Application Note

Scale-down Virus Filter Integrity Testing
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>3</td>
</tr>
<tr>
<td>Summary</td>
<td>3</td>
</tr>
<tr>
<td>Definitions and Purpose of Filter Installation or Integrity Testing</td>
<td>3</td>
</tr>
<tr>
<td>Process Filter Integrity Testing</td>
<td>4</td>
</tr>
<tr>
<td>Scale-down Filter Testing</td>
<td>4</td>
</tr>
<tr>
<td>Parenteral Drug Association (PDA) Recommendations</td>
<td>5</td>
</tr>
<tr>
<td>Conclusion</td>
<td>5</td>
</tr>
<tr>
<td>References</td>
<td>5</td>
</tr>
</tbody>
</table>
Purpose

The purpose of this document is to address questions regarding the need for installation testing or integrity testing of scaled-down virus filters (disc assemblies, Minidisc capsules) used in virus spike retention studies, particularly after virus challenge (i.e. “post use”) it provides a scientific rationale as to why correlated integrity tests are not applicable to laboratory scale-down filter models used in virus spike challenge studies conducted to validate virus filter use in GMP production.

Summary

There are presently no documented regulatory GMP requirements specific to the use or testing of virus-retentive filters in biopharmaceutical manufacturing. Nevertheless, GMP requirements for integrity testing of bacteria-retentive sterilizing filters are widely applied also to virus filters and are expected under general GMP operation. These expectations include conducting a physical integrity test of production scale virus filter installations after use in manufacturing of an active pharmaceutical ingredient (API), intermediate or final drug product. In these production applications, the physical integrity test should be correlated to virus retention performance (i.e. log reduction factor). This correlation serves as a surrogate for actual virus challenge of the production filter in order to confirm filter performance (viral clearance) according to validated process claims for each production batch. Correlation of integrity test parameters for Pall production scale virus filters (Ultipor® VF grades DV50 and DV20 and Pegasus™ grade ULV6) are documented in the respective Pall filter validation guides.¹

Qualification and evaluation or validation of pharmaceutical manufacturing equipment, e.g. virus filters are required under GMP process validation. Unlike in GMP manufacturing, qualification or evaluation/validation testing involves actual challenge of scaled-down virus filters (disc assemblies, Minidisc capsules) using model viruses spiked into the process fluid. Spiked fluids are passed through scaled down virus filters under simulated process conditions to assess filter retention capability and predict filter performance in production. Actual viral clearance (log reduction factor) by the scaled-down filter sample is determined by analysis of influent and effluent viral titers, either by direct infectivity assay, or where qualified as suitable, by alternate tests such as PCR.

Before starting a virus spike challenge test on a scaled-down virus filter, the installation integrity of the unit should be confirmed according to the manufacturer’s specification (a water wet pressure pressure hold test in the case of Pall Ultipor VF and Pegasus virus filters). This serves to avoid invalid results from non-integral filter assemblies. After completion of the virus spike challenge of the scaled-down virus filter however, performing a virus retention-correlated integrity test, or even an installation test of the scaled-down filter is not required for several reasons. First, integrity testing is an indirect physical test performed before (or most importantly after) filter use in GMP manufacturing because an actual microbial challenge (bacterial or viral) is counter-indicated. Second, during qualification/validation testing of the scaled-down virus filter, an actual microbial challenge (virus spike) is performed. Integrity tests, as an indirect measure, are correlated to microbial (in this case viral) clearance by the filter but are not an actual demonstration of clearance. Where actual microbial (e.g. viral) clearance data is generated in qualification or evaluation/validation studies, it supersedes data from an indirect physical test and is itself the basis for any microbial clearance claim.

Definitions and Purpose of Filter Installation or Integrity Testing

It is important to recognize the two different kinds of filter “integrity” tests applied to membrane filter assemblies. An “installation” test (i.e. an “installation integrity test”) is one that confirms filter grade, proper assembly and absence of gross leaks and defects. In contrast, an “integrity” test (i.e. a “correlated integrity test”) provides all that, plus is supported with data relating its’ test parameters and limit value to specified filter performance claims (in this case, expected minimum titer reduction of a model virus or bacteriophage under defined challenge test conditions). Any filter “integrity” test, e.g. “bubble point”-type, Forward Flow “diffusion”-type, Pressure Hold or Decay-type (also “diffusion” based) or particle challenge-type test, can be either an “installation integrity” test or a “correlated integrity” test depending on the availability of appropriate correlated performance data and the consequent ability of the test to predict specified microbial retention performance. Air or liquid flow rate (permeability)-based tests are generally “installation” tests only.
It is also important to recognize the purpose of either installation or correlated integrity tests as applied in GMP production. Regulatory GMP guidelines for manufacture of drug and biological products that are sterilized by filtration require manufacturers to conduct a post-use “integrity” test of the sterilizing process filters that is correlated to bacterial retention, in order to confirm process filtration performance (i.e. sterilization). To varying degrees, regulatory GMP guidelines also recommend conducting some type of physical integrity test prior to filter use. While there are no comparable regulatory guidelines that address integrity testing of virus filters, it is commonly presumed by regulators and industry that a similar practice would apply.

**Process Filter Integrity Testing**

The ultimate “integrity” test of a production filter that would be predictive of its’ sterilizing or viral clearance capability is to challenge that filter with a high level of bacteria or viruses suspended in the actual product fluid, confirming its’ retentive properties, and then using that same filter for drug product filtration. This is obviously neither practical nor acceptable in a GMP production environment for many reasons, including that it would leave the process equipment and filter highly contaminated, with the filter close to plugging before it can be used.

