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The Science, Implications and Implementation of PUPSIT (Pre-Use Post Sterilization Integrity Testing) – A 3 Part Webinar Series

Sept 1: ***The Role of PUPSIT in the Assurance of Sterilising Filtration***

Sept 8: ***Assessing the Risk of Filter Masking***

Sept 21: ***Practical Implication and Decision Making of PUPSIT***

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Welcome/Introduction

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Sterile Filtration Quality Risk Management (SFQRM) Consortium

Companies have struggled with the implementation of the PUPSIT(Pre-Use Post Sterilizaiton Integrity Testing) requirement as EU and other regulatory authorities have increased their enforcement of its use for sterile products.

To address this issue PDA and BioPhorum formed the Sterile Filtration Quality Risk Management (SFQRM) consortium in 2017.

The consortium brought together a group of over 50 subject matter experts, over a 3-year period, and are now ready to share their groundbreaking results and insight.

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Today's Expert Q&A Panel

Dieter Bachmann	Director, Aseptic Processing, Johnson and Johnson
Hal Baseman	Chief Operating Officer at Valsource Inc.
Steve Ensign	Senior Consultant Engineer, Eli Lilly
Maik Jornitz	President and CEO of G-CON Manufacturing Inc.
Stephen Lexa	Associate Senior Consultant, Quality, Eli Lilly
Marjo Peters	Director, Drug Product Technical Steward Europe, AstraZeneca
Brian Thome PhD.	Principal Engineer, Parenteral Manufacturing Sciences, Biogen
Carl Weitzmann PhD.	Associate Director, Process Technology Platform, Sanofi Pasteur
Thao Vinh-Le	Senior Manager, Secondary Transversal Support – MSAT, GSK Vaccines

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Today's Presenter

Will Peterson
Associate Director of Engineering, Sterile Product Manufacturing
Merck & Co.

Will Peterson is a founding participant of the SFQRM consortium and member of the leadership team. He is a contributing author on multiple publications released by the consortium in 2020. Will's career at Merck & Co. has had a special focus on sterilizing filtration for over a decade, serving as an internal engineering consultant for a global network of manufacturing and research sites that produce sterile products. Much of his time has been spent selecting filters, designing filtration processes, troubleshooting integrity tests, and establishing company-wide standard approaches sterile filtration on both the quality/compliance side as well as the engineering/operations side.

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-Panelist Bios-

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Dieter Bachmann

Director, Aseptic Processing
Johnson and Johnson

Dieter is Director Aseptic Processing at J&Js corporate Sterility Assurance group with a main responsibility for providing standardization, science and education across J&J in the field of aseptic processing technologies. He is a Pharmacist by training with 30+ years of experience and holds a PhD in Pharmaceutical Formulation Technologies. Dieter has worked with small family-owned companies as well as in global business. Since joining Johnson & Johnson in 1998 he held several positions in R&D, Operations and Quality of J&Js Pharma and Medical Device franchises. Alongside business Dieter always engaged in associations work. For 10 years Dieter used to work as a Swiss national delegate on developing monographs for the European Pharmacopeia (EP) at EDQM in Strassburg. He is a frequent presenter and active member of PDA and ISPE. Dieter engages at the German DIN/NA063 and ISO TC198. Since 2019 Dieter is the global convenor for ISO TC198/WG9 Aseptic Processing.

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Hal Baseman

Chief Operating Officer at Valsource Inc

Mr. Baseman is the Chief Operating Officer at Valsource Inc. with over 40 years in pharmaceutical industry. He has held PDA positions as Board Chair, SAB Co-chair, Co-lead for Aseptic Processing Points to Consider, Process Validation IG, TR 22, 44, and 60, and is a long standing member of TRI faculty. Hal co-chairs the Annex 1 response team, Portfolio Steering Committee, and MSOP and is a member of the QRM for Aseptic Processing Standards task force and the PUPSIT consortium committee. Hal holds MBA from LaSalle University and B.S. Biology from Ursinus College.

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Steve Ensign

Senior Consultant Engineer

Eli Lilly

Mr. Ensign has over 30 years of experience in the pharmaceutical industry and has had numerous assignments in engineering projects and process, TSMS, manufacturing, leadership and Six Sigma (Black Belt) in the parenteral operations area. Previous assignments have included new product development, scale-ups, building and starting up new facilities. His current position is working to increase pre-filled syringe capacity in the US and Europe for current and new products.. Mr. Ensign received a B.S. in Mechanical Engineering from the University of Illinois in 1988 and Six Sigma Black Belt certification in 2005.

