeia ("USP"), FDA, CDC, state pharmacy boards and associated inspectors, have a long history of honorable efforts to create regulations, standards and enforcement that improve patient care while meeting and promoting the ethics of "do no harm." Importantly, this includes the making of sterile preparations intended to provide a high level of safety and efficacy for patients who receive them. These efforts should be applauded for the sincerity, time and concern involved in "minimizing harm, including death" (USP Chapter 797 2023), to the patients served and clinicians who treat them. Still, many issues remain as a direct result of people striving to meet what are, sometimes, difficult, if not impossible, standards and procedures designed to meet resulting requirements. These also have the effect of making patient access to critical sterile preparations difficult, if not occasionally inaccessible, to patients.

As a result, doctors, nurses, pharmacists, and others in the healthcare industry frequently face major issues relative to patient safety, supply chain shortages and high pharmaceutical drug costs in addition to patient access to compounded and re-packaged preparations. Concerns over contaminated preparations that can cause severe harm to their patients and those events which cause supply chain interruptions of critical and necessary medications are sadly, all too common in contemporary medical practice. Today, these are a constant concern for clinicians.

Fortunately, recognizing the vision of the FDA and authors of the U.S. Pharmacopeia Standards, such regulations and standards provide an opportunity for healthcare medical device manufacturers to create new technologies and products having significant potential to minimize these issues.

This paper is intended to provide information in support of providers considering use of a new technology and products, which are designed to meet FDA regulations and USP Chapter 797 Standards while helping providers achieve their respective oaths and ethics to "do no harm."

Background

The USP Standard is a well written, albeit a long and sometimes difficult to parse document that has been proved to improve preparation sterility when strictly followed. Consequently, "503B Outsourcing Facilities came into existence in 2013 as a result of the Drug Quality and Security Act (DQSA). It created Section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C), prompting extensive regulatory changes in the safe and effective compounding of drugs and medicines" (Fagron, 2025).

Prior to this time, hospitals and retail pharmacies made sterile preparations in a "clean room" that consisted of working in a designated area under a laminar flow hood.

Outsourcing facilities strive to assure that the preparations sold meet the USP 797 Standards. These companies are well known and include names such as, but are not limited to, Fagron Compounding Services, Pine Pharmaceuticals, Leiter's Health, QuVa Pharma, and ImprimixRx (a Harrow Company).

One unintended result of USP Chapter 797 was limited patient access to sterile preparations made by a relatively small number of 503B pharmacies. These tend to be geographically isolated and difficult for many patients to reach. Such is the case even in

relatively large urban areas including Orange County, CA, San Diego, CA and most of Utah outside of Salt Lake City (e.g.). Such locations may require patients to drive long distances while losing significant time to simply arrive at such a pharmacy. Frustratingly, if a patient fails to arrive by 6 PM on a Friday, these pharmacies are commonly closed for entire weekends until the following business day. Most of these locations are also closed on holidays. Some of these compounded medicines are needed on an emergency basis (e.g. fortified antibiotics for serious eye infections).

As well, history has proved that, with even the highest quality regulations, dedication to using the best equipment and providing concerted training with regular short-term inspection cycles, such measures have not universally solved problems associated with preparation, product sterility and delivery issues. Recalls of compounded or re-packaged drug lots involving discovered contaminated preparations and resulting product backorders have plagued the healthcare industry since. Just over the last two years, large recalls of prefilled Avastin (Pine Pharmaceuticals) and numerous other drugs have resulted from an inability of at least some 503B pharmacies to meet the cGMP standards at various times (e.g.).

Providers and the FDA are aware of the consequences of these recalls including drug and medical device shortages. As a result, the complications in treating patients in need of those items can be serious. In fact, acquiring such can suddenly become difficult, if not impossible, over extended periods of time.

As introduced supra, problems associated with current medicine preparation processes are fundamentally the result of a lack of an inherent, effective "safeguard" (defined herein as "technology or process which assures safety and efficacy for an intended use"). While current preparation processes have a form of a safeguard, which is applied before shipment, it is generally made by performing a sampling test of finished preparations. Generally, such testing cannot be universally effective and, therefore, must depend upon statistical analyses. The observation that states, "If it can happen, it will," encompasses inadvertent and all other types of disparate acts that result in preparation sterility degradation. To provide a system or process which can be used with safety requires the provision of such safeguards being an inherent part of the preparation process.

A new patented technology called "PALA Technology" (AseptiKits, LLC – a wholly owned subsidiary of Thorne Medical, Inc.) provides a line of products that enable sterile processing without a clean room or laminar flow hood and each has safeguard features. These products are all FDA cleared as "convenience kits." This means that components

involving contact with pharmaceutical drugs are already evaluated and "approved" by the FDA based on FDA approved medical devices that involve use of those components.

Every medicine-contacting device is pre-sterilized and kept so by being disposed in the closed and sealed environment of a medical grade header bag. The only matter pathway into the plastic bag is through a .22-micron sterilizing grade filter which assures a Sterility Assurance Level ("SAL") of "at least 10^{-6} throughout the preparation process (Propharma, 2024). A "bubble test" to assure filter integrity can also be done as taught in the Instructions for Use ("IFU") for each product.

The USP Chapter 797 Introduction and Scope section states, "this chapter must be followed to minimize harm, including death, to human and animal patients…)." Also, USP provides a comment in the Introduction, "The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited as long as they are noninferior to those described herein" suggesting a low standard for acceptance.

New emerging technologies are often disruptive to the status quo. This is true of the PALA Technology given that it solves several cited reasons for drug re-packaging, other preparations, and common reasons for misuse of vials as cited by the FDA. These include:

- "To meet the needs of specific groups of patients (e.g., pediatric patients or patients receiving drugs for ophthalmic use) who require smaller doses of approved sterile drug products that may not be available commercially;
- To reduce medication errors associated with drawing up a dose from a vial at the point of patient care;
- To reduce the availability of drug products that could be abused when controlled substances are left over in a vial after a dose is drawn out;
- To provide a particular sized container to fit into a particular device to administer the drug (such as a particular pain medication pump);
- For convenience for the practitioner administering an injection to a patient; to reduce waste and conserve drug supplies;
- And in some cases, to reduce cost" (FDA, 2017).

The Problems with Current USP Standards and cGMP

Please note: Virtually all medical device and compounding companies experience backorders and recalls for a variety of reasons. The following examples are used only to highlight issues faced by these companies as they strive to meet standards and the

difficulties involved in doing so. In no way should these be considered as cause for concerns about the efforts made by these organizations to meet the standards and regulations. That being said, these examples are not surprising, but they are alarming.

It should be noted that the FDA tracks supply chain interruptions. An example can be found at https://www.fda.gov/medical-devices/medical-device-safety/medical-device-supply-chain-and-shortages

In December 2024, Fagron Compounding Services experienced contamination issues and was issued an FDA Warning Letter. It is important to note that even when significant testing procedures are followed, it does not mean that all preparations in each product lot are sterile. In a recent warning letter by the FDA the following quote is instructive:

"Please note, microbial contamination, when present, is not uniformly distributed within a batch; therefore, it may not be identified in a sterility test. Compounding facilities producing drug products intended to be sterile under insanitary conditions should not rely upon or cite a passing sterility test result as an indication of product sterility." (FDA, 2024 – See Appendix A).

In 2024, Leiters Health initiated a recall for several of its compounded products. An FDA Warning Letter was issued that included the following statement:

"Risk Statement: There is a reasonable probability that the use of the defective vancomycin and fentanyl IV bags will be associated with life-threatening adverse events" (FDA 2024).

In October 2023, Pine Pharmaceuticals issued a recall following an inspection by the FDA. One year later, Pine issued a statement that it would no longer re-package Avastin and other ophthalmology products. These events created major backorders for Avastin and 1 mL two-part syringes commonly used for filling Avastin. Prices for prefilled syringes from other 503B pharmacies rose from about $40 per syringe to over $60 per syringe for many purchasers.

These events highlight ongoing and significant concerns involving the fact that large recalls impact the drug supply chain. The FDA monitors drug recalls and supply chain issues. These can be found on the FDA website using the link below:

https://dps.fda.gov/drugshortages

Drug recalls have involved many causes. However, drug recalls caused by contaminations and drug dose errors are well recognized by the FDA. In fact, the FDA states, "for example, failure to properly manipulate sterile drug products under appropriate aseptic conditions could introduce contaminants that could cause serious patient injury or death" (FDA 2017).

Significance and Roles Relative to Enforcement Discretion

It is important to note that, while USP Chapter 797 and PALA Technology products apply to similar themes and standards, they are categorically different as shown in Table 1 below.

As a basic comparison, the Chapter 797 Standard focuses on making sterile preparations in a clean room and under a laminar flow hood. In contrast, PALA Technology products are designed and *intended for use without a clean room or a laminar flow hood*. USP Chapter 797 cites potential contamination risks associated with "critical sites" (see USP Definition below):

"Critical site: A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, and beakers) or openings (e.g., opened ampules and needle hubs) that are exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination" (USP Chapter 797, 2023).

