WHITE PAPER

Best Practices for Validated Sterilization of Alternating Tangential Flow (ATF) Devices

Sterilization of ATF Devices

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Abstract

Alternating Tangential Flow (ATF) devices play a vital role in upstream bioprocessing, enabling high-efficiency cell retention, nutrient exchange, and waste removal in perfusion culture systems. When implemented with multi-use bioreactors, stainless steel ATF devices must be sterilized between production runs to ensure compliance, safety, and performance.

This white paper details a validated steam sterilization process tailored to protect the integrity of ATF device components while achieving the sterility assurance levels required for cGMP environments. It highlights key process considerations, including temperature control, load configuration, and pressure regulation to prevent damage to sensitive hollow fiber membranes.

Cycle Terminology

- **Preheat (Conditioning)**
  Indirect dry heating prepares the chamber and load upon cycle initiation, minimizing condensate formation during the later process and aiding in drying efficiency.
- **Purge (Conditioning)**
  Steam displaces ambient air from the chamber and filter housings. Full removal of residual air is essential to achieving uniform sterilization.
- **Pre-Vacuum**
  Alternating vacuum and steam injections carefully remove trapped air and allow gradual pressure equalization across the filter membranes, protecting structural integrity.
- **Heat Up**
  The temperature and pressure ramp up to setpoints while removing any condensate via the drain bleeder.
- **Dwell (Sterilization Plateau/Exposure Phase)**
  The chamber maintains a validated setpoint temperature and dwell according to the programmed cycle for a designated time to ensure microbial kill.
- **Drying/Cool Down**
  Passive or assisted cooling brings the system back to ambient conditions while preventing recontamination or membrane damage.

Introduction

Used alongside bioreactors in perfusion-based cell culture, Alternating Tangential Flow (ATF) devices enable continuous product harvest and media exchange, improving cell density, yield, and cost-efficiency. ATF systems are commonly used for the production of biologics, such as monoclonal antibodies, vaccines, and enzymes.

Devices from leading ATF manufacturers, like Repligen and Spectrum Labs, integrate hollow fiber filters, some of which are as narrow as 0.65 µm. These hollow fiber filters are particularly sensitive to thermal and mechanical stress. They function by creating a bidirectional flow of media across a filtration membrane using a diaphragm pump, significantly reducing membrane fouling while enabling high-density cell culture.

Unlike single-use ATF assemblies, stainless steel ATF devices are designed for repeated use and must undergo validated sterilization between batches. Saturated steam sterilization remains the preferred method for durable process equipment, but special adaptations are necessary to preserve ATF device integrity during the process. Traditional steam sterilization cycles must be adapted to accommodate the filters' delicate membrane structures while ensuring validated sterilization of the ATF assembly.

Preparation

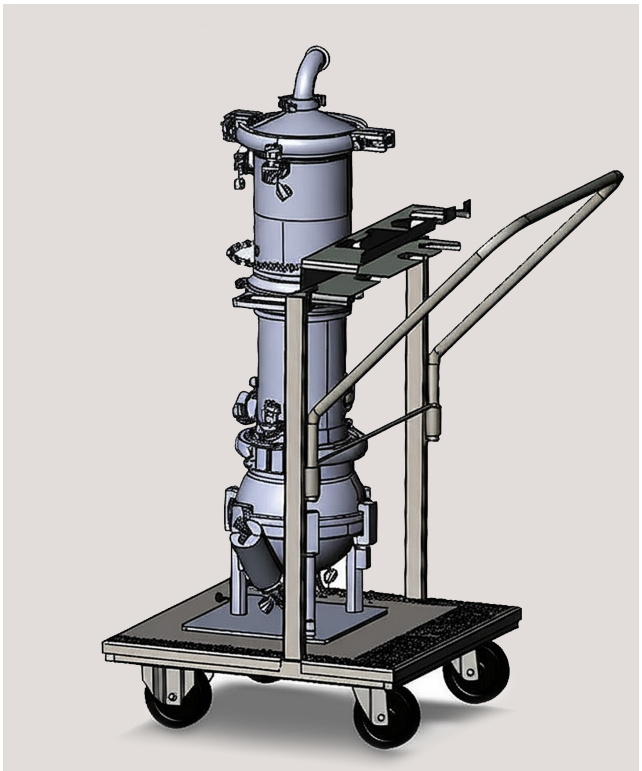
Before sterilization, the ATF device should be:

- Fully assembled and integrity tested according to the supplier's recommendations
- Free from residual product or fluid
- Properly configured for steam access and drainage

Specialized Loading and Handling Considerations

As there can be external filters attached to the ATF filtration housing, each with individual flexible hoses, some procedural attention needs to be taken to ensure a repeatable and reliable process. External filters have to be in a vertical position to ensure condensate drainage. Due to complex tubing and the presence of external filters, a purpose-built trolley or rack system is recommended for secure, ergonomic loading.

- Filters should be held vertically to facilitate condensate drainage.
- Tubing must be secured and uncluttered to allow for complete air removal.



A custom trolley design improves safety and ergonomics with builtin clamps for stability and defined locations for clipping hoses.

Temperature and Pressure Validation

ATF devices are typically sterilized using a vacuum-saturated steam process, modified to protect delicate fibers while achieving full air removal and load sterility.

The process works by initially preheating the chamber load contents using 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.

Once initially warmed, the air is removed from the chamber using a steam purge or flush, followed by a carefully controlled series of ramped vacuum and steam pulses to remove the remaining air from deep within the load.

With the air removed, the process brings the load up to sterilization temperature for the set time period.

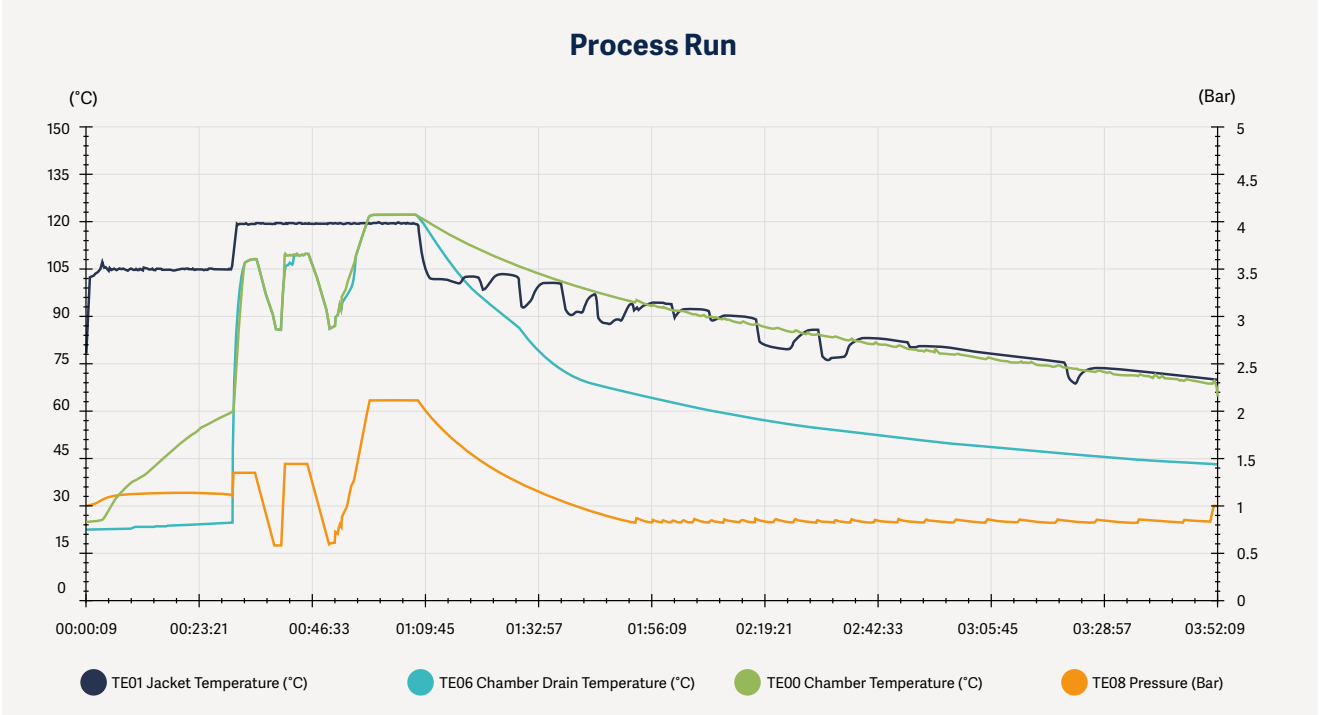
In the post-sterilization phase, the load is both dried and cooled prior to pressure equalization.