Maik W. Jornitz

President and CEO of G-CON Manufacturing Inc

Mr. Jornitz is a technical expert with over 30 years of experience in bioprocesses, especially sterilizing grade filtration and single-use technologies, including regulatory requirements, integrity testing, systems design, and optimization. Jornitz has published 11 books, 18 book chapters and over 100 scientific papers. He is the former Chair of the PDA Board of Directors and Science Advisory Board, and member of multiple PDA Task Forces. He is working member of Biophorum, ASTM, an advisory board member of the Biotechnology Industry Council, ICAV and multiple science journals. He recently has been recognized as one of the top ten global industry influencers. As a faculty member of various training activities, including PDA TRI, he trains members of the industry and regulatory authorities on a frequent basis. He received his M.Eng. in Bioengineering at the University of Applied Sciences in Hamburg, Germany and accomplished the PED program at IMD Business School in Lausanne, Switzerland

Stephen Lexa

Associate Senior Consultant, Quality, Eli Lilly

Mr Lexa has spent over 12 years in parenteral manufacturing spanning clinical, commercial, and extemporaneous prep applications. He has experience in new facility construction as well as sterile area renovations. Steve has held a variety of operations and quality leadership and project roles, including those involving facility/equipment design and quality system integration. He also provides expertise in areas of sterility assurance, risk-management principles, and applied risk tools.

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Marjo Peters

Director, Drug Product Technical Steward Europe, AstraZeneca

Marjo Peters is part of the Global Technical Operations group for Drug Products and Combination Products at AstraZeneca. As part of her current role she is responsible for the technology transfer and technical support for the commercial manufacture of biological products at the European manufacturing sites (both internally and CMO's) for AstraZeneca. She is based out of the Nijmegen Manufacturing Facility located in the Netherlands, where she previously worked as Director of Manufacturing, Science & Technology for 10 years. Before joining AstraZeneca, Marjo worked for Organon (a Dutch based pharmaceutical company), where she was involved in the formation of a small scale Biopharmaceutical CMO called BioConnection.

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Brian Thome PhD.

Principal Engineer, Parenteral Manufacturing Sciences, Biogen

Brian is a process engineer who has worked across the fill finish spectrum over his twelve year career in the biopharma industry including formulations, lyophilization, process development, analytics and technology transfer. The last ten years have been spent at Biogen where he has led tech parenteral drug product technology transfers to external manufacturing partners as part of the launch of three commercial products. He currently leads a team responsible for process validation and ongoing technical process ownership for Biogen's commercial parenteral products. Brian is from Seattle, Washington, USA and currently lives in Zürich, Switzerland. He received his doctorate in Chemical Engineering from Washington State University.

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Carl Weitzmann PhD

Associate Director, Process Technology Platform

Sanofi Pasteur

Carl Weitzmann is Associate Director in the Process Technology platform at Sanofi Pasteur, located at the vaccines production site in Swiftwater Pennsylvania, with responsibility for filtration processes. He has held positions at Wyeth (Pearl River) and at Sanofi in R&D QA, R&D Process Development, and Manufacturing Technology, spanning development and technology transfer of multiple vaccine and biological products. He holds a Ph.D. in Biochemistry from the University of Pennsylvania, with a strong background in enzymology, protein chemistry, and molecular biology, 20 years' experience in the pharmaceutical industry dealing with process, aseptic process, cleaning, and filter validation, and 10 years' experience in filter manufacture and validation.

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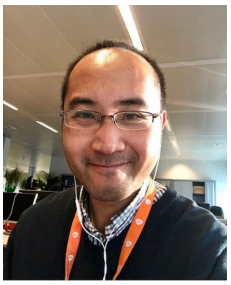

Thao Vinh-Le

Senior Manager, Secondary Transversal Support – MSAT
GSK Vaccines

Thao Vinh-Le is a Certified Industrial Pharmacist with a master degree in Pharmaceutical Engineering and Industrial Technology. Having over 19 years of (bio)pharma international experiences and over than 10 years within GSK Vaccines – MSAT team which is mainly in charge of Transversal Project, Quality Improvement Program and Troubleshooting in Commercial Manufacturing Process. Over the last 4 years, Thao has acting more specifically as the GSK Vaccines PUPSIT expert, following the PUPSIT risk evolution and in charge of the development of the PUPSIT technology deployment.

