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Technical Regulatory Document

PUPSIT Risk Assessment

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EU GMP Annex 1: Manufacture of Sterile Medicinal Products (2022)[1] allows greater flexibility on the requirement for performing Pre-Use, Post Sterilization Integrity Testing (PUPSIT) based on risk assessment. The rationale for performing PUPSIT is two-fold: (i) to detect the presence of a non-integral filter after sterilization (which could occur from the sterilization process, transportation, handling or installation of the filter), and (ii) for situations where the process fluid, or impurities in the process fluid, could potentially mask a defect in the filter post-use. Such masking would increase the risk of the marginal damage not being detected by the post-use integrity test. This paper provides guidance for factors to consider when performing a PUPSIT risk assessment.

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-manufacturing 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 perform PUPSIT, nor will they accept the argument that it is too risky or too hard to do PUPSIT. A risk assessment submitted to the relevant regulatory authority for review and comment must be data-driven based on the individual process risks.

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" that should be considered for a 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:
Filter manufacturing involves multiple checkpoints during the manufacturing process to assure the filter is integral and meets QC specifications. This should include an integrity test as part of the release criteria for 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 this risk assessment.

Filter transportation, storage, unpacking and installation:
Filter manufacturers and end users must ensure that the filters are integral in their original packaging and 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 during storage and movement inside the end-user's facility. The use of an in-situ pre-use, pre-sterilization integrity test will detect damage 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 manufacturing process. The risk assessment should consider that 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. This is applicable to filter sterilization performed by both the filter manufacturer as well as the end-user.
- How the sterilization conditions are monitored and controlled.
- What actions are taken if the conditions are outside the sterilization 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 implementation of automated systems. However, redundant filtration on its own will reduce the 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, process fluid components, and proper sizing can all impact the propensity of process fluids to mask a defect. A risk assessment should include data to determine the likelihood of filter plugging (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 review of the differential pressure for pump driven filtration (or flow decay for pressure-driven filtrations) will improve the detection of unexpected filter plugging and/or potential defect 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 the Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container[3], the bioburden concentration in the process fluid must be below 10 cfu/100 mL. A complete risk assessment should include a full qualitative and quantitative 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) filter disc. The filter discs 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 (2022). (https://health.ec.europa.eu/system/files/2020-02/2020_annex1ps_sterile_medicinal_products_en_0.pdf).
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.
3. Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (2019), EMA/CHMP/CVMP/QWP/850374/2015