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# Implementing and Managing Pre-use Post-sterilization integrity testing. (PUPSIT)

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## Agenda

1. **Regulatory Environment**
2. **PUPSIT Why & Debate**
3. **Executing PUPSIT**
4. **Design considerations**
5. **Implementation aspects**
6. **Conclusion**

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# 1. Regulatory Context



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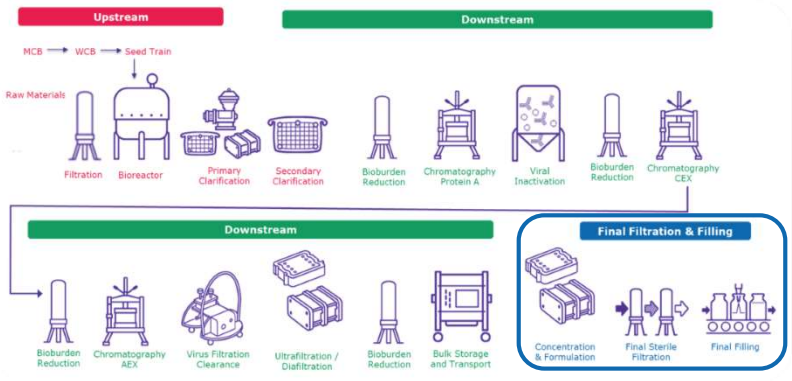
## Introduction

- What is PUPSIT?

- P. Pre
- U. Use
- P. Post
- S. Sterilization
- I. Integrity
- T. Testing

- Where is PUPSIT



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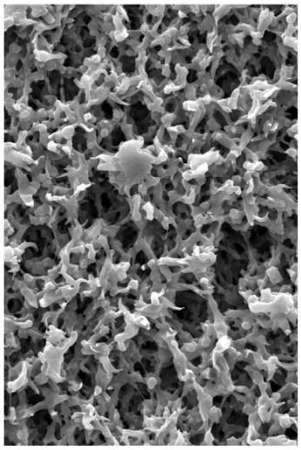
# Sterile Filter Definition - more than just "0.22 µm"



**EU GMP, Annex 1, 2022**
"Sterilizing grade filter – A filter that, when **appropriately validated, will remove a defined microbial challenge** from a fluid or gas producing a sterile effluent. Usually, such filters have a pore size equal or less than 0.22 µm."

**FDA cGMP, Guidance for Industry, 2004**
"A sterilizing grade filter should be **validated to reproducibly remove viable microorganisms** from the process stream, producing a sterile effluent. Currently, such filters usually have a rated pore size of 0.2 µm or smaller."

**EMA, Guideline on sterilisation of the medicinal product, 2015**
Filter retention capacity to be validated by challenging the filter membrane with justified indicator organism (*Brevundimonas diminuta*) at a minimum concentration of **$10^7$ CFU per $cm^2$** of filter surface area.

**A Liquid Sterilizing filter should be validated**

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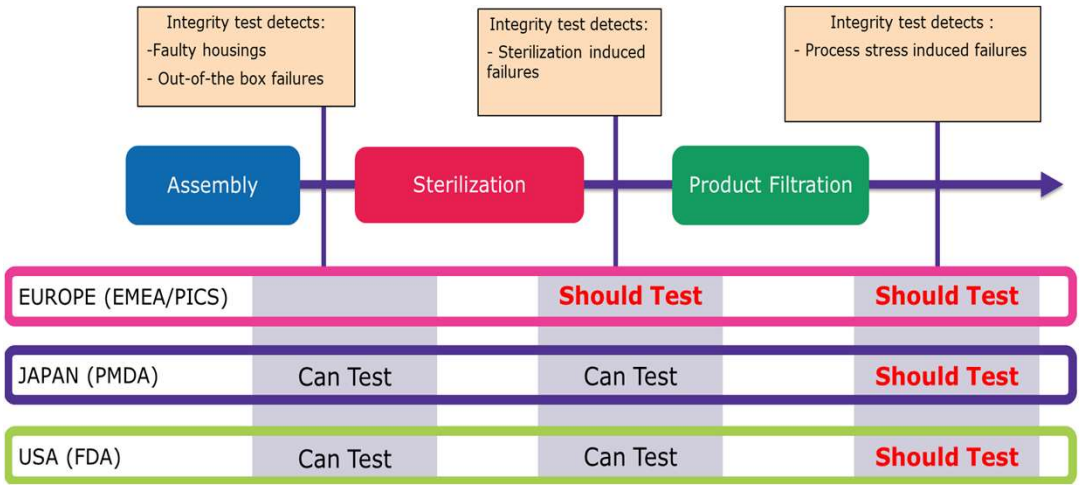
# When to Integrity Test Sterilizing grade filters? Regulatory Perspective