There are no "critical sites" involved during use of PALA Technology product because such surfaces are never exposed to environments where contamination can occur during proper use. The bag and all interior components/containers (e.g. eye drop bottles, syringes, IV bags, elastomeric balls and vials) are pre-sterilized. Sterility is maintained inside the PALA bag by an integral .22-micron sterilizing grade filter for delivery into receiving. All containers are filled, capped, and sealed from the exterior of the bag prior to opening.

Importantly, PALA Technologies dramatically simplify compounding. All Instructions for Use for each product are provided on a single sheet of paper compared to the 797 Standard which is described in a long document that also results in long SOPs involving extensive training to meet the Standard's requirements. It is well known in medicine that the simpler the procedure, the less likelihood of a medical error, in this case, potentially serious and life-threatening medication errors.

Table 1: Comparison of PALA Technology Products versus USP Chapter 797 – a few basics

Description	USP Chapter 797 Feature	PALA Technology Products
Clean room and laminar flow hood	Required	Designed to make sterile preparations without a clean room or laminar flow hood
User technique	Numerous requirements to assure sterility – highly vulnerable to user technique errors	User technique independent – closed system. Containers are filled, capped, and sealed from outside of the bag, prior to opening the bag
Terminal sterilization	Preferred, difficult, sterilization methods can negatively affect drugs. Use of filters does not mean sterility under 797 (not integral or a closed system)	Integral .22-micron sterilizing grade filter provides "equivalent" of terminal sterilization of all preparations delivered into the containers in the bag
Critical sites vulnerable to contamination	Multiple as identified in the Chapter definition	None – closed system and .22-micron filter provides Sterility Assurance Level of at least 10^{-6} ("SAL") safety
Sterility confirmation	Sample testing – "sterility is not uniformly distributed within a batch; therefore, it may not be identified in a sterility test"	Sterility is assured by PALA Technology product designs having an SAL of "at least 10^{-6}
User error medication risks	Somewhat high – numerous steps and complicated procedures and known to increase probability of medication errors	Low. Simple use procedures (one-page IFU). Fewer steps = lower probability of medication errors
Training	Extensive. Long, multiple SOPs, long 797 document instructions.	Minimal. Single page IFU. Short videos and in-services offered as needed.
Regulatory path	Regulated by state pharmacy boards and/or FDA inspections for USP Chapter797 compliance. Verification and certification required.	FDA cleared medical device. Complies with GMP and testing requirements including a sophisticated QA program meeting industry standards for sterile medical device manufacturing.

USP Chapter 797 requires sterility testing, but as indicated supra, “microbial contamination, when present, is not uniformly distributed within a batch; therefore, it may not be identified in a sterility test” (FDA 2024, See Appendix A). PALA Technology medical device sterility testing under a rigorous QA program assures that the product meets or exceeds sterile medical device standards.

PALA Technology products are FDA cleared and regulated by the FDA whereas state pharmacy boards serve to regulate pharmacy compounding relative to USP Chapter 797 compliance which, by instruction, includes use of clean rooms and laminar flow hoods. These standards are contained in a long, well and tightly written document that involves long SOPs, extensive training and frequent testing (e.g.) that involve clean rooms and laminar flow hoods.

USP 797 states that terminal sterilization is optimal and preferred whenever possible. However, most drugs are not stable enough to withstand most forms of sterilization. In fact, most drugs are sterilized using .22-micron filters in the manufacturing process, the very method used by PALA Technology products to assure sterility.

In effect, PALA Technology Kits qualify as FDA cleared medical devices that are “clean rooms in a bag.” Use of the product combined with its design for terminal sterilization for all solutions entering the bag exceed USP Chapter 797 standards. This means that FDA cleared PALA Technology products are best characterized as outside the scope of the USP 797 Standard.

Communications and Enforcement Discretion

Communications relative to new technologies relating to USP Chapter 797 can be challenging for pharmacists. As a starting point, the following is a helpful statement from a member of the Expert Committee at USP to AseptiKits:

“Please note that USP has no role in enforcement and cannot opine on whether practices or products meet our standards, that is the role of regulators. Please note that CSPs must be prepared according to <797>, and not <795>, and the chapter do not allow the preparation of CSPs under <795>. Also note in the introduction and scope section of <797>, there is an alternative technologies clause that allows for the use of technologies not mentioned in the chapter as long as they are non-inferior to what is in the chapter and validated for the intended purpose. It is up to regulators to determine what meets the requirements for “non-inferior” and “validated.”

To date, it appears that multiple state pharmacy boards have taken the same or a similar position and will not determine requirements for “non inferior” and “validated” products relative to the USP Chapter 797 Standard compliance. These often cause fear and concern among those wanting to improve patient care while having unresolved questions relative to whether a new technology meets USP standards (e.g.) or how PALA Technologies fit within a given practice. Such concerns are well resolved by the definition of enforcement discretion as applied by the FDA and other regulatory agencies (e.g. state pharmacy boards).

The following definition applies well to PALA Technology products and is well expressed by The Hartford:

What Is Enforcement Discretion?

> *“As an agency responsible for ensuring public health and safety, if the FDA believes a product risk is low or could have a significant benefit to the public, it will exercise enforcement discretion on certain requirements allowing a company to bypass its typical regulatory pathway. Enforcement discretions can be applied in a variety of ways, including downgrading the level of regulation, waiving compliance with certain regulatory requirements or issuing a notice of enforcement discretion under specific circumstances” (The Hartford, 2023).*

The National Institutes of Health states:

> *“FDA issues guidance documents to inform the public about the product categories for which they intend to exercise enforcement discretion. These guidance documents clarify which products fall under enforcement discretion and under what conditions. When the enforcement discretion guidance is followed, those designated products can be manufactured, imported, and distributed in the U.S. immediately, meaning innovators do not need advance approval from FDA. Typically, these guidance documents explain the use of discretion by FDA regarding the enforcement of some regulatory requirements, such as otherwise mandatory pre-market submissions (e.g., 510(k)s), registration and listing, and quality management system requirements” (National Institutes of Health, 2024).*

Note that All PALA Technology products meet or exceed FDA requirements as provided in FDA guidance documents including GMP practices, testing and use of OEM supplied

components from already FDA approved devices manufactured by large and reputable medical device companies to meet or exceed industry standards.

The same rules apply equally to state regulations. When a state (e.g. a state pharmacy board) states that it will not "opine" relative to compliance with a given regulation, it means that the device (in this case an FDA cleared medical device) falls under "regulatory discretion" as described supra. An example of such an expression is contained in the language from an email response from a Utah pharmacy board member. Interestingly, the regulatory discretion is well stated for those understanding the message and meanings behind the language.

> *"Hello,*
>
> *Thank you for contacting the Utah Division of Professional Licensing.*
>
> *The Division and Board cannot not and does not review or endorse products and unfortunately this will not be an agenda topic for a board meeting.*
>
> *I recommend reaching out to the professional pharmacy associations in Utah and the individual pharmacy systems.*
>
> *Board member participation is voluntary and almost all actively work in retail and hospital pharmacy systems. They definitely could learn about the product through their jobs and employers.*
>
> *Best Regards"*

In other words, the State Pharmacy Board chose not to review the product or "opine" relative to regulatory compliance meaning that the PALA Technology products fall under regulatory discretion as FDA cleared medical devices as described supra. "Reaching out" to individual pharmacy systems communicates permission to sell, at least under "enforcement discretion."

Issues surrounding "Misuse of Vials"

Another issue surrounds the misuse of vials. Clinicians are sometimes tempted to use a single dose vial by making multiple entries to save costs, to save drug during drug shortages and out of convenience. The Joint Commission stated the following:

"The misuse of vials primarily involves the reuse of single-dose vials, which are intended to be used once for a single patient. Single-dose vials typically lack preservatives; therefore, using these vials more than once carries substantial risks for bacterial contamination, growth and infection" (Joint Commission, 2014).

For clinicians, dedicated to "do no harm," these should cause serious concerns and require careful consideration.

The significance of this issue and the ability of PALA Technology to provide a viable solution cannot be overstated. The identified needs to "justify" misusing such vials without the PALA Technology presents a serious risk. However, PALA Technology provides a solution where a single entry into the vial can be made and then sterility assured by using the PALA Technology kits and "equivalent terminal sterilization" (based on USP Chapter 797 definitions) provided to assure that sterility is maintained during drug preparation. Such practices will save time, save lives, and provide a means for healthcare providers to properly treat their patients while avoiding vial misuse.

AseptiKits contacted a consulting company called "Propharma." Propharma is the largest company of its kind and is involved in the regulatory process to advise relative to FDA, USP and other compliance questions. A white paper was provided by Propharma relative to USP Chapter 797 compliance and is available upon request. This document is discussed in greater detail in this document under the heading. "FDA and USP Chapter 797 Considerations."

Fig. 1. ALAdrop for compounding eye drops.

Purpose of 503B Pharmacies

The FDA describes outsourcing pharmacies (“503B Pharmacies”) as shown below:

> *“The Drug Quality and Security Act, signed into law on November 27, 2013, created a new section 503B in the Federal Food, Drug, and Cosmetic Act. Under section 503B, a compounder can become an outsourcing facility.*
>
> *The law defines an outsourcing facility as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of section 503B.*

Drugs compounded by an outsourcing facility can qualify for exemptions from FDA approval requirements and the requirement to label products with adequate directions for use, but not from current good manufacturing practice (CGMP) requirements.

