BIOTECH

Technical Regulatory Topic

USTR 3678

Use of Intermittent Filtration Cycles in Product and Process Related Filter Validation

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Contents

1 Objective

This document defines the approach to integrate intermittent filtration cycles into product and process related validation studies according to biopharmaceutical filter users' processes.

2 Background

Most sterilizing grade filtrations that are requested to be validated are related to the final filtration stage of liquid pharmaceutical manufacturing in an aseptic process according to regulatory requirements. The final filter is very often located directly in front of the filling line, or it may even be a part of it.

The liquid product flow in filling lines or filling systems is typically not continuous. The flow is stopped and started regularly, either after filling up a surge tank or whilst changing the filled vials, ampoules, or bottles for new empty ones. These stop and starts are performed in regular intervals and describe intermittent cycles. The time for 'off' (flow stopped) and the time for 'on' (flow active) combined are defined as one cycle. Numerous cycles may be applied during filling of a pharmaceutical drug product into small vials, an essential part of the manufacturing process.

The sterilizing grade final filtration step if placed between the bulk volume and the filling needles will be impacted by the intermittent cycles. Any stop and start event will be accompanied by changes in differential pressure and may cause hydraulic shocks. Thus, intermittent cycles might have an impact on the performance of the filter and should be considered as a worst-case parameter for the validation of that filtration step.

This document describes the different options to simulate an intermittent filtration during validation.

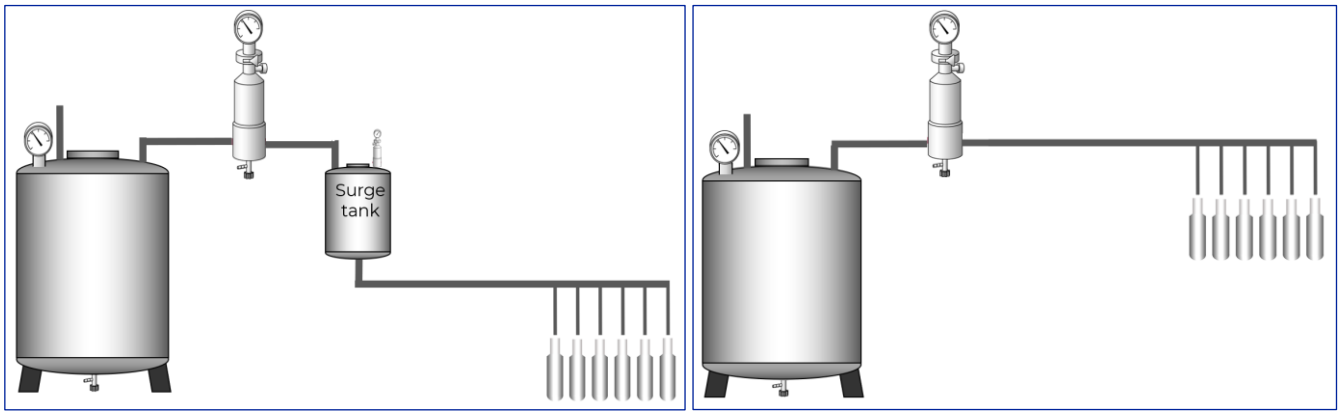
3 Filling Applications

Filling applications can be designed differently. Some filling machines contain a small volume surge tank (e.g. 5 L volume) and product is pumped into the filling needles directly from this tank. Filling of the surge tank typically is level dependent. Reaching a minimum level starts the filling and achieving the maximum level leads to a stop in filling. In another kind of filling machine, the liquid is transferred directly from the bulk tank into the filling needles.

The position of the sterilizing grade final filter is between the bulk tank and the filling needles, typically as shown in Figure 1.

Figure 1

Typical positions of sterilizing grade filters in filling lines



4 Consideration of Intermittent Cycles for Filter Validation Tests

4.1 Validation Tests

Intermittent cycles cause changes in flow rate and differential pressure on the sterilizing grade filter during drug product manufacturing. As previously mentioned, these changes are part of the process and therefore should be considered during validation testing.

The flow rate or differential pressure changes may impact the result of investigations performed for product and process related filter validation. Table 1 shows a list of tests and the necessity for consideration of intermittent cycles.

