PDA Update on Pre-Use Post-Sterilization Integrity Testing

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Agenda

- Current Annex 1; PUPSIT implications
- December Annex 1; PUPSIT revision and comments submitted
- PDA PUPSIT Initiatives:
  - PDA/BPOG Memorandum of Understanding
  - Filter manufacturers joint statement
  - Filter blocking trial initiative

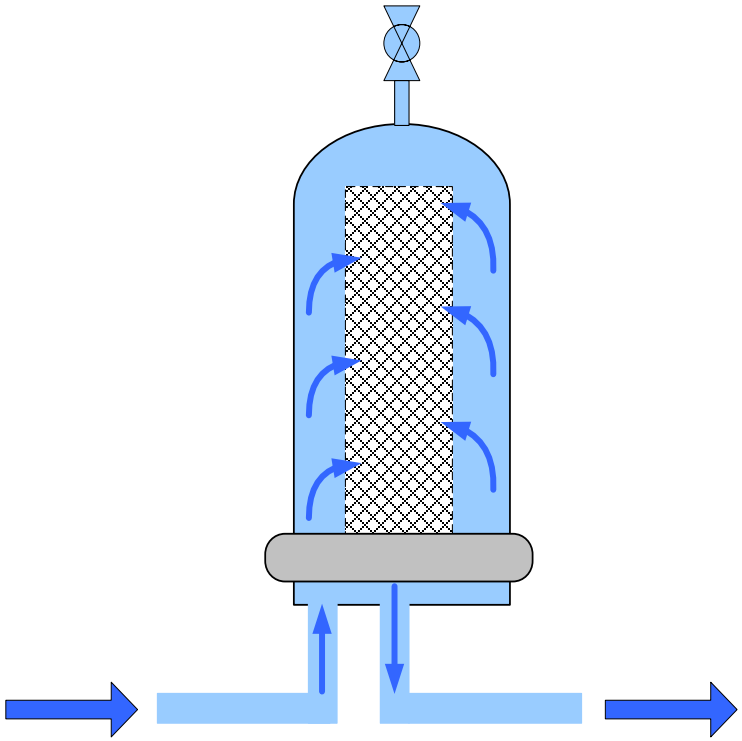
Statement within current Paragraph 113

113. The integrity of the **sterilised** filter should be verified **before use** and should be confirmed immediately after use by an appropriate method such as bubble point, diffusive flow or pressure hold.

Integrity Testing

All integrity tests listed require at least:

- wetting of the filter with appropriate fluid, commonly water and fluid volumes
- atmospheric pressure on the filtrate side



Statement within current Paragraph 113

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What are the risks not to pre-use test ?

- Filter fails post-use test
  - if possible, reprocessing required
  - if filled or reprocessing not validated, batch needs to be discarded

  → *economical burden*

- Filter passes post-use test, but has been non-integral during filtration

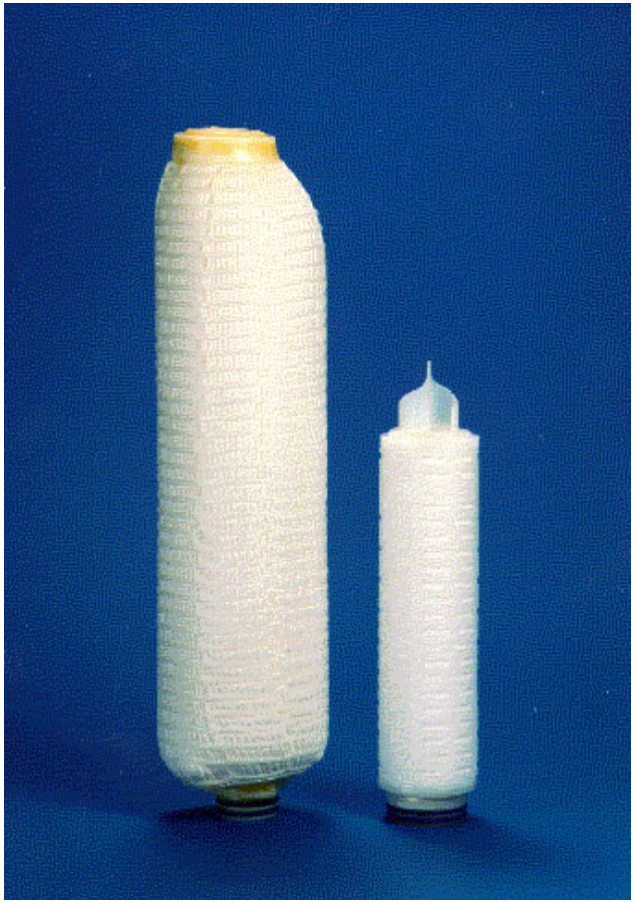
  → *hypothetical, literature search and enquiries with filter manufacturers have not revealed such incident*