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Parenteral Drug Association

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The role of PUPSIT for sterility assurance during sterilising filtration.

Presenter
William Peterson
Associate Director – Sterile & Validation COE
Merck MSD

Q&A Panel:
01 September 2020

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Abstract

Since 1998, the EU Guidelines to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use, Annex 1 (Manufacture of Sterile Medicinal Products) or "Annex 1" has contained the requirement for verifying the integrity of a sterilizing grade filter before use and after its sterilization.

The requirement remained in the 2008 revision and in the 2017 and 2020 draft revisions to Annex 1. Concerns by European and other Health Authorities over the risk of filtration failure resulted in an increase in enforcement of this requirement. This enforcement started a discussion within the industry of the of the challenges, benefit, and aseptic process related risk of PUPSIT.

The resulting debate has exposed a need for scientific evidence to support and 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. This webinar will be the first in a series presenting the background of, reasons for, challenges to, and approach for mitigating the risk of sterilizing filtration, that has prompted the use of PUPSIT. Subsequent webinars will present the scientific findings resulting from these efforts and a plan for using that information to make better filtration and PUPSIT related decisions.

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Agenda

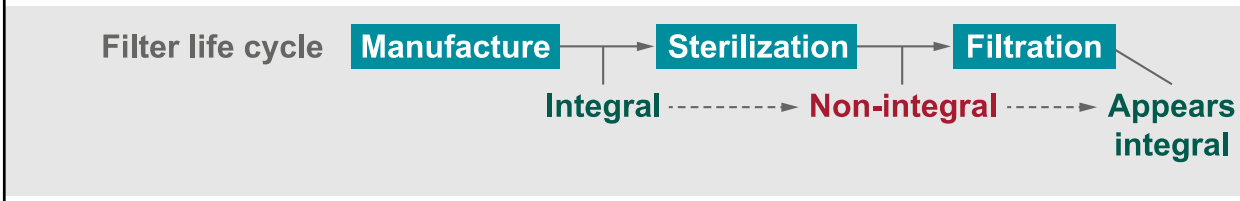
- Overview PUPSIT
- Regulatory Background
- Value of SFQRM Consortium effort and path forward

Filter integrity testing: protects the patient by ensuring sterility

Post-use filter integrity testing is sufficient to detect filter failure and ensure patient safety *unless there is a possibility that a filter passing the post-use test could have allowed bacterial penetration during the course of filtration*

This possibility is called the "blinding" or "flaw masking" hypothesis:

- A flawed filter is used during a filtration process
- Flaws allow microbiological contamination to pass during filtration, resulting in non-sterile filtrate
- Flaws are later closed or clogged by product debris.
- Closed flaws go un-detected by post-use test: Test Passes



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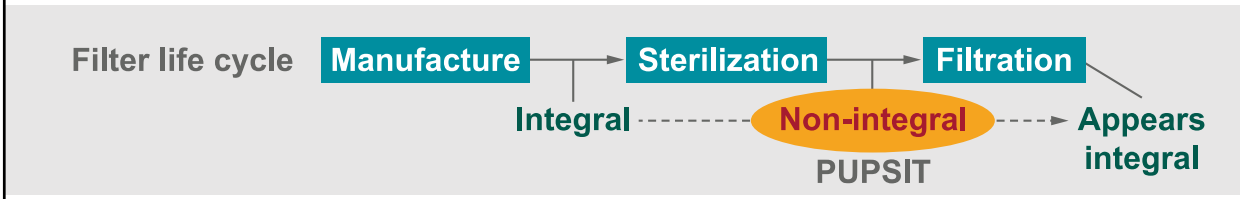
PUPSIT is a mitigation for the flaw masking hypothesis

"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 that could mask flaws
- 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
- Material must be present that can plug the defect to such an extent that it is not detectible by post-use integrity testing

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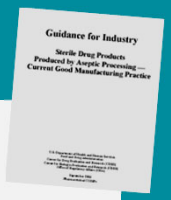
Regulatory requirements

EU GMP: The integrity of the sterilized 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

EU GMP Annex 1 for the manufacture of sterile medicinal products, February 2008



US FDA: Integrity testing of the filter can be performed prior to process and **should be routinely performed post-use**.

US FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, 2004

Where sterility is claimed: IT before use is recommended, after use is required

Industry guidance

PDA® TR26 – 2008 Sterilizing filtration of liquids

- Where the claimed purpose of the filter is to sterilize, **pre and post filtration** integrity tests **should be performed**.
- Prefiltration integrity test may be performed prior to sterilization of the filter and, preferably, after sterilization.
- Steps should be taken to ensure that the **downstream side of the system remains sterile** when performing a post sterilization, pre-use integrity test.

PDA® TR 66 – 2014 Single-use systems

- It is **less important** to conduct a **pre-use integrity test** of a sterilizing filter that has been **sterilized with gamma radiation.**
- The pre-use test has a primary purpose of detecting a damaged filter, a purpose that has roots in steam sterilization, which has known mechanisms by which filters can be damaged. These **mechanisms do not exist with gamma radiation sterilization**. *p 33*

ISO® 13408

- The filtration system should be designed to permit in-place integrity testing as a closed system prior to filtration.

ISO® 13408, 2003

PDA® recommends IT pre-use and post-use.
Industry guidance emphasizes that maintaining process sterility is of critical concern

Inspectors' guidelines

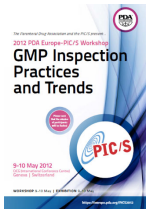
PIC/S **:** … the integrity of each individual product filter used for routine production should be tested before and after use.

Recommendation on the validation of aseptic processes July 2009

PIC/S **:** However, if a system of two filters with redundancy is used (the second filter is used for security, if one fails the required SAL is still achieved), sampling should be performed upstream of these filters in order not to compromise the filtration step.

GMP annex 1 rev 2008, Interpretation guide (PI-032A 1) Dec 2009

The debate



Historical positions

Industry position on PUPSIT

- Low value, flaw masking is uncommon
- PUPSIT adds risk, may disrupt aseptic pathway, adds complexity and interventions, stresses filter

European regulatory position on PUPSIT

- Essential: filtration is risky, flaw masking is a risk
- Industry just does not want to do it, risk assessments are biased

U.S. FDA position

- Nothing official
- Processes should be risk based

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Background: collaboration

BPOG and PDA MOU Dec. 2017 to create common position, support of work streams, and publish results

Deliverables

A) Communication (s) to the wider industry and regulatory authorities the consortium rationale, mission, approach, progress and conclusions and call for participation of regulators;

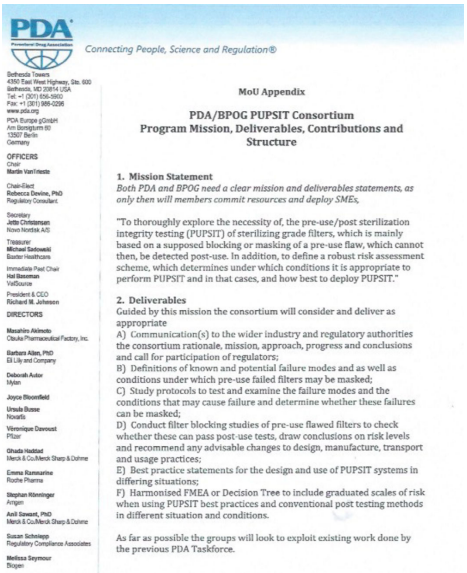
B) Definitions of known and potential failure modes and as well as conditions under which pre-use filters may be masked;

C) Study protocols to test and examine the failure modes and the conditions that may cause failures and determine whether these failures may 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 change to design, manufacture, transports and usage practices.

E) Best Practice statements for the design and use of PUPSIT systems in differing situations;

F) Harmonized GMEA or Decision Tree to include graduated scales of risk when using PUPSIT best practices and conventional post testing methods in different situation and conditions.



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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.

