FILTRATION AND PRE-USE POST STERILIZATION INTEGRITY TESTING

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2023 Annex 1 Workshop Series (Singapore)

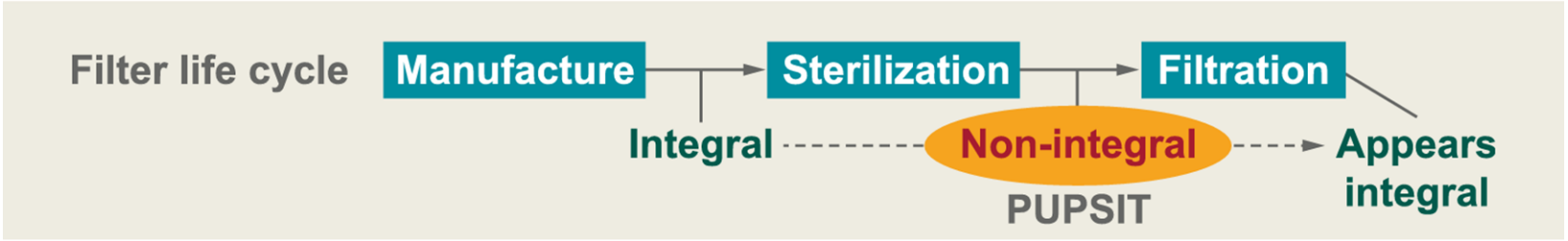
Agenda

- Annex 1 and PUPSIT
- SFQRM Task Force
  - Flaw Masking studies
  - BCT Data mining
  - Best Practice
  - Risk Assessment
- Conclusion & Summary

First things first – what is PUPSIT?

"Pre-Use, Post-Sterilization Integrity Testing."

- Used to confirm that a filter is integral after it has been sterilized, but before it is exposed to product
  - **Flaw Masking Hypothesis**: *The possibility that a filter passing the post-use test could have allowed bacterial penetration during the course of filtration*
- Used *in addition* to a post-use filter integrity test



However, for flaw masking to occur:

- Flaw must be present during filtration, despite pre-use integrity testing and sterilization processes validated to not damage the filter.
- Flaw must be large enough to pass microbiological contamination
- Flaw must be small enough to be closed by clogging/fouling
- Material must be present that can plug the defect to such an extent that it is not detectible by post-use integrity testing

The newest version of PUPSIT in Annex 1

- **EU ANNEX 1 – 22 August 2022**

- 8.87 The integrity of the **sterilized** filter assembly should be verified by integrity testing before use **(PUPSIT)**, to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. Test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test.
- It is recognized that pre-use post sterilization integrity testing (PUPSIT) may not always be possible after sterilization due to process constraints. In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of non-integral filtration system.

When PUPSIT and Masking became a topic -> 2007

EU GMP guide annexes: Supplementary requirements: Annex 1: Manufacture of sterile medicinal products

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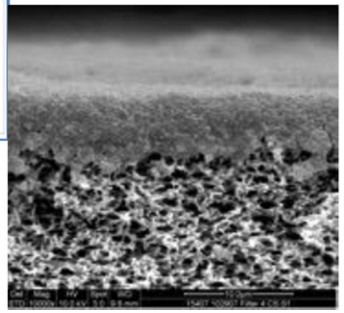
1. How should the integrity of sterilising filters be verified? H+V June 2007

Annex 1, paragraph 85 states, 'the integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble-point, diffusive-flow or pressure-hold test.'

The filter-sterilisation process may be physically stressful for the filter. For example, high temperatures during the process may cause the filter to distort, potentially leading to fluid pathways that allow the passage of particles greater than 0.2 µm in size. The performance of a filter can improve with use, as particles begin to block individual pathways and remove larger pathways that smaller particles could successfully navigate. For these reasons, filters should be tested both before use but after sterilisation and again after use.

Furthermore, testing should be performed *in situ* in order to verify the integrity of the filter complete with its housing.