Statement within current Paragraph 113

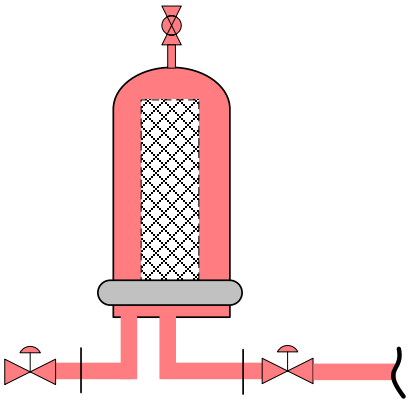
113. The integrity of the **sterilised** filter should be verified before use and should be confirmed immediately after use by an appropriate method such as bubble point, diffusive flow or pressure hold.

Why would a filter fail after sterilization ?

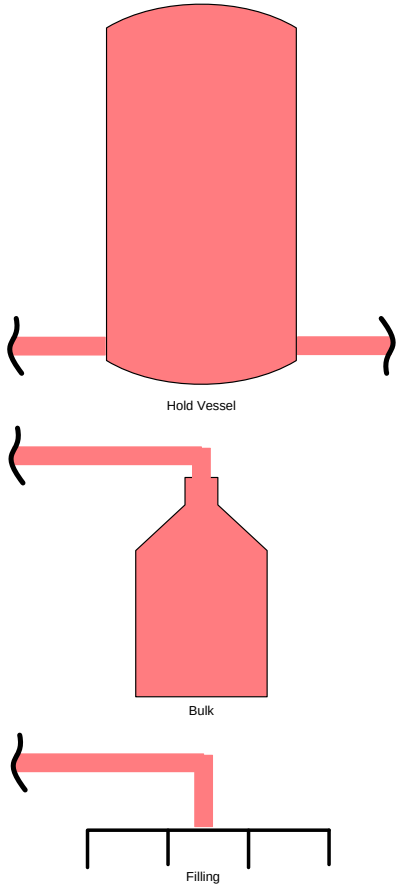
- Most common reasons:
  - ignored filter manufacturer's technical specifications
  - improper end-user training
  - improper sterilization process design and/or qualification
    - temperature
    - pressure



Pre-use Test Implications for a Sterilized Process



- Downstream side gains higher complexity, higher complexity means higher risk
- Wetting fluid potentially dilutes product
- Pressure on sterile side requires to be atmospheric, adding vent complexity and no control over possible ingress
- Downstream volume requires to be large enough (difficult with SUT)



