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Sterile filtration and Quality Risk Management

Understanding the role of PUPSIT in your contamination control strategy and compliance with EU GMP Annex 1.

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Quality is not finite

Process control during the manufacture of sterile products is essential to assure product quality and to deliver safe drugs and therapies. Specific controls that relate to every aspect of production, including the facilities, systems, materials, equipment, and procedures that are required, evolve in response to increased knowledge, continuous improvement, new challenges, new technology or new solutions. With input from the industry, suppliers, and specialist interest groups, these grow from local solutions to become increasingly commonplace and ultimately to influence the global regulatory guidance. With this flow, the industry evolves, passively sharing best practices to develop ever-safer processes.

At times in this cycle, there are periods of uncertainty, especially as novel manufacturing methods and new modalities arise. There can occasionally be differences in the guidance issued from different regulatory agencies; the interpretation of this guidance and the subsequent local enforcement of it. Global harmonization takes time. However, where there is a clear scientific rationale and an achievable solution, it is inevitable, but not immediate. During this process, there are milestones that mark the transition from isolated applications to being acknowledged as best practice and then becoming an industry benchmark.
The update to EU GMP Annex 1, Manufacture of Sterile Medicinal Products, is one such milestone.

Defining a single path from the guidance

Various levels of guidance are available from a wide variety of sources. It is the skill of process developers, quality, validation, and regulatory groups to navigate these texts when establishing optimal processing procedures and compiling the supporting documentation for regulatory scrutiny relevant to the milestone in question.

Process decisions supported by sound scientific judgement and strong data are needed to satisfy regulatory agencies. However, given that very specific knowledge is often required to determine the suitability of the proposed rationale, such solutions are often discussed, and then globalized via specialist industry bodies.
One example of this process is the long-standing discussion relating to the implementation of pre-use, post-sterilization integrity testing (PUPSIT). The recent update to EU GMP Annex 1 is informed by these discussions and the data generated as part of this process. This provides greater clarification of this subject and puts quality risk management and periodic review of the contamination control strategy at the heart of this guidance. This includes confirming the integrity of critical filters used as part of this strategy.

Establishing a contamination control strategy

Since 1963, the principles that underpin current good manufacturing practices (cGMP) for pharmaceuticals have evolved, and continue to evolve, to address specific industry needs and to deliver ever safer products to the public. This is a never-ending journey. Regional variations are not uncommon, however all processes aim to ensure the delivery of products with the appropriate quality attributes by establishing a state of control.

These controls are established to assure the safety, purity, and efficacy of the product. Any potential risk should be diligently reviewed to establish an action that is designed to control or eliminate this risk. This principle of Quality Risk Management (QRM), in combination with the well-informed identification, and scientific assessment of risk, informs both the need for specific controls and the necessary strategy required to achieve it.

'Contamination Control Strategy (CCS): A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in- process controls, finished product specifications, and the associated methods and frequency of monitoring and control.' EU GMP Annex 1

The role of filtration for bioburden control in QRM and CCS

Filters are, by definition, designed to separate the wanted (typically an active ingredient) from the unwanted (typically some form of contaminant). When tasked to reduce or eliminate bioburden, they are reliant upon other process components to maintain the state of low bioburden that they achieve. This can be as simple as preventing potential recontamination of the filtered fluid direct from a non-sterile atmosphere or from contact of the process fluid with non-sterile surfaces. It is common for filtration controls to be implemented at many points in an average process. Their use can quickly lower bioburden wherever potential recontamination may occur and minimize the potential for increase during any hold steps.

Filters are typically designed to remove specific contaminants with a defined level of retention performance. The level of retention required by the process is established from a knowledge of the likely level of contamination and the acceptable level of that contaminant. Where potential contamination has a high impact on the critical quality attributes of the drug product, the level of acceptance may be set at zero. In these critical applications the filtration process is typically accompanied by other actions designed to validate, monitor, and document the performance of the filter.

Sterilizing grade filters are one such example and are found throughout most pharmaceutical processes. When they are deemed critical to quality, their performance is also validated, the influent level of bioburden is measured, and their integrity at the point of use is confirmed, recorded, and reported as part of the batch release criteria. When used correctly, they contribute to the assurance of sterility of the final product and are an intrinsic part of the manufacture of sterile medicinal products.