Table 1

Validation tests and consideration of intermittent cycles

Test Type	Target of Test	Intermittent Cycles To be Considered?	Justification
Bacterial retention	Performance of the filter: Complete retention of bacteria	Yes	Changes in flow rate or differential pressure (flow/no flow) may impact performance.
Compatibility	Chemical resistance against product liquid	No	No impact on filter chemistry.
Extractables	Release of substances into product liquid	No	No impact on extraction of filter substances. Tests are performed with constant liquid movement.
Adsorption	Removal of substances from product liquid	Potentially	Stops and starts may impact adsorption and desorption of components. However, it will not be possible to simulate that during testing. If a topic of concern, the filter user should check during manufacturing process.
PWIT	Determination of product wet integrity test (PWIT) parameters	No	No impact on filter wetting and diffusive flow.

4.2 Risk for Filter Performance

The impact of intermittent cycles on filter performance, especially on bacterial retention, can only be assumed based on some observations and reports from both industry and biopharmaceutical filter users in the past (no references available). A reliable and documented body of evidence has not been found.

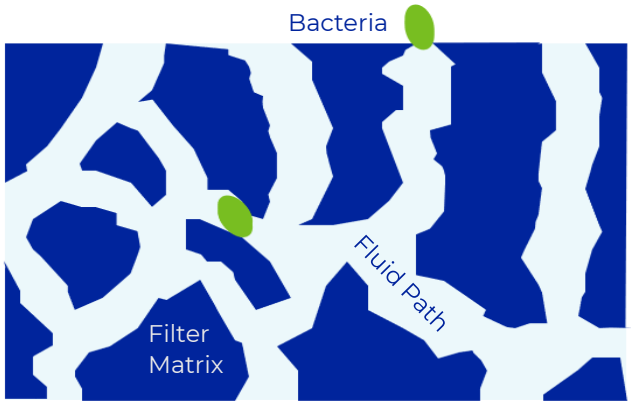
There may be various effects, either separately or in combination, that could have an impact on bacterial retention. Bacterial retention in liquids is based on two main filtration mechanisms:

- Direct interception:
  Particles/bacteria are larger than the fluid path (pores). They are stopped by the filter and cannot penetrate further into the matrix (see Figure 2).

  Direct interception is typically not impacted by differential pressure or flow rate (as long as the filter matrix is stable).

Figure 2

Bacterial retention by direct interception

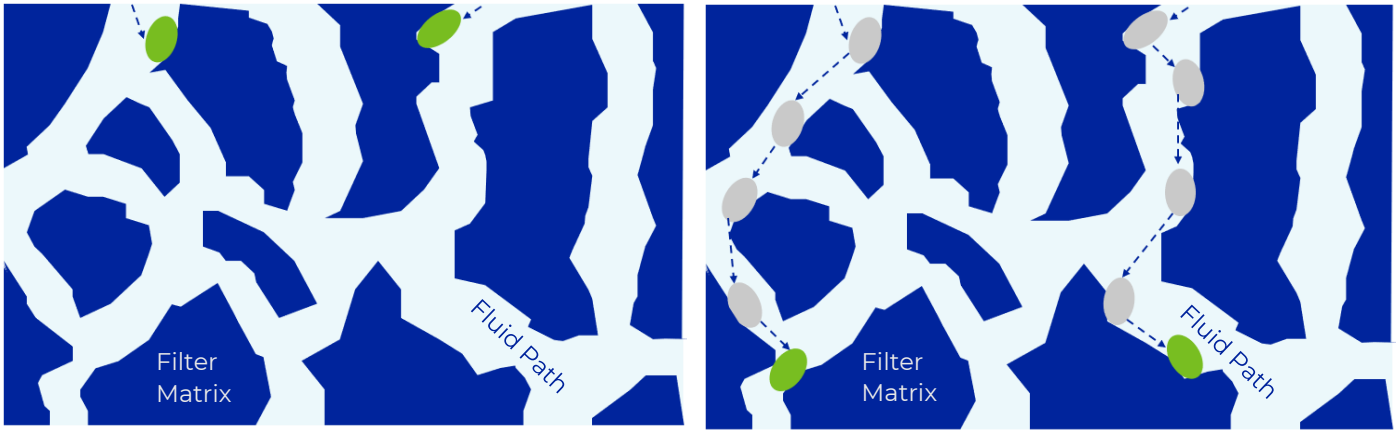


- Inertial impaction:
  Particles/bacteria are smaller than the filter pores but cannot follow a tortuous fluid path due to their mass. Consequently, they come in contact with the pore walls. The final retention mechanism here is the adsorption of the particle/bacteria to the pore wall maintained by the interaction of different forces.