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# 2. Why PUPSIT?





## Purpose of Integrity Test for Critical Filters?

**Pre-use Test :**

- Confirmation of **manufacturers specifications**
- Detects **leaks** due to poor setup (gasket, o-ring, seals)
- **Before sterilization** : verify filter was not **damaged** during **transport / installation**
- **After sterilization** : verify **sterilization** method **did not compromise** filter **integrity**

**Post-use Test**

- Verify **filtration process** did not **damage** filter
- Verify filter did **retain bacterial contamination**
- Verify **product is safe** to be administered to patient

1980's Membrane disc holder

Early days of Housings & Cartridges

Self Contained Devise (Capsules)

# Filter Life Cycle

## What is "Blinding" / "Flaw Masking"

| | Manufacture | Sterilization | Filtration | |
|---|---|---|---|---|
| No Damage | Integral | Integral | Integral | No Risk |
| Transportation / Installation Damage | Non-Integral | Non-Integral | Non-Integral | Business Risk |
| Sterilization Stress | Integral | Non-Integral | Non-Integral | Business Risk |
| Process Stress | Integral | Integral | Non-Integral | Business Risk |
| Flaw Masking | Non-Integral | Non-Integral | Appears Integral | Patient Risk |



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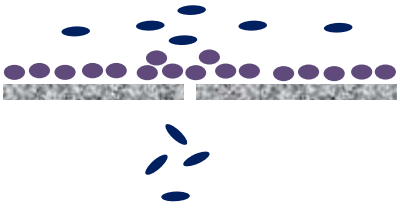
# Conditions Necessary for Flaw Masking

| | Manufacture | Sterilization | Filtration | |
|---|---|---|---|---|
| Flaw Masking | Non-Integral | Non-Integral | Appears Integral | Patient Risk |

- Flaw must be **large** enough to pass **microbiological contamination**
- Flaw must be **small** enough to be closed/masked by **clogging**
- Material/Particle burden must be present that can plug the defect/filter to such an extent that it is **not detectable by post-use FIT**

False positive FIT





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# Industry debate

## Biophorum & PDA SFQRM production 2017 - Now

PDA Research

2017 PDA PUPSIT Survey

BioPhorum

PUPSIT Survey 2019

Blinded results for discussion

PDA Journal of Pharmaceutical Science and Technology

Datamining To Determine The Influence Of Fluid Properties On The Integrity Test Values

PDA Journal of Pharmaceutical Science and Technology

Test Process and Results of Potential Masking of Sterilizing Grade Filters

NF EN ISO 13408-2
18 May 2018

Aseptic Processing of health care products – Part 2 : sterilizing filtration

Points to Consider for Risks Associated with Sterilizing Grade Filters and Sterilizing Filtration

Points to Consider for Implementation of Pre-Use Post-Sterilization Integrity Testing (PUPSIT)

Some Industry insights

- **Low value**, flaw masking is **uncommon**
- PUPSIT adds **risk**, may compromise aseptic pathway
- Adds **complexity**, stresses filter