"Quality Risk Management (QRM): A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle." ICH Q9

EU GMP Annex 1

Annex 1 has been revised on numerous occasions (1997, 2008, 2022) with each revision accommodating advances in technology, understanding and industry trends.

The most recent update due for implementation in 2023 contains numerous changes. Many of these aim to address points of ambiguity and adapt language to align with technical and regulatory precedents to achieve greater clarity. The requirement for pre-use, post-sterilization filter integrity testing (PUPSIT) is among the areas that receive adjusted wording.

Pre-use, post-sterilization integrity testing (EU GMP Annex 1, Sterilizing Grade Filters Used for Aseptic Manufacturing)

2008	2022
"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 time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals."	"The integrity of the sterilised 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 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. 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 recognised that pre-use post sterilisation integrity testing (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 non-sterility…"

While the change is relatively small, the new clarity signals intent to both reinforce the guidance and to ensure that risk assessments, and the good science that informs them, underpins the chosen action.

The work behind the change

The rewording belies the depth of the scientific investigations behind the change. In 2017 the PDA/BioPhorum working group, Sterile Filtration Quality Risk Management (SFQRM) consortium was formed and investigated the long discussed theoretical mechanism of filter flaw masking. This hypothesis proposed the possibility of a filter containing a flaw, not present at the point of manufacture, being created, and subsequently masked by extensive plugging of the filter with a process component present during the filtration. This masking would then result in the flaw not being identified by routine post-use filter integrity testing. The published report[ref] provides data that indicates that this mechanism of failure is genuine, but, that the risk is extremely low for most processes. However, while the risk is considered extremely low, it can exist. Therefore, in the absence of process data confirming its absence, a change in procedure to add an additional layer of control may be beneficial and is proposed.

So, is there a regulatory divergence relating to PUPSIT?

There is not a global consensus on the use of PUPSIT as a specific method to control the residual risk associated with the existing filter integrity testing regime. Through the BioPhorum/PDA SFQRM interest group there is data that better defines the nature of the risk. As routine review is a fundamental part of an effective contamination CCS, this newly defined risk should naturally be included in such a review and risk assessment. If we remain agnostic about the need for, and nature of any control, this means that all manufacturers of sterile drug products could reasonably be expected to be aware of the new data and to have answers to some standard questions, irrespective of the local regulatory guidance specific to PUPSIT. Such questions may include:

Documenting points of risk as part of QRM

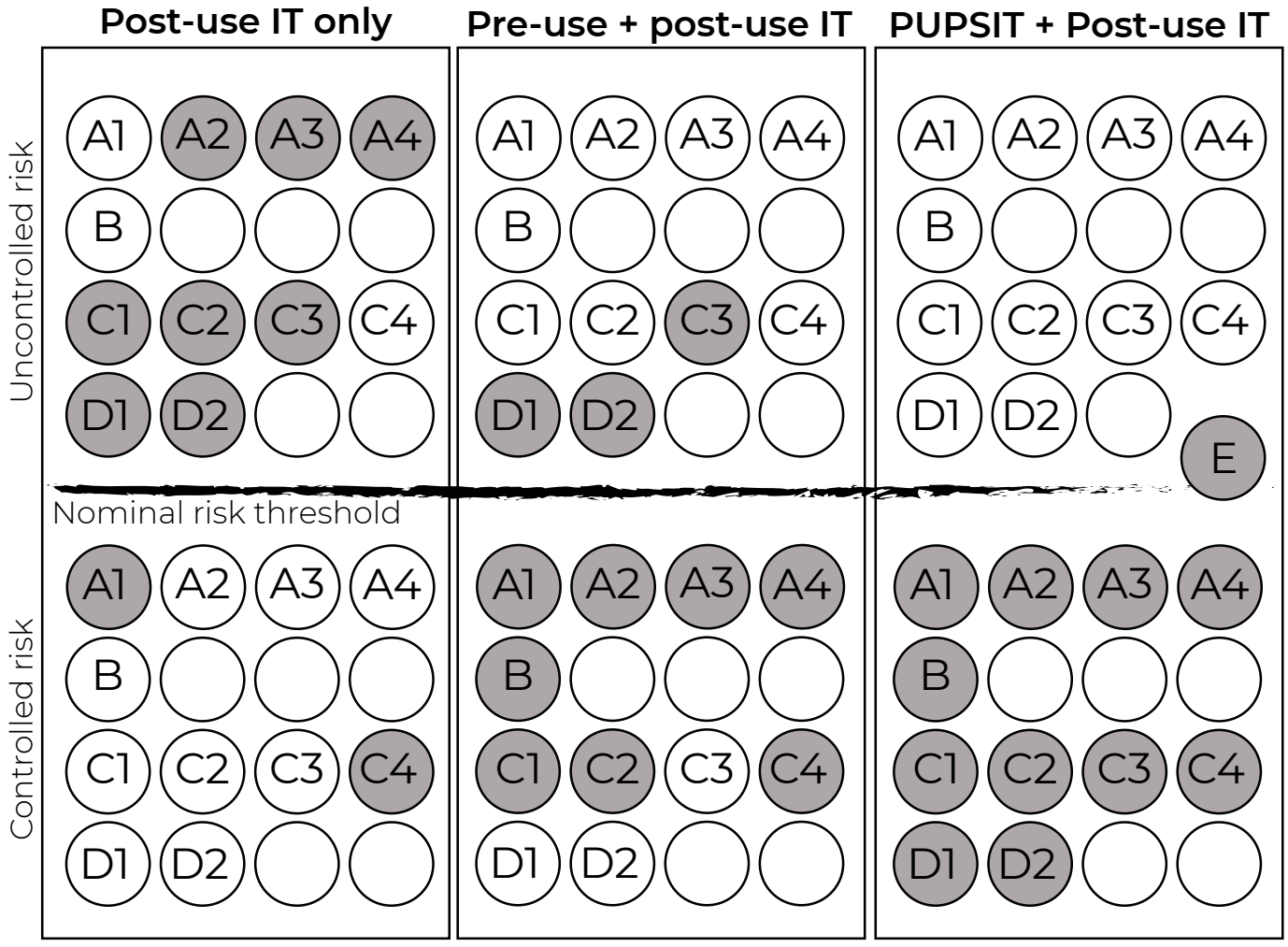
Filter focused risk summary from point of manufacture to point of use

	Nature and location of risk	Nominal risk	Potential impact	Mitigating data, preventative or corrective action
A1	Defective filter supplied	Low	IT failure post-use; Batch loss or batch reprocessing if permitted	Membrane manufacture QC, 100% filter IT and bacterial challenge sample testing is part of manufacturer's release criteria. Cert of conformance supplied and included in batch records. Audited supplier quality systems.
A2	Filter damaged during assembly or packaging of single-use system	Low		Pre-use IT confirms the absence of any defect before use. System leak testing guards against potential non-filter related flaws.
A3	Filter damaged during shipment	Low		External visual inspection for physical damage on receipt; Pre-use IT; Risk assessment for shipping and / or transportation validation study.
A4	Filter damaged during storage	Low		Pre-use IT; Storage procedures adhere to specified storage conditions and shelf life claims.
B	Filter damaged during transfer into manufacturing	Low		Visual inspection; Manual handling training; Pre-use IT.
C1	Filter damaged during installation	Low		Visual inspection; Operator training; System shadow board; Pre-use IT.
C2	Filter damaged during sterilization (gamma / x-ray)	Very low		Core validation data and irradiation dose monitoring; Pre-use IT / Post-use IT.
C3	Filter damaged during sterilization (steam)	Med		Sterilization validation and monitoring; Pre-use IT / Post-use IT.
C4	Damaged during process (including preparative processes for filter IT)	Very low		Core filter validation data; Process monitoring or critical parameters; Automation and associated PQ data.
D1	Process fluid contains potentially masking components to reduce sensitivity of post-use IT.	Very low	Sterility potentially compromised, potential patient safety risk	Define safe filtration design space to avoid critical fouling. Review if prefiltration / serial / redundant filtration can reliably remove masking species. Size filter to reduce impact of fouling, PUPSIT to confirm filter is flaw-free immediately before use.
D2	Post-use IT fails to identify filter flaw	Very low: No data to support the hypothesis (excluding flaw masking)		No action.
E	Risk of sterility breach from PUPSIT	Low		Optimized process design & components; SUS leak testing; Control bioburden of wetting fluid; Automation; Operator training.

