EJPPS – European Journal of Parenteral and Pharmaceutical Sciences Volume 25 Issue 1
https://www.ejpps.online/
https://doi.org/10.37521/ejpps

Opinion Paper

Pupsit and justifications to do otherwise

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PUPSIT - the debate is still ongoing

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The pre-use post sterilization integrity testing (PUPSIT) the wording in the new draft of Annex1 is significantly different than the current Annex 1 2008 wording. And again, the draft 2020 version is different to both the 2008 issued and 2017 draft.

> Annex 1 2008 - "*113. 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*."[1]

From 1998 to 2017, because of the wording in Annex 1, it was easy to genuinely feel compliant with regard to sterile filter integrity testing requirements when testing the filters off-line before and after use. In the case of gamma irradiated single use filters, sterile's manufacturers could consider themselves compliant in taking the filter manufacturers certification with regard to pre-use testing.

The MHRA state that on line PUPSIT has been their expectation since 1998. However, sterile's manufacturers could not be expected to understand this from the 2008 Annex 1 text as it was not this definitive. The MHRA expectation clarity pre 2017 was obtained from website Q&A, conferences, 1:1 from the inspector either in or outside an inspection. Once made clear there is no debate, regardless of what is written in Annex 1. A manufacturer must comply with the expectations of the competent authority who issues the MIA and inspects their site.

Then Annex 1 Draft Dec 2017 was issued.

> Annex 1 Draft Dec 2017 "*8.84 The integrity of the sterilized filter assembly should be verified by testing before use, in case of damage and loss of integrity caused by processing, and should be verified by on line testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test. It is recognised that for small batch sizes, this may not be possible; in these cases, an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved. There should be written integrity test methods, including acceptance criteria, and failure investigation procedures and justified conditions under which the filter integrity test can be repeated. Results of the integrity tests (including failed and repeated tests) should be included in the batch record."*

The 2017 Annex 1 (8.84) draft made it quite clear that PUPSIT was required and this integrity testing was to be on line. Anything else was possible with justification. I like this *"just do it or justify otherwise"* approach. It reduces time wasting internal debates in the manufacturing companies.

The unambiguous clarity of regulations is not limited to EUGMP Annex 1 2017:

ISO 13408-2 Aseptic Processing of health care products Part 2: Filtration

8.10 "The filtration system should be designed to permit in place integrity testing as a closed system prior to filtration

9.5 "Physical Testing of a sterilising filter in situ should be conducted before use after sterilisation where the design of the filtration system permits"

Then Annex 1 Draft Dec 2019 was issued.

Annex 1 Draft Feb 2020: *"8.88 The integrity of the sterilized filter assembly should be verified by integrity testing before use, to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. 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 pre-use post sterilization integrity testing (PUPSIT) may not always be possible after sterilization 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 of non-sterility.*

The 2020 Annex 1 (8.88) draft seems to have stepped a bit back to 2008. The key difference is the word on-line – the new draft allows for the filter and housing be removed to a separate place for testing as a norm negating the stated requirement to risk assess this. It makes sense that the norm testing should be performed in situ in order to verify the integrity of the filter complete with its housing and line connections.

What complicates the issue is that the FDA, while part of the PICs team that issued Annex 1 draft 2017, has no requirement for pre-use, on-line testing. Recently a PDA group[2] has been set up a collaboration to:

"The overall objective of this collaboration is to perform a series of integrated and interdependent workstreams that will provide industry and regulators alike with information that can be used to make informed decisions on how best to control and prevent sterilizing grade filter failures or improve detection of failures. It is not anticipated that any individual workstream will result in definitive positions, but rather that the output of all workstreams are needed to form a valid, scientific position".

There are few, if any, evidence-based publications about situations that will create filter "holes" >0.2 µm. However, there are many reports of gamma irradiation damage, filter flaw masking, transport damage and assembly damage. These reports state that filters can change their efficacy during the filtration process via blockage hence the before and after integrity test. I have no doubt that these reports are true, but these reports have not been turned into evidence-based publications. It is because of this lack of public evidence that there is disagreement between competent authorities about PUPSIT being mandatory.

Because of the PUPSIT clarification seen in Annex 1 (Nov 2017 draft) the filter manufacturers have done a lot of work on PUPSIT configurations. All filter suppliers can now supply or will co-develop closed systems. This makes PUPSIT possible for most processes making it difficult to justify the use of any other system. GMP requires that pharmaceutical manufacturers keep pace with technology and best practice, given that this ability to test is readily available, it makes no sense to back away from this position.

It is the sterile manufacturers that are accountable for the sterility of their products and they must manufacture products in accordance with the regulatory interpretation of the competent authority issuing their MIA. For the MHRA the approach has been consistent since 1998. Other competent authorities, even those within PICs, are less consistent.

Sources

1. Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 1 Manufacture of Sterile Medicinal Products 2008
2. PUPSIT and the Annex 1 Revision. Tina Morris, PDA, Maik Jornitz, G-Con, Gabriele Gori, GSK, and Hal Baseman, ValSource | Aug 29, 2019

[1] Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 1 Manufacture of Sterile Medicinal Products.2008
[2] PUPSIT and the Annex 1 Revision. Tina Morris, PDA, Maik Jornitz, G-Con, Gabriele Gori, GSK, and Hal Baseman, ValSource | Aug 29, 2019