**How to make PUPSIT safe & easy**

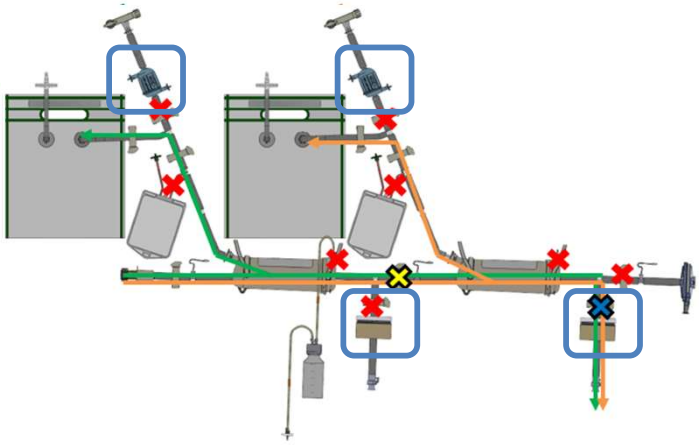




# 3. Executing PUPSIT

## PUPSIT steps

- Wet and vent the product filter
- Integrity test the product filter
- Blow down the filter to dry (optional)
- Wet and vent (optional) the product filter with product
- Discarding first aliquot (optional)
- Integrity test the vent and barrier filters







# 4. Design considerations

# Wide Array of Filtration System Options

## Process Design Considerations

### 1. Number of filters in system

- **Single stage**
- **Dual stage**
- **Redundant**

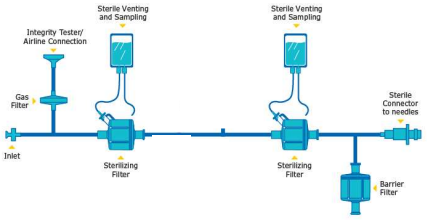
### 2. Flushing

- Flush bag or barrier filter

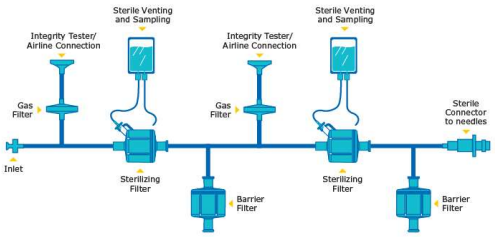
### 3. Product Recovery

- Blow down through filter
- Blow down after filter

**Not Designed for PUPSIT**




**Designed for PUPSIT**



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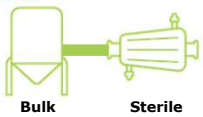
# Designs for final filtration systems

## Single Filter



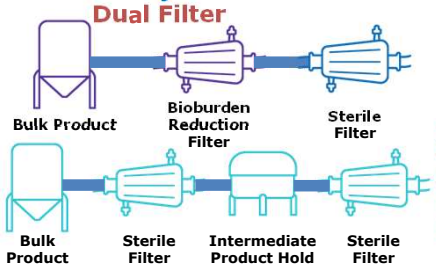

**BENEFITS**

- ✓ Minimum hold-up volume
- ✓ Minimum flushing requirements
- ✓ Ease of handling and operation
- ✓ Lower filter cost

**CONSIDERATIONS**

- × No back-up in the event of primary filter failure
- × Minimal feed bioburden control
- × High probability of filter plugging

## Dual Filter



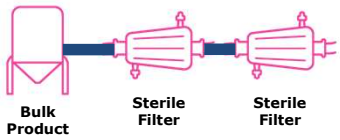

**BENEFITS**

- ✓ Compliance with regulatory guidance for <10 CFU/100 ml
- ✓ Minimizes plugging risk for secondary filter

**CONSIDERATIONS**

- × No back-up in the event of primary filter failure
- × Higher hold-up volume
- × Higher cost
- × Higher system complexity

## Redundant




**BENEFITS**

- ✓ Compliance with regulatory guidance for <10 CFU/100 ml
- ✓ Low plugging risk for primary filter
- ✓ Potential batch recovery if one filter fails integrity test

**CONSIDERATIONS**

- × Higher hold-up volume
- × Higher cost
- × Higher system complexity



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# Process Design Considerations