Outsourcing facilities:

- Must comply with cGMP requirements;
- Are inspected by FDA according to a risk-based schedule; and
- Must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound" (FDA 2022).

There are several important points to make relative to the "current Good Manufacturing Practices" ("cGMP") as described by the FDA compared to PALA Technology:

1.) The "current" GMP does not include use of PALA Technology Kits which provide a higher standard for compounding at a lower cost. Manufactured products are terminally sterilized as are other sterile medical devices.
2.) PALA Technology Kits are designed to provide low-risk compounding including, but not limited to:
    a. Closed system, sterile preparation environment
    b. Terminal sterilization for solutions passing through a .22-micron sterilizing grade filter.
    c. User technique independent compounding
    d. No "critical access site" exposures during compounding
3.) The cGMP standard is based on USP Chapter 797 which describes compounding in a clean room and under a laminar flow hood, neither of which are needed when using PALA Technology Kits. In effect, PALA Technology Kits provide an FDA cleared medical device clean room.
4.) cGMP is not compatible with terminal sterilization of drugs using conventional or USP 797 described procedures while PALA Kits use an integral .22-micron filter as an "equivalent" terminal sterilization process. This is dramatically different compared to cGMP. Note: Most terminal sterilization processes, e.g. gamma, ETO and steam are destructive to most drugs.
5.) The SOP(s) for a PALA Technology Kit can be reduced to a single page Product IFU document (provided in every case of PALA Technology Kits sold) versus an entire "book" addressing USP 797 requirements.

6.) While sterile preparations can be made using PALA Technology Kits and sold outside of a facility, the primary intent of PALA Technology designs is focused on in-house use.
7.) PALA Technology Kits require minimal FDA or state inspector involvement given the simplicity of the product use and proved finished sterility of preparations after use. In effect, SOPs can simply be summed up in the one paper IFU provided for each PALA Technology product.

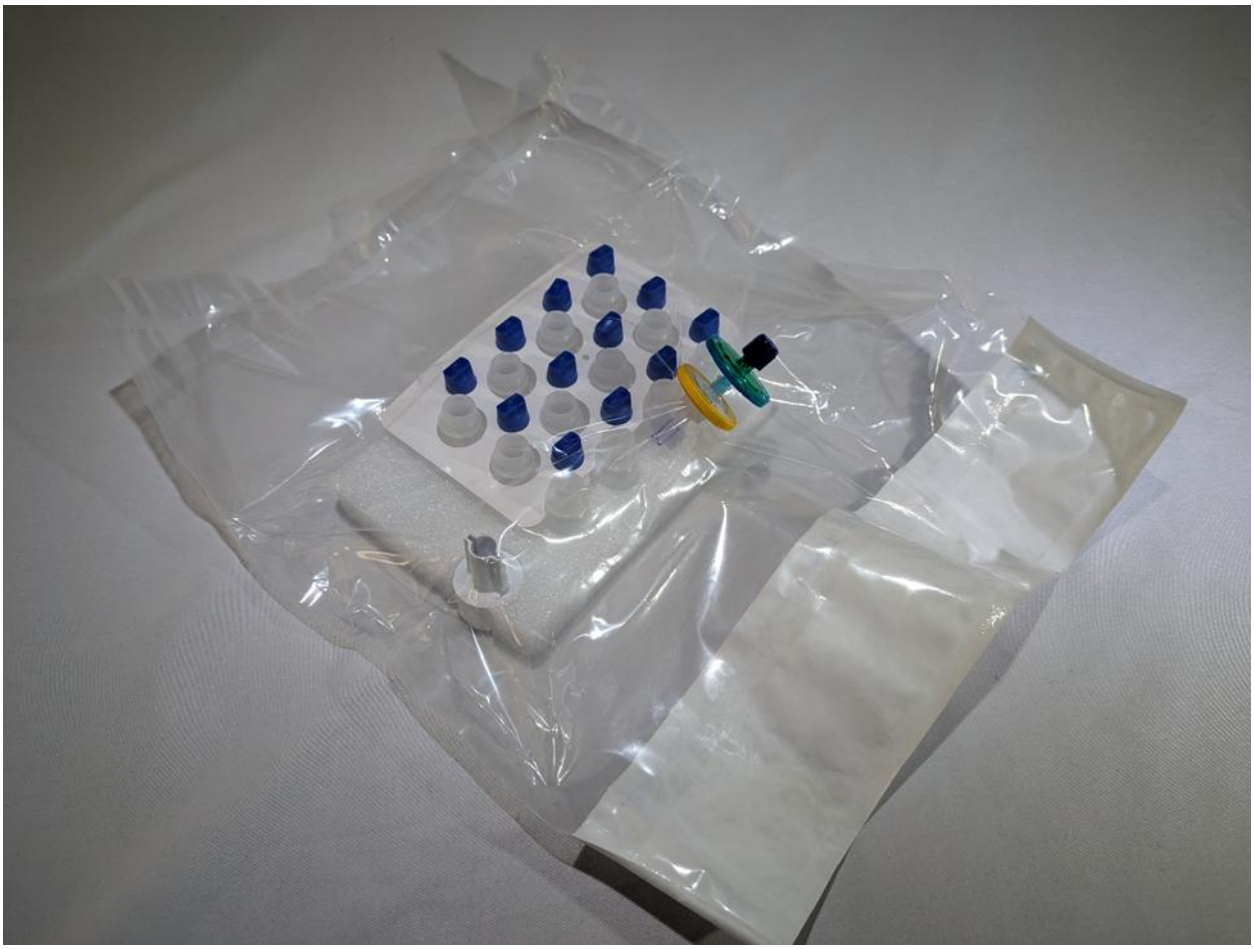


Fig. 2. PALA Kit for serum tears preparations

In other words, the 503B designation appears to either not apply or, possibly, may be managed with communications to the FDA relative to drugs to be re-packaged, reconstituted or compounded. An FDA 503B filing for the current designation is likely a reasonable path. However, that does not appear to fit well within current regulations due

to the lower risk and higher sterility standards achieved with use of the FDA cleared PALA Technology as a medical device. In these cases, PALA Technology products Intended Use statements speak to this issue e.g. “for making sterile preparations without a clean room and/or laminar flow hood.”

FDA and USP Chapter 797 Considerations

Essential to any regulatory evaluation, it is important to understand what the FDA regulates in this field.

- The first and best-known FDA function is that of determining safety and efficacy of medical devices and drugs. The FDA has multiple “classes” of concern in this area based on risk versus benefits.
- The second FDA function of note involves facility inspections. Critical to these inspections include a review of quality assurance programs including SOPs and a review of how well a manufacturer or pharmacy follows its programs. This includes documentation of product complaints and responses to product that falls outside of the parameters required based on standards. A key standard relative to 503B pharmacies is compliance to USP 797. This includes a wide range of details, documentation, and a review of results. Often, inspections extend to more careful inspection details, especially when a break in technique or errors are discovered.

Similar inspections are done by state pharmacy boards in 503A pharmacies.

PALA Technology products simplify inspections given that there is no clean room, no laminar flow hood and no need to review long SOPs. The only required SOP is to follow the IFU for the PALA Technology Kits used. As FDA cleared and registered medical devices, this process is simplified. AseptiKits has met with multiple FDA personnel, including inspectors, who responded positively to the simplified inspection process and preparation procedures that assure preparation sterility with every proper use.

To date, interactions with state pharmacy boards and related organizations suggest that PALA Technology products will reduce inspection costs on the state level as well and fall under “enforcement discretion”.

Given that USP Chapter 797 is critical to the success of any sterile preparation operation and recognized as important to the FDA, Propharma produced a white paper offering its position on the PALA Technology Kits. A copy of the Propharma conclusions are shown below (a copy of the full document is available upon request):

"4. CONCLUSION

The ALAdrop and PALA 12 Convenience Kits are a technology that allows the user to have the equivalent of a desktop aseptic processing area. Clinicians transfer the collected autologous serum samples to the kit using the provided syringe. The sample passes through either one or two filters that are attached to the bag and is collected within the ophthalmic dropper bottles. Caps are placed on the bottles and secured in place using the provided ratchet. Once all bottles are filled, capped, and tightly closed, the bag is then opened (breaking the seal of the sterile environment) for retrieval of the bottles.

The ALAdrop and PALA 12 Convenience Kits are not a pharmaceutical drug product, yet the overall validation process follows some of the same principles of drug product sterility assurance (i.e., validation of sterilization process, validation of the sterilizing filter). ETO sterilization of the kit has been demonstrated to provide a sterile closed bag system for the processing of autologous serum eye drops, without impact to the form or function of the kit (Rane et al. 2023-attachment 2).

Furthermore, the sterile environment within the bag is maintained via use of the connected 0.22-micron filter. The use of a 0.22-micron sterilizing grade filter within a closed system achieves preparations having a sterility assurance level (SAL) of at least 10^{-6}, which is the equivalent to a moist heat terminal sterilization cycle using an autoclave.

Given the above, these closed systems comply with USP <797> for the compounding of sterile preparations" (Propharma, 2024).