1. **Preheating (Conditioning)**
   Indirect dry heat warms the load to reduce thermal shock and pre-evaporate moisture.

2. **Air Removal (Steam Purge + Pulsed Vacuum)**
   Downward steam displacement removes bulk air, followed by ramped vacuum/steam pulses to evacuate air from internal filters and tubing. Pulse rates are carefully controlled to avoid damaging fiber bundles.

3. **Heat-Up and Sterilization Dwell**
   Chamber temperature rises to the sterilization set point (typically 121°C), held for a validated dwell time. Temperature spread must remain within ±1°C across the load, per EN285:2016.

4. **Cooling and Drying**
   Passive or assisted cooling (via jacket or air fan) returns the load to ambient temperature. Condensate is vented to prevent residual moisture. Dryness is critical for maintaining filter performance and validation.



The process trend illustrates a typical process using default parameters. The pretreatment phase is naturally convected dry heat and the post sterilization phase is natural cooling.

Process Control Considerations

Temperature Distribution

In any sterilization process, the temperature distribution in compliance with recognized standards such as EN285:2016 is paramount. There are several factors that can affect the distribution, but in any saturated steam vacuum process, air removal is key.

Since the AFT device requires control of the pressure rates with limited vacuum depth during the pulsing phases, a tight temperature spread throughout the load needs to be carefully validated.

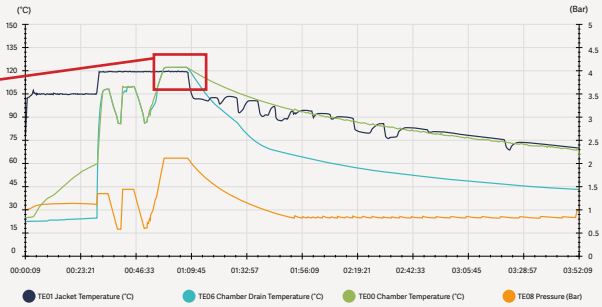
Process Times

The overall process time for these devices can be several hours. This is due to several factors including:

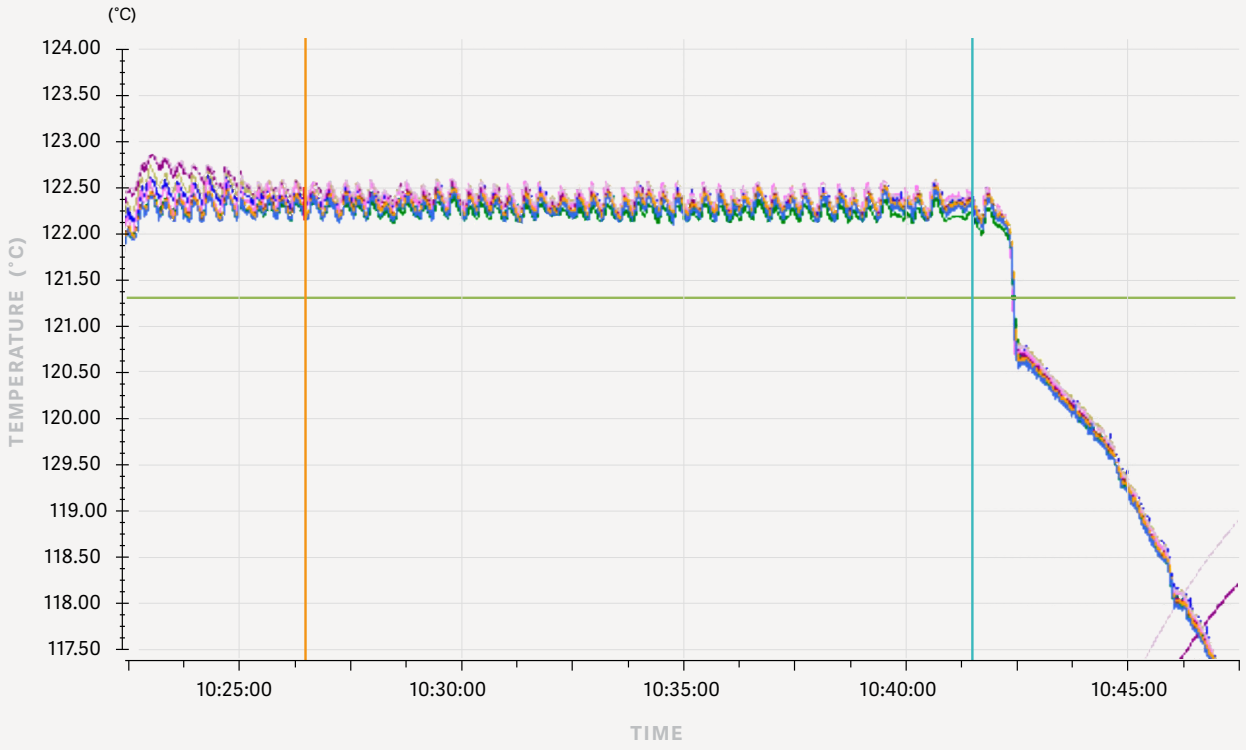
- Preheating time required to initially warm the device
- Ramped pressure changes to reduce stress on the fibers
- Time required for drying and cooling