Concern: Bridging covers a smaller flaw



Why consider PUPSIT

- **Expected by EU regulators, because it was perceived that..**
  - **Sterilisation** is an **aggressive process**, and it is **not always very well controlled**
  - **Filter manufacturing** is **not always consistent**
  - There is *some* anecdotal evidence that *marginal defects* **can blind during the filtration process** and may not be detected in the post-use tests

➢ The resulting debate has exposed a need for scientific evidence to support an effective risk-based approach to PUPSIT use.

➢ To help meet that need, BioPhorum and the PDA formed the **Sterile Filtration Quality Risk Management (SFQRM)** Consortium, which has been working to provide objective, unbiased, scientific data to help guide informed decisions about sterile filtration control measures.

SFQRM Consortium

Sterile Filtration Quality Risk Management

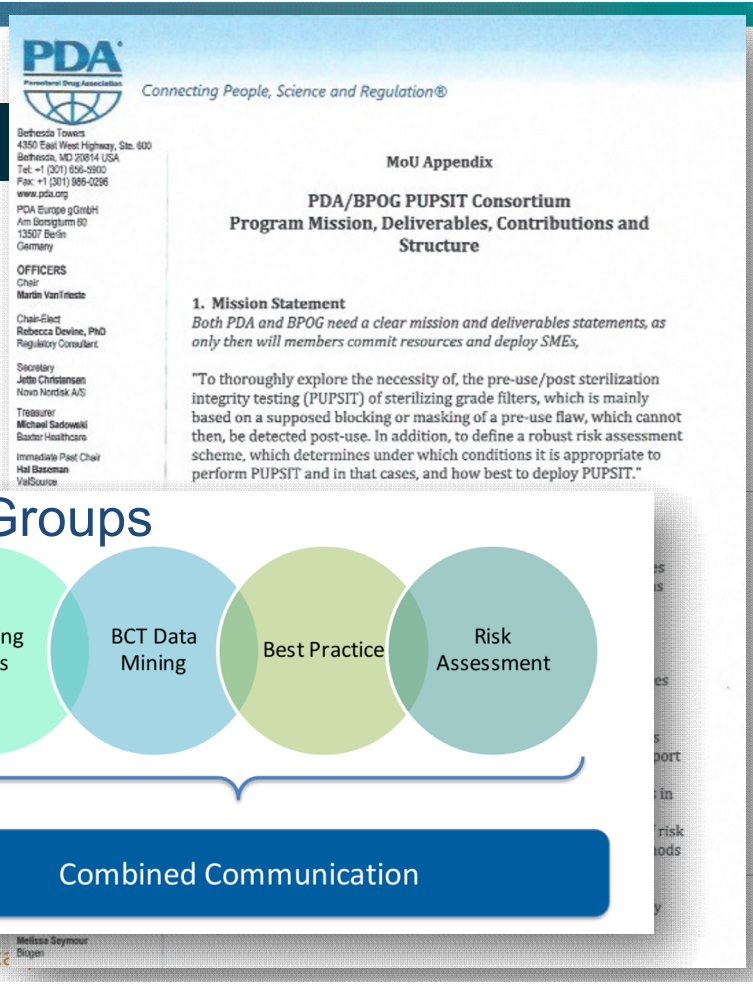
– **BioPhorum and PDA signed MOU Dec. 2017**

Main goal

To gather scientific data and evaluate potential risks to provide more guidance to industry on the merit of PUPSIT in sterility assurance

Workstream Deliverables;

- ✓ **Flaw masking studies**
- ✓ **Bacterial Challenge Test Data mining**
- ✓ **Best Practice**
- ✓ **Risk Assessments**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MoU Appendix

PDA/BPOG PUPSIT Consortium
Program Mission, Deliverables, Contributions and Structure

1. Mission Statement

Both PDA and BPOG need a clear mission and deliverables statements, as only then will members commit resources and deploy SMEs,

"To thoroughly explore the necessity of, the pre-use/post sterilization integrity testing (PUPSIT) of sterilizing grade filters, which is mainly based on a supposed blocking or masking of a pre-use flaw, which cannot then, be detected post-use. In addition, to define a robust risk assessment scheme, which determines under which conditions it is appropriate to perform PUPSIT and in that cases, and how best to deploy PUPSIT."