Of note is the fact that the simpler the procedure, the lower the likelihood of a medication error. This is well borne out in the evidence of errors, recalls and supply chain issues since 2013.

Figure 3. VitrALA for sterile intravitreal drug preparations.

PALA Technology – Offering A Higher Standard for Sterile Preparations

PALA Technology Kits feature single use, closed-system products using a header bag and integral 0.22-micron sterilizing grade filter. These products enable clinicians to prepare sterile solutions without a clean room or laminar flow hood. These are commonly referred to as “a clean room in a bag.”

Perhaps an apt comparison of PALA Technology Kits to cGMP and USP Chapter 797 Standards is to indicate two major differences:

1. PALA Technology Kits are FDA cleared products designed to provide sterile compounding in a closed system using a “new technology” without a clean room or laminar flow hood. These Kits are shown to be “non inferior,” reliable and USP Chapter 797 compliant (Propharma, 2024).

2. USP Chapter 797 Standards describe a lengthy process involving a clean room/laminar flow hood, and pass-through window operations, SOPs, extensive training, frequent testing, certification and inspections to reasonably achieve consistent sterile preparations. As shown supra, these processes sometimes, and without warning, often break down resulting in large drug and medical device recalls that cause major interruptions in the supply chain while placing patients at risk for serious infections and harm, including death.

PALA Technology Kits provide features that set it apart from current cGMP and USP Chapter 797 described processes as shown in Table 2 below:

Table 2: Features and Benefits

Features	Benefits
Everything inside the bag is sterile	Maintains sterility of components
Fluids passing through the 0.22-micron filter are sterilized to an SAL of "at least 10^{-6}"	Sets a higher standard for sterile preparations
User technique independent sterility	Avoids touch and other harmful microbial contaminations
Designed for existing user technique	Intuitive use
Ergonomic design	Easy-to-use
Reduces drug waste	Lowers drug and device costs, maximizes drug utilization
Supports drug and device supply chains	Reduces probability of large recalls
Complies with FDA regulations, USP, and CDC standards	Sets a higher standard for sterile preparations
Reduces processing steps	Simplifies drug preparation – known to reduce preparation errors
All preparations are capped and sealed before opening the bag	Assures a finished sterile preparation
A simple post-fill bubble test verifies filter integrity	Verifying indicator of sterile processing

Figure 4. Syrikit 1 mL x 20 each

Summary and Conclusions

The FDA, USP, CDC and state pharmacy boards have demonstrated a long history of honorable work to minimize potential patient harm while promoting standards intended to improve patient care.

503B pharmacies began making sterile preparations around 2013 and have experienced numerous challenges trying to meet USP Chapter 797 standards while complying with cGMP practices. These pharmacies face incredibly difficult challenges in consistently providing consistently sterile preparations.

Despite all efforts, contaminations and drug errors have resulted in supply chain interruptions, serious patient risks and there are no guarantees that even if a product lot tests negative for microbial contamination that some preparations within that lot could still be contaminated.

Interruptions in the medical device and pharmaceutical supply chain also cause serious concerns for clinicians trying to serve important patient needs. The causes of these recalls should also cause worry about preparations that may be contaminated that slip through testing.

The costs associated with these issues are significant in terms of destroyed drugs and devices tied to such recalls. 503B costs that must be passed along to caregivers and ultimately third-party payors and patients can be crippling.

The more complicated a procedure, the more likely for errors to occur. Therefore, it is not surprising, but often alarming, or deeply concerning, that these things occur on a too frequent basis in these environments.

USP and FDA recognize the value of new technologies that improve sterility while simplifying procedures and alleviating such pressures on healthcare systems. In fact, to the credit of USP, the standard for "non inferior" for new technologies is a low bar to reach and leaves the door open for improved products and processes.

AseptiKits created and developed its PALA Technology which resolves the many issues discussed supra. Its closed system i.e. "clean room in a bag" with inherent safeguards, assures sterility via its integral .22-micron sterilizing grade filter and closure system to cap and seal all preparations prior to opening a bag. PALA Technology products are proved to be reliable, effective, simple, and low cost.

While the regulatory path may appear to be somewhat unclear, what is obvious is that members of the FDA who have seen and understood the new PALA Technology have been universally supportive of the PALA Technology Convenience Kits use and the potential for resolving many of the major issues facing healthcare today.

AseptiKits™, the product innovator and designer, is a wholly owned subsidiary of Thorne Medical, Inc.

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PALL Sterilizing-Grade Filter Specification

PALL Medical

25 mm Acrylic Fluid Filter

Product Design and Performance Advantages

- Supor® and Versapor® are both compatible with Gamma and Ethylene Oxide sterilisation methods
- Choice of pore sizes enables retention of particles bacteria and fungi
- Range of inlet and outlet luer connectors and housing colors available

Customer Qualified Applications

- Pharmacy Admixture
- Small Volume Sterilisation
- Low volume pain control
- Low volume injectables

Product Specifications

Materials of Construction
Filter Membrane: Supor Polyethersulfone, Versapor Acrylic Copolymer membrane and Polyester Screens
Filter Housing: Modified Acrylic

Biological Safety
Materials of construction have been evaluated in accordance with United States Pharmacopeia (USP) Biological Reactivity Tests, *In Vivo* <88> (USP Class VI-121 °C Plastic tests) and/or relevant sections of the ISO 10993 series of standards.

Material Content Declaration
Materials of construction do not contain:
- Natural latex or latex derivatives
- PVC or hydroxyvinyl chloride
- DEHP- Diethylhexylphthalate
- BPA - Bisphenol A
- TSE - Transmissible spongiform encephalopathy
- BSE - Bovine spongiform encephalopathy

Effective Filtration Area/ EFA
Approx. 2.8 cm^2

Pyrogenicity
< 0.25 EU/mL using the LAL test method

Inlet/Outlet Connectors
FLL: **F**emale **L**uer **L**ock
MLL: **M**ale **L**uer **L**ock
MLS: **M**ale **L**uer **S**lip

Water Bubble Point
Supor Membrane: 0.2 µm: ≥ 3.1 bar (46 psi)
5.0 µm: ≥ 0.2 bar (3 psi)
Versapor: 5.0 µm: ≥ 0.034 bar (0.5 psi) (≥ 1.0" Hg)

Retention properties
0.2 µm Supor membrane is retentive of *B.diminuta* and meets requirements for a sterilizing grade filter per modified ASTM F838-15a test methods

Sterilization Compatibility
Ethylene Oxide or Gamma irradiation

Water Flow rate
Supor Membrane: 0.2 µm: ≥ 180 mL/min at 3.1 bar (45 psi)
5.0 µm: ≥ 1500 mL/min at 3.1 bar (45 psi)
Versapor: 5.0 µm: ≥ 970 mL/min at 3.1 bar (45 psi)

PROTECT WHAT MATTERS - EVERY DAY

PALA Technology Kits and USP Chapter <797> SWOT Analysis

The following SWOT Analysis highlights the challenges faced by new and even documented superior features of a more advanced technology compared to the challenges of making sterile preparations in a Class 5 clean room and under a laminar flow hood as described in USP 797.

Pharmacists must deal with the difficult decision of following a riskier procedure that is highly reliant on following USP 797 or using a product that offers a substantially higher level of safety.

Strengths	Weaknesses	Opportunities	Threats
Lower cost	Fear of USP 797/State Boards of Pharmacy by pharmacists and other clinicians	Growing awareness of PALA Technology Direct comparisons of <797> and PALA Technology Kits. Work with FDA and 503B pharmacies	State Boards of Pharmacy being resistant to PALA Kits – overly dedicated to '797'.
Closed system	NA	Superior to USP 797	Fearful pharmacists
User technique independent	NA	Superior to USP 797	Fearful pharmacists
Terminal sterilization 'equivalent'	NA	Superior to USP 797	Fearful pharmacists
Reduces drug waste	NA	Superior to USP 797 – No significant recalls or supply chain interruptions. Work with FDA and 503B pharmacies	Fearful pharmacists
Potential increase in BUD	NA	Superior to USP 797	Fearful pharmacists
Broad use will reduce recalls and supply chain interruptions	Fear of USP 797/State Boards of Pharmacy	Superior to USP 797	Fearful pharmacists

Areas of Critical Need

USP Chapter 797 standards have re-configured availability of sterile preparations in demographics that have seriously affected the ability of clinicians to deliver quality care to local patients.

In addition, other needs, on both a national and international scale have become obvious. Much of this has to do with affordability relative to USP 797 compliance. Other issues are the result of natural disasters, need for improved military health support and the challenges of providing care in remote locations where clean rooms are not available. This is especially true in countries where clean rooms and laminar flow hoods are not commonly found.

