Pre-Use Post Sterilization Integrity Testing (PUPSIT)

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What is PUPSIT?

• Pre-Use Post-Sterilization Integrity Testing (PUPSIT)
Presentation main topic points

1. Current regulatory agency view point
2. Rational for performing PUPSIT
3. How to perform PUPSIT
4. Risk assessment for PUPSIT
1. Current regulatory agency viewpoint
In 2002 it was already in the TGA GMPs

AUSTRALIAN CODE OF GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS

16 August 2002

85. 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 during routine manufacturing from this 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.
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Annex 6

WHO good manufacturing practices for sterile pharmaceutical products

7.7 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. 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 these during routine manufacturing should be noted.
8.10 The filtration system should be designed to permit in-place integrity testing as a closed system prior to filtration. Care should be taken not to compromise the sterility of the filter.

9.5 The validated physical integrity test of a sterilizing filter shall be conducted after each use without disturbing the filter in its housing. Physical integrity testing of a sterilizing filter in situ should be conducted before use after sterilization where the design of the filtration system permits. Care should be taken not to compromise the sterility of the filter.
9.5.2 In addition to the validation of the filter type the integrity of each individual product filter used for routine production should be tested before and after use.

9.6 Vent Filters

9.6.1 It is important that the integrity of critical gas and air vent filters is confirmed immediately after the filling and if it fails, the disposition of the batch determined. In practice vent filters fail the integrity test more frequently than product filters as generally they are less robust and more sensitive to pressure differentials during steam sterilisation.
Regulatory requirements are not homogeneous worldwide (US FDA)

- FDA
  - 2004 Aseptic Processing Guidelines

After a filtration process is properly validated for a given product, process, and filter, it is important to ensure that identical filters (e.g., of identical polymer construction and pore size rating) are used in production runs. Sterilizing filters should be routinely discarded after processing of a single lot. However, in those instances when repeated use can be justified, the sterile filter validation should incorporate the maximum number of lots to be processed. Integrity testing of the filter(s) can be performed prior to processing, and should be routinely performed post-use. It is important that integrity testing be conducted after filtration to detect any filter leaks or perforations that might have occurred during the filtration. *Forward flow and bubble point* tests, when appropriately employed, are two integrity tests that can be used. A production filter’s integrity test specification should be consistent with data generated during bacterial retention validation studies.
Regulatory requirements are not homogeneous worldwide (India FDA)

7.2. Unit-sterilizers shall be double-ended with suitable inter-locking arrangements between the doors. The effectiveness of the sterilization process shall be established initially by biological inactivation studies using microbial spore indicators and then at least once a year by carrying out thermal mapping of the chamber. Various sterilization parameters shall be established based on these studies and documented. For membrane filters used for filtration, appropriate filter integrity tests that ensure sterilization shall be carried out before and after filtration.

10.5 Filtration (membrane).

(i) Solutions for Large Volume Parenterals shall be filtered through a non-fibre releasing, sterilizing grade cartridge/membrane filter of nominal pore size of 0.22 μ for aseptic filling whereas 0.45 μ porosity shall be used for terminally sterilized products.

(ii) A second filtration using another 0.22 μ sterilizing grade cartridge / membrane filter shall be performed immediately prior to filling. Process specifications shall indicate the maximum time during which a filtration system may be used with a view to precluding microbial build-up to levels that may affect the microbiological quality of the Large Volume Parenterals.

(iii) The integrity of the sterilized filter shall be verified and confirmed immediately after use by an appropriate method such as Bubble Point, Diffusive Flow or Pressure Hold Test.
Regulatory requirements are not homogeneous worldwide (CFDA)

6.3 “The integrity of the sterilizing grade filter should be verified by proper method **after use**. Results of these checks should be included in the batch record. An appropriate method includes bubble point, diffusive flow and pressure hold test”
Article 25 [Integrity test time] After the sterilization filter is used, the integrity of the filter must be checked and recorded immediately with appropriate method. Prior to use of the sterilization filter, a risk assessment shall be carried out to determine whether the integrity test is to be implemented before or after sterilization. When performing a pre-use integrity test after sterilization, measures are required to ensure sterility of the filter downstream. Commonly used integrity test methods include bubbling point test, diffusion flow/forward flow test or pressure maintenance test.
**Rationale for Recommendation**

Whereas a PUPSIT could provide added assurance of a filter's integrity throughout processing and reduce the risk of product loss, the risk of implementation of such a test must be assessed for each process and manufacturing site. A PUPSIT procedure may result in a higher risk to product quality. Integrity tests of filters after sterilization and pre-use in many cases may increase the actual risk of product contamination due to downstream manipulations and/or the addition of equipment into the downstream process, and this contamination might not be detected afterward. There is no scientific evidence that a non-integral filter pre-use will not be detected by a post-use integrity test.

