
PDA
Parenteral Drug Association


BioPhorum

Assessing the Risk of Filter Masking

Test Description and Results

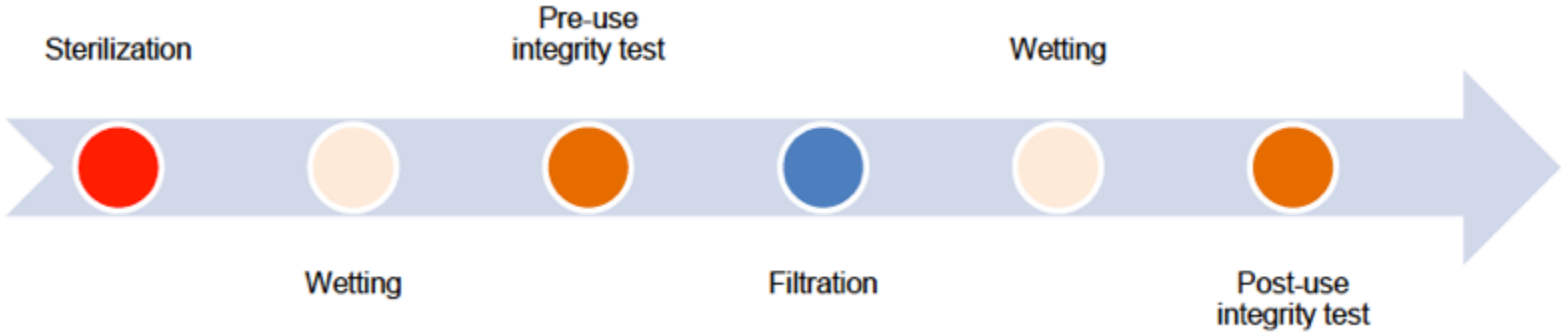
Agenda

- Annex 1 PUPSIT
- Reasons stated to use PUPSIT
- PUPSIT Task Force – Working Blocks
- Studies & Results
  - Masking Studies
  - Data Mining
- Conclusion
- Q & A

First Things First – What is PUPSIT ?

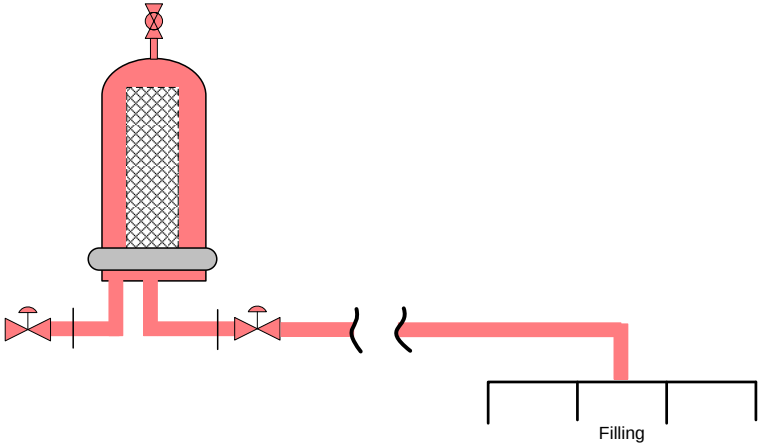
PUPSIT = Pre-use/Post Sterilization Integrity Test

Used to determine whether the terminal sterilizing grade filter in front of filling is integral after the sterilization of the filter.



Annex 1 PUPSIT Paragraph - Past

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.

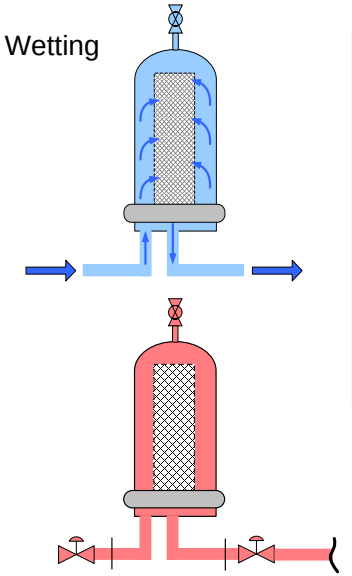


Caveat:

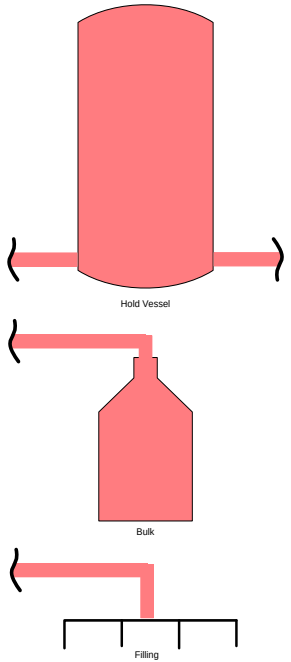
The filter has been sterilized by either gamma, autoclaving or in-line steam sterilization

It is critical that Filtrate Side is sterile and requires to stay sterile, however PUPSIT requires manipulations on the sterile filtrate side

Pre-use Test Implications*



- Wetting fluid reaches the sterile filtrate side
- Wetting fluid potentially dilutes product
- Pressure on sterile side requires to be atmospheric
- Downstream volume requires to be large enough
- Cooling time to obtain appropriate temperature



*To be reiterated in the Points to Consider for Implementation of Pre-Use Post-Sterilization Integrity Testing (PUPSIT)

The Possible Need 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

→ *Unknown occurrence, but main concern by regulatory authorities*

When Masking became a Topic

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

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Collapse all items in this list

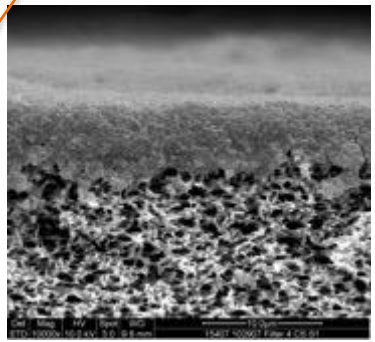
1. How should the integrity of sterilising filters be verified? H+V June 2007

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.

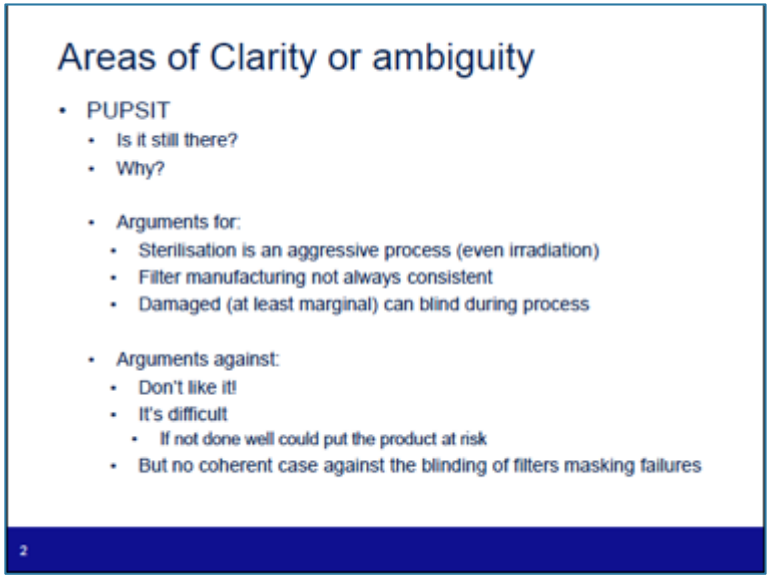
Furthermore, testing should be performed *in situ* in order to verify the integrity of the filter complete with its housing.