The following are locations and environments where PALA Technology products can serve to improve healthcare while meeting USP 797 standards as well as FDA regulations:

1. Critical access hospitals: For many such places, the cost of USP 797 compliance exceeds the ability for such places to provide needed care. PALA Technology products can provide the ability of such hospitals to offer such services without compromising sterile preparation quality.
2. Indian Health Services: Provides improved access to care across a wide range of needs, even in remote locations. Such products could dramatically improve services on a localized as well as broader scale.
3. Natural disaster relief (e.g. hurricanes and earthquakes where power is unavailable to run a clean room and meet standard): Sterile preparations can still be provided even under the most severe environments to meet all patient needs relative to sterile preparations.
4. Military sites: Both active duty in remote “MASH-type” locations, military bases and navy ships. The need to drop “sub-797 standard clean rooms and laminar flow hoods” can be virtually eliminated.
5. Local retail pharmacies – Many sterile preparations require patients to travel long distances to get even emergent medications (e.g. fortified antibiotic eye drops for severe eye infections), or basic care items. This appears to be as true in large urban locations (e.g. Orange County, CA) as well as low population states e.g. Alaska, Utah, Montana and Nevada). Instructions for Use and Filter Bubble Test

USP <797> Compliance Labels and PALA Products Sales Brochures

AseptiKits*

SYRIKIT* Syringe Sterile Preparation Convenience Kit

Thorne Medical, Inc.
DBA AseptiKits, LLC
101 N 700 W
North Salt Lake, UT 84054-2736
USA
Email: sales@aseptikits.com
Phone: 844-863-5170

Symbol Definitions

Attention, See Instructions For Use	STERILE EO Sterile by Ethylene Oxide		Single Use
Do Not Resterilize	Do Not Use If Package is Damaged	LOT Lot Number	Use By
REF Reorder Number	Rx ONLY For Use By or on the Order of a Qualified Prescribing Clinician	Quantity	Manufactured by
Pyrogen Free	DEHP Free DEHP Free	Latex Info Not Manufactured With Natural Rubber Latex	Patent Information

INDEPENDENTLY VERIFIED BY NEW TECHNOLOGY NONINFERIOR
USP 797 COMPLIANT
CLOSED-SYSTEM FILTER STERILIZATION

PALA TECHNOLOGY

Patent Pending

Intended Use
SyriKit Syringe Sterile Preparation Convenience Kit is intended for the preparation of sterile-filled syringes.

Description
SyriKit Syringe Sterile Preparation Convenience Kit includes sterile syringes inside a header bag. The header bag features an integrated 0.22 micron sterilizing-grade filter to sterilize fluids as they enter the kit and syringes. Syringes are capped prior to opening the header bag to maintain sterility.

Kit Contents
- header bag
- integrated 0.22 micron sterilizing-grade filter
- Luer adapters
- sterile syringes
- syringe caps
- cap holder

Warnings
1. Visually inspect the header bag and filter seal.
2. Do not use if damaged.
3. Do not exceed 75 PSI (5.2 Bar).
4. Single-use. Do not reuse.
5. Follow institutional protocols for cross-contamination from penicillin and related agents, mutagenic agents, drugs with narrow therapeutic indexes, and high potency drugs.
6. Verify filter patency with a bubble test after syringes are filled. Do not use syringes if the filter fails a bubble test.

Cautions
1. Do not use SyriKit Syringe Sterile Preparation Convenience Kit near sharp objects.
2. Do not apply excessive force while injecting fluids through the syringe filter.
3. Assure that syringe caps are securely affixed after press fitted on each dose syringe.
4. Always follow institutional protocols relative to patient and care giver safety.
5. Do not attempt to disconnect pre-assembled components except as instructed.
6. When compounding multiple solutions, thoroughly mix all solutions before dispensing through the filter and into individual dose syringes to assure concentration integrity.
7. Store preparations in compliance with FDA guidance or USP Chapter 797.

Instructions for Use
1. Unfold the kit onto a flat, clean surface.
2. Inspect the header bag and filter seal for damage. Do not use if damaged.
3. Draw a volume of drug into an external source syringe and connect it to the filter.
4. Prime the filter assembly.
5. Move a syringe to the filter location with the cap near the cap holder.
6. Insert the cap into the cap holder and remove the cap.
7. Connect the syringe to the filter assembly.
8. Fill the syringe as prescribed.
9. Remove the syringe from the filter assembly and cap.
10. Remove the cap and syringe from the cap holder.
11. Move the filled syringe away from the filter assembly for ease of use.
12. Prepare the next syringe, repeating steps 5 through 11 for each syringe.
13. Fill the internal large volume syringe last to store any remaining drug.
14. Verify filter patency with a bubble test after syringes are filled. Do not use syringes if the filter fails the bubble test.
15. Open the header bag and remove the syringes.
16. Label and store the syringes as per institutional protocol.

Part Number: SP0118 Rev B

SYRIKIT*

1mL Syringe
Sterile Preparation
Convenience Kit

AseptiKits*

1 1mL Syringes
(QTY: 20)

REF 0103-001

SKU 0103-001-01

INDEPENDENTLY VERIFIED
USP 797 COMPLIANT
CLOSED-SYSTEM FILTER STERILIZATION
NONINFERIOR
ENHANCED
NEW TECHNOLOGY

PALA TECHNOLOGY

STERILE EO

DEHP Free

Latex Info

See IFU

Rx ONLY

AseptiKits, LLC
101 N 700 W Ste A
North Salt Lake, UT 84054
844-863-5170
www.aseptikits.com

Sterile Barrierz, MTI, Inc.
101 N 700 W Ste A
North Salt Lake, UT 84054

8 50066 03120 9

Made in USA.

GTIN: 00850066031209
LOT: ------ EXP: 2028-01-30

(01) 00850066031209(10) 00000(17) 20280130

AseptiKits, LLC is a wholly-owned subsidiary of Thorne Medical, Inc.

SP0116-012 Rev. B

Summary and Conclusions

This document focused on three primary goals. These included:

1. Respectfully acknowledge the efforts, wisdom, good will and challenges involved in creating the 797 standard to make sterile preparations safe for patients who need them; the need to inform and assist inspectors to assure that the standard is being followed and recognize that, despite the best of intentions and efforts by firms that make sterile preparations - the standards are extremely difficult to consistently achieve. Despite the best of efforts, the resulting in FDA Warning Letters, critical drug recalls and supply chain interruptions (e.g.) describe an environment requiring improved tools that can meet the critical objectives of providing sterile preparations.
2. Provide data, evidence and other information that makes the case for use of an alternative technology that meets or exceeds USP 797 requirements, i.e. PALA Technology-based products that meets all regulatory requirements and thereby provide confidence among clinicians and regulators of the improved safety of PALA Technology products.
3. Offer overwhelming supporting information for state pharmacy boards, FDA, inspectors, pharmacists, and other clinicians that provides for a better understanding of how USP Chapter 797 relates to the new PALA Technology products, thereby providing a clear justification for use of PALA Technology products as each sees fit without fear of regulatory disciplinary action.

These efforts are believed to demonstrate needs for improved technologies and communications that solve many of the issues faced in medical practice today. The PALA Technology products offer a correction to issues that appeared to be unresolvable otherwise.

In other words, the intensity, genius, and firmness of support for USP 797 gives insight to the idiom that no strength of desire, merit of brilliance, depth of study nor weight of management can, through the control and authority of regulation, make perfect a widely used process that is inherently imperfect.

It became clear that an improved, superior “alternative technology” that meets or exceeds USP Chapter 797 is needed.

Both USP and FDA recognized the potential harm which can result from “insanity conditions” and the inability to assure that the breadth of preparations cannot be guaranteed to be sterile based on sample testing.

It is believed that the information contained herein, including that provided by FDA, USP, certified regulatory consultant organizations and supported by numerous clinicians exemplify the conclusions that PALA Technology products provide a superior standard for making sterile preparations than can be provided using clean rooms and laminar flow hoods.

It is expected that, as the PALA Technology products are used, that patient safety will be dramatically improved while drug use will become more efficient, drug waste minimized as supply chains provide for greater access without the levels of drug, and medical device losses caused by recalls related to preventable medication errors and contaminations (e.g.).

PALA Technology products offer a superior level of sterile preparation safety across a wide range of applications including eye drop bottles, syringes, elastomeric balls, vials and IV bags (e.g.). These products will enable improved care for our military, Indian Health Services, international health services, disaster relief, remote care, and Critical Access Hospitals.

One final note: PALA Technology products provide substantial savings, both in material, and labor costs.

These efforts exemplify the AseptiKits Mission Statement as stated below:

> *“The mission of AseptiKits is to develop and provide high quality medical devices that make sterile preparations affordable and convenient for all patients who need them and for the clinicians who prepare them.”*

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Appendix A: Fagron FDA Warning Letter (as cited in AseptiKits White Paper)

WARNING LETTER

Fagron Compounding Services, LLC dba Fagron Sterile Service MARCS-CMS 698861 — DECEMBER 19, 2024

Delivery Method:
VIA Electronic Mail
Product:
Drugs

Recipient:
Jason McGuire
Senior Vice President, Operations
Fagron Compounding Services, LLC dba Fagron Sterile Service

8710 East 34th Street North Wichita, KS 67226-2636United States

Issuing Office:
Center for Drug Evaluation and Research (CDER)

United States

WARNING LETTER
WL # 698861
12/19/2024

Dear Mr. McGuire:

You registered your facility with the U.S. Food and Drug Administration (FDA) as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353b][1] on October 2, 2015, and most recently on October 18, 2024. From June 18 to June 28, 2024, an FDA investigator inspected your facility, Fagron Compounding Services, LLC dba Fagron Sterile Services, located at 8710 East 34th Street North, Wichita, KS 67226. During the inspection, the investigator collected evidence that drug products you produced failed to meet the conditions of section 503B of the FDCA necessary for drugs produced by an outsourcing facility to qualify for exemptions from certain provisions of the FDCA. In addition, the investigator noted serious deficiencies in your practices for producing drug products intended or expected to be sterile, which put patients at risk.