- *At all points in the life cycle of each critical filter and associated components (from the point of manufacture to the point of use post-use testing), have you evaluated all the potential failure modes?*
- *What is the likelihood and the effect of any failure mode upon your process?*
- *What data do you have to support this?*
- *What controls do you, and your suppliers, have in place to control these risks?*
- *Is there anything specific to your process that may reduce the effectiveness of any of these controls? (i.e could your process fluid mask any filter flaw during post-use IT?)*
- *What data do you have, or would you need, to support this evaluation?*
- *What is the new risk associated with any additional control and how can this be mitigated?*

The first two of these questions set the scene for much of the existing regulatory guidance relating to critical filtration. It is easy to lose sight of the fact that, while the expectation of post-use filter testing predates today's formal risk-based approach, it is an effective risk control to guard against the filter not performing as expected. Filter integrity testing is not the only control that may be required, and we will review other factors in the later section.

Figure 1 Visualization of changing risk with filter integrity test regime



Adding PUPSIT without adding risk

Attempting to perform a post-sterilization filter integrity test without careful consideration on the potential impact of the sterile pathway carries new risk. This risk only increases if applied in conjunction with redundant or serial filtration. There are, however, proven solutions that work in both single-use and traditional hard-piped processes. These, coupled with suitable supplier data packages and optional additional testing such as single-use system leak testing, provide a practical ready-made solution to the challenge. When supported by the right scientific and technical expertise, the appropriate knowledge transfer, and operator training, adding PUPSIT to your process does not have to be daunting. This addition also provides a good opportunity to future-proof an area of the process that will, no doubt, receive a renewed regulatory focus during inspections as a result of Annex 1 updates.

Is PUPSIT the only solution?

The scientific answer to this is no. The risk associated with flaw masking has currently only been confirmed if two conditions prevail: (1) a filter has a flaw, and (2) the filter is exposed to a very high levels of filter plugging which is unlikely to simulate a typical controlled manufacturing process . Avoiding this through characterization of the 'safe' filter operating space, including the necessary process monitoring and control, and reporting suitable data in the batch records, seems an acceptable solution. Filter blockage may also be prevented through increased filter sizing or prefiltration.

Figure 2 A typical system design supporting PUPSIT in single-use processes

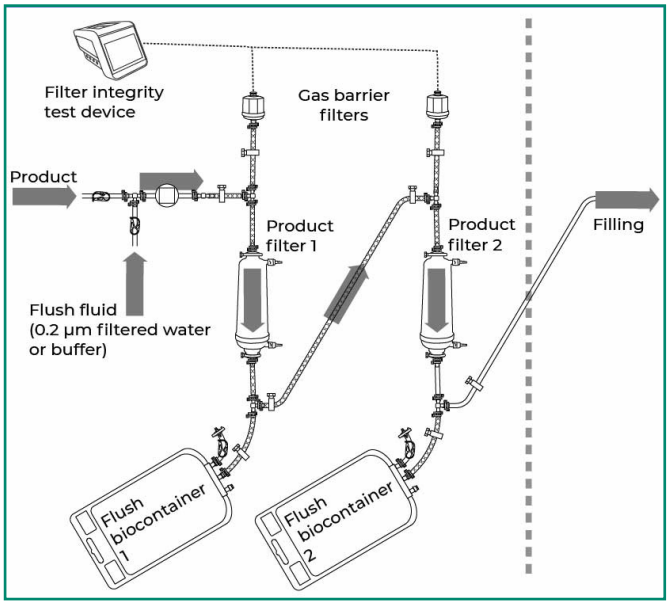
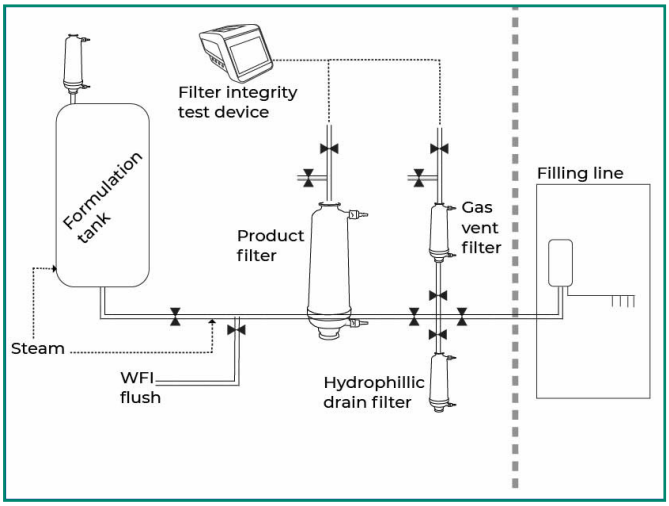