Concern: Bridging covers a smaller flaw



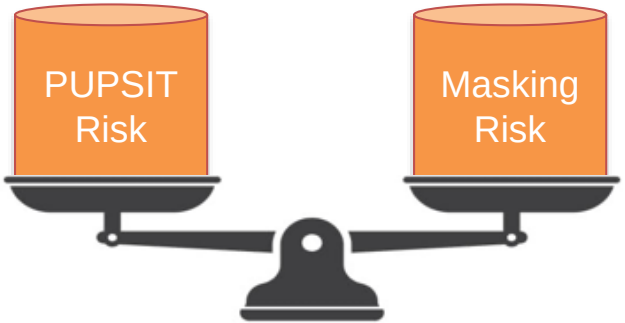
The Masking Prospect triggered Enforcement

- Sterilization processes and filter manufacturing inconsistencies pose a risk of flawed filters being used
- Anecdotal evidence of filter flaw masking was mentioned by regulators and the basis of the need of PUPSIT
- With the filter flaw masking potential, European regulators started enforcing the use of 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
- …



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

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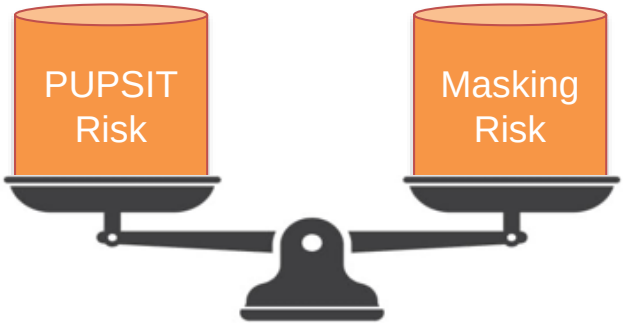

We needed scientific data for a resolution !

RESOLVE®

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

1st Step – PDA/Biophorum SFQRM Initiative

Memorandum of Understanding

Defined tasks:

- 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

Connecting People, Science and Regulation®

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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."