  Differential pressure or flow rate are likely to impact inertial impaction and the retention of the bacteria by adsorptive effects. Bacteria that are adsorbed at the pore wall during liquid flow may become desorbed if the flow rate or differential parameters change during a stop ('off') and a further start of flow ('on'). In such a case, the bacteria could make their way through the membrane over the filtration time increasing the risk of bacterial penetration (see Figure 3).

Figure 3

Potential impact of intermittent cycles on inertial impaction for bacterial retention



Both mechanisms are dependent on further parameters, such as composition and physical properties of the liquid, and properties of the membrane etc.

Due to this potential risk of bacterial penetration associated with intermittent cycles, they should be considered for relevant investigations during product and process specific filter validation.

As explained in Section 4.1 the most relevant test for consideration of intermittent cycles during validation is the bacterial retention test which tests the main aspect of filter performance. Thus, the following explanations refer only to bacterial retention tests.

4.3 Bacterial Retention Test Phases and Intermittent Cycles

Bacterial retention test configurations are chosen dependent on the outcome of viability tests and are defined as non-bactericidal, moderately bactericidal, and bactericidal test designs.

Moderately bactericidal and bactericidal test configurations include two process steps: a pre-conditioning phase using process fluid without bacterial addition for the full process time followed by a short challenge phase with inoculated process fluid (moderately bactericidal) or inoculated surrogate fluid (bactericidal). The non-bactericidal test configuration has only one process step: the challenge phase for the full process time with bacteria added to the product liquid.

The bacterial retention test phases during which the intermittent filtration cycles should be considered are defined in Table 2.

Table 2

Consideration of intermittent cycles during bacterial retention tests

Non-Bactericidal	Moderately Bactericidal	Bactericidal
	Pre-conditioning Phase	**Pre-conditioning Phase**
	In Product Process simulation without bacteria • Has to simulate **all process parameters** to check their impact on the test filter • Intermittent cycles are part of the process → **To be considered**	In Product Process simulation without bacteria • Has to simulate **all process parameters** to check their impact on the test filter • Intermittent cycles are part of the process → **To be considered**
Challenge Phase	**Challenge Phase**	**Challenge Phase**
In Product • Containing bacteria • Intermittent cycles are part of the customer's process → **To be considered**	In Product • Containing bacteria • Intermittent cycles provide the risk of bacterial penetration → **To be considered**	In Surrogate • Containing bacteria • Intermittent cycles provide the risk of bacterial penetration → **To be considered**

As intermittent cycles are part of the biopharmaceutical filter user's drug product manufacturing process it is good practice to consider these cycles also during the bacterial challenge test for filter validation. The impact of changes in differential pressure or flow rate are relevant for both the process simulation during filter pre-conditioning and during the bacterial challenge phase. Thus, it should be regarded for all steps of a bacterial retention test.

5 Simulation of Intermittent Cycles During Validation

5.1 Method of Intermittent Cycles in the Commercial Filling Process

In commercial pharmaceutical filling processes intermittent cycles can be applied in different configurations:

- Filtration driven by pressurization of a tank:
  - Valve upstream of filter (see Figure 4)

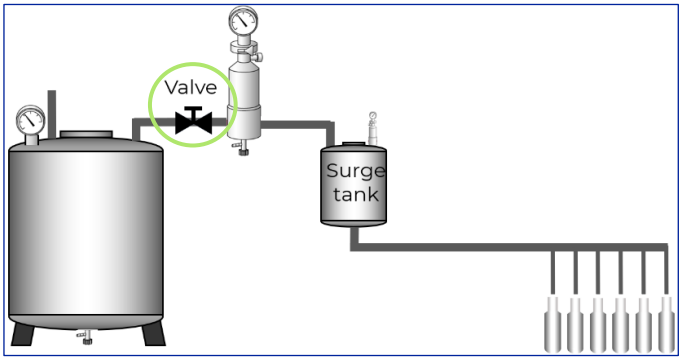
    Stop of flow ('off'):

    Differential pressure (dp) will decrease slowly – depending on the flow of the remaining liquid to downstream side.

    During 'off' phase the filter will be exposed to no dp at zero system pressure.

