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PUPSIT:
CONSIDERATIONS IN IMPLEMENTATION

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Executive Summary

There has been significant debate over the years between regulatory agencies and the pharmaceutical industry regarding the advantages and disadvantages related to patient sterility risk with performing Pre-Use Post-Sterilization Integrity Testing (PUPSIT) of sterilizing-grade filters. This white paper will not add to this specific discussion; instead, the purpose of this document is to provide the reader with items to consider when determining how to implement PUPSIT in a robust manner for their particular application in instances where the decision is to perform PUPSIT.

Background

Regulatory Guidance Associated with PUPSIT

Section 113 of EU GMP Annex 1, Manufacture of Sterile Medicinal Products (November 2008) states for filtration of medicinal products which cannot be sterilised in their final container "the integrity of the sterilized 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." [1]

The word "sterilized" in this statement indicates that a pre-use integrity test should be performed on the filter after the filter has been sterilized but before the filter is used for the filtration of the process fluid being sterilized.

Understanding Integrity Testing of Filters

Integrity tests are performed on sterilizing grade filters to provide assurance that defects are not present in the filter or installation which could compromise the ability of the installed filter to retain microorganisms.

Integrity testing involves a thorough wetting of the filter media with a wetting fluid followed by the introduction of a pressurized test gas on the inlet (non-sterile side) of the filter while maintaining the outlet (sterile side) of the filter at a lower known pressure (typically atmospheric pressure). This creates differential pressure across the wetted filter media during the test. The rate at which the test gas passes through the wetted filter is calculated and used to determine whether or not the filter being tested is "integral," meaning the tested filter is capable of retaining microorganisms to the required level. *There are two common methods used to perform an integrity test:*

Bubble Point Method. The test is performed by slowly ramping up the differential pressure across the wetted filter media while monitoring the rate of change in the determined flowrate of the test gas passing through the filter media. This method determines the differential pressure at which the flow of test gas through the wetted media transitions from only diffusive flow to a combination of diffusive flow and bulk flow, an indication that liquid has been displaced from some of the pores in the filter media. The output generated from this method is the "bubble point pressure," the pressure at which the test gas starts to pass through the filter media via bulk flow. Although unique for each filter media, a typical bubble point integrity test acceptance criteria value for a 0.22 µm sterilizing grade filter might be 50 psig. Therefore, a bubble point integrity test value > 50 psig would be considered integral.

Diffusion Method. The test is performed at a predetermined differential pressure across the wetted filter media. This differential pressure is below the pressure required to displace liquid from the pores of the filter media (the bubble point); this test is typically performed at ~ 80% of the bubble point pressure for the filter media being tested. The passage of the test gas through the wetted filter media at this reduced differential pressure is controlled by the diffusive flow. The acceptance criteria using the diffusion integrity test method is dependent upon the surface area of the filter element (a larger surface area has a larger diffusion rate) and the test pressure. Although unique for each filter type and size, a typical diffusion integrity test acceptance criteria value for a 10" 0.22 µm sterilizing grade filter might be 13 mls/minute at a differential pressure of 40 psig. Therefore, a diffusion integrity test value < 13 mls/minute when tested at 40 psig would be considered integral.

Filter manufacturers perform bacterial retention studies on different lots of filter media with different integrity test values. With this data, the relationship between integrity test values and bacterial retention can be developed. Using this data, manufacturers generate bubble point and diffusion integrity test acceptance criteria for the filters. A satisfactory integrity test provides a high degree of assurance that liquid passing through the filter media will be free of viable microorganisms (sterile).

Note: For a more detailed understanding of the bubble point and diffusion integrity test methods see PDA Technical Report #TR-26[2].

Complicating Factors

At a high level, the integration of a pre-use integrity test on a filter after it has been sterilized but before it has been used to filter the process solution doesn't seem all that complicated. One has to wet the filter media with the wetting fluid, apply a differential pressure across the filter with a test gas, and determine the flowrate of test gas passing through the filter media to determine if the filter is integral. *Three factors which make this activity more complicated are as follows:*

1. The integrity test must be performed in manner that maintains the sterility of the filtration operation.
2. The integrity test must be performed in a manner that will not negatively impact the process fluid being filtered.
3. The integrity test should be performed in a robust reproducible manner that will limit the impact on the product yield and/or cycle time of the manufacturing operation.