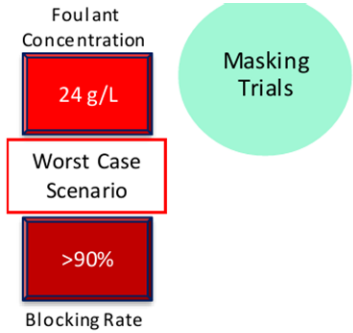
Melissa Seymour
Biogen

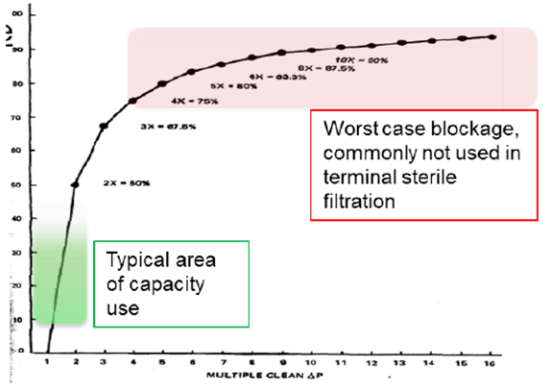
Flaw Masking trial, phase 1 test

- Filter manufacturers collected marginal flawed 10” filter cartridges
- Filters were water wetted and integrity tested (Bubble Point)
- Ovaltine 24g/L concentration – complex foulant containing cocoa powder, protein, sucrose, etc. A worst case product stream for most pharmaceuticals
- The filters were subjected to the blocking solution at constant pressure (10 psig) till >90% blocking rate
- Post-use the filters were flushed with water (50L/m^2) and integrity tested (Bubble Point)
- Both integrity tests were performed with automated integrity test systems

→ 24 filters tested → 2 passed post-use (>90% blocked)

Prior to this experiment, masking was only theoretical!

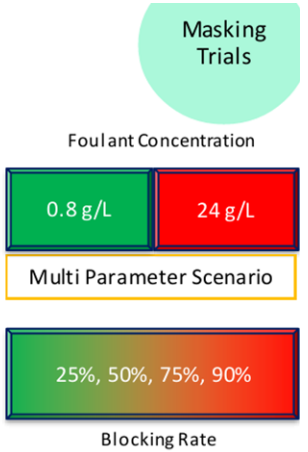


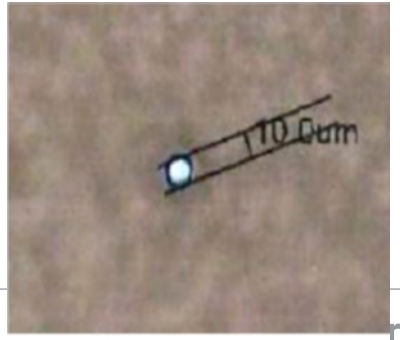


Flaw Masking trial, phase 2 test

- Filter manufacturers collected 47 mm disc filters and a defined 10 micron hole was laser drilled into it
- Filters were water wetted and integrity tested (Bubble Point)
- The filters were subjected to the blocking solution (at 24 g/L and 0.8 g/L concentration) at constant pressure (10 psig) at 25%, 50%, 75% and 90% blocking rate
- Post-use the filters were flushed with water (50L/m^2) and integrity tested (Bubble Point)
- The integrity tests were performed with automated integrity test systems and manual

→ 8 filters tested at 24 g/L → all failed
44 filters tested at 0.8 g/L → 2 passed (81%, 97% blockage)



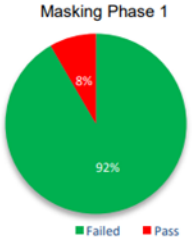


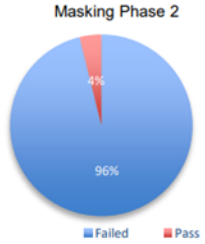
47 mm laser drilled membrane disc

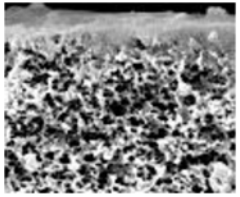
Flaw Masking trial - summary

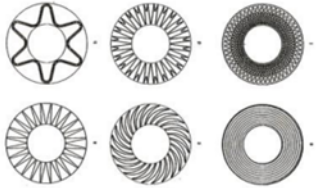
- ✓ Masking of filter flaws can happen under extreme circumstances of fouling and blocking of a sterilizing grade filter
- ✓ The masking possibility depends very much on the process, product and filter capacity conditions
  - Foulant concentration
  - Filter combination and membrane composition
  - Pressure conditions (cake compaction)