**Number of filters in system**

- Single stage
- Dual stage
- Redundant

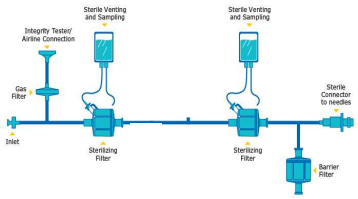
**Flushing**

- **Flush bag or barrier filter**

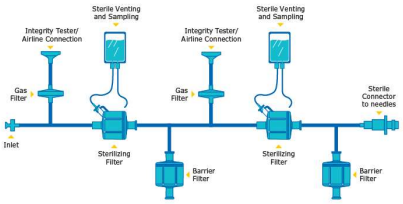
**Product Recovery**

- Blow down through filter
- Blow down after filter

**Not Designed for PUPSIT**




**Designed for PUPSIT**



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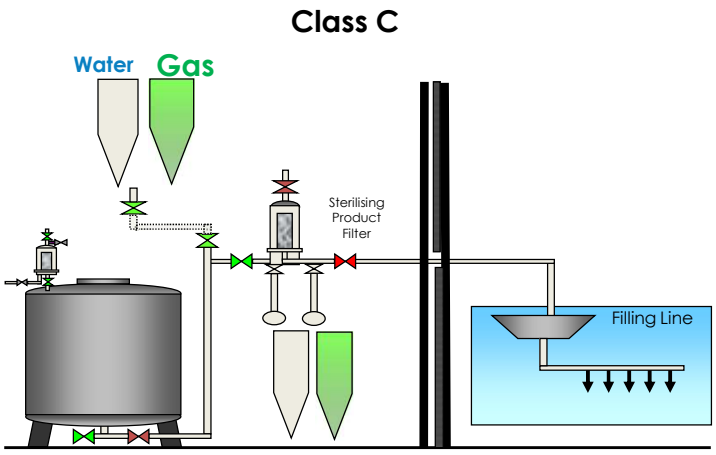
# Practical Challenges when Performing PUPSIT

- Remove –
  - Wetting Liquid
  - Test Gas
- While Maintaining downstream
  - Sterility
  - Atmospheric pressure (test)



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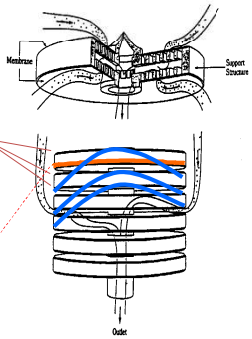
# What is a Barrier Filter?

One disk pair

Barrier filters can pass both liquid and gas.