However, a PUPSIT may provide the opportunity to detect non-integral filters after sterilization and prior to use, thus preventing potential product loss (in case a refiltration is not possible) and preventing introduction of contamination into an aseptic area.
2. Rational for performing PUPSIT
Rational for performing PUPSIT

1. Broken membrane due to sterilization?

- Yes, but this kind of failure would be detected by the post use testing.

- A hydrophilic membrane can typically withstand up to 25 SIP cycles ⇒ It is very unlikely that a validated and monitored within specification SIP disrupts the membrane.
2. A minor failure on the membrane could be masked by the clogging

➢ In theory possible, but extensive SSB trials have showed that even when clogging of the membrane takes place a broken membrane is still detected as such after filtration (publication submitted by M. Jornitz and M. Stering, publication date still TBD).

➢ In addition the last filtration step must not be clogging.

➢ The post use test must be performed immediately after use to avoid precipitation or denaturation of product.
3. How to perform PUPSIT
Pros:

➢ No real constraints in terms of resistance due to hard piping.

➢ Wetting liquid can be evacuated towards a large sterile vented vessel.

➢ The system can be pressurized after testing to maintain sterility.

➢ The installation may be automated.
Cons:

➢ The protective filters have to be tested. Should they be tested pre or post use of the product filter?

➢ Risk of dilution of drug product unless the filter is dried or the first volume is discarded.
PUPSIT - Stainless steel
PUPSIT - Single Use System (SUS)

- Pros:
  - The installation may be automated in the future = risk reduction
Cons:

- Difficult handling and complex setup = risk for operator mistakes.
- Pressure constraints.
- Limited wetting volume due to bag size, unless a hydrophilic filter is used.
- The protective filters have to be tested. Should they be tested pre- or post use of the product filter?
- Risk of dilution unless the first volume is discarded; the filter can hardly be dried.
Perhaps you want this...

- Redundant or serial sterile filtration
...but what you need is this!
The setup of PUPSIT also depends on the type of final filtration

There are several types of sterile filtration:

- Single step sterile filtration

- Single step sterile filtration with bioburden reduction (0.45 or 0.2 µm)
The setup of PUPSIT also depends on the type of final filtration

- Continued:
  - Redundant sterile filtration
  - Serial sterile filtration
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<thead>
<tr>
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<th>Single step</th>
<th>BioB. reduction</th>
<th>Redundant</th>
<th>Serial</th>
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<tr>
<td>Before</td>
<td>Only one</td>
<td>Just the sterilizing grade</td>
<td>Both filters</td>
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4. Risk assessment for PUPSIT
Key points to consider when risk assessing PUPSIT

- Risk of a "false pass" type result.
- Sterilisation type used for filters?
- False pass in Post Use test due to clogging of filter (main reason for PUPSIT)
- Loss of sterility on downstream
- The PUPSIT introduces more connections and pipe work/tubing
- Failed post use IT of 2 filters (in redundant filtration mode)
- Commercial risk
If you want to know more about PUPSIT risk assessment...
Take home message

• If you want to export to the EU or following the WHO guidelines you must perform PUPSIT. These regulatory requirements are unlikely to be changed in a near future.

• If you are following the India FDA guidelines you must perform FIT before filtration.
  ✓ If you are using stainless steel housings you can FIT before SIP
  ✓ If you are using SUS you have to perform PUPSIT

• Regardless if you are planning to perform PUPSIT or not it is strongly recommended to do a risk assessment e.g. a FMEA
  ✓ Risk mitigation from a general perspective
  ✓ Risk mitigation due to additional contamination risk when performing PUPSIT
ANY QUESTIONS?

Thank you for your attention