Biotech

Technical Regulatory Document

PUPSIT Risk Assessment

Document Number:	USTR3453
Revision Number:	0
Date:	18-Mar-21
Author:	Brian Joseph

EU GMP Annex 1: Manufacture of Sterile Medicinal Products[1] is currently under revision, and the current draft wording allows more flexibility on the requirement for performing Pre-Use, Post Sterilization Integrity Testing (PUPSIT) based on risk assessment. The driving force for performing PUPSIT is to detect the presence of a marginally non-integral filter after sterilization, where the process fluid, or impurities in the process fluid, could potentially mask a damage or a defect. Such masking would increase the risk of the marginal damage not being detected by the post-use integrity test. When performing a process risk assessment, two factors need to be considered:

1. The chance of there being a damage present capable of being masked.
2. Whether the process fluid can plug damage.

There have been a lot of questions as to what may be considered an acceptable risk assessment. Firstly, a risk assessment must demonstrate a complete understanding of the drug-making process in order to understand the potential risks to the drug product leading ultimately to potential risks to the patient. It is important to understand that a proper risk assessment is analogous to a puzzle composed of many parts. A single piece of the puzzle will not be accepted by regulators on its own as a reason not to do PUPSIT, nor will they accept the argument that it is too risky or too hard to do PUPSIT. The risk assessment must be a data-driven argument based on the individual process risks, that can be submitted to the relevant regulatory authority for review and comment.

This document provides guidance on what components should be part of a PUPSIT risk assessment. Although this is not a comprehensive list, it will provide many of the “puzzle pieces” for a proper risk assessment. In fact, PUPSIT is one of the pieces, among many others, for completion of the complex puzzle to ensure safe and reliable manufacturing of sterile products.

Filter manufacturing:
Most filter manufacturers perform an integrity test as part of the manufacturing release criteria for their sterilizing grade filters. In many cases, the release criteria are more conservative than the validated limits, thereby adding a safety margin for the detection of marginal defects. Such a test will detect any defects in the filter manufacturing process, preventing a defective filter from being supplied to the end user. The presence of this manufacturing integrity test, and the validated steps that are performed by the filter manufacturer after the integrity test are performed, should be included as part of his risk assessment.

Filter transportation, storage, unpacking and installation:
Filter manufacturers and end users must ensure that the filters are integral inside in their original packaging to show that the packaging properly protects the filter from physical damage that can occur during shipping between the filter manufacturer’s facility and the end user’s facility, and storage and movement inside the end-user’s facility. However, the use of an *in-situ* pre-use, pre-sterilization integrity test will detect damages that may have occurred during the shipment process, receiving and storage by the end user, as well as handling and installation by the end user. This test, combined with evidence of a well-controlled sterilization process, will reduce the risk of a damaged filter being used in the drug manufacture process. The risk assessment should consider that such a pre-sterilization integrity test is only applicable to filters that are delivered as non-sterile standalone filters (e.g., not part of a gamma-irradiated single-use system). A risk assessment should also include detailed procedures to show how the filters are handled in the facility and how to manage process excursions (i.e., dropped filters).

Filter sterilization:
A well-controlled and understood sterilization process is critical in ensuring a filter is not damaged prior to use. Improper sterilization can potentially cause damage to the filter, resulting in a compromised drug product. If filter damage is detected during the post-use test, the consequence is typically a loss of product, financial loss, and possibly a shortage of drug products to the patients. Documentation on the validated sterilization process should show:

- Sterilization conditions are within the specifications of the filter and do not affect the integrity of the filter.

- How the sterilization conditions are monitored and controlled.
- What actions are taken if the conditions are outside the design space.

Filter configuration:
When PUPSIT is performed manually on a redundant filtration configuration, the integrity test itself may increase the risk to the final product due to additional complexity of connections and valve manipulation. Risks associated with manual value manipulation can be reduced by automated systems. However, redundant filtration on its own will reduce risk of product contamination. If a single filter contains damage, installing a second filter in series will reduce the likelihood that both filters are not integral and will thereby provide additional assurance that the system will sterilize the drug product. In addition, as the second filter in the series is protected by the first filter, the likelihood of masking a defect in the second filter by particles or fouling of the filters during filtration is significantly decreased.

Filtered product:
Aside from filter considerations, process fluid characteristics must be considered as part of the risk assessment. It has been demonstrated that a filter must be significantly plugged in order to mask a defect[2]. Proper filter selection, product components, and proper sizing can all impact the propensity of process fluids to mask a defect. A risk assessment should include plugging data (pressure differentials for pump-driven systems or decreased flow in pressure-driven process filtrations) obtained from such sources as filterability trials, validation studies, or collected during process filtration. Little or no plugging during filtration will decrease the likelihood that minor damage or defect, if one is present, will be masked. A properly sized filtration system will reduce the likelihood of filter masking if a defect is present. The control and registration of the differential pressure for pump driven filtration (or flow decay for pressure-driven filtrations) will improve the detection of unexpected filter plugging or masking conditions.

A complete understanding of the potential bioburden in the fluid can help ascertain the risk of a damaged filter to the drug product. As per Annex 1, the bioburden concentration in the process fluid must be below 10 cfu/100 mL. A complete risk assessment should include a full understanding of the potential bioburden in the process fluid.

The point at which the filtration is performed in the process must also be considered. Masking of a filter at final fill poses a greater risk to the patient than at an intermediate step, such as buffer filtration.

If, based on the product composition and the propensity of plugging the filter, the fluid is determined to be high risk for masking, then a dedicated investigation (masking study) can be performed to evaluate the risk of filter masking for a given product solution during sterile filtration. Such a study could include filtering a sample of the process fluid through a damaged (laser drilled) disc. The filters can be integrity tested after filtration to see if the damage can still be detected. Evidence of masking will necessitate incorporating PUPSIT as part of the drug manufacturing process.

References

1. Commission E. *EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Annex 1: Manufacture of Sterile Medicinal Products*. (https://ec.europa.eu/health/documents/eudralex/vol-4_en).

2. Ferrante S, McBurnie L, Dixit M, Joseph B, Jornitz M. *Test Process and Results of Potential Masking of Sterilizing-Grade Filters*. PDA J Pharm Sci Technol 2020; 74(5):509-523. DOI: 10.5731/pdajpst.2019.011189.

Corporate Headquarters
Port Washington, NY, USA
+1.800.717.7255 toll free (USA)
+1.516.484.5400 phone

European Headquarters
Fribourg, Switzerland
+41 (0)26 350 53 00 phone

Asia-Pacific Headquarters
Singapore
+65 6389 6500 phone

Visit us on the Web at www.pall.com/biotech

Contact us at www.pall.com/contact

International Offices
Pall Corporation has offices and plants throughout the world in locations such as: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, India, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Poland, Puerto Rico, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, the United Kingdom, the United States, and Venezuela. Distributors in all major industrial areas of the world. To locate the Pall office or distributor nearest you, visit www. Pall.com/contact.

The information provided in this literature was reviewed for accuracy at the time of publication. Product data may be subject to change without notice. For current information consult your local Pall distributor or contact Pall directly.

Filtration. Separation. Solution℠