FDA issued a Form FDA 483 to your facility on June 28, 2024. FDA acknowledges receipt of your facility's responses, dated July 19, 2024, August 30, 2024, September 27, 2024, and October 25, 2024. FDA further acknowledges that on August 15, 2024, your firm initiated a voluntary recall of four lots of Lidocaine HCl Injection, 2% due to lack of sterility assurance. Based on this inspection, it appears you produced drugs that violate the FDCA.

A. Compounded Drug Products under the FDCA

Under section 503B(b) of the FDCA, a compounder can register as an outsourcing facility with FDA. Drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility qualify for exemptions from the drug approval requirements in section 505 of the FDCA [21 U.S.C. § 355(a)], the requirement in section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] that labeling bear adequate directions for use and the Drug Supply Chain Security Act requirements in section 582 of the FDCA [21 U.S.C. § 360eee-1] if the conditions in section 503B of the FDCA are met.[2]

An outsourcing facility, which is defined in section 503B(d)(4) of the FDCA [21 U.S.C. § 353b(d)(4)], is a facility at one geographic location or address that — (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. Outsourcing facilities must comply with other applicable provisions of the FDCA, including section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (CGMP), and section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions. Generally, CGMP

requirements for the preparation of drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

In addition, for a compounded drug product to qualify for the exemptions under section 503B, the labeling of the drug must include certain information (section 503B(a)(10) of the FDCA [21 U.S.C. §353b(a)(10)]).

B. Failure to Meet the Conditions of Section 503B

During the inspection, the FDA investigator noted that drug products produced by your facility failed to meet the conditions of section 503B. For example, the investigator collected evidence of the following deficiencies with your facility's drug product labels:

1. The drug product label did not include the dosage form. Examples include: Tropicamide 1%/Cyclopentolate 1%/Phenylephrine 2.5%/Ketorolac 0.5%, 5mL and Fentanyl Citrate 2mcg/mL (100mcg/50mL)/Ropivacaine HCl 0.15% (1.5mg/mL) (75mg/50mL).

2. The drug product label did not include the established name of the drug. Examples include: Tropicamide 1%/Cyclopentolate 1%/Phenylephrine 2.5%/Ketorolac 0.5%, 5mL; Sodium Citrate 4% (40mg/mL) containing Gentamicin 320mcg/mL Injection, 3mL, 5 mL, and 30 mL; and Epinephrine (1mg/mL), Sterile Solution for Injection.

3. The drug product label did not include a list of active ingredients identified by established name. Examples include: Tropicamide 1%/Cyclopentolate 1%/Phenylephrine 2.5%/Ketorolac 0.5%, 5mL; Sodium Citrate 4% (40mg/mL) containing Gentamicin 320mcg/mL Injection, 3mL, 5 mL, and 30 mL; and Epinephrine (1mg/mL), Sterile Solution for Injection.

Further, the investigator collected evidence of the following deficiencies with your facility's container labels:

1. The container from which the individual units of the drug are removed for dispensing or for administration did not include directions for use, including, as appropriate, dosage and administration. Examples include: Epinephrine (1mg/mL), Sterile Solution for Injection; Phenol Injection 6% (60 mg/mL), in Sterile Water for Injection, 10 mL in Multi-Dose Vial; Sodium Citrate 4% (40mg/mL) containing Gentamicin 320mcg/mL Injection, 3mL, 5 mL, and 30 mL; and Dexamethasone Sodium Phosphate 10 mg/mL Solution for Injection, 2 mL in Multi-Dose Vial.

2. The container from which the individual units of the drug are removed for dispensing or for administration did not include a list of active ingredients identified by established name. Examples include: Tropicamide 1%/Cyclopentolate 1%/Phenylephrine 2.5%/Ketorolac 0.5%, 5mL; Sodium Citrate 4% (40mg/mL) containing Gentamicin 320mcg/mL Injection, 3mL, 5 mL, and 30 mL; and Epinephrine (1mg/mL), Sterile Solution for Injection.

Because your compounded drug products have not met all of the conditions of section 503B, they are not eligible for the exemptions in that section from the FDA approval requirements of section 505, the requirement under section 502(f)(1) that labeling bear adequate directions for use, and the Drug Supply Chain Security Act requirements described in section 582 of the FDCA.

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator observed that.

1. You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area.

2. Your firm produced drug products while construction was underway without adequate controls to prevent contamination of the product environment and products.

The FDA investigator also noted CGMP violations at your facility, that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

2. Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).

3. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a revised draft guidance, *Current Good Manufacturing Practice — Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act*. This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.

Under section 301(a) of the FDCA [21 U.S.C. § 331(a)], the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, it is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

Unapproved New Drug Products

You do not have any FDA-approved applications on file for drug products that you compound.[3] Under sections 505(a) and 301(d) of the FDCA [21 U.S.C. §§ 331(d)] a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA under section 505 of the FDCA is in effect for the drug. Marketing of these products, or other applicable products, without an approved application violates these provisions of the FDCA.

Misbranded Drug Products

You compound drug products that are intended for conditions not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use cannot be written so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses causing them to be misbranded under section 502(f)(1) of the

FDCA.[4] The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. Further, it is also a prohibited act under section 301(k) of the FDCA to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.

D. Corrective Actions

We have reviewed your facility's responses to the Form FDA 483. We acknowledge your firm's recall of four lots of Lidocaine HCl Injection, 2% due to lack of sterility assurance.

Some of your corrective actions appear adequate; however, we cannot fully evaluate the adequacy of the following corrective actions due to lack of adequate supporting documentation. Pertaining to the *Chaetomium globosum* recovery referenced, you stated the operator "was in training at the time of the recovery." The investigation into the recovery, DEV-2024-0174, states the operator, "was not fully trained" and "left unsupervised by a qualified trainer, which is a deviation" from procedure. Your firm identified this deviation after reviewing footage of batch **(b)(4)**. However, upon discovering this deviation, your investigation did not expand to other lots produced or operations conducted by the "not fully trained" operator.

Some of your corrective actions appear deficient. You stated in your response, "For the personnel samples, the samples were taken after the completion of the **(b)(4)** process, prior to removal of waste and disinfection/sanitization of the ISO 5 hood and equipment. In review of the batch record, the operators for Succinylcholine lot **(b)(4)**, Rocuronium lot **(b)(4)** and Lidocaine lot **(b)(4)** had performed staging, support and **(b)(4)** activities prior to taking the glove samples. This included sanitizing materials into the hood, removing filled bags, insertion of sterile needle into the bag ports and batch record documentation. None of these activities impacted the filling of the child batches as each child batch did not have a recovery and sterility testing for each passed." We disagree with your assessment. The operator was involved in critical process parameters, including **(b)(4)** of the parent batch. This parent batch was used to fill four child batches. The child batches were not **(b)(4)**. We acknowledge your recall of child batches of the parent lot: Lidocaine HCl 2%, Lot# **(b)(4)**, within expiry on August 9, 2024.

Please note, microbial contamination, when present, is not uniformly distributed within a batch; therefore, it may not be identified in a sterility test. Compounding facilities

producing drug products intended to be sterile under insanitary conditions should not rely upon or cite a passing sterility test result as an indication of product sterility.

We acknowledge your commitments in response to our concerns noted with your upcoming facility expansion. During the next FDA inspection, we will assess the potential impact of the upcoming planned construction activities on the quality of sterile drug products that were produced and distributed to patients.

In addition to the issues discussed above, you should note that CGMP requires the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. See section 501 of the FDCA. If you choose to contract with a laboratory to perform some functions required by CGMP, it is essential that you select a qualified contractor and that you maintain sufficient oversight of the contractor's operations to ensure that it is fully CGMP compliant. Regardless of whether you rely on a contract facility, you are responsible for assuring that drugs you produce are neither adulterated nor misbranded. [*See* 21 CFR 210.1(b), 21 CFR 200.10(b).]

In addition, regarding issues related to the conditions of section 503B of the FDCA, some of your corrective actions appear adequate: You have initiated CAPA-2024-0105 and CAPA-2024-0106 to address label issues concerning dosage form, established name of the drug and directions for use. However, no corrective actions have been provided to the agency to address label issues concerning a list of active ingredients identified by established name.

Should you continue to compound and distribute drug products that do not meet the conditions of section 503B, the compounding and distribution of your drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the Drug Supply Chain Security Act requirements.

FDA strongly recommends that your management undertake a comprehensive assessment of operations, including facility design, procedures, personnel, processes, maintenance, materials, and systems. In particular, this review should assess your aseptic processing operations. A third-party consultant with relevant sterile drug manufacturing expertise should assist you in conducting this comprehensive evaluation.

E. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility. You are responsible for investigating and determining the causes

of any violations and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law, including FDA regulations.