Liquid Condensate

3 x Hydrophilic membranes

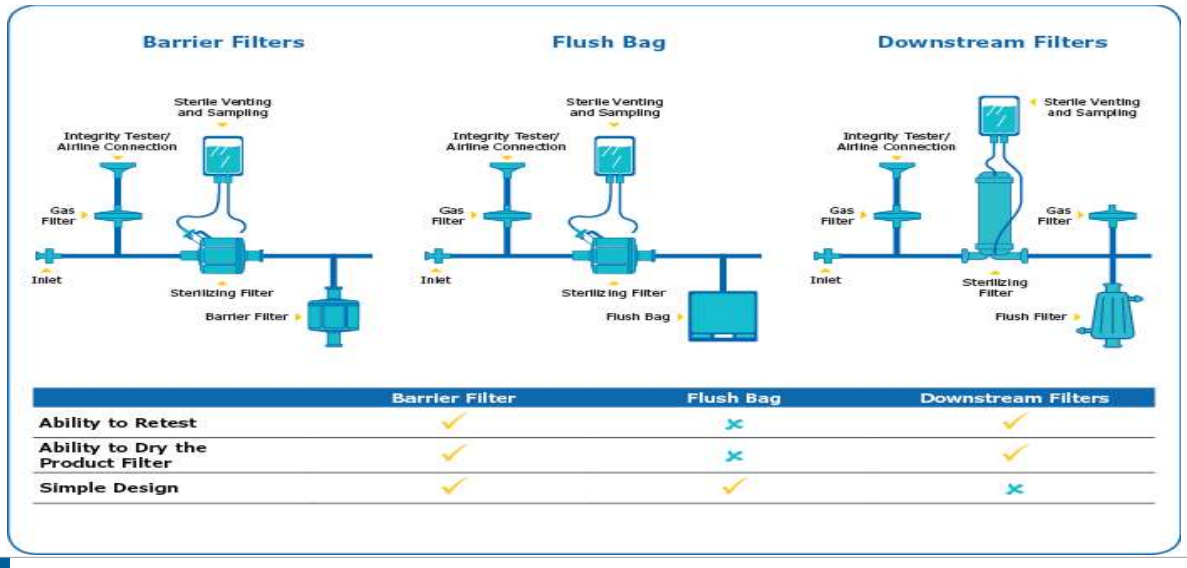
Gas

1 x Hydrophobic membrane





# Comparison of all 3 Options:



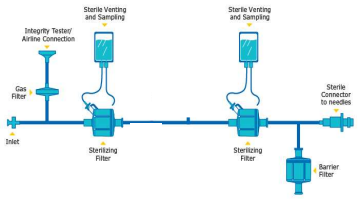

| | Barrier Filter | Flush Bag | Downstream Filters |
|---|---|---|---|
| Ability to Retest | ✓ | ✗ | ✓ |
| Ability to Dry the Product Filter | ✓ | ✗ | ✓ |
| Simple Design | ✓ | ✓ | ✗ |

# Process Design Considerations

**Not Designed for PUPSIT**

**Number of filters in system**

- Single stage
- Dual stage
- Redundant



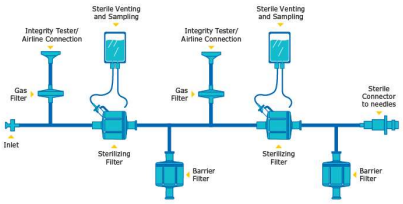

Flushing

- Flush bag or barrier filter

**Designed for PUPSIT**

**Product Recovery**

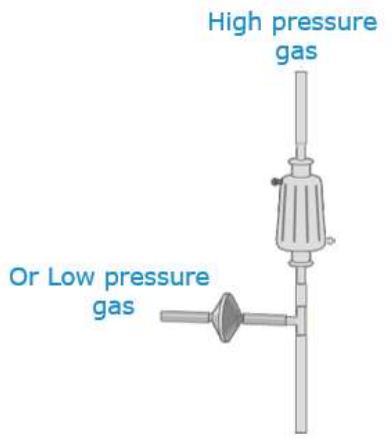
- **Blow down through filter**
- **Blow down after filter**






# Recovery: Post Process Product Recovery

- During processing the entire system is flooded with product
- Gas **will not** pass through the wet membrane **below** the bubble point pressure
- To displace downstream liquid with gas requires either **exceeding the bubble point** OR applying low pressure through the vent between the product filters displaces downstream liquid



## Post Process Product Recovery

| Blow-down through final filter (Exceed filter bubble point>50 psi) | Blow-down after final filter (Air introduced downstream) |
|---|---|
| + No added downstream fittings | + Low pressure |
| + No downstream manipulations | + Low shear/foaming |
| | + No added filter validation concern |
| – Requires proper validation | - Requires sterile gas filter |
| – Risks product foaming | •That will require testing |
| – Downstream component pressure limits | – Requires downstream fittings and manipulations |





# 5. Implementation aspects

# Integration of PUPSIT into the Manufacturing Operation

- The implementation of a PUPSIT process can have a **significant impact** on the manufacturing operation.
- PUPSIT-related decisions such as how wetting is performed, whether redundant filtration is implemented, and if an extended air blow is performed to facilitate drying (to avoid product dilution), can significantly affect important manufacturing parameters such as the **cycle time and process yield**.
- When designing a PUPSIT process, the primary goal is to design a system that **minimizes the patient sterility risk and business risk.**

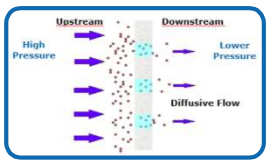




# Integrity test

## What test method is best for Single-Use Assemblies?

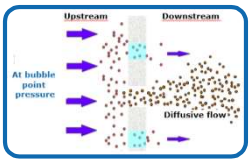
### 1 Diffusion




- **PRO'S**
- Lower **test pressure** → reduced stress on SUS
- **Less gas** volume generated **downstream**
- Minimize need / size for **flush bag**
- Minimize the risk of **back pressure**
- Faster
- Resilient to product excipient adsorption
- Softer **wetting conditions** required