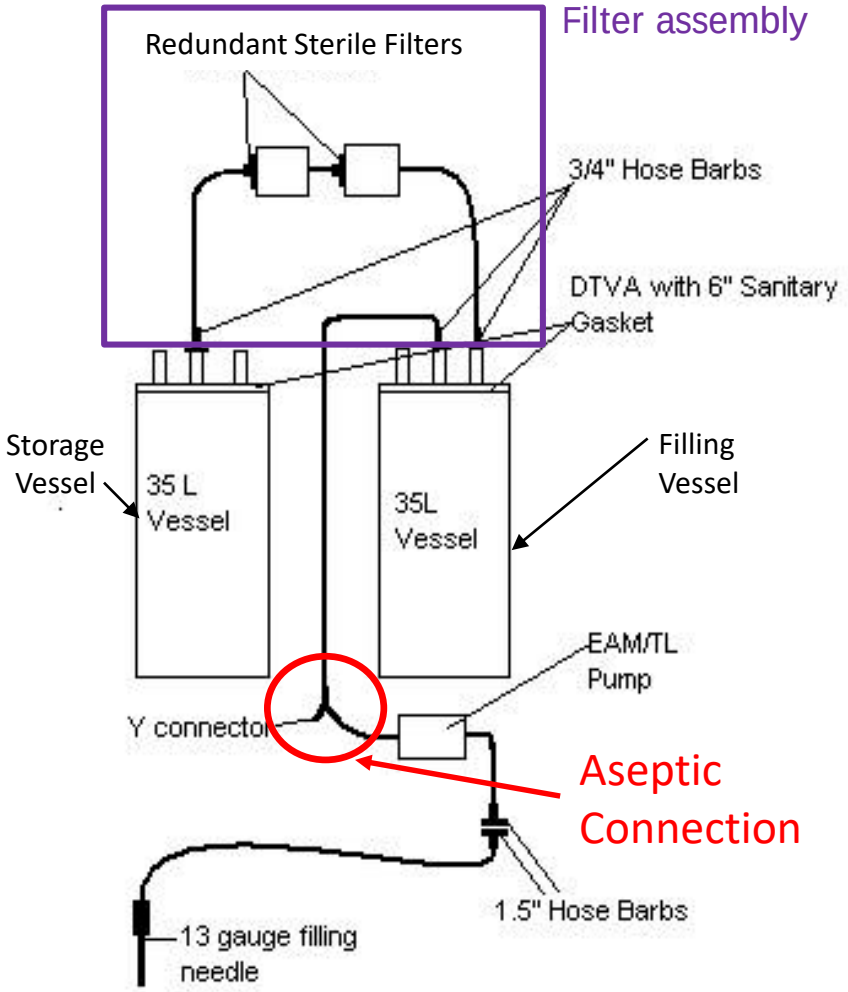
Risk Assessments showed an increase in Risk ≠ Patient Safety

Can the process design be modified to accommodate the pre-use test ?

Yes, with complexity though…..

An example:

