Best Practices for Sterilization of Prefilled Syringes

APPLICATION BRIEF

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Optimizing Terminal Sterilization

Abstract

As the use of prefilled syringes continues to grow due to their convenience, safety, and ease of administration compared to traditional injectables, the need for a reliable sterilization process becomes critical.

To reduce risks associated with aseptic production and filling of syringes, terminal sterilization is preferred. With a variety of syringe nests available on the market, there is a need to establish a sterilization process that is compatible with the most popular types and can provide validated sterility.

This brief outlines a recommended sterilization method using a steam-air mixture cycle with controlled support pressure.

Designed to be compatible with commonly used syringe nest formats, this process minimizes stopper movement, maintains container integrity, and supports compliance with validation protocols such as thermal mapping and bio-indicator testing.

Steam Sterilization Cycle Phase

- **Preheating**
  Upon cycle initiation, the chamber and its contents are warmed using indirect dry preheating. This reduces the level of condensation formed later during the process.
- **Heat Up**
  During the heat ramp phase, the temperature and pressure are increased to achieve the desired setpoint while any condensate formed is removed via the drain bleeder.
- **Exposure Phase**
  According to the programmed cycle, temperature and pressure dwell are precisely maintained in the chamber and load for the preset time.
- **Drying/Cool Down**
  In the final phase of the procedure, the load is returned to ambient temperature and pressure with care taken to ensure any condensate is removed. For this cycle, the internal fan(s) are used for active cooling of the chamber and the load.
- **Support Pressure**
  Support pressure is carefully controlled in order to minimize stopper movement within the syringe barrel. To achieve this, an air steam mixture process is used.

Introduction

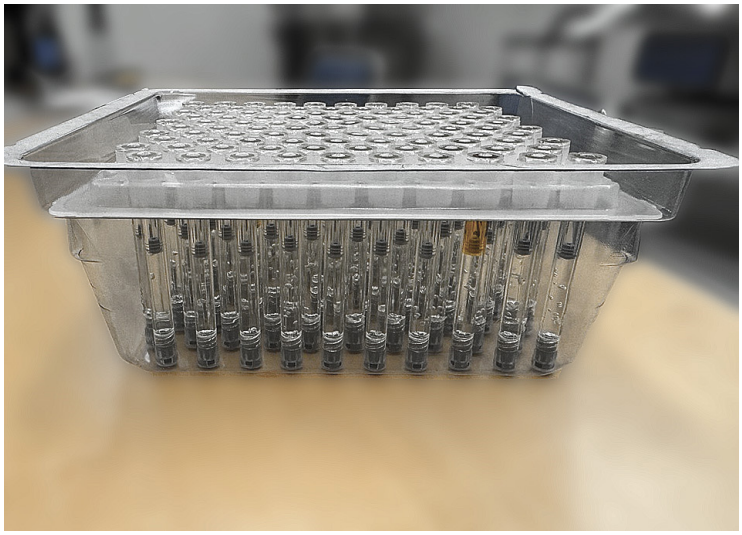
For pharmaceuticals and drug products, aseptic processing and validated sterilization processes are essential. This is especially true in the case of more sensitive drug products. For many pharmaceutical products, the final fill-finish step is terminal sterilization. This takes place once the pharmaceutical product is packaged. Especially in the case of sensitive products and packaging itself, terminal sterilization is a demanding process. It is also an essential method to provide a quantifiable sterility assurance level (SAL).

Prefilled syringes offer numerous benefits, including increased drug preparation efficiency, reduced waste, reduced dosage error, and easier administration. However, terminal sterilization of prefilled syringes is a demanding process that brings with it many challenges pharmaceutical manufacturers must overcome.

Prefilled syringes are often packaged by drug manufacturers in nests of 100 units. This helps enable high-throughput handling for injectable products.

When conducting terminal sterilization of prefilled injectable pharmaceuticals, manufacturers must account for many factors to ensure SAL.

This document describes a sterilization process developed specifically for prefilled syringe nests. This validated terminal sterilization method utilizes a steam-air mixture that includes integral air support pressure to minimize the stopper movement and prevent associated potential barrel-induced contamination and/or leakage.