- **CON'S**
- Silicone tubing permeability to gas ~ 1 ml/min.m

### 2 Bubble Point




**PRO'S**
- Resilient to **temperature variation**
- **Invariant** for one membrane/fluid combination
- **Independant** from filter surface area

**CON'S**
- Higher **pressure** level
- **Large gas** volume displaced
- May requires large flush bag
- Risk for back pressure
- Slower
- Impacted by polysorbate/Tween adsorption
- Strong **wetting conditions** required

## What fluid to use for filter wetting

### 1 Water

- **PRO'S**
- Inexpensive fluid
- Unlimited amount for flushing
  - large filtration system
  - E&L removal
  - Repeated wetting
- Test specification published
- No risk for flaw masking

- **CON'S**
- More sophisticated design
  - Water in & out
  - Air in & out
- Risk of dilution
- Filter blow down
  - Duration 15' to 3h
  - Mechanical stress 4 bar
  - Qualification

### 2 Product

**PRO'S**

- Leaner design
- No dilution
- No drying
- Negligible risk of flaw masking

**CON'S**

- Product specific FIT limit
- Product discard for E&L removal
- Negative impact of PUPSIT on product (foam)
- Product filling "at risk" till PUPSIT result

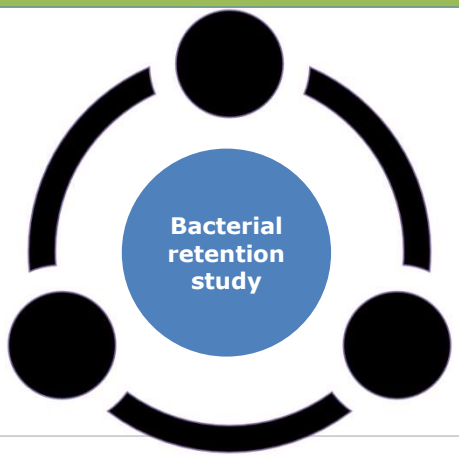
Product value dependant





## Filter validation and PUPSIT

**Check point 2** - For bacterial-retention studies to simulate the worst-case operating parameters, additional bacterial-retention testing may be considered, but only **in cases where the product expelled during the integrity test is added to the product pool.**




**Check point 1** - If process fluid is used as the wetting agent for PUPSIT, **the differential pressure across the filter that the process fluid is exposed to during the integrity test may be significantly greater than** the differential pressure that would otherwise occur during the normal filtration operation.

**Check point 3** - If a process uses **WFI to wet** the filter for integrity testing and is subsequently "blown out" using a compressed gas or any other blow-out step following filtration, **this pressure should be considered during filter test assessments** as it may be greater than the pressures the filter experiences during normal filtration.

# Change Control Considerations in Maintaining a Robust PUPSIT Process - a review

- Once a PUPSIT process is implemented in the manufacturing operation, any changes to the system must be evaluated by an **SME for potential impact** on the integrity test process, integrity test results or acceptance criteria as part of a robust change control system.
- Although not exhaustive, the following items should be evaluated for impact on the PUPSIT operation:
  - Change in the **formulation** of the wetting fluid
  - Change in the **temperature** of the wetting fluid
  - Change of the **test gas or test gas temperature**
  - Change in the pipe routing on the outlet of the filter being integrity-tested (**potential backpressure**)
  - Change in **vendor material** for single-use systems
  - Change in the configuration of the **test program** used in the integrity tester
  - Change in the **manufacturer of the sterilizing filter** used for the process stream
  - Change in the **moisture content or temperature** of the air used for drying
  - Change in the volume of the downstream collection vessel



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# 6. Conclusion



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## Take away Message

- PUPSIT should be performed - Annex 1, 2007
- Single-Use facilitates implementation of PUPSIT
- Benefits of PUPSIT are debated
- Annex 1 Rev 2022 opens door to alternative approaches



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# Thank You!





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