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SFQRM team

Christoph Knoop	AbbVie	Bryan Schneider	Ferring	Marc Steffens	Roche
Ciaran Burke	Allergan	Yair Dishair	Ferring	Kewei Yang	Roche
Robert McMahon	Alexion	Julien Van de Walle	GSK	Carl Weitzmann	Sanofi
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
Dina Rusu	Bayer	Dieter Bachmann	Janssen	Leesa McBurnie	Meissner
Brian Thome	Biogen	Martin Frei	Lonza	Stephanie Ferrante	Millipore
Caroline Eichberger	BMS	Gabriele Roidl	Lonza	Randy Wilkins	Millipore
Lei Ling	BMS	Sanghee Yang	Lonza	Brian Joseph	Pall
Chris Knutsen	BMS	Antonio Orlandi	Lonza	Mandar Dixit	Sartorius Stedim
Roentgen Hau	Celgene	Will Peterson	Merck MSD	Magnus Stering	Sartorius Stedim
Carol Kidwell	CSL Behring	Louise Lunn	Novo Nordisk	Maik Jornitz	G-CON Manufacturing
Steve Ensign	Eli Lilly	Carsten Dam-Mikkelsen	Novo Nordisk	Glenn Wright	PDA
Steve Lexa	Eli Lilly	Sean Tomlinson	Pfizer	Hal Baseman	ValSource
Peter Berzins	Eli Lilly	Vincent Van Dijck	Pfizer	Kelly Waldron	ValSource
Nunzio Zinfollino	EMD Serono	Katrien Suy	Pfizer	Jeff Gaerke	CA Inc
Adamo Sulpizi	EMD Serono	Michel Shroyen	Pfizer	Jannika Kremer	BioPhorum

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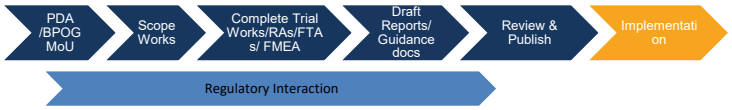
Collaboration team strategy

25 Biomanufacturers
4 Suppliers + 3 PDA
30+ Representatives
Various Work Groups



1. Change focus from PUPSIT to SFQRM
2. PUPSIT is not a process, it is a control measure
3. Prevention of failure is superior to detection
4. Low value efforts are harmful to patient safety, because they take resources away from more valuable efforts
5. Develop scientific data/evidence to determine and defend positions
6. Present results and encourage industry dialog
7. Align regulatory concerns to specific actions/deliverables

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Listening to regulator's position

1. *Filter manufacturing, transport, and usage is relatively uncontrolled and risky*
2. *Filter flaw and blinding risks cannot be eliminated and are potentially catastrophic*
3. *PUPSIT works, it is more effective than other control measures*
4. *Industry risk assessment are biased, flawed, and have predetermined outcomes*
5. *PUPSIT is not risky, not a burden, and not complex*
6. *Industry simply "does not want to do PUPSIT"*
7. *More scientific data and evidence are needed*

Not all regulators have the same opinion or position.

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SFQRM Deliverables Updates

- Masking studies
- Data mining
- Risk assessments
- Best practice
- Ancillary efforts

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Masking studies

Test flawed filters after exposure to proteinaceous foulant solution

Two populations of flawed filters were used:

1. Marginally OOS filter cartridges rejected from filter manufacturing lines
2. Disc filters with defects generated by laser-drilling 10 micron holes

Results

1. **Cartridges**: Despite exposure to 24g/L foulant concentration and 90%+ flow decay, only 2 out of 24 cartridge filters demonstrated apparent flaw masking (pre-use **failure** followed by a post-use **pass**). 19 experienced a *reduction* in bubble point after exposure to the foulant
2. **Discs:** No passing post use tests on blockage rates up to 75% whether challenged with 0.8 g/L or 24 g/L foulant solutions. At blockage levels above 75%, only 2 out of 27 demonstrated passing post-use integrity tests

While masking can be made to occur, it is not likely to occur under typical drug manufacturing conditions.

Full study published in the PDA Journal of Pharmaceutical Technology June 2020 *Test Process and Results of Potential Masking of Sterilizing Grade Filters*. Authors Stephanie Ferrante (Millipore Sigma), Leesa McBurnie (Meissner), Mandar Dixit (Sartorius Stedim), Brian Joseph (Pall), Maik Jornitz*(G-CON)

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Update: masking study

Next steps

- Repeat at conditions approaching commercial usage, using commercially flawed filters and laboratory flawed, laser drilled disc filters

Discussion

- Difficult to find or produce flawed filters, and they would not have passed manufacturer release tests
- Masking may occur under **extreme, non-commercial** conditions
- Flaws likely to be uncovered by pre-use (pre-sterilization) testing
- Would need to establish correlation between laboratory produced flaws and commercially occurring flaws
- Results can provide guidance to industry to determine if their filtration conditions pose risk