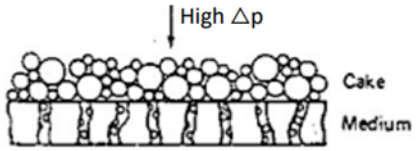
Masking Trials







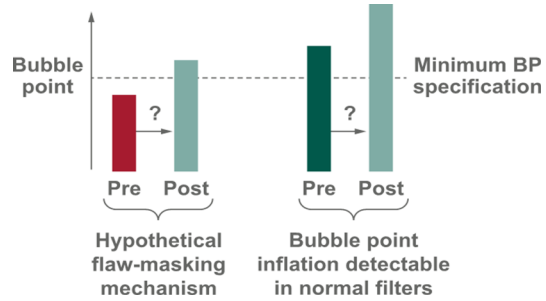


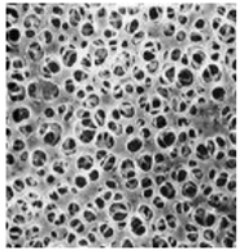


BCT Data mining

To determine the influence of fluid properties on the integrity test values

BCT Data Mining





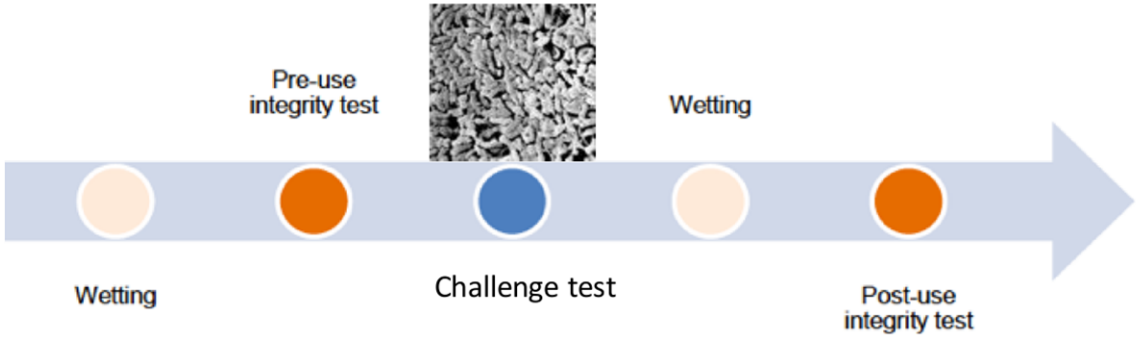
Is the post-test BP the same as the pre-test BP ?

Extensive integrity test value shifts may be indicative of filter masking

BCT Data mining – Database of filter validation testing

BCT Data Mining

- The data mining integrity test data source were the pre- and post product bacteria challenge test integrity tests performed in filter process validation
- The bacteria challenge tested level is > 10^7 cfu B. dim. per cm^2 filtration area with various products

