WHITE PAPER - STERILITY

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March 29, 2024

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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

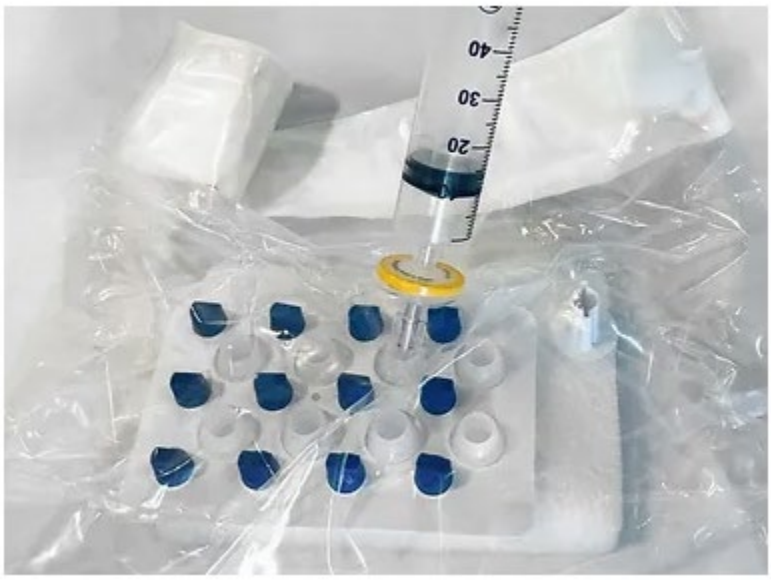
Clinicians transfer the collected serum samples to the kit using the provided syringe. The sample passes through two filters that are attached to the bag and is collected within the ophthalmic dropper bottles. Caps are placed on the bottles and secured in place using the provided ratchet. Once all bottles 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.