With modern sterilizer technologies, there are three methods that can be employed to reduce the process time.

Process Run



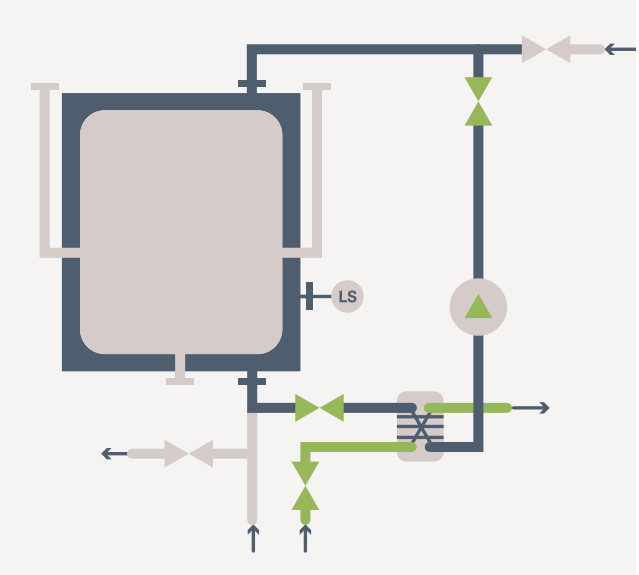
Example Validation



Thermocouple mapping has demonstrated consistent sterilization temperatures across filter assemblies within the allowable ±1K range during the exposure phase. Controlled overshoot and dwell time ensure effective microbial inactivation without overburdening the filter structure.

