White Paper

Title: **Filter Validation Guidelines**

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Purpose

The purpose of this document is to provide general guidelines for validating a filter to be used with a particular dissolution method.

Definition(s)

Control is a sample of known concentration. It should include all excipients present in a normal sample.

Standard is a solution of known concentration of the API. The solution should not include any excipients.

Sample is a mixture collected from a dissolution vessel. The concentration of a sample is initially unknown and must be calculated using a standard.

In-Line Syringe Filter refers to filters typically installed on the end of a syringe using a luer-lock fitting.

(**Sample Probe) Tip Filter** refers to filters that are placed on the tips of sample probes.

Detail

All dissolution methods require filtration. Filtration removes particles from the media and stops the dissolution process in the filtered sample. This makes choosing a filter a critical part of developing a dissolution method. Showing scientific justification for use of a given filter is a requirement for GLP/GMP.

A filter validation process should look at the following:

- **Efficiency** – Does the filter remove enough particles to prevent further dissolution of the sample?
- **Leachability** – Does the filter add any components to the sample as it is filtered?

- **Rinse Volume Test/Adsorption** – How much of a rinse does the filter need to ensure the sample is the same concentration as what is present in the vessel?

  If an automated system is used, and filters will be reused for samples, the following should also be evaluated:

- **Rinse Volume** – How much media is required to rinse the filter in order to ensure the sample is representative of what is in the dissolution vessel?
- **Reuse** – How many times can a filter be reused without it clogging or affecting the concentration of the sample?
- **Tip Filter** – Should a tip filter be used in order to preserve the life of the in-line filter? The tip filter must be validated with the in-line filter.

Each step of the process should be documented so that justification for each point can be shown. When performing testing, it is recommended to perform evaluations in triplicate (three times for each filter type).

1. **Choose a filter material:** The filter material should be chemically compatible with the API, excipients, and dissolution media. At the beginning of the process it is best to pick multiple candidates.
2. **Choose a pore size:** Pore size should be based largely on the requirements of the analytical method.
   a. UV spectrophotometry usually requires at least 10 micron filters.
   b. HPLC typically requires 0.45 micron filters to avoid blocking or damaging the column.
   c. UHPLC (UPLC™) typically requires 0.2 micron filters to avoid damage to the columns.
3. **Select at least 2 manufacturers:** Selecting more than 1 manufacturer allows for two advantages.

a. If there is a difference in the filter performance, it will show which manufacturer is superior for the method.

b. If the filter performance is the same, then it provides a backup filter to be used in case there is a shortage of the primary filter.

Some filter manufacturers offer membrane filters with a built-in pre-filter. The pre-filter is typically a material with a larger pore size (5 micron) which can filter out larger particles without becoming clogged. This allows the membrane filter to be used primarily for smaller particles, which in turn extends filter life. Use of a tip filter on the end of a sample probe would fulfill the same function as a built-in pre-filter; however, it should be validated with the in-line syringe filters.

4. **Efficiency Test:** This test should ensure that the dissolution process is being stopped by removing all the particles from the sample. The test should be run with a control at roughly 50% dissolved.

a. Pull 3 aliquots as close to simultaneous as possible.

b. Filter each of the aliquots as soon as they are pulled.

c. Analyze the first aliquot immediately.

d. Ultrasonicate the second aliquot for 5-10 minutes to attempt to dissolve any particles the filter did not remove. Then analyze the second aliquot.

a. Ultrasonicate the third aliquot for 10-15 min to attempt to dissolve any particles the filter did not remove. Then analyze the third aliquot.

	Pass	Fail
Efficiency Test	Each aliquot shows a nearly identical concentration.	The second and/or third aliquot(s) show significantly higher concentrations than the

		first.

5. **Leachability Test:** This test should help ensure the filter is not adding material to the sample, which may interfere with the results.
   a. Prepare a suitable volume of dissolution media for filtering.
   b. Collect 3 separate aliquots of the dissolution media each using a different filter of the same type. These will be your filtered blank samples.
   c. Prepare a standard using the dissolution media.
   d. Collect 3 separate aliquots of the standard, each using a different filter of the same type.
   e. Analyze the 3 filtered blanks, and 3 filtered standards against one unfiltered blank and one unfiltered standard.

Leachability Test	Pass	Fail
Blank	The concentration of the unfiltered blank is nearly identical to the filtered blanks.	The filtered blanks show a significantly higher reading than the unfiltered blank.
Standard	The concentration of the unfiltered standard is nearly identical to the filtered standards.	The filtered standard shows a higher reading than the unfiltered standard.

6. **Rinse Volume Test:** While the leachability test is done to ensure that nothing is being added to the sample from the filter, the rinse volume test is to ensure that the process of filtering does not affect the concentration of the sample. Filters often must be rinsed with a minimum volume in order to saturate the membrane with the API.

