Pre-Use Post Sterilization Integrity Test – PUPSIT

What is the Cytiva's Position on PUPSIT?

Document Number:	USTR 3650
Revision Number:	1.1
Date	March 16, 2022
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Please Note: The position of the Regulatory Authorities on PUPSIT is covered in document reference – RPSCPPS_01.

Cytiva Biotech's Position on PUPSIT

Pre-Use Post Sterilization Integrity Test (PUPSIT) is applicable in Europe, as indicated in the EU-GMP guidelines intended for Sterilized Filters (2009, Vol 4 Annex 1, paragraph 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 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.*

A post sterilization integrity test provides meaningful data about filter integrity, Cytiva Biotech therefore advocates and supports the application as recommended by the above guideline. Integrity testing is recommended in the Cytiva Biotech Instructions for Use (USD 2441a):

> *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 post-use. Consider application specific regulatory and technical guidelines for process design details, including your process-specific risk assessment.*

A post sterilization integrity test can be meaningful in detecting 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). However, if not performed properly, PUPSIT may introduce risk for sterility breach. The risk may be further increased where complex systems, such as a system containing redundant filtration, are used.

The European Medicines Association (EMA) have expressed concerns regarding 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.

Data supporting this "self-repair" mechanism is currently not available, since if there is a PUPSIT failure, the end user does not use the filter for processing their drug product. To verify, or refute, this theory by laboratory testing is most likely not representative of all possible filtration processes and process conditions.

However, Cytiva Biotech filter validation studies have shown filter membranes retain their pore flow pathway morphology after both steam exposure and gamma irradiation. Despite these results, this validation study cannot preclude the possibility of damages 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 damaged filter could be used for critical filtration and that the damage will only be detected during the post use integrity test.

Thus, a business 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. However, Cytiva advise that PUPSIT should be applied when using its products for confirmation of their integrity before introducing product to the filter.

The risk assessment should include the review of the filtration conditions and parameters to evaluate the potential particulate level, blocking potential of product liquid components.

The successful implementation of PUPSIT in critical applications confirms that the risk of sterility breach is mitigated when adequate technological controls (i.e. system design, in-situ leak testing, validation, operator training) are used.