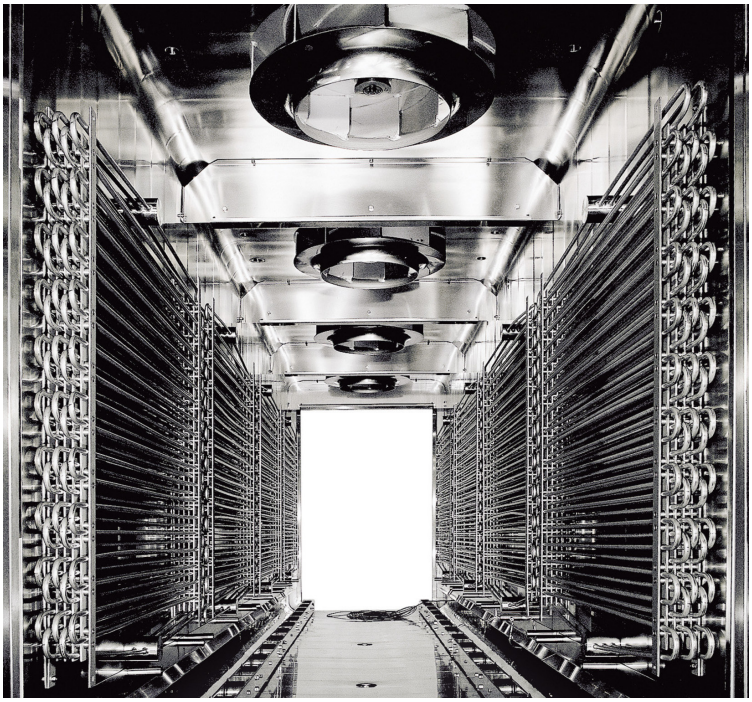
Option 1 – Assisted Jacket Cooling

The final device cooling phase in the standard cycle setup is by far the longest part of the process, taking as much as 50 percent of the total time. One method for reducing the final cooling time is to use indirect assisted cooling via jacket cooling rather than just natural cooling.
This method cools both the chamber and load at a much faster rate, but care must be taken to avoid condensation on the load, so it can only be used once all the process steam has been removed.



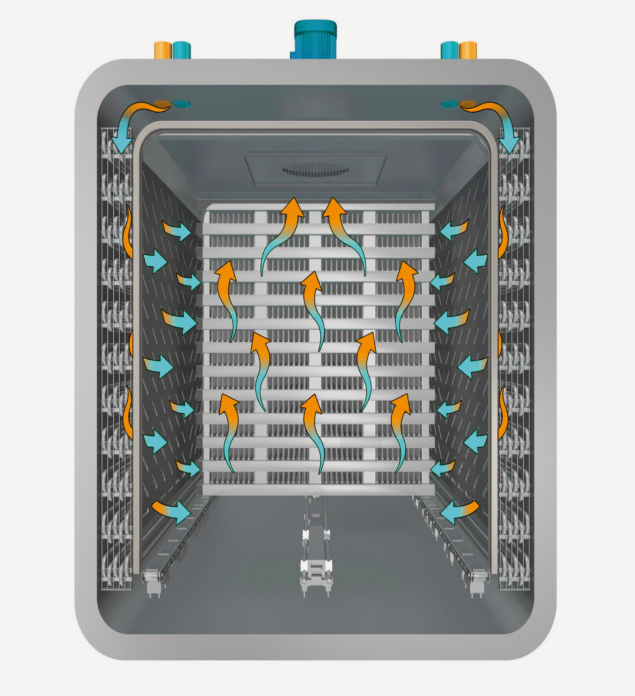
Option 2 – Forced Air Cooling

With the addition of an internal chamber recirculation fan, the cooling phase time can be reduced further through forced convection. Furthermore, a high movement of air in the chamber can also reduce the drying time.



Option 3 – Forced Air Dry Preheating and Cooling

A chamber fan can also be used to significantly reduce the time required for preheating. This, in conjunction with internal heat exchangers, provides the fastest possible cycle times with reductions in times for preheating, drying, and cooling.



Getinge Bioreactor Systems

Getinge sterilizers are engineered to support advanced sterilization requirements for multi-use ATF devices and bioreactor accessories.

Getinge sterilizers are fully compatible with other upstream components such as bioreactor vessels, headplates, and tubing assemblies. This allows biopharmaceutical manufacturers to adopt a unified sterilization protocol across devices.

Glass and Stainless Steel Bioreactors
Getinge's portfolio includes both stainless steel bioreactors (BioBench / BioPilot / BioProduction) and glass bioreactors (Applikon), enabling flexible integration of ATF systems for any scale of upstream processing. Learn more at getinge.com/from-culture-to-cure

Conclusion

Validated steam sterilization of stainless steel ATF devices is essential for maintaining cGMP compliance, product safety, and device longevity. Because of the sensitivity of hollow fiber filters, sterilization processes must be carefully configured to balance sterility assurance with mechanical integrity.

Getinge's cGMP sterilizers provide the control, reliability, and documentation required for complex bioprocessing applications, including those involving multi-use ATF systems. With advanced cycle features, flexible loading solutions, and compatibility with a wide range of bioreactor technologies, Getinge supports efficient, validated sterilization in the most demanding environments.

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