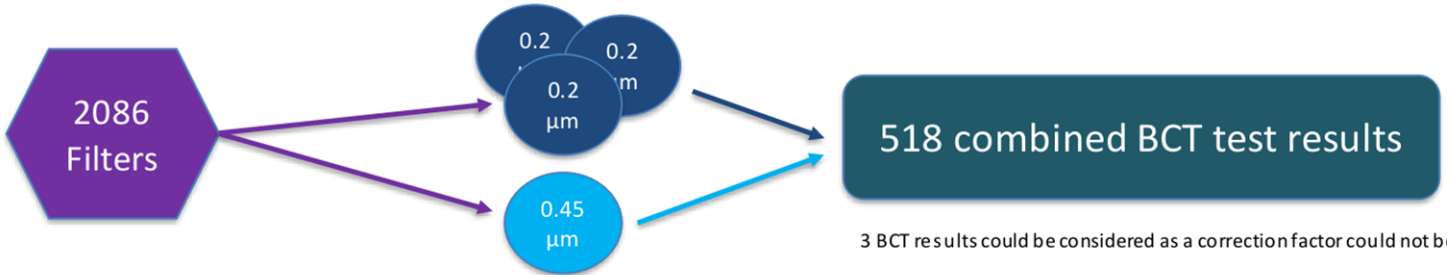


BCT Data mining – Data collection

BCT Data Mining

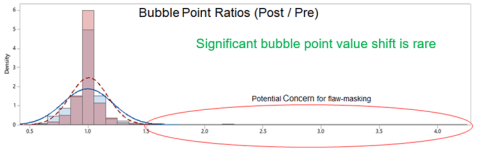
- Data have been submitted by two filter users and all four participating filter manufacturers' filter validation laboratories, with each BCT consisting of three 0.2-micron filters and one 0.45 micron filter (control filter)

- This data set includes pre-test and post- test BPs on 2086 filters (1,571 x 0.2 micron filters and 515 x 0.45 micron filters), representing 531 BCTs on 518 different fluids. The data set actually comprises 518 average corrected ratios from the combined test and control filters for each test (3 x 0.2, 1 x 0.45 micron)



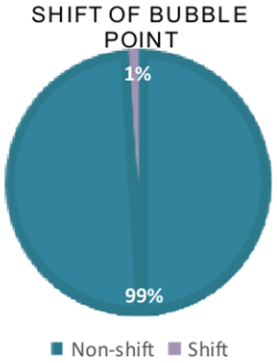
3 BCT results could be considered as a correction factor could not be determined

BCT Data mining – Results



BCT Data Mining

- Out of 518 average Bubble Point ratio data points (2086 filters), there are 5 outliers (<1%) where the Bubble Point shifted
- Reviewing the outliers, the fluids used were high foulant fluids and cause pore plugging
- In addition, the conditions of a bacteria challenge test are extreme, and not representative typical production conditions
- As with the Masking trials the Bubble Point shift experienced is rare



Best Practice : Points to Consider (PtC) – PUPSIT Implementation

Best practice PtC

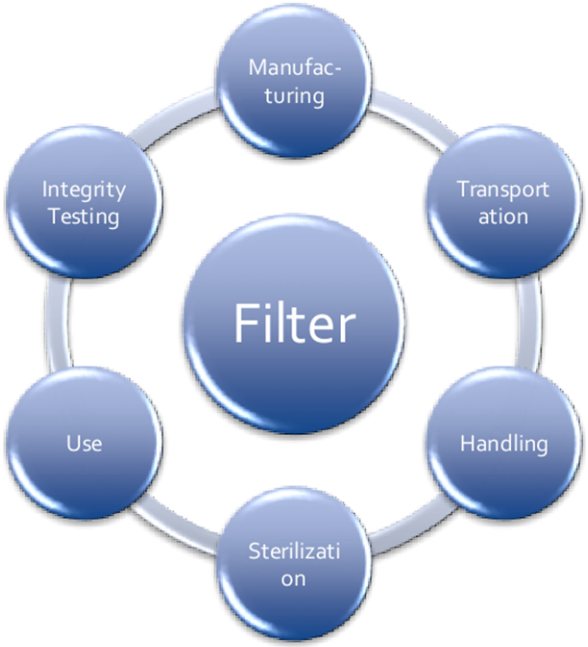
- Was required to address a multitude of questions
  - PUPSIT risks
  - PUPSIT installation
  - Flushing
  - Drying
  - Testing redundant filters
  - Pressure conditions
  - Etc…
- To raise the awareness about the actions which require to be taken
- To be able to add some guidance and alignment

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

Best Practice

Contents

Risk assessment



Risk Assess-ment

Includes:

- Filter Manufacturers "Quality" Survey Response
- Detailed quality control steps during the manufacturing process
- Filter use control sheets (preventative & detection) have been established, incl.:
  - ✓ Receiving
  - ✓ Storage
  - ✓ Transfer to Manufacturing
  - ✓ Filter installation
  - ✓ Wetting
  - ✓ Drying
  - ✓ Vent & Flush
  - ✓ Product filtration
  - ✓ Post-use test

Risk assessment : FINDINGS

The primary findings from the FTA and risk control mapping exercises were:

Risk Assess-ment

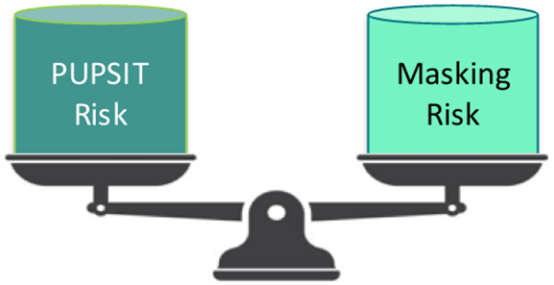
- There are many opportunities for failure of the sterilizing grade filters throughout the value stream, and
- These opportunities can be effectively controlled

A typical unit operation/process step contained an average of nineteen (19) individual faults that could ultimately lead to the failure of a filter to sterilize product.

Each fault had an average of four (4) redundant risk controls (not including of sterility testing of sterilized drug product) that served either to prevent the fault from occurring, or to enable the detection of the fault with sufficient time to correct before patient safety would be in jeopardy.

PUPSIT: The Risk balance…

- Increased complexity of the filtration set-up
- Manipulation of the sterilized filtrate side
- Microbial ingress of the filtrate side
- Product dilution with wetting fluid
- With product wetting, unknown effects on the product by the test gas and time
- …



We needed scientific data for a resolution !

- Flawed filter will not be detected by the post-use test
- Microbial penetration potential not being detected
- Sterilization process detriments are not detected
- …

Bringing it all Together

- PUPSIT use and implementation requires a multitude of considerations to function safe and sound
- The implementation is not easy, but rather complex and will increase the complexity on the filtrate side of the sterilizing grade filter. Retrofitting older facilities may require significant engineering changes
- Wetting solution choice requires detailed analysis in regard to the activities after PUPSIT, which should not influence the quality of the filter and filter's retentivity
- Redundant filter system become even more complex and in instances end-users moved to a single filtration step
- There is no easy "one-fits-all" solution, every application needs to be evaluated

Best Practice

The Final... : ***REALLY*** Final version of Annex 1

8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilising grade filter that is used to sterilise a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test**. It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints** (e.g. the filtration of very small volumes of solution). In these cases, **an alternative approach may be taken providing that a thorough risk assessment has been performed** and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to:

i. In depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized.

ii. In depth knowledge and control of the supply chain to include:

- Contract sterilisation facilities.
- Defined transport mechanisms.
- Packaging of the sterilised filter, to prevent damage to the filter during transportation and storage.

iii. In depth process knowledge such as:

- The specific product type, including particle burden and whether there exists any risk of impact on filter integrity values , such as the potential to alter integrity-testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test.
- Pre-filtration and processing steps, prior to the final sterilising grade filter, which would remove particle burden and clarify the product prior to the sterile filtration.

Summary

- PUPSIT has been in Annex 1 since the beginning but sporadically enforced when the Q&A 2007 was published with the suggestion of masking possibilities and scientific evidence of masking and perceived risks were needed
- SFQRM group established the scientific evidence, plus looked at the risks and installation implications involved. The data and information can be used as a basis to evaluate every terminal filtration application and run a risk assessment to determine whether PUPSIT would be of need or not
- Workshop questions are:
  - What are the challenges or concerns you face in implementing PUPSIT ?
  - Have you utilized or considered the data submitted by SFQRM to run a risk-based assessment instead of generally implementing PUPSIT ?
  - What was the most helpful argument to avoid PUPSIT implementation ?
  - What else would be needed to convince the regulatory authorities ?

Acknowledgement

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SFQRM Team

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PDA

Thank You