NOTE: This test also fulfills the adsorption test of the filter validation.

a. Prepare a standard at lowest expected concentration for the dissolution test (e.g., the first sample time point).

b. Manual Sampling

   i. Using a 10 mL or larger syringe, fill the syringe with the standard.

   ii. Dispense 1 mL aliquots into test tubes or vials for analysis.

   iii. Analyze each aliquot. When the results match the concentration of the standard, the minimum rinse volume for the filter has been determined.

c. Automated Sampling

   i. Determine the empty tubing volume.

   ii. Prime the lines with a blank solution (20 mL for most samplers).

   iii. Wipe off probes and move them to the standard solution.

   iv. Rinse with the volume determined in step 6.c.i.

   v. Collect a sample.

   vi. Wipe off the probes and move them to the blank solution.

   vii. Prime the lines with blank solution again to remove the standard from the lines.

   viii. Repeat steps 6ciii through 6.c.vii, increasing the volume in step 6.c.iv by 1 mL each time.

   ix. Analyze each aliquot. When the results match the concentration of the standard, the minimum rinse volume for the filter and sampler has been determined.

	Pass	Fail
Rinse Volume Test	The concentration of the filtered samples is nearly identical to the concentration of the standard.	The concentration of the filtered samples is significantly below the concentration of the standard.

7. **Filter Reuse (Stage 1):** Reusing filters is an excellent way to cut costs; however, the user must ensure that the reuse has been scientifically shown not to affect dissolution results.

   Warning: It is not permissible to reuse filters for different vessels or different dissolution testers. Reused filters should be reused on the same tester and vessel. Never reuse a filter for multiple dissolution tests.

   a. The first stage of testing filter reuse is to ensure that sample concentrations are not affected if a filter is used multiple times.

   b. Prepare 3 standards at 10%, 50%, and 100% concentrations.

   c. Using the same filter for each standard, collect an aliquot of the 10%, 50%, and 100% standards. Ensure the rinse volume is adequate by performing the rinse volume test (step 6) prior to running this test.

   d. Analyze each aliquot and ensure the results match with the standard.

Filter Reuse (Stage 1)	Pass	Fail
10%	The concentration of the filtered samples is nearly identical to the concentration of the standard.	The concentration is significantly lower than the standard. Recheck rinse volume.
50%	The concentration of the filtered samples is nearly identical to the concentration of the standard.	The concentration is significantly lower than the standard. Recheck rinse volume.
100%	The concentration of the filtered samples is nearly identical to the concentration of the standard.	The concentration is significantly lower than the standard. Recheck rinse volume.

8. **Filter Reuse (Stage 2):** Assuming the filter passed the first stage of the reuse test, the next test is a mechanical check to see when a filter will clog due to particles.

   NOTE: Tip filters will remove any larger particles before they can reach the filter. In many cases, this will greatly extend the mechanical life of the filter. Tip filters should be validated as part of the same process as the in-line filters.

   a. Prepare a dissolved sample in a dissolution vessel at 100% dissolved.

   b. Pump the unfiltered sample through a filter until the filter clogs. It is recommended to evaluate 6-8 filters to account for any manufacturing differences.

i. If sampling manually, when the syringe becomes twice as hard to push through the filter, the filter should be considered clogged. Refill the syringe as necessary while testing.

ii. Using the transfer command of the AutoPlus, observe the system until the system clogs. This can be determined by listening for a rapid clicking as the valves are forced open by the back pressure in the system.

c. Determine the lowest volume that caused a filter to clog. It is recommended to subtract 20% from the lowest volume as a measure for how much sample can pass through a filter safely.

i. If performing validation on an automated system, calculate the total volume pumped through the filter at each sample point (rinse w/ filter + sample collection) to determine how many times the filter can be reused.

d. Repeat step 8.b with the reuse specification determined from step 8.c. The test should complete without any need to replace filters. If a filter clogs, reduce the number of times it is reused and repeat step 8.c.

	Pass	Fail
Filter Reuse (Stage 2)	The test is completed reusing the filters the number of times determined in step 8.c.	A filter clogs prior to the point determined in step 8c. Repeat the evaluation with a lower number of reuses or lower volume of filtered material.

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Conclusions

As with any stage of dissolution method development, filter validation should be fully documented and justified. Each step in the process should show why a filter was chosen and why other filters were omitted.

Recommended Reading

- USP Chapter <1092> The Dissolution Procedure: Development and Validation
- Hanson Research Technical Bulletin 1001

Technical Support

If additional technical support is required, please contact Hanson Research at www.hansonresearch.com/tsr.htm or email techsupport@hansonresearch.com.

Disclaimer

The reader must understand the following about this document:

1. This document is meant to provide guidance for those new to filter validation. This document is not meant to cover every possibility or condition.
2. The guidelines provided in this document may not be suitable for all products.
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