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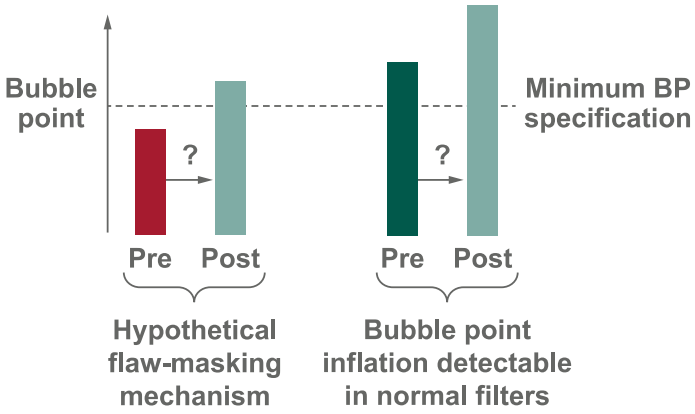
Bacterial Challenge Test (BCT) Data Mining

Routinely performed BCT typically have both “pre” and “post” use integrity test results. Can we pull this data and see if exposure to the product “inflates” the bubble point?



Integrity test value shift may be indicative of filter masking

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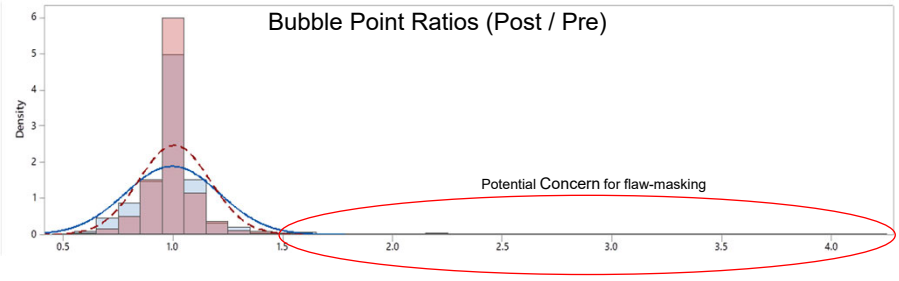
Bacterial challenge test data mining

Results

2,080 data sets have been collected and statistically analysed from a multitude of different 0.2 micron and 0.45 micron filters utilized with different fluid streams.



Discussion

- Showed that significant bubble point value shift is rare and predictable
- This is only a risk for fluids with a flaw-masking mechanism and if filters begin in the damaged state. End-users should assess this risk for themselves and weigh against risk of executing PUPSIT.
- In combination with masking studies this provides valuable information for companies to select the correct and most effective means to determine if products or processes are at risk of blinding and how to prevent blinding effects.

Full study published in the PDA Journal of Pharmaceutical Technology May 2020
Datamining To Determine The Influence Of Fluid Properties On The Integrity Test Values. Authors: Brian Thome, Brian Joseph, Dawood Dassu, Jeff Gaerke, Leesa McBurnie, Mandar Dixit, Magnus Stering, Sean Tomlinson, Scott Mills, Stephanie S Ferrante, Carl Weitzmann

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Survey and risk assessments

Objective

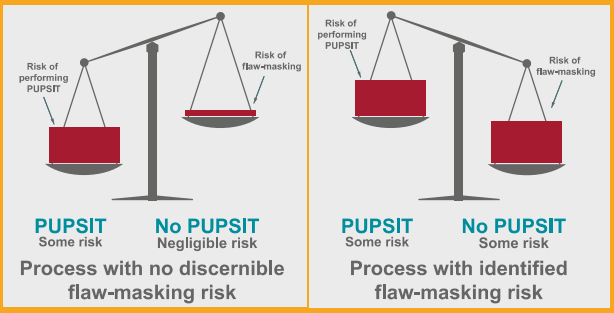
Determine failure modes and risks associated with filter manufacturing & usage. Identify actions to improve filter manufacturing and usage control and prevent filter flaws

Study

Using separate FTA tools, manufacturers and users assess risk of filter flaws as a result of manufacturing and usage

Results

Separate assessments completed for manufacturing, transport, handing, and use of cartridge filters and SUS assemblies.



Discussion

- In most cases, failure modes appear to be well controlled.
- Data will help inform risk identification and analysis for those instances in which specific detection controls, such as PUPSIT, are necessary for inclusion in the overall filtration control strategy.
- Examples may also be used by filter manufacturers as a guide for process improvement and by users as a guide for audit and selection of filter manufactures.

Published in PDA Technical Journal June 2020:
"Risks associated with Sterilizing Grade Filters and Sterilizing Filtration" Lead author Kelly Waldron, Valsource + 21 contributing authors, including both manufacturer and filter manufacturers, from the SFQRM Consortium team.