In lieu of such testing therefore, a non-destructive physical air/liquid displacement test (e.g. “bubble point”-type) or diffusion test (e.g. Forward Flow/Diffusion or Pressure Hold/Decay) is applied from the upstream side of the process filter to enable either pre-use or post-use installation or correlated integrity testing. Alternatively, a microbial or particle challenge test can be applied post-use. Such destructive tests are not applicable to pre-use testing due to their adverse impact on the filter and requirement to recover samples of the filter effluent, which can compromise downstream sterility in sterile operations. Application of a post-use microbial or particle-based integrity tests may also require cleaning of the used production filter prior to post-use testing to properly assess the integrity of the filter at the beginning of the process.

Correlated integrity test parameters for process scale filters are appropriately developed by direct microbial challenge and correlation to integrity test values of process scale filter modules or cartridges or sufficiently large scale models that still incorporate process scale module or cartridge manufacturing conditions.

**Scale-down Filter Testing**

Given that performance of microbially retentive process scale filters cannot be validated by direct microbial challenge with drug product in situ, it is recommended practice for the purposes of filter qualification and process validation to conduct laboratory evaluation/validation studies on scaled-down filter assemblies, whereby microbial spike challenges are conducted in actual drug product under simulated model process conditions. Such scaled-down filter assemblies must incorporate the same membrane grade as the corresponding production scale process filters. Once microbial retention by the filter membrane grade is qualified under actual drug product and process conditions, conducting a correlated “integrity test” on the process scale filter installation in production (correlated to the filter supplier’s standard challenge condition) is considered sufficient to predict or confirm validated retention performance of the production filter assembly.

With regard to the scaled-down filter units, a pre-use installation test is considered prudent to assure proper assembly and freedom of gross leaks or defects prior to conducting the microbial challenge test. For virus filters, such tests are typically Pressure Hold-type tests and/or Permeability tests (water or buffer flow rate at specified pressure differential). A pre-challenge correlated integrity test may also be applied if available, but is unnecessary and not required because it is an indirect substitute for the actual microbial challenge, which is conducted subsequently. Similarly, there is no need for a post-challenge correlated integrity test because the microbial challenge results themselves define the filter’s performance, not an indirect physical test.

Furthermore, correlated physical integrity tests for production-scale sterilizing and virus filters such as Forward Flow/Diffusion and Pressure Hold/Decay tests are difficult to scale down to small area filters because the test value becomes increasingly low and difficult to determine accurately. While this limitation is not seen with microbial or particulate retention-type integrity tests, those tests are less preferred because they are destructive and not applicable to pre-use testing, require cleaning of the filter prior to post-use application, cannot be conducted in situ at GMP production scale without contaminating process equipment and are cumbersome and expensive to conduct in situ or off-line at production scale.
Laboratory scale studies conducted to qualify process equipment and validate their use in a GMP production environment do fall under GMP regulation, however there is no requirement to conduct an indirect integrity test of laboratory scale-down filters challenged for evaluation/validation purposes, precisely because the scale down filters are subject to the actual microbial challenge that supersedes the need for an indirect physical integrity test.

**Parenteral Drug Association (PDA) Recommendations**

This topic was addressed by the ad hoc PDA Virus Filtration Committee and incorporated into PDA Technical Report (TR) 41 “Virus Filtration” (Revised 2008). Section 6.5.2 on Integrity Testing in Development states:

“Because of the inaccuracy associated with the very small signal obtained when performing integrity tests on small-scale devices, it is common for a true, scaled integrity test value not to be required in one’s documentation of filter comparability. (Integrity testing at manufacturing-scale level is addressed in Section 7.) For scale-down devices, installation testing alternatives include a pressure hold test, in which no pressure decay is measurable over the time of the test, or a bubble point test, in which visually detected air flow through the filter indicates a defective filter unit. As an additional check on the filter, it may be useful to perform a permeability measurement with clean water. Since permeability normalizes for surface area, the scaled down device permeability may be directly compared to the range expected of the process-scale device. If the small scale device permeability falls outside of this range, the filter test support apparatus should be checked for problems, and the filter may need to be replaced or more fully wetted before use. Lastly, one may check filter documentation to determine if the scaled-down filter is intended for use as a model for the process-scale filter.”

**Conclusion**

Physical integrity tests of production scale filters used in manufacturing are a GMP requirement that serves as an indirect substitute for actual microbial challenge in order to assess microbial retention capability for the filter’s use with each production batch. In laboratory studies conducted on scaled-down filter assemblies to qualify or evaluate/validate filter performance, a pre-use installation test is prudent to confirm assembly integrity, however, availability of direct microbial challenge retention results post-challenge supersedes the need to conduct indirect correlated integrity tests after microbial challenge (post-use) and is not a GMP requirement.

**References**

1. Pall Filter Validation Guides for Ultipor VF grades DV50 and DV20 and Pegasus grade ULV6 filters (Contact Pall for appropriate guide for selected filter).
New York – United States
800.717.7255 toll free (USA)
516.484.5400 phone
516.801.9548 fax
biotech@pall.com e-mail

Portsmouth – Europe
+44 (0)23 9230 3303 phone
+44 (0)23 9230 2506 fax
BioPharmUK@europe.pall.com e-mail

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