Preparation

Prefilled syringe nests are often housed tip down in tubs for protection. Before sterilization, nests must be removed from tubs, secured in a nest sleeve, and inverted so the tip faces upward.

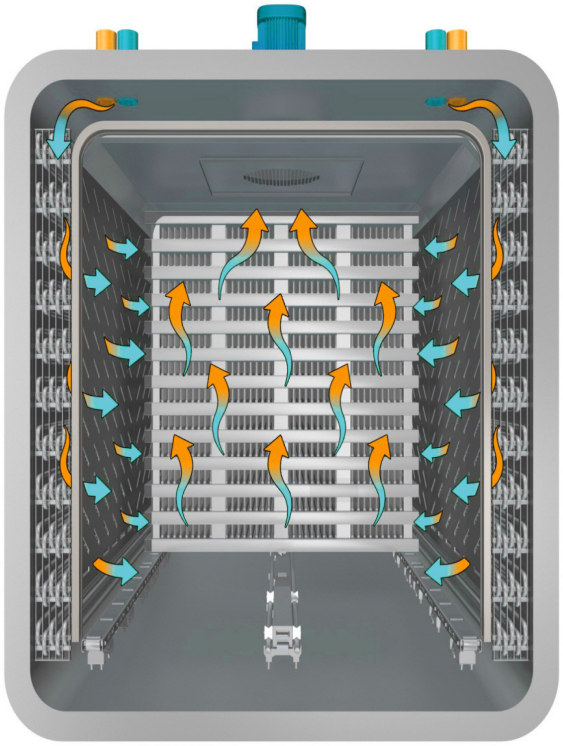
This orientation allows for proper condensate drainage and consistent processing. Once secured, nests are then loaded into racks or trays within the sterilizer.

Sterilization Process

Due to the movable plunger in the syringe, it is important to apply support pressure during the cycle. A steam-air mixture process is therefore recommended. This also brings several other potential advantages with the following characteristics:

Steam-Air Sterilization Process Benefits:

- Dry preheating improves load dryness
- Ensures temperature uniformity, even in larger chambers
- Support pressure minimizes syringe stopper movement
- Active fan cooling helps shorten total process times
- Condensate management helps ensure dry loads



Controlling Stopper Movement

As the syringes are heated during the process, changes occur within the syringe and its contents, resulting in stopper movement that can increase contamination risks:

- The syringe barrel increases in volume
- The liquid volume inside the syringe increases (this typically exceeds barrel volume expansion)
- The vapor pressure of the liquid increases

If not controlled, the movement can result in leakage and increase the potential risks for barrel induced contaminants. It can also enable the formation of bubbles and an uneven appearance in some product types. To manage these effects, sterile air support pressure needs to be accurately controlled during the entire heating and cooling process to ensure the stopper location is maintained in the optimal position for a given temperature. While thermal expansion always results in some movement, this method helps constrain the stopper's final location to close tolerances of the initial position.