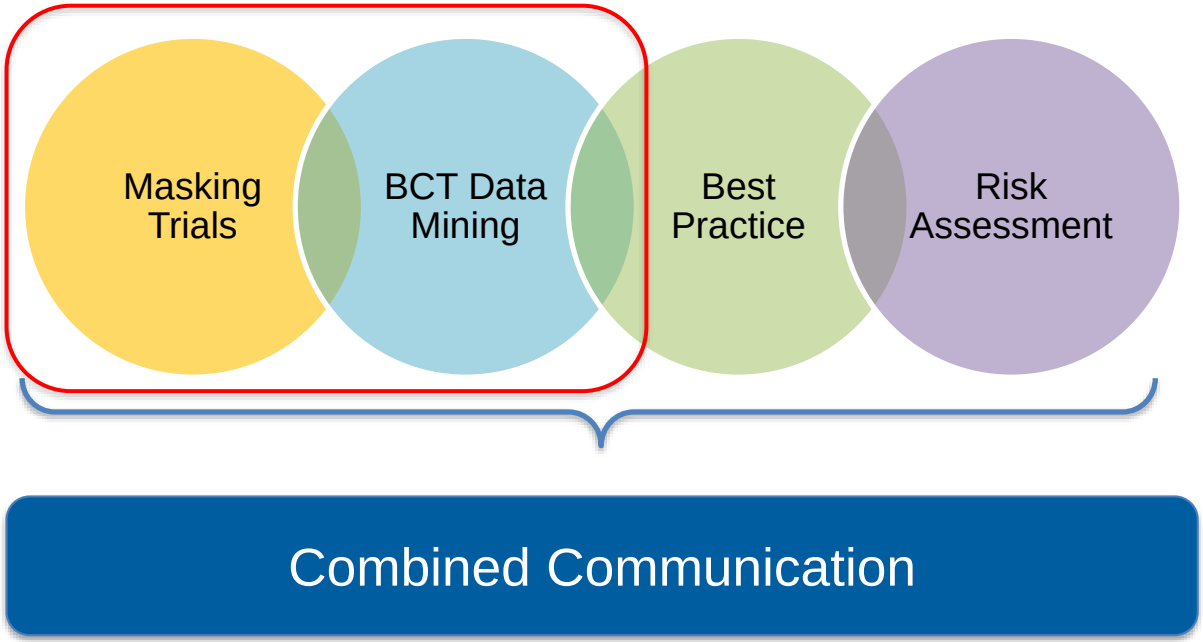
2. Deliverables

Guided by this mission the consortium will consider and deliver as appropriate

A) Communication(s) to the wider industry and regulatory authorities the consortium rationale, mission, approach, progress and conclusions and call for participation of regulators;
B) Definitions of known and potential failure modes and as well as conditions under which pre-use failed filters may be masked;
C) Study protocols to test and examine the failure modes and the conditions that may cause failure and determine whether these failures can be masked;
D) Conduct filter blocking studies of pre-use flawed filters to check whether these can pass post-use tests, draw conclusions on risk levels and recommend any advisable changes to design, manufacture, transport and usage practices;
E) Best practice statements for the design and use of PUPSIT systems in differing situations;
F) Harmonised FMEA or Decision Tree to include graduated scales of risk when using PUPSIT best practices and conventional post testing methods in different situation and conditions.

As far as possible the groups will look to exploit existing work done by the previous PDA Taskforce.

2nd Step – PDA/Biophorum SFQRM Task Groups



Masking Trial Work – Data Mining Work

- Blocking/masking trials performed with various filters to see whether masking is possible
- Filter suppliers were essential to gain flawed filter elements
- Test protocol was established and reviewed by European regulators

- Data of product bacteria challenges tests were collected to see whether pre-use and post-use integrity test data shift
- Data were collected from a multitude of trials with various solutions

Masking Trial Work

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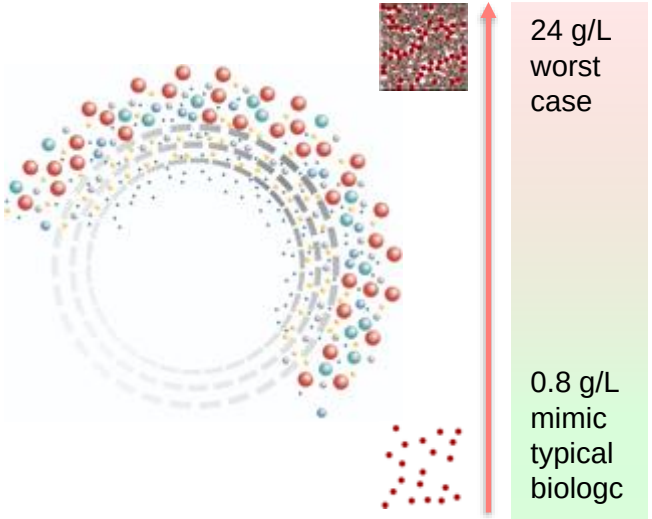
Determination of Test Parameters