Variations in the design of the equipment train associated with the filtration operation, process stream requirements, and manufacturing operational philosophies all have a significant impact on how PUPSIT is incorporated into a manufacturing process. Because of this, there is not a "one size fits all" solution for how to implement PUPSIT. Instead, there are several attributes related to the filtration operation that one must consider when determining the best means to implement PUSPIT.

Attributes to Consider in Pupsit Implementation

Selection of Wetting Fluid Used to Perform PUPSIT

Typically, either high purity water or the process solution being sterile filtered is used to wet the filter media in preparation for performing PUPSIT.

Advantages to using water as the wetting fluid:

- Filter supplier published integrity test acceptance criteria is based on water as the wetting fluid.
- High purity water is typically less expensive than the process fluids being filtered.
- In some processes, a flush of the filtration system may be required to remove leachables from the filtration assembly components. If this is required, it is possible that this flush can be performed with water as part of the filter wetting operation eliminating the need to use process fluid for this flush.

Disadvantages to using water as the wetting fluid:

- Upon completion of PUPSIT, the filter will remain wetted with water potentially causing product dilution of the process fluid.
- If water is removed via an air blow, this can take multiple hours impacting the step cycle time.
- Utility arrangement and control scheme required to produce a robust air blow process that results in a reproducible level of filter dryness can be challenging.

Advantages to using the process solution as the wetting fluid:

- Filtration operations which use the process solution as the wetting fluid are often less complicated than those which use water.

Disadvantages to using the process solution as the wetting fluid:

- Flushing with process fluid can waste valuable process fluid.
- If process fluid is used to wet the filter, testing must be performed to determine the process fluid wetted integrity test acceptance criteria.
- The process fluid wetted integrity test acceptance criterion is valid over a pre-determined temperature range (generally +/-4˚C). If there is not sufficient control over the temperature of the process fluid used to wet the filter during PUPSIT, it may be required to determine the process fluid wetted integrity test acceptance criteria at more than one temperature range and then use the measured temperature of the process fluid during wetting to determine the correct acceptance criteria.
- Any changes to the manufacturing process or process solution formulation must be evaluated to determine if a new process fluid wetted integrity test values are required.

Concerns with Dilution of the Process Fluid as a Result of PUPSIT

The impact of residual water on dilution of the process fluid is dependent upon the configuration of the process equipment train downstream of the sterilizing filter. As an example, if the discharge from the sterile filter supplies a 1 L hold reservoir that directly supplies a filling line the impact of the residual water from the filter on the dilution of the process stream would be much greater than if the filter discharges into a 1,000 L well-mixed hold tank

Starting Design of the Filtration Operation and Means of Sterilizing

Process design affects how PUPSIT is integrated. Examples include:

- Fully automated hard piped stainless-steel systems sterilized via steam in place (SIP).
- Semi-automated combination of stainless-steel components and disposable tubing sterilized via a combination of autoclave and SIP.
- Manual operation with mostly single-use disposable components with minimal stainless-steel components sterilized via a combination of gamma irradiation and autoclave.

Test Gas Used to Perform PUPSIT

The most common test gas used in integrity test operations is air. However, some process fluids are sensitive to oxygen, and therefore, alternative gasses, such as nitrogen are used.

Note :it is important to understand that changing the test gas will impact the acceptance criteria when performing an integrity test using the diffusion integrity test method.

Whether or not to perform Redundant Filtration

To minimize the business risk of losing a batch due to a post-use integrity test failure, some pharmaceutical manufacturers install a second redundant sterilizing filter in series before the final sterilizing filter. A post-use integrity test on the redundant filter is only required if the post-use integrity test of the final filter fails.

Performing a pre-use test integrity test on both sterilized filters each batch is complex. The requirement to perform PUPSIT on the two filters in series complicates the design of the filtration assembly significantly because it must be designed so the components between the redundant filter and the sterile filter remain sterile throughout the filtration operations (including PUPSIT).