You should take prompt action to address any violations. Failure to adequately address any violations may result in legal action without further notice, including, without limitation, seizure and injunction.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to address any violations. Please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. This letter notifies you of our concerns and provides you an opportunity to address them. If you believe your products are not in violation of the FDCA, include your reasoning and any supporting information for our consideration. If you cannot completely address this matter within fifteen (15) working days, state the reason for the delay and the time within which you will do so.

Your response and any questions regarding the contents of this letter should be sent to compoundinginspections@fda.hhs.gov. In your response, refer to the Warning Letter Number above (#698861) and include a subject line that clearly identifies the submission as a Response to Warning Letter.

Sincerely,
/S/

F. Gail Bormel, JD, RPh
Director
Office of Compounding Quality and Compliance
Office of Compliance
Center for Drug Evaluation and Research

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1 See Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

2 We remind you that there are conditions, other than those discussed in this letter, that must be satisfied to qualify for the exemptions in section 503B of the FDCA.

3 The specific products made by your firm are drugs within the meaning of section 201(g) of the FDCA [21 U.S.C. § 321(g)] because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases and/or because they are intended to affect the structure or any function of the body. Further, they are "new drugs" within the meaning of section 201(p) of the FDCA [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for their labeled uses.

4 Your compounded drug products are not exempted from the requirements of section 502(f)(1) of the FDCA by regulations issued by the FDA (see, e.g., 21 CFR 201.115).

Appendix B: Propharma White Paper

WHITE PAPER - STERILITY

Prepared for:

AseptiKits, LLC
101 North 700 West Ste A
North Salt Lake, UT 84054

March 29, 2024

propharma

TABLE OF CONTENTS

1. PURPOSE/SCOPE....3
2. BACKGROUND....3
PALA 12 Convenience Kit....3
ALAdrop Convenience Kit....4
3. COMPLIANCE WITH USP <797>....5
4. CONCLUSION....7
5. REFERENCES....8

LIST OF FIGURES

Figure 1: PALA 12 Convenience Kit....3
Figure 2: ALAdrop Convenience Kit....4

1. PURPOSE/SCOPE

AseptiKits developed a unique system for filling autologous serum eye dropper bottles within a closed system and seeks confirmation that this kit complies with standards within USP <797> Pharmaceutical Compounding – Sterile Preparations.

2. BACKGROUND

PALA 12 CONVENIENCE KIT

AseptiKits developed unique serum eye dropper convenience kits. The Portable Aseptic Level Assurance (PALA 12) Convenience Kit allows clinicians to process autologous blood serum eye drops in a portable closed system sterile environment. The kit consists of a pre-sterilized bag containing trays, ophthalmic dispenser bottles, caps, syringes, a ratchet for securing the caps to the filled bottles, and two filters in series (Figure 1).

Figure 1: PALA 12 Convenience Kit

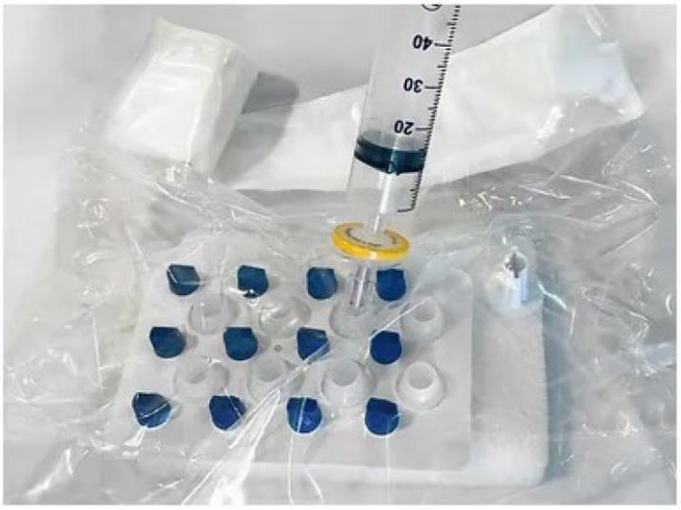
Clinicians transfer the collected serum samples to the kit using the provided syringe. The sample passes through two filters that are attached to the bag and is collected within the ophthalmic dropper bottles. Caps are placed on the bottles and secured in place using the provided ratchet. Once all bottles are filled, capped, and tightly closed, the bag is then opened (breaking the seal of the sterile environment) for retrieval of the bottles.

Previously, the kit consisted of two 0.22-micron filters that were used in series within the closed system. The design has recently changed to one 0.8-micron filter on top (for removal of particulates) and a 0.22-micron sterilizing grade filter on the bottom (for removal of microorganisms). In the event that the 0.22-micron filter becomes clogged during filling of the bottles, AseptiKits recommends the clinician use another kit to continue processing the autologous serum samples.

ALADROP CONVENIENCE KIT

The Aseptic Level Assurance (ALAdrop) Convenience Kit is also a closed bag system which consists of a pre-sterilized bag containing a tray, ophthalmic dispenser bottles, caps, syringes, a ratchet for securing the caps to the filled bottles. Unlike the PALA-12 however, the ALAdrop kit utilizes one 0.22-micron sterilizing filter (Figure 2). ALAdrop is intended for use in mixing pharmaceutical drugs and enables clinicians to prepare sterile eye drops outside of a clean room or laminar flow hood, for treating specific eye issues.

Figure 2: ALAdrop Convenience Kit



The procedure for using this kit is similar to that for PALA-12. The collected serum sample is transferred to the kit using the provided syringe. The sample passes through the sterilizing filter that is attached to the bag and is collected within the ophthalmic dropper bottles. Caps are placed on the bottles and secured in place using the provided ratchet. Once all bottles are filled, capped, and tightly closed, the bag is then opened (breaking the seal of the sterile environment) for retrieval of the bottles.

As of March 11, 2024, and as discussed in AlvaMed's Regulatory Analysis Report (Rane et al. 2023), there remains no FDA product classification for these types of convenience kits (ALAdrop, PALA-12), and as such, are exempt from premarket notification for devices (refer to: FDA's Product Classification Database).

3. COMPLIANCE WITH USP <797>

This paper will discuss ALAdrop and PALA 12 kits in the context of the following sections of USP<797> for compounded sterile preparations (CSPs):

- Ethylene Oxide (ETO) Gas Sterilization/Sterility Testing
  ETO sterilization is a common method of sterilizing medical devices that uses a combination of vacuum, humidity, gas, and temperature to inactivate microorganisms. Typically, the temperatures utilized are lower than what would be required for other terminal sterilization processes, thereby making ETO sterilization a viable option for items that are moisture and/or heat sensitive.
  AseptiKits uses a third-party facility for ETO sterilization of their kits, and the sterilization process has been validated at that site. Using the validated sterilization cycle (time, temperature, humidity, vacuum), the bags are consistently sterilized prior to shipment to testing sites or other facilities. Biological indicators utilized during the sterilization procedure demonstrated the lethality of the cycle (Nelson Labs STP0079). Further, sterility testing of the kits afterward, using the method in USP <71>, confirmed that the kit has been adequately sterilized (Rane et al. 2023-attachment 9).
  ETO sterilization is known to leave behind trace amounts of residue. It is standard practice that, following exposure of an item to the ETO gas for a specified amount of time, the chamber containing the sterilized item is aerated to remove traces of the ETO gas. It is important to monitor any residue and potential impact to the end user of the sterilized item.
  Aseptikits sponsored a study to measure the levels of residual ETO on their sterilized kits. The test was conducted under GMP regulations, and each sample was tested for ethylene oxide and ethylene chlorohydrin, as noted in the lab report (Slaba 2024). The report shows little to no residue was found following extractions at various timepoints. Therefore, it is not anticipated that residual ETO would have an impact on the end user or function of the kit.

- Filter sterilization/filter validation
  Once the kit has been sterilized using ETO, the interior environment of the bag must remain sterile for the duration of serum processing.
  The serum is transferred to the bag using a syringe and enters the bag via the attached filters (Figure 1 and Figure 2). For the PALA-12, the first filter that the serum passes through has a pore size of 0.8 microns for removal of particulates. The second filter (attached in series) has a pore size of 0.22 microns, which is a sterilizing grade filter. The ALAdrop has one 0.22-micron sterilizing grade filter. This is critical for maintaining a sterile environment within the bag.
  The 0.22-micron filter was validated as capable of retaining a microbial challenge of $> 1 \times 10^8$ colony forming units (cfu) for all samples tested (Saunders 2016). The use of a

0.22-micron sterilizing grade filter within a closed system achieves preparations having a sterility assurance level (SAL) of at least 10^{-6}, which is the equivalent to a moist heat terminal sterilization cycle using an autoclave.

In separate laboratory studies, a bacterial preparation was injected through the filters and into the eye drop dispenser bottles following the kit's Instructions for Use. The contents of the dispenser bottles were subsequently taken and tested for bacterial contamination. No bacterial growth was detected in either of the two independent studies (Rane et al. 2023; Norrdin 2022), thus providing additional assurance that the 0.22-micron bacterial retention filter functioned as intended contributing to the maintenance of a sterile environment within the bag.

Another factor in the use of filters for sterilization is whether or not the filter integrity is maintained during the process. A breach of the filter could result in contamination passing through to the sample. It is unclear whether post-use integrity testing was previously conducted. If not, this is recommended. If sterility testing of the final bottle contents fails (i.e., shows microbial growth), the filter integrity should be assessed as part of the investigation.