Masking Trials

Test Fluid

Ovaltine™: proteinaceous malt, cocoa extract → mimics biologics solution well

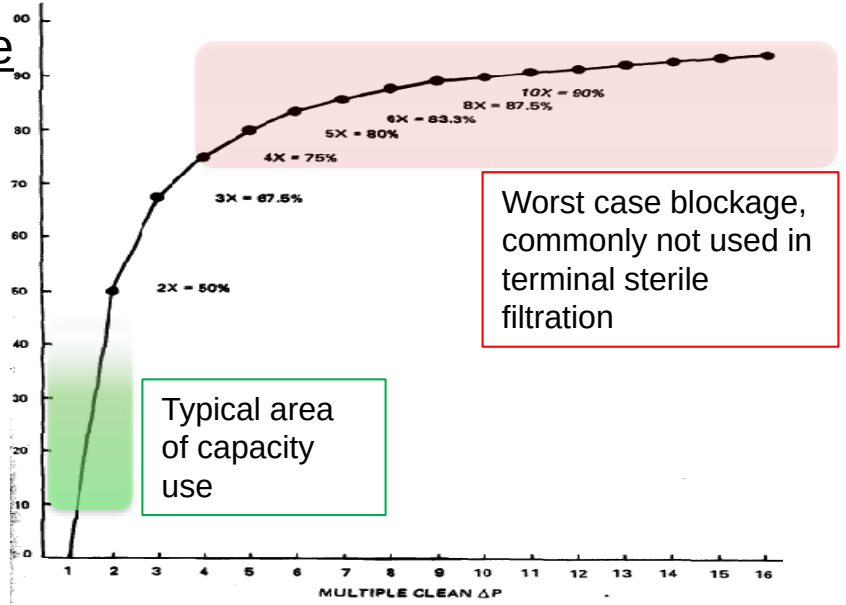
Foulant concentration



24 g/L worst case

0.8 g/L mimic typical biologc

Blocking rate



Worst case blockage, commonly not used in terminal sterile filtration

Typical area of capacity use

Masking Trial, Phase 1 – Test Protocol

Masking Trials

- Filter manufacturers collected marginal flawed 10” filter cartridges
- Filters were water wetted and integrity tested (Bubble Point)
- The filters were subjected to the blocking solution (Ovaltine 24g/L concentration) 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

Masking Trial, Phase 1 - Results

Masking Trials

Phase 1 Masking Trials, 10” filters, worst case scenario

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

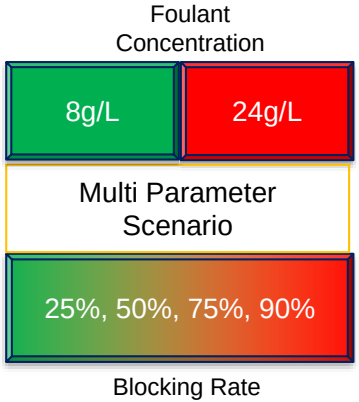
Outcome summary:

- We verified that worst case blocking rate and foulant concentrations can block minor flaws
- We understand that a terminal filtration step would not see such blocking rate
- Next step Phase 2 trials at different blocking rates and foulant concentrations

Masking Trial, Phase 2 – Test Protocol

Masking Trials

- 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

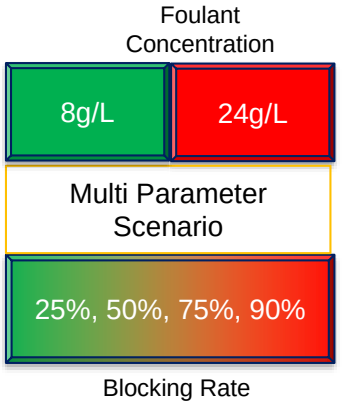


Masking Trial, Phase 2 - Results

Maskin
g Trials

Phase 2 Masking Trials, 47 mm discs, laser drilled flaw

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



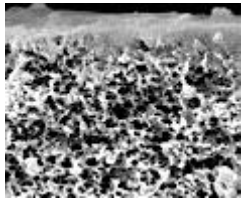
Outcome summary:

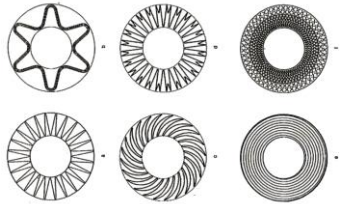
- We verified that only at very high blocking rates filter flaws may be masked
- It does not necessarily always happen as 16 of 47 mm disc filters at a blockage rate >80% failed the post-use test
- Filter flaw masking is very dependent on the product and process conditions

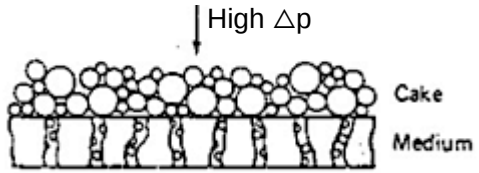
Masking Trial – Summary

Masking Trials

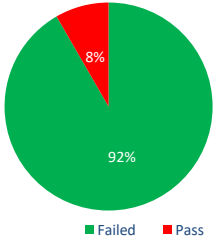
- ✓ Masking of filter flaws can happen under extreme circumstances of fouling and blocking of a sterilizing grade filter
- ✓ The masking possibility depends very much on the process, product and filter capacity conditions
  - Foulant concentration
  - Filter combination and membrane composition
  - Pressure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