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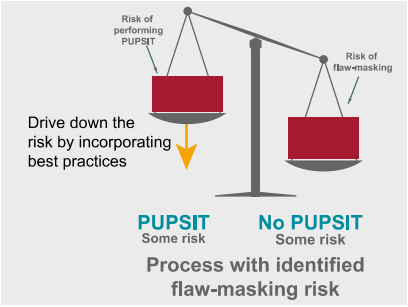
Best practice/points to consider

Objective

When a User *does* implement PUPSIT, how can they best minimize added risk & complexity?

Deliverable

Prepare guidance on best practice for design and operation of PUPSIT



Results

- Comprehensive Best Practice Document
- Based on and linked to PUPSIT FMEA that uncovers associated risks, and means to control and reduce risks
- Compiled by Industry Experts

Next steps

Reinforces complexity of PUPSIT and need for sophisticated approach

Published: *Points to Consider for Implementation of Pre-Use Post-Sterilization Integrity Testing (PUPSIT).* Authors: Hal Baseman, ValSource, Steve Ensign, Eli Lilly and Company, Stephanie Ferrante, Millipore Sigma, Jeff Gaerke P.E., CAI, Maik Jornitz, G-CON Manufacturing Inc., Tina Morris, PDA, Will Peterson, Merck Sharp & Dohme, Thao Le Vinh, Glaxosmithkline

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Publications overview

Document	Acceptance/Publication
Datamining to Determine the Influence of Fluid Properties on the Integrity Test Values	Published in the PDA: link here
Test Process and Results of Potential Masking of Sterilizing Grade Filters	Published in the PDA: link here
PDA Points to Consider for Risks Associated with Sterilizing Grade Filters and Sterilizing Filtration	Published in the PDA: link here
PDA Points to Consider for Implementation of Pre-Use Post Sterilization Integrity Testing (PUPSIT)	Published in the PDA: link here
PDA Journal: Test Process and Results of Potential Masking of Sterilizing Grade Filters, Part 2 (probably new name when published)	To publication stage late 2020 / early 2021
Capstone Article: The Use of Scientific Data to Assess and Control Risks Associated with Sterilizing Filtration	Published in the PDA Letter June 2020: link here

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Summary and conclusion of workstream deliverables

- Flaw masking is possible in rare circumstances
- For the vast majority of filtered solutions, flaw masking cannot and will not occur
- Users must make a process-specific assessment of the flaw masking risk
- If there is a reasonable risk of flaw masking that cannot be adequately reduced using process controls, the default position should be to perform PUPSIT
- However, if there is negligible risk of flaw masking (many instances) we recommend that users should take a risk-based approach to the implementation of PUPSIT due to the strong case for added process risk + complexity

The question is *not* whether PUPSIT can uncover a filter integrity failure, *nor* whether there is a theoretical possibility of a flawed filter passing a post-use integrity test, *nor* the impact of such an occurrence.

The question is whether PUPSIT is the best choice to prevent such an occurrence in an actual filtration process from affecting product sterility, without adding additional risk.

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Update: ancillary activities

BioPhorum participant surveys

- Sterility assurance related failures linked to PUPSIT
- Effort and resources needed to install and perform PUPSIT

Communication with Inspectors Working Group leadership

- i.e. Editorial Letter/ FF21 pre-read.
- Pre-view by regulators of all SFQRM Consortium publications
- Regular teleconference meetings, 3 this year thus far.

Value of effort

Regulators concern	Workstream link/answer
1. Filter manufacturing and usage risk	1. FTAs show risks are well controlled
2. Filter blinding risks are real	2. Studies show blinding is rare under very specific conditions
3. PUPIST effectiveness	3. Stress prevention over detection
4. Biased risk assessments	4. Use study results to make Ras objective
5. PUPSIT is risk free and easy	5. Surveys, best practice and FMEA
6. Industry against PUPSIT	6. BPOG PDA effort unbiased, including best practice
7. More scientific data and evidence needed	7. Laboratory studies and data analysis
Differing regulatory opinions	**Commentary, dialog, & education**

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Changing Positions? – A Side-by-side comparison Annex 1 draft 2017 and draft 2020

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 recognized 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

8.88 The integrity of the sterilized filter assembly should be verified by integrity testing before use, 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 (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 non-sterility. Points to consider in such a risk assessment should include but are not be limited to:

i. In depth knowledge and control of the sterilization 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 sterilization facilities.
- Defined transport mechanisms.
- Packaging of the sterilized filter, to prevent damage to the filter during transportation and storage.

iii. In depth process knowledge such as:

- The specific product type, including particulate 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 sterilizing filter, which would remove particulate burden and clarify the product prior to the sterile filtration.