Ambient conditions

Elevated temperature without support pressure

Elevated temperature with support pressure active

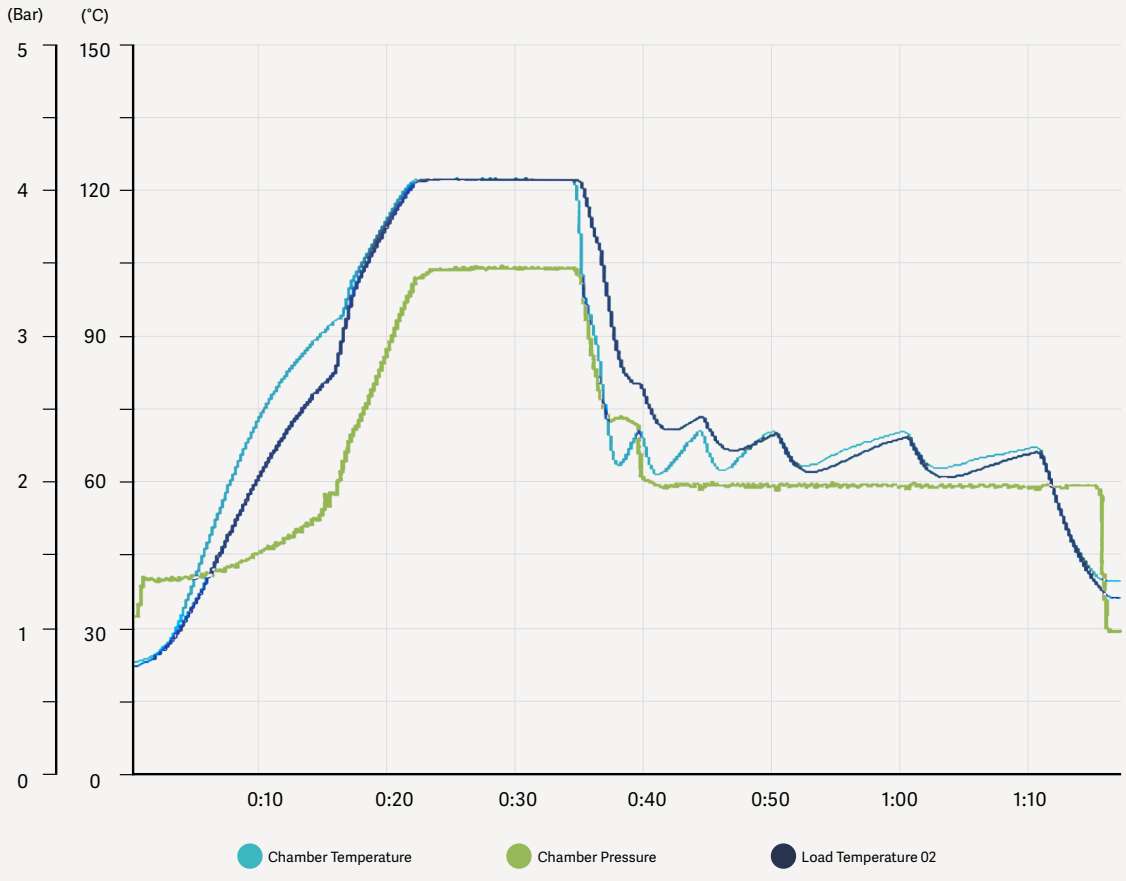
Steam Sterilization Process

The process works by initially preheating the chamber and load contents using a dry heat. This not only begins the warming of the load, it also reduces the condensate that will be produced during the steam part of the cycle, and hence also assists with the drying process later on.

The heat-up phase brings the load to temperature and needs to be adjusted to suit the load specifics. For example, products that thermally degrade may require fast heating and cooling times. Care also needs to be taken to ensure all parts of the load are uniformly heated to ensure a tight control of F0 (thermal lethality).

The post-sterilization phase is cooling, where the load is both dried and cooled prior to pressure equalization.