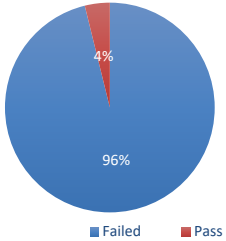




Masking Phase 1



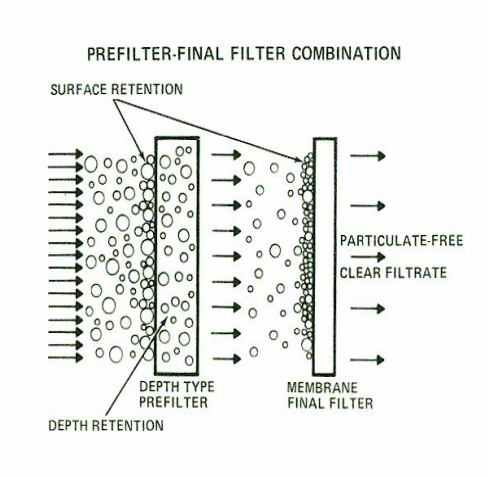
Masking Phase 2



Masking Trial – Summary, cont.

Masking Trials

- ✓ Filterability trials and understanding of one's product and process conditions support the risk assessment whether masking is a possibility or not
- ✓ Risk assessments of the risks of PUPSIT implementation versus masking risk probability will allow a proper judgement to assure patient safety
- ✓ Reduction of foulant materials by preventative measures like prefiltration in front of the sterilizing grade filter will avert the risk of masking



Data Mining Work

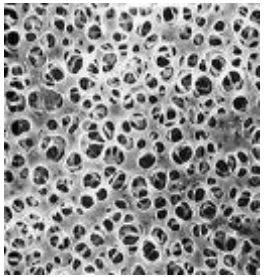
- Data of product bacteria challenges tests were collected to see whether pre-use and post-use integrity test data shift
- Data were collected from a multitude of trials with various solutions

Data Mining

BCT Data Mining

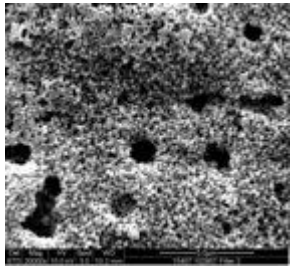
To determine the influence of fluid properties on the integrity test values

