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Pharma & Biopharma
Manufacturing &
Testing Services

Application Note

When do you need to consider revalidating the performance of your sterilizing-grade filter?

Introduction

Any product or process change that could potentially affect the cGMP compliance of a validated process or system should be evaluated and a risk assessment should be performed to evaluate the impact. Here are some key points to consider.

Which change might require revalidation?

Filter validation assesses the filter performance for a given product and process. Therefore, a change in any of these three variables must be examined.

- Product change
  - Any change to the product formulation including changes in API or excipient concentration and pH will require full set of re-validation, unless bracketed testing has been previously performed on product variables. As for extractables, a new study should be conducted only if the change would affect the choice of model solvents or if it was a leachables study.
  - If changes affect the worst-case product posology then the Patient Safety Assessment may need to be updated. These changes include increasing the maximum drug dosage per day, increasing the frequency and duration of treatment, or changing the target population.
- Filter change
  - If the membrane and membrane area are the same and only the device changes, from a cartridge to a capsule for example, only extractables/leachables studies, compatibility test, product diffusion, and patient safety assessment may need to be repeated.
  - If the filter membrane type changes, this will require all filter validation studies to be repeated.
  - If pore size changes, the entire re-validation set must be done with the exception of compatibility and extractables which do not necessarily require a new study.
  - If change affects filter size and thus filtration surface area, bacterial retention testing may have to be repeated if there is a subsequent increase in the process operating parameters (e.g. volume/surface area, pressure, flow rate, filtration temperature or filtration time). Updates to the extractables/leachables, product diffusion, and patient safety reports may also be needed.
- Process change – Assuming all other variables (such as filter and product) constant:
  - If there are increases in key process parameters such as flux (flow rate/surface area), pressure, filter/product contact time, or volume/surface area which exceed the conditions of the previous testing will require bacterial retention revalidation. Compatibility and extractables studies might also need to be repeated in specific cases.
  - Per the 2008 Revised PDA Technical Report 26, when the validated temperature range is exceeded, the entire filter validation should be repeated.
  - If changes affect in the sterilization method or increases in sterilization conditions such as time and temperature will require revalidation for extractables and leachables. Sterilization conditions impact the types and quantity of extractables and leachables.
  - If changes decrease the volume processed through the filter including flush amount, minimum tank volume or batch size then the Patient Safety Assessment may need to be updated.

The following chart gives you some indications of the tests which might have to be re-validated depending on the changes made.

Changes to Consider		Bacterial Retention	Product Bubble Point	Product Diffusion	Compatibility	Extractables & Leachables & Patient Safety
Product	**Change in product formulation** (concentration, pH,…)	✔	✔	✔	✔	✔
	Change in posology (dosage, frequency)					✔ May need an update of the Patient Safety report
Filter	**Change in filter membrane** (type / materials of construction)	✔	✔	✔	✔	✔
	Same membrane - Change in device type (from a capsule to a cartridge for instance)			✔ May need a letter with data to update the original report	✔	✔
	Same membrane - Change in pore size	✔	✔	✔	✔ May need a letter with data to update the original report	✔ May need a letter with data to update the original report
	Same membrane - Change in filtration surface area	✔* *If filtered volume / surface area is increased		✔		✔ May need a letter with data to update the original report
Process	**Increase in flux** ie. increased flow rate per surface area	✔				
	Increase in total filter/ product contact time	✔			✔* *If it exceeds contact time achieved during testing	✔* *If it exceeds the time provided in original report
	Increase in control pressure	✔				
	Increase in batch volume without a scaled increase in filter surface area	✔				
	Change in sterilization conditions generally increase in time, temperature, or number of cycles					✔* *If the new sterilization conditions exceed those provided in the original report
	Change in filtration temperature	✔	✔	✔	✔* *If temperature is increased	✔* If temperature is increased
	Change in sterilization method					✔

Methodology

There should be a change control program which triggers a review of validation documentation. Risk assessment should be done to identify the systems and processes that are critical to the manufacture of safe and efficacious drugs and have the highest chance of a change to the validation status.

The validations for these pieces of equipment should be on a routine revalidation schedule or a more routine validation review. Autoclaves, for instance, are typically on an annual revalidation cycle while filters are not. However, changes to the filtration process can change the state of the validation and go unnoticed. It is important to periodically review filter validations especially when there are proposed process changes or excursions.

The following are suggestions on how to evaluate your current filter validation status:

- Identify all currently manufactured products.
- Have they been validated? If so:
  - Review older validations against the current process conditions.
  - Have there been filtration process changes?
  - Has the product formulation changed since the validation? (Changes in formulation can be seen as “new” products).
  - Is there a change in posology? Does a new dosage exists?
- Have all filtration processes been validated?

For more information on the various studies:

- Bacterial retention testing
- Extractables studies
- Leachable studies
- Patient safety assessment
- Compatibility studies
- Product specific integrity test

Please contact your local Sales representative.

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