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Annex 1 2020 Draft

Changes to new draft	Expanded language on PUPSIT
	The section is more risk oriented and less restrictive
	Default is still PUPSIT, however, new draft open up for risk based approach when it is not reasonable or not possible to do PUPSIT.
Discussion	Guidance gives examples of what to include in RA, what is not contained in the examples is risk to the integrity of filter by using filter
	Language has many “for example” clauses – this opens up for interpretation by inspectors. We would like to suggest that regulators soften and/or remove “examples”
	Reference to small batches however leaves it open for different regulatory interpretations – recommend to remove specific reference
	Would like to try to include the consideration of risk from PUPSIT to the aseptic process – Likely a hard sell, as no company wants to discuss introduction of risk during PUPSIT implementation.
	Desire to not to make PUPSIT the default, but the entire contamination control strategy

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Path forward

- Publish all results and reports, linking all of the workstream deliverables
- Encourage dialog from industry based on deliverables
- Shift to educating regulators on interpretation of results and acceptance of risk based alternate approaches

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Thank you

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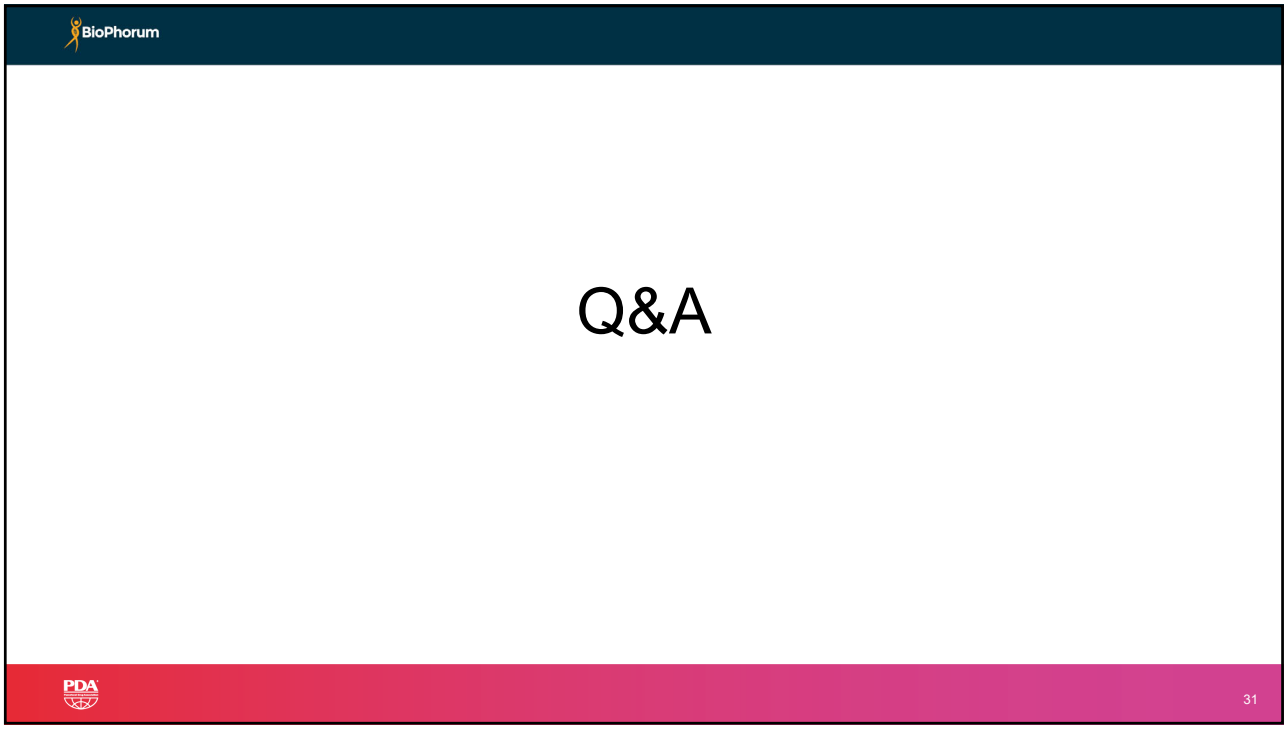

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