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



BP new filter

BP blocked filter

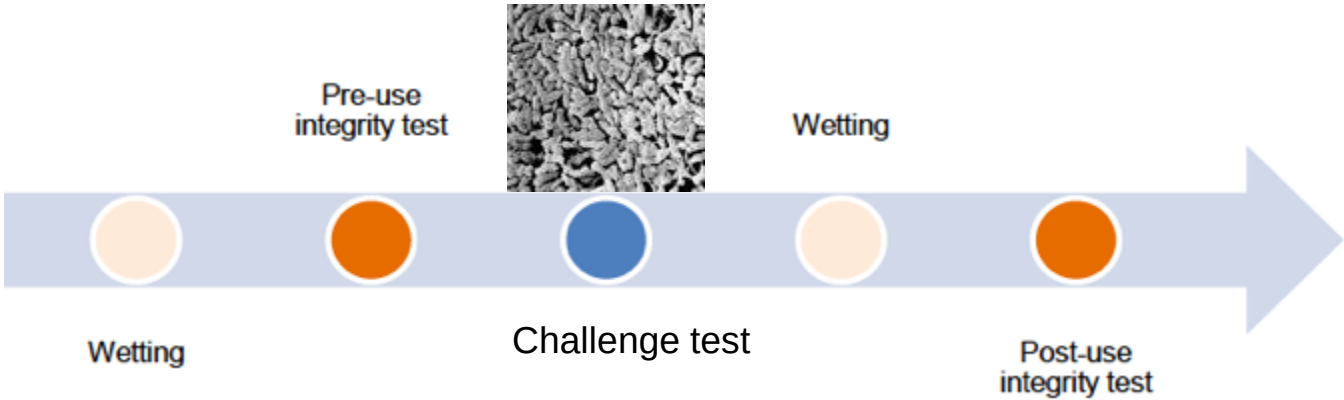


Integrity test value shift may be indicative of filter masking

Data Mining – Data Base

BCT Data Mining

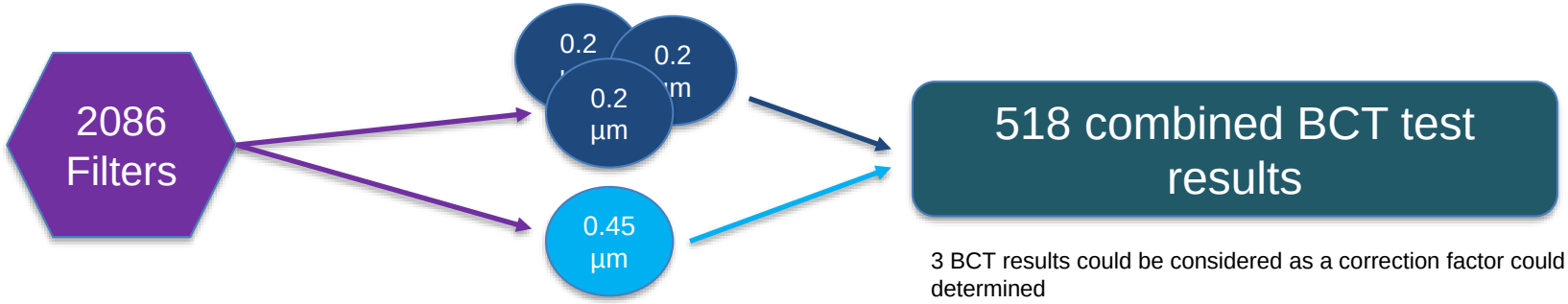
- The data mining integrity test data source were the pre- and post product bacteria challenge test integrity tests performed in filter process validation
- The bacteria challenge tested level is > 10^7 cfu B. dim. per cm^2 filtration area with various products



Data Mining – Collection

BCT Data Mining

- ✓ Data have been submitted by two 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

Data Mining – Collection, cont.

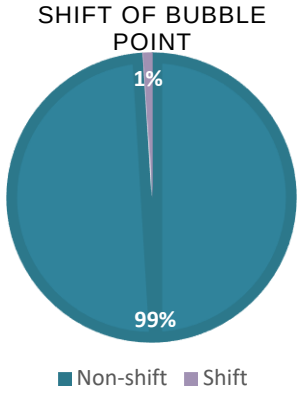
BCT Data Mining

- Various 0.2 and 0.45 micron filter compositions and materials were used
- A large variation of fluids were used, under different process conditions
- If product wetting was used for the post-use integrity test, a correction factor was taken into consideration to be able to compare the result with the water-wet pre-use test
- The integrity test used was Bubble Point, since the filters were disc filters

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, it seems 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

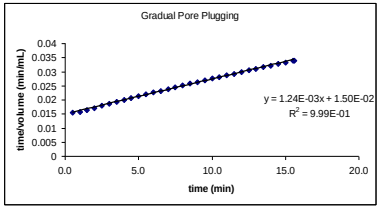


Conclusion

- The masking trial and the data mining results showed that under extreme conditions a filter flaw can be masked, or a Bubble Point test result can shift
- These conditions are rare and can be tested to determine the likelihood of occurrence
- If a risk assessment, including filterability tests show a higher risk of filter fouling steps can be taken to prevent fouling, for example prefiltration or higher filter surface areas
- Fouling respectively masking is a measurable risk and can be implemented into the process validation of sterilizing grade filters

BCT Data Mining

Masking Trials



Acknowledgement

SFQRM Team							
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John Kautz	Astra Zeneca		Simon Hanslip	GSK		Shyam Mehta	Teva
Marjo Peters	Astra Zeneca		Carsten Knapp	GSK		Olivier Dupont	UCB
Christian Neuhofer	Bayer		Thao Le Vinh	GSK		Cecile Nicolas	UCB
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Lei Ling	BMS		Sanghee Yang	Lonza		Brian Joseph	Pall
Chris Knutsen	BMS		Antonio Orlandi	Lonza		Mandar Dixit	Sartorius Stedim
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Steve Lexa	Eli Lilly		Sean Tomlinson	Pfizer		Hal Baseman	ValSource
Peter Berzins	Eli Lilly		Vincent Van Dijck	Pfizer		Kelly Waldron	ValSource
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Thank you