PALL Biotech

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 'What is Pall's position on PUPSIT?'.

1 Position of Regulatory Authorities and Guidance on the Regulations

1.1 Europe

Pre-Use Post Sterilization Integrity Test (PUPSIT) is recommended in Europe, as indicated in the 2009 of the EU-GMP guidelines (Vol 4 Annex 1, paragraph 113 for sterilizing grade filters used for aseptic manufacturing). Paragraph 113 states:

> *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 from this during routine manufacturing 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.*

The European Medicines Agency (EMA) GMP/GDP Inspectors Working Group has provided additional insight into this recommendation on the EMA website[1]. Under the 'Questions and answers' section of the EMA website, the working group has 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.*

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 will be 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.

1.2 USA

The regulatory authority in the United States, the Food and Drug Administration (FDA), current Good Manufacturing Practice (GMP) regulations, Code of Federal Regulations (CFR) 21 Parts 210[2] and 211[3] (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)[4] 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 both integrity testing prior to use and post filtration is recommended but not required, proposing the importance and value of this practice to detect any leaks or perforations resulting during the filtration process.

1.3 Japan

The Japanese regulatory authority, Pharmaceuticals and Medical Devices Agency (PMDA), gives integrity testing information in their Guidance for Industry – Sterile Drug Products Produced 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, and should also be tested pre-use, if appropriate.

1.4 China

The National Medical Products Administration, formerly the Chinese FDA, does not specify any requirements for pre-use integrity testing, including PUPSIT, in the Good Manufacturing Practice for Drugs (2010 Revision; MOH Decree No. 79)[5].

2 References

1. 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:-manufacture-of-sterile-medicinal-products-section

2. https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=fe9f19ce57a95b93ef219876bace9a16&ty=HTML&h=L&mc=true&r=PART&n=pt21.4.210#_top

3. https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=1aabf7933f9119add40df9d196a5bd7b&ty=HTML&h=L&mc=true&r=PART&n=pt21.4.211#_top

4. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice

5. http://subsites.chinadaily.com.cn/nmpa/2019-07/25/c_390613.htm

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