USTR 3650

Pre-Use Post Sterilization Integrity Test - PUPSIT

What is Pall's Perspective on PUPSIT?

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Please note: The position of the Regulatory Authorities on PUPSIT is covered in Pall document reference USTR 3649.

Pall's Perspective on PUPSIT

While it has not been universally adopted or policed, a Pre-Use Post Sterilization Integrity Test (PUPSIT) has been required for final sterilizing grade filters used on products manufactured or sold in Europe since 2003. This is described in Annex 1 of the European Union Good Manufacturing Practices (EU-GMP) guidelines. A new revision of Annex 1 was published in 2022 and is due for implementation in 2023. The relevant section (Vol 4 Annex 1, paragraph 8.87) now states:

> "*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 on 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.*"

A pre-use post-sterilization integrity test provides meaningful data confirming filter integrity at the point of use and mitigates the risk of a non-integral filter being inadvertently used. Pall therefore recommends the use of PUPSIT as a method to control the residual process risk associated with post-use filter integrity testing. Pall also acknowledges that other solutions such as the use of redundant filtration, when coupled with suitable data, understanding, and risk assessment, may be applied as an alternative to, or used in addition to, PUPSIT. As such Pall supports the application as recommended by the above guideline, and recommends such integrity testing in the Pall Instructions for Use for capsules and cartridges:

> "Sterilizing and virus grade filters should be integrity tested pre-use, if applicable after sterilization to ensure that the individual filter is capable of performing its stated function, and integrity tested post-use. Consider application specific regulatory and technical guidelines for process design details, including your process-specific risk assessment."

The European Medicines Association (EMA) has expressed concerns regarding the possibility of expanded flow pathways after thermal exposure. The rationale expressed by EMA Good Manufacturing Processes/Good Distribution Practice Inspectors Working Group supports a PUPSIT recommendation because of a perceived risk of pore size distortion during filter-sterilization followed by the risk of a defect masking during filtration. In effect, this becomes a kind of self-repair mechanism.

However, Pall filter validation studies have shown filter membranes retain their pore flow pathway morphology after both steam exposure and gamma irradiation. Despite these results, these studies cannot preclude the possibility of damage incurred during transport, installation, or by deviations in pressure, beyond acceptable limits, during steam sterilization. If the filter is tested prior to sterilization only, it is possible that a filter damaged as a result of sterilization could be used for critical filtration, and that the damage will only be detected during the post-use integrity test.

Controlling Risks Associated with PUPSIT

A pre-use post-sterilization integrity test can detect damage that occurs to the filter during the sterilization process or during any step since the previous integrity test (for example: packaging, shipping, storage, installation). Its inclusion reduces the risk of any such damage not being identified until post-use testing. However, if not performed properly, PUPSIT may introduce a new risk of sterility breach. This risk may be further increased where complex systems, such as a system including redundant filtration, are used. Actions that may mitigate this risk include carefully optimized system design, automation and operator training.

In 2017, PDA and the BioPhorum Operations Group began a collaborative effort and defined workstream deliverables which were designed to (a) better understand the potential risk of masking of a filter flaw, and (b) minimize such risks where they could potentially occur. The results of these studies [1] indicated that masking of flawed filters leading to a false confirmation of post-use filter integrity could occur with high fouling feeds that could cause premature filter blockage. These conditions would typically be indicated by very low filter capacity as a result of the high degree of blocking species. In a validated process, sterilizing grade filters are not typically subjected to such conditions and appropriate sizing ensures that filters do not plug prematurely. However, Pall acknowledges the potential risk and concludes that that masking of flawed filters requires both a very small defect and a solution containing a higher degree of fouling species. The prevalence of both is considered low but should be confirmed by suitable process data and an accompanying risk assessment.

Thus, a decision on whether or not to apply PUPSIT should be made on a risk assessment basis. This risk assessment should follow the principles and tools for quality risk management as described in ICH Q9 to enable an effective and consistent risk-based decision regarding the quality of the filtered product by reference to a quality management process. The risk assessment should also include review of the filtration conditions and parameters, and an evaluation of the plugging potential of the process fluid, as indicated in EU GMP Guide Annex 1 paragraph 8.87.

Pall is committed to a risk-based approach in the design of final filtration systems which may determine a requirement for PUPSIT as part of the end-users contamination control strategy. Pall also strongly recommends other filter performance risk controls such as appropriate process specific validation to confirm bacterial retention, performance operator training to assure accurate execution of critical tasks and the adoption of automated solutions to further control human risk factors.

References

[1] S. Ferrante, L. McBurnie, M. Dixit, B. Joseph and M. Jornitz, “Test Process and Results of potential Masking of Sterilizing Grade Filters,” *PDA Journal of Pharmaceutical Science and Technology,* May 2020.

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