Venting the Downstream Side of the Filter Being Tested during PUPSIT

Integrity testers generate and measure the pressure of the test gas supplied to the inlet of the filter being tested. It is common that the pressure supplied from the integrity tester is the same as the differential pressure across the filter because the downstream (sterile) side of the filter being tested is vented and therefore at atmospheric pressure. If the downstream side of the pressure is kept at a fixed pressure that is not atmospheric pressure, an offset value is entered to compensate for this.

As an example, assume that the filter being integrity tested is configured so the piping on the downstream side of the filter being tested turns and goes up in elevation 7 feet above the outlet of the filter before being discharged into a sterile vented vessel. If this discharge piping is filled with water during filter wetting process and the piping remains liquid-filled during the integrity test, the added liquid head will result in ~ 3 psig of backpressure on the filter being integrity tested. If this is not compensated for, the reported bubble point value will be three psig higher than the actual integrity test value.

There are a number of ways to vent the downstream side of the filters being integrity tested. *Common ways include the following:*

- Venting into an expandable bag with a vent filter on it.
- Venting into a rigid waste container with a vent filter on it.
- Venting into a downstream process fluid vessel with a vent filter on it.
- Venting through a sterilizing vent filter.

Note: specialized vent filter elements designed for PUPSIT are available that include both hydrophobic and hydrophilic filter media in a single filter element. An advantage to this type of sterilizing vent filter is that a single filter will allow the passage of both the liquid wetting fluid and the test gas during the integrity test.

Note: If a sterilizing vent filter is used, a post-use integrity test must also be performed on the vent filter to assure that the system remained sterile during the integrity test operation.

Process Fluid Consumption

Thorough wetting of the sterilizing filter media is important for robust, reproducible integrity test determination. As an example, for a 10" sterilizing grade filter element, a recommendation to supply a flush flowrate of 7 lpm for 5 minutes is common.

When process fluid is used as the wetting fluid, there are significant cost drivers to minimize the amount of process fluid directed to waste as a result of performing PUPSIT.

In some cases, this quantity is minimized by directing the process fluid used to wet the filter to the downstream hold vessel used for manufacturing instead of directing it to waste. When this is done, the quantity of process fluid transferred and the sterility of the downstream equipment is at risk until PUPSIT is completed successfully.

Another means to minimize the quantity of process fluid directed to waste involves modifying the wetting process to enable robust wetting of the filter media with a reduced volume of wetting fluid. *Some examples are:*

1. Positioning an in-line filter element so that the hollow core on the sterile side of the in-line filter element is directed upward during the wetting operation. This orientation allows the wetting fluid to easily displace the air in the hollow, which facilitates wetting of the filter media
2. With tee style filter housings, filling with wetting fluid, applying top pressure, and holding for a period reduces the quantity of fluid required for wetting.

Note: There are drivers to have the filter oriented in a different position (e.g., with the core of the filter directed downward) at other times during the filtration operation (e.g., during the execution of the integrity test and during an extended air blow if the filter is dried). If this is the case, the filter assembly is designed to be rotated.

Capacity/Cycle Time Considerations

Performing PUPSIT within the filtration operation requires additional steps. Potential additional tasks required and cycle time impact includes:

- **Performing the integrity test → 0.5 hours.** If the integrity test passes the first time, the test generally takes around 0.5 hours to set up and run.
- **Drying → 0.5-3 hours**. If water is used as the wetting fluid, the process may require that the filter be dried upon completion. Depending on the level of dryness required, drying could take up to 3 hours.
- **Venting of test gas from filter housing → 0.25 hours.** After performing the integrity test, the non-sterile side of the filter housing will be full of the test gas. This must be vented out of the housing so that the full surface area of the filter can be used during filtration.
- **Performing integrity test of any sterile vent filters associated with PUPSIT → 1 hour.** This testing is typically performed off-line so doesn't directly affect cycle time.

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References:

[1] Annex 1: Manufacture of Sterile Medicinal Products. Volume 4, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. European Commission: Brussels, Belgium, November 2008; http://ec.europa.eu/health/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf.

[2] Technical Report No. 26: Sterilizing Filtration of Liquids. Parenteral Drug Association: Bethesda, MD, 2008.

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