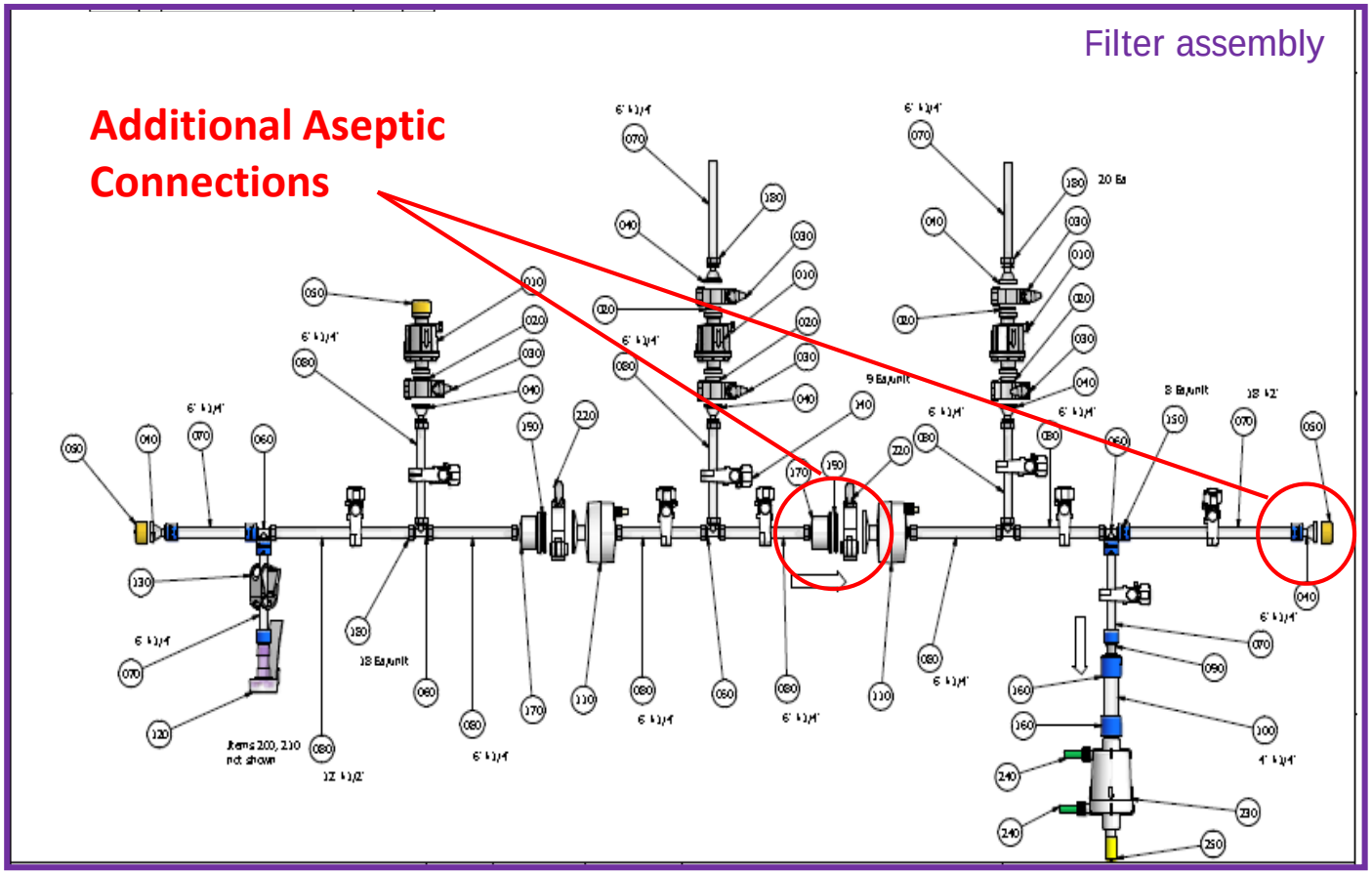
From here….



Commercial Production Since 2001
Number of Batches
~90/year
Number of Units Filled ~100K/year

Number of Media Fill Positives 0
Number of Sterility Test Positives 0
Number of Field Complaints/Issues related to sterility assurance 0

To there….



Additional Components:

2 Vent Filters
1 Hydrophobic Filter
1 Hydrophilic Filter
3 Sanitary Connects
2 2-way valves
Bottled WFI
Compressed Air

Concerns

- There is a risk (which has been demonstrated with risk assessments) that integrity testing, manipulations etc. resulting from post-sterilization/pre-use integrity testing can introduce downstream contamination.
  - PDA Journal of Pharmaceutical Science and Technology, Vol. 66, No. 5, September–October 2012, *Pre-use/Post-sterilization Integrity Testing of Sterilizing Grade Filters,* PDA Pre Use/Post-Sterilization Integrity Test Task Force.

Category	w/ Test	w/o Test	Rational
Severity	4	4	If the filter fails or microbial ingress happens, it has a major effect in both cases
Frequency	3	2	Microbial ingress into the downstream side has occurred, for this reason the downstream side is commonly held under pressure after steam sterilization. This overpressure is replaced by atmospheric pressure during the pre-use test (3). Since steam sterilized downstream processes are commonly held at overpressure the likelihood of ingress is lower (2).
Detectability	3	1	If there is a microbial ingress due to downstream manipulation, when the test is performed, it will not be detected (3). If the filter is flawed due to the steam sterilization process it will be readily detected by the post-use test (1).
Risk level	36	8	Risk assessment would not recommend a pre-use/post-sterilization test.