Figure 3 A shadow board concept in use with a PUPSIT capable SUS and automated filtration skid

Figure 4 A typical system design supporting PUPSIT in hard-piped processes



"The approach for small batch sizes: It is recognised that for small batch sizes, this (PUPSIT) 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". EU GMP Annex 1, section 8.84

The Annex 1 revision does highlight one condition under which an exception can be made. This stresses the importance of risk assessment, however, it raises new questions. Is this exception only permitted where PUPSIT solutions for small batch sizes are not available, and are these exceptions limited to only small batches? Similarly, what is defined as 'small'? Will this be determined in terms of an absolute volume, or will exceptions be more readily accepted for advanced therapy medicinal products (ATMP) or high concentration formulations where the full-scale volume may naturally be lower than for more traditional drugs?

While not referred to within EU GMP Annex 1 revision, the use of a second retentive (redundant) filter does seem to respond to most of the questions raised by the risk assessment. This may reasonably be expected to remove any potentially masking

components that increase the risk of not identifying a reduction in filter performance.. When applied, it should result in the post-use filter integrity test being capable of identifying the presence of a filter defect that was present before processing. There is, however, no data available to validate these assumptions, nor any current signal that this solution will be globally accepted by inspectors.

Is there a conclusion?

The need for a defined and documented contamination control strategy, informed through the application of Quality Risk Management principles, and supported by good data-driven science, is at the heart of recent updates to regulatory guidance. When applied to critical operations, such as those surrounding the final sterilizing grade filtration, residual risks associated with existing process designs and procedures can be identified and assessed.

The collection of controls and requirements that surround the use of sterilizing grade filters at points critical to product quality are a good case study of this progression. For more than 40 years, the benefit of microbially retentive filters to the product quality and safety has been embraced. In this time, we have seen changes in the format of the filters to simplify their use and to safeguard their performance. We have seen changes in their core performance specification from 0.45 µm to 0.2 µm and even 0.1 µm ratings being required, as our knowledge of potential penetration increases. Guidance regarding the documentation of the filter performance has also developed, encompassing process-specific validation and filter integrity testing.

PUPSIT is the latest example of this evolution and has achieved a point of technical maturity, For most processes its inclusion can be achieved with the right knowledge and support. It is, however, not the only control and the acceptance of alternate, solutions will be clarified in time. For now, a well-designed process that carefully applies PUPSIT, is likely to be safer than one without. Similarly, a process that is owned by those who acknowledge and seek to understand any risk to quality, is likely to be more robust than one owed by those that just follow the essential guidance without true understanding. Even if nothing changes in the process itself, the science and data that underpins the conclusion to take action, or to take no action, increases knowledge. Applying this knowledge through the CCS safeguards quality.

To conclude, the questions of whether PUPSIT is necessary or is mandated are largely irrelevant in comparison to the ability to scientifically answer the question: ‘Am I doing everything I can to identify, understand and control all potential risks to product quality?’

PUPSIT may be one current focal point, but this question will be applied to many other points of risk control. QRM principles, coupled with better understanding, will drive changes in many areas, and this will be especially true as specific challenges associated with the manufacture of novel modalities are explored, mature and become the next focus of evolving regulatory guidance.

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