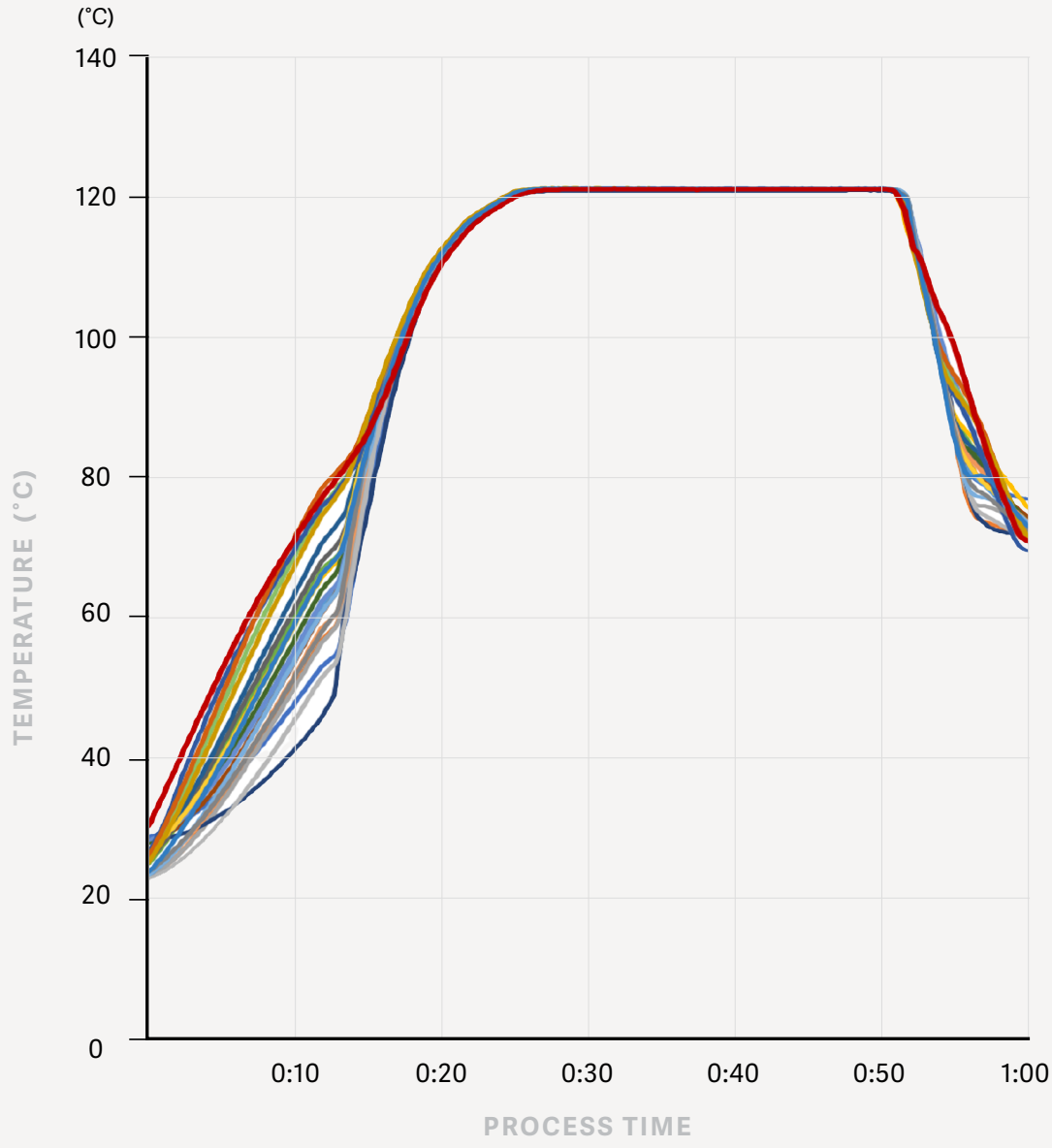
Support pressure is maintained during the entire process as required.



Trend to illustrate a sterilization cycle with dry pre-heating to 80 °C and active fan cooling included for efficient process times.

Process Validation

Since the effectiveness of the process is paramount, the system and load must be fully qualified to the appropriate norms and regulations. Typically, this includes thermal mapping for minimum and maximum loads, stability studies, and bio-indicator challenges in appropriate parts of the load. This ensures sterilization efficacy and compliance with global standards. Additionally, clean media sampling and testing must be performed.



Thermal mapping of 24 thermocouples (TC) placed inside a typical 2mL prefilled syringe nest during validated sterilization cycle in a 9 cubic metre chamber.

Automated Handling For High Volumes

Since prefilled nests are commonly used for high-volume production, a fully or semi-automated process that includes nest handling is an increasingly common option for manufacturers.

With logistical automation and filling line integration, there comes the potential for other system enhancements, including:

- Traceability
- Re-stacking into the original tubs
- Inspection systems
- Batch process reports
- Final packaging integration
- Manufacturing Execution System (MES) integration

