BIOTECH

Technical Regulatory Topic

USTR 3649

Pre-Use Post Sterilization Integrity Test - PUPSIT

What is the Position of the Regulatory Authorities on PUPSIT?

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Please note it is Pall's position that filters should be integrity tested as PUPSIT and this is covered in an additional document ‘USTR 3650 What is Pall’s Perspective on PUPSIT?’.

1 Position of Regulatory Authorities and Guidance on the Regulations

1.1 Europe

Pre-Use Post Sterilization Integrity Test (PUPSIT) has been recommended in Europe for approximately 20 years and is recommended again in the 2022 version of the European Union Good Manufacturing Practices (EU-GMP) guidelines (Vol 4 Annex 1 [1], paragraph 8.87).

Paragraph 8.87 states:

> "8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilising grade filter that is used to sterilise a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk on a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to:
>
> i. In depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized.
>
> ii. In depth knowledge and control of the supply chain to include:
> - Contract sterilisation facilities.
> - Defined transport mechanisms.
> - Packaging of the sterilised filter, to prevent damage to the filter during transportation and storage.
>
> iii. In depth process knowledge such as:
> - The specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity-testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test.
> - Pre-filtration and processing steps, prior to the final sterilising grade filter, which would remove particle burden and clarify the product prior to the sterile filtration."

Back in 2012 the European Medicines Agency (EMA) GMP/ Good Distribution Practice (GDP) Inspectors Working Group provided additional insight into this recommendation on the EMA website [2]. Under the 'Questions and Answers' section of the EMA website, the working group responded to the question "how should the integrity of sterilising filters be verified?" as follows:

> "The filter-sterilisation process may be physically stressful for the filter. For example, high temperatures during the process may cause the filter to distort, potentially leading to fluid pathways that allow the passage of particles greater than 0.2 µm in size. The performance of a filter can improve with use, as particles begin to block individual pathways and remove larger pathways that smaller particles could successfully navigate. For these reasons, filters should be tested both before use but after sterilization and again after use."
>
> "Furthermore, testing should be performed *in situ* in order to verify the integrity of the filter complete with its housing."

Since then when the draft of the Annex 1 published in 2022 was in discussion, additional concerns were raised about the potential for filter flaw masking. Therefore, while testing the filter before sterilization is acceptable, going forward it may no longer be acceptable as the only pre-use integrity test.

This recommendation is effective for any products or manufacturing processes that are registered or changed after this regulation was implemented. It applies to companies that either manufacture in Europe, or to companies that import their products into Europe.

It is worth noting, that companies in other countries that are members of Pharmaceutical Inspection Co-Operation Scheme (PIC/S) will also be expected to do PUPSIT, or have a suitable risk assessment performed if not (e.g. Australia, Canada). Some PIC/S inspectors have been increasingly expressing expectations for companies to employ this testing procedure in other countries, although it is not a requirement in these countries.

1.2 USA

The regulatory authority in the United States, the Food and Drug Administration (FDA), current Good Manufacturing Practice (cGMP) regulations, Code of Federal Regulations (CFR) 21 Parts 210 [3] and 211 [4] (respectively titled: Current Good Manufacturing Practice In Manufacturing, Processing, Packing, Or Holding Of Drugs; General and Current Good Manufacturing Practice For Finished Pharmaceuticals) do not specify requirements for filters with respect to pre-use testing, either before or after sterilization.

However, in the current version of the FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – cGMP, Chapter IX, Section B 'Filtration Efficacy' (2004) [5] states:

> "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 appropriate 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."

This means that integrity testing prior to use is recommended but not required, but is mandatory to be performed post filtration, proposing the importance and value of this practice to detect any leaks or perforations resulting from the filtration process.

1.3 Japan

The Japanese regulatory authority, Pharmaceuticals and Medical Devices Agency (PMDA), gives integrity testing information in their Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing Chapter 17.1.4 Routine Procedures, Section 3 (2011):

> "3) Filter integrity test - Filters should be verified for integrity after filtration processing (after use of filters) without disassembling the entire filter. Integrity should also be confirmed prior to the filtration process (before use of filters), as appropriate, by evaluating potential risks inherent to the process."

While this is not a legal requirement, it is a recommendation that filters be tested post-use in the same filter housing. The filters should also be tested pre-use, after the risks generated from a more complex filtration system setup are balanced with the benefits that could be achieved in terms of increased process reliability.

1.4 China

The National Medical Products Administration (NMPA), formerly the Chinese FDA, published the Sterilization and Filtration Technology Application Guide in 2018 [6] with an update in terms of PUPSIT requirements. Chapter 6-Use of Sterile Filters and Systems, Section 6.3-Integrity Testing states:

> "After using the sterilize filter, its integrity must be tested and recorded immediately with appropriate methods. Before using the sterilize filter, a risk assessment should be conducted to determine whether the integrity test should be carried out and whether it should be carried out before or after the sterilization. When conducting the integrity test after sterilization and before use, measures need to be taken to ensure the sterility of the downstream of the filter."

Additionally, Chapter 4-Filtration Process and System Design, Section 4.2-Filtration System Design states:

> "If the disposable filtration system is used and the integrity test or pre-washing before use is required, the following factors should be considered in the design: the pressure resistance of the upstream connecting

pipeline, the sterility of the downstream, and the downstream can provide enough space (such as installing a sterilizing barrier filter or a corresponding volume of sterile bag) for exhaust and drainage. If a disposable sterile connection device is used, it shall be documented that there is no risk of microbial contamination."

And Chapter 6- Use of Sterile Filters and Systems, Section 6.6-Disposable Filtration System states :

"When deciding whether to conduct integrity test before using the disposable filtration system, risk assessment should be conducted based on the following factors (but not limited to the following factors):

- Assess the impact of filter integrity failure, including the possibility of introducing non-sterile products into sterile areas.
- Assess the risk of pollution caused by additional components and operations.
- Potential damage detected.
- The possibility of damaging the downstream sterility of the filter during the integrity test before use and after sterilization.
- Whether the wetting liquid will dilute the product or affect the product quality attribute.
- Impact of additional time on time-sensitive process."

2 References

[1] European Commission, “The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use - Annex 1 Manufacture of Sterile Medicinal Products,” 2022. [Online]. Available: https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf.

[2] European Medicines Agency, “Guidance on good manufacturing practice and good distribution practice: Questions and answers,” [Online]. Available: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers#eu-gmp-guide-annexes:-supplementary-requirements:-annex-1:-manufact. [Accessed 04 January 2023].

[3] Code of Federal Regulations, “Part 210-Current Good Manufacturing Practice In Manufacturing, Processing, Packing, or Holding of Drugs; General,” [Online]. Available: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-210#_top.

[4] Code of Federal Regulations, “Part 211- Current Good Manufacturing Practice for Finished harmaceuticals,” [Online]. Available: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-211#_top.

[5] U.S. Food & Drug Administration, “Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice- Guidance for Industry,” October 2004. [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice.

[6] National Medical Products Administration, “Sterilization and Filtration Technology Application Guide,” 2018. [Online]. Available: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20180911170301439.html.

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