Most of the other aspects of USP<71> are facility-specific (i.e., personnel training and evaluation, personal hygiene and garbing, certification, establishing beyond-use dates, etc.) and, therefore, beyond the scope of this document.

4. CONCLUSION

The ALAdrop and PALA 12 Convenience Kits are a technology that allows the user to have the equivalent of a desktop aseptic processing area. Clinicians transfer the collected autologous serum samples to the kit using the provided syringe. The sample passes through either one or two filters that are attached to the bag and is collected within the ophthalmic dropper bottles. Caps are placed on the bottles and secured in place using the provided ratchet. Once all bottles are filled, capped, and tightly closed, the bag is then opened (breaking the seal of the sterile environment) for retrieval of the bottles.

The ALAdrop and PALA 12 Convenience Kits are not a pharmaceutical drug product, yet the overall validation process follows some of the same principles of drug product sterility assurance (i.e., validation of sterilization process, validation of the sterilizing filter). ETO sterilization of the kit has been demonstrated to provide a sterile closed bag system for the processing of autologous serum eye drops, without impact to the form or function of the kit (Rane et al. 2023-attachment 2).

Furthermore, the sterile environment within the bag is maintained via use of the connected 0.22-micron filter. The use of a 0.22-micron sterilizing grade filter within a closed system achieves preparations having a sterility assurance level (SAL) of at least 10^{-6}, which is the equivalent to a moist heat terminal sterilization cycle using an autoclave.

Given the above, these closed systems comply with USP <797> for the compounding of sterile preparations.

5. REFERENCES

FDA/CDRH website – FDA's Product Classification Database: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm

Nelson Labs STP0079: Biological Indicator (BI) Sterility Test Final Report.

Norrdin, R. San Diego Eye Bank Report 2022.

Rane S. et al. Alvamed - AseptiKits Regulatory Analysis Report. March 8, 2023.

Saunders, D. "Evaluation of Brevundimonas diminuta retention efficiency of Pall filters with 0.2 µm Supor™ membrane and acrylic housing." Pall Technical Report. July 2016.

Slaba, M. "Sterilant Gas Residue Analysis Final Report." Nelson Labs. February 2024.

USP <797> Pharmaceutical Compounding – Sterile Preparations. Official as of May 1,2024.

Appendix C: Peak Consulting Letter

PEAK
REGULATORY CONSULTING

April 14, 2025

Re: Use of the AseptiKits Convenience Kits in leu of an ISO Class 5 Clean room environment

To Whom it May Concern,

The AseptiKits Convenience Kits are sterile, single use, closed system flexible bags with an integral 0.2-micron syringe filter with proprietary holding tray(s). The AseptiKits Convenience Kits enable pharmacies and other clinicians in other healthcare environments to transfer compounding solutions through the sterilizing grade filter into the sterilized bag using sterile and aseptic techniques. The use of AseptiKits Convenience Kits is done on-site while maintaining the compounding sterility requirements laid out in USP <797>, without the need for an ISO Class 5 clean room or laminar flow hood.

The AseptiKits Convenience Kits use off the shelf FDA 510(k) cleared or 510(k) exempt components in the fluid pathway for filling bottles/syringes that are manufactured in an ISO 13485 cleanroom and are supplied by large medical device manufacturers (for example, Merit Medical and Millipore Sigma). Syringe products using the Aseptic Level Assurance (ALA) technologies that are currently in development, are designed using 510(k) cleared or 510(k) exempt components in the fluid pathway and meet requirements as required for Class 2 products as a convenience kit. This also includes the AseptiKits syringe application kits which include a silicone-oil-free kit (e.g. VitrALA) having a primary intended use for intravitreal injections.

FDA Regulations:

The sterile preparation AseptiKits Convenience Kits are regulated by the FDA as a medical device under the following regulations and controls. As such, the products and facility are registered with the FDA and are controlled and maintained under cGMP and QMS requirements per 21CFR 820 and ISO 13485:2016.

Common Name:	System/Device, Pharmacy Compounding
Regulation Number:	880.5440 – Intravascular Administration Set
Product Code:	NEP
Classification:	Class 2 – Exempt
Submission Type:	510(k) Exempt

FDA guidance "Sterilized Convenience Kits for Clinical and Surgical Use; Final Guidance for Industry" issued January 7, 2002

USP Regulations:

The USP, as an organization, is not an enforcement agency and as such does not have any legal right or obligation to opine an official opinion on whether practices or products meet their standards. That is the role of regulators, such as the FDA, as noted above.

In particular, the purpose of USP <797> is to prevent harm and fatality to patients that could result from microbial contamination (nonsterility), excessive bacterial endotoxins, content errors in the strength of correct ingredients, and incorrect ingredients in compounding sterile preparations (CSPs). In particular, aqueous injections for administration into the vascular and central nervous systems, which pose the greatest risk of harm to patients if there are issues of nonsterility and large errors in ingredients.

Peak Regulatory Consulting, LLC
370 South 300 East | Salt Lake City, UT 84111

In relation to the AseptiKits Convenience Kits, the USP Expert Committee has stated that compounding sterile preparations (CSPs) must be prepared according to the USP <797> requirements. They note that in the introduction and scope section of USP <797>, there is an alternative technologies clause that allows for the use of technologies not mentioned in the chapter, as long as they are non-inferior to what is in the chapter and validated for the intended purpose for which it is designed.

As noted by the USP Expert Committee, the subject Convenience Kits would be considered as one of those alternative technologies. Specifically, the AseptiKits Convenience Kits maintain a controlled sterile environment (SAL 10^{-6}) equal to or better than an ISO Class 5 clean room environment (non-inferior), as well as having been validated for its intended use through rigorous testing, including packaging and material integrity and the sterilization process, in accordance with the FDA guidance "*Sterilized Convenience Kits for Clinical and Surgical Use; Final Guidance for Industry*" issued January 7, 2002.

The following table compares the USP <797> compliance requirements of an ISO 5 Compounding Aseptic Isolator (CAI) and the AseptiKits Convenience Kits.

Table 1: Non-Inferior Comparison to ISO 5 Compounding Aseptic Isolator (CAI)

USP <797> Feature	CAI (Compliant)	AseptiKits Convenience Kits	Comparison
ISO Class 5 Maintenance	HEPA filtration and pressure control	Sterile closed environment maintains sterility (SAL 10^{-6}) equal to or better than an ISO Class 5 cleanroom environment	Viable alternative non-inferior and validated technology
Environmental Monitoring	Daily air and surface sampling	Sealed and contained sterile environment, no access to external air or environment	Viable alternative non-inferior and validated technology
Personnel Access	Through glove ports, maintaining sterility	Through sterile 0.2-micron syringe filter sterile port	Viable alternative non-inferior and validated technology
Construction	Polypropylene or stainless steel, easy to disinfect	Tyvek/ polyethylene	Viable alternative non-inferior and validated technology
Certification	Meets cGMP, IEST, ASTM, ISO 14644-1 standards	Meets cGMP, ASTM F1140, ASTM F2096, ASTM F1886, ASTM F88, ISO 11607, ISO 11135, and ISO 11137 standards	Viable alternative non-inferior and validated technology

Utah State Pharmacy Board:

Individual State Pharmacy Boards are not enforcement agencies and as such have no legal right or obligation to opine an official opinion on whether practices or products meet their standards and whether products should or should not be allowed on the market. That is the role of regulators, such as the FDA, as noted above.

For example, the Utah State Pharmacy Board under the direction of the Utah Division of Professional Licensing, has emphasized that the "Division and Board cannot and does not review or endorse products". They further note that the board members' participation is voluntary, and almost all actively work in retail and hospital pharmacy systems and that most pharmacists will likely learn about the AseptiKits Convenience Kits through their jobs and employers. Thus implying they would expect the use of the AseptiKits Convenience Kits would become common place among pharmacists.

Conclusion:

The only enforcement agency related to the use and marketing of the Convenience Kits is the FDA. AseptiKits has complied with and demonstrated the safe and effective use of their Convenience Kits, and are legally registered with the FDA, and actively maintain their cGMP Quality Management System documentation in accordance with 21 CFR 820 and ISO 13485:2016. The USP and State Pharmacy Boards have no legal jurisdiction or enforcement capability or responsibility over the marketing and use of products that have demonstrated compliance with their standards. It is for the reasons outlined herein, that the AseptiKits Convenience Kits can legally and lawfully, in compliance with USP <797> and the FDA regulations and guidance documents, stated previously, be marketed for its intended purpose.

Sincerely,

Spencer Walker, MSc.
CEO/ Founder

PEAK Regulatory Consulting
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Appendix D: Links to FDA Warning Letters Cited Under the Heading: Sources of Insanitary Conditions in USP 797 Certified Facilities

General FDA Warning Letter Link: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters

For a complete list of insanitary 503 B FDA Warning letters enter the following key words in the search bar – "503B Insanitary." The specific complete FDA Warning Letters for each cited document may be found be searching each based on the date and/or company as shown supra. At this writing there were 78 Warning Letters shown for this search. Many of the cited examples listed supra can be found under the heading "Adulterated Drug Products."