Conclusion

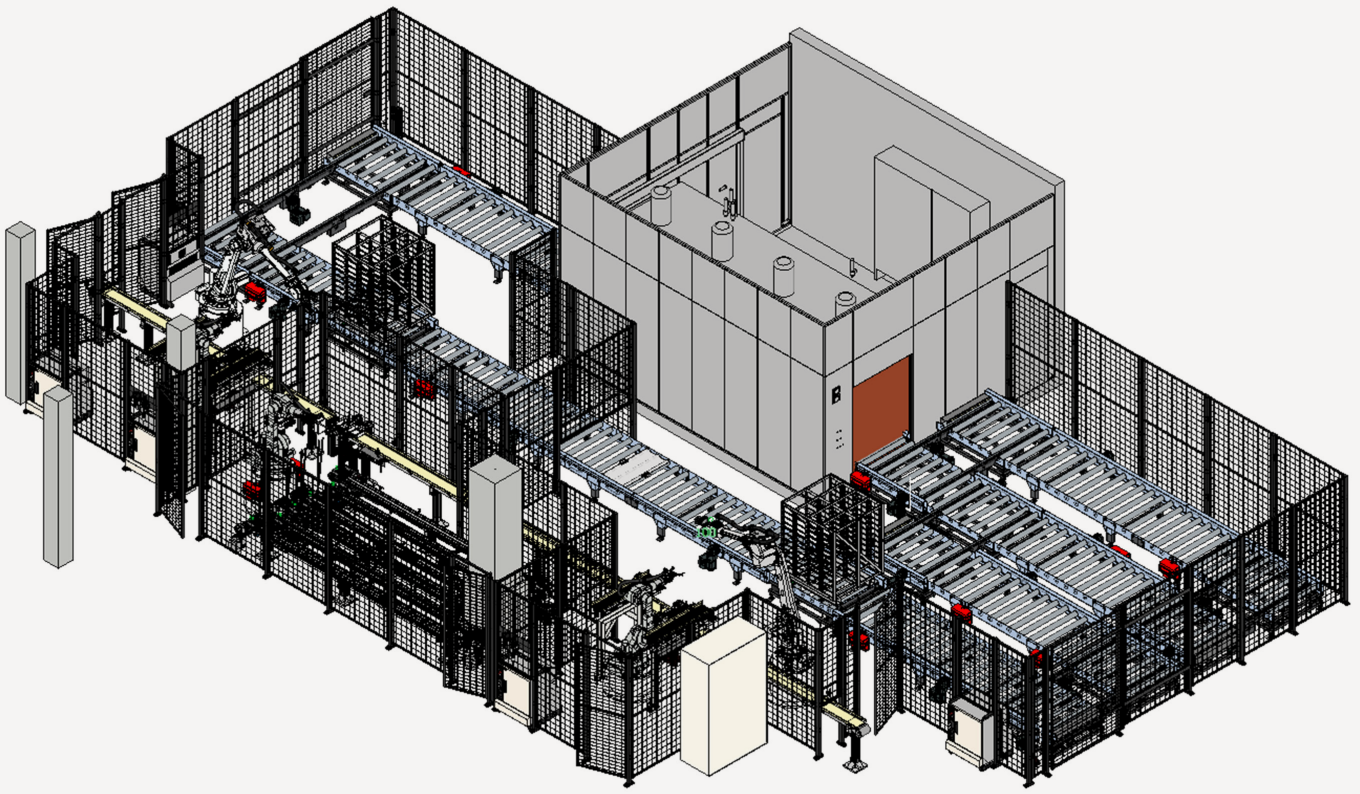
The sterilization of prefilled syringe nests requires precise control over temperature, pressure, and support conditions to ensure product integrity and consistent sterility outcomes. The steam-air mixture cycle, paired with controlled air support pressure and dry preheating, offers a proven method for minimizing stopper movement, preventing leakage, and maintaining syringe cleanliness throughout the sterilization process.

This approach supports a wide range of syringe nest formats and is compatible with automated or manual handling systems. By validating process parameters through thermal mapping and bio-indicator studies, manufacturers can achieve a robust, repeatable sterilization cycle that meets regulatory and quality assurance standards.

Summary and Best Practices

- To ensure optimal results, the following best practices are recommended:
- Invert and Secure Nests: Always orient syringes tip-up and use sleeves to secure devices prior to sterilization.
- Use Dry Preheating: Begin the cycle with dry heat to reduce moisture accumulation and accelerate drying.
- Apply Support Pressure: Maintain air support pressure throughout the cycle to minimize plunger displacement and preserve fill volume.
- Utilize Active Cooling: Use internal fans to accelerate load cooling and minimize overall cycle time.
- Validate Thoroughly: Perform thermal mapping and biological indicator testing to confirm cycle efficacy for all load types and configurations.
- Consider Automation: Integrate automated handling, inspection, and re-stacking systems to increase throughput and reduce human error.

By implementing these best practices, manufacturers can confidently sterilize prefilled syringe nests while protecting product quality and ensuring compliance with global sterilization requirements.



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