- There may be a risk (which has never been demonstrated) that a non-integral filter before use can become integral by the time of post-use testing.
  - No published scientific journal or article have been found

Annex 1 revision with respect to PUPSIT

8.84 The integrity of the sterilized filter assembly should be verified by testing before use, in case of damage and loss of integrity caused by processing, and should be verified by on line testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test. It is recognised that for small batch sizes, this may not be possible; in these cases an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved. There should be written integrity test methods, including acceptance criteria, and failure investigation procedures and justified conditions under which the filter integrity test can be repeated. Results of the integrity tests (including failed and repeated tests) should be included in the batch record.

Annex 1 PDA Comments

Part 1: describing the necessary qualification/process validation needs

8.84 The filter and filter assembly preparation, sterilization, and use for sterilization of the product should be qualified to ensure that the filter and assembly maintain their integrity throughout the entire process. This should include a well-documented risk based assessment of and corresponding control strategy implementation to address potential filter and assembly defects and filtration failures caused by manufacture, handling, storage, sterilization, and use of the filter and assembly prior to and during product filtration. Control strategies should include efforts to prevent such defects and failures, as well as test the filter and assembly at appropriate phases of the process, including testing prior to the filter sterilization, immediately after use, and where the risk assessment indicates the need, after the filter sterilization.

Annex 1 PDA Comments, cont.

Part 2: addressing the integrity test

8.85 Filter and assembly integrity methods and systems should be designed, installed and operated to be effective for their purpose and where appropriate, fit for use in an aseptic process and controlled environment. There should be written integrity test methods, including acceptance criteria, failure investigation procedures and justified conditions under which the filter integrity test can be repeated. Results of the integrity tests (including failed and repeated tests) should be included in the batch record.

PDA PUPSIT Initiatives

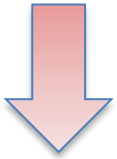
MoU BPOG

Following activities are worked on and supported by both membership:

- Joint communication into the industry
- Definition of known and potential filter failures modes
- Masking studies – protocol establishment and tests at PDA TRI
- Best practice design of a PUPSIT
- Risk assessment template

PDA PUPSIT Initiatives, cont.

During the Annex 1 conferences statements were made to justify the PUPSIT
These statements were anecdotal and erroneous, but triggered the need for response



This resulted in a joint statement by four filter manufacturers: Meissner, Millipore, Pall, Sartorius

The statement addresses the statements, clarifies those, which voids those as justification for the PUPSIT
The statement has been published in the PDA Letter under the Filtration IG hospice

PDA PUPSIT Initiatives, cont.

One main argument made for PUPSIT, is the blinding of a flaw, so the post-use test cannot find the flaw

- Blinding trial test protocol → review and approval by the filter suppliers
- Once approved we send it to MHRA → review and approval by MHRA
- In the meantime we collect 10” sterilizing grade filter samples from the filter manufacturers. These filters need to be failed filters for testing.
- Once the protocol is approved and filters are collected, we start the trial work in PDA TRI
- The results of the tests will be published without naming the filter types and companies

PDA's Proposal

The need of a pre-use integrity test of a sterilized filter should be left to the discretion of the filter user and should not be mandatory.

The decision to perform or not perform a pre-use/post-sterilization integrity test should be made by the filter user upon thorough, documented risk-based analysis in accordance with ICH guidelines. When it has been demonstrated, for example, that the likely risk of contamination or a breach in sterility would increase if implemented, a pre-use/post-sterilization integrity test shall be avoided.

Based on the risk analysis, a control strategy should be implemented, that includes validation, in-process monitoring and control of temperatures and pressures during sterilization to ensure that the vendor recommended parameters have not been exceeded.

Why leave it to the End-User ?

- Because they know there processes best
- Because they run existing processes successful and reliable
- Because they know a risk when they see a risk
- Because they care about the one person they work for….The Patient !

Thank you

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