Figure 4

Filtration driven by pressurization of a tank – valve upstream of



  - Valve downstream of filter (see Figure 5)

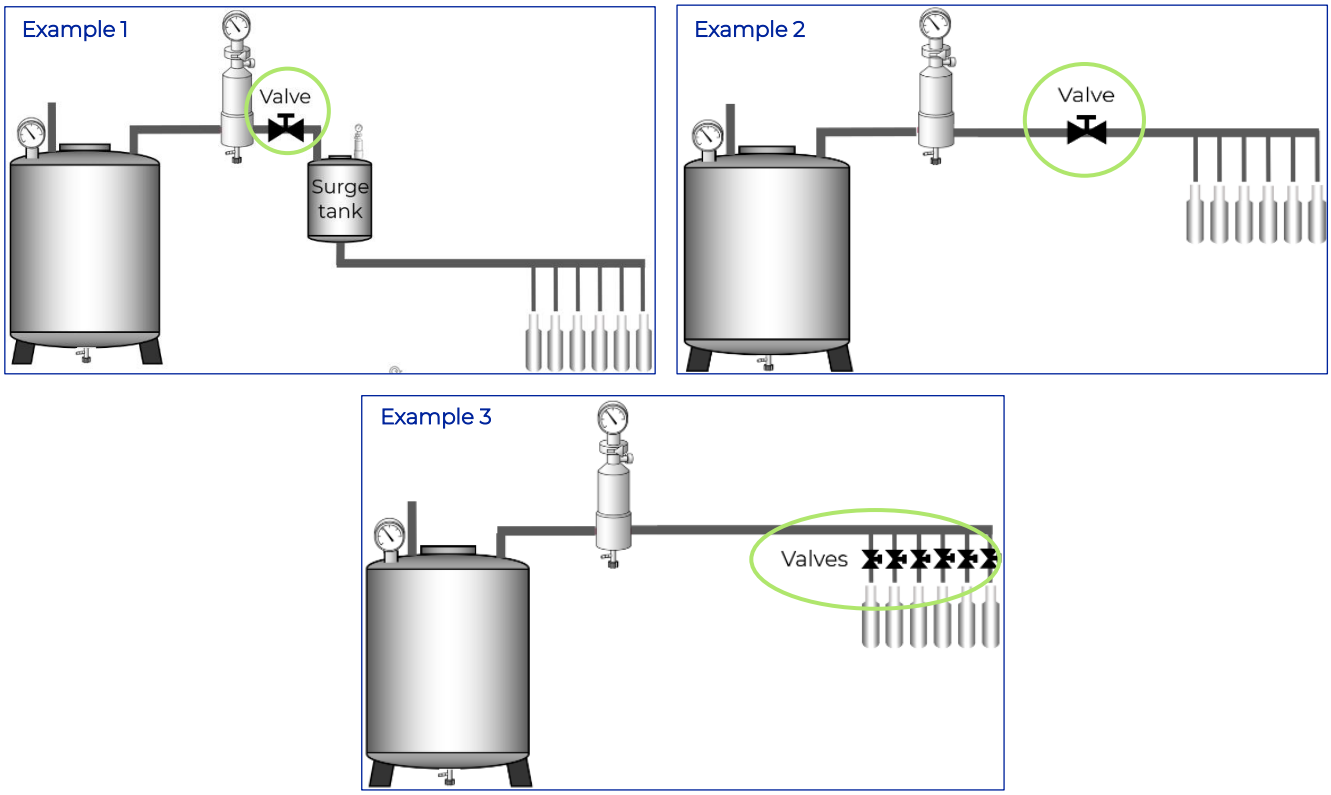
    Stop of flow ('off'):

    Differential pressure will decrease to zero immediately (no flow).

    During 'off' phase the filter will be exposed to no dp at full system pressure.

Figure 5

Filtration driven by pressurization of a tank – valve downstream of filter



- **Filtration driven by pump:**
  - Pump upstream of filter (see Figure 6)

    Stop of flow ('off'):

    - Differential pressure will decrease slowly – depending on the flow of the remaining liquid to the downstream side.
    - During 'off' phase the filter will be exposed to no dp at zero system pressure.

  - Pump downstream of filter (see Figure 7)

    Pump draws liquid through the filter – can only achieve 1 bar dp, if no further pressurization of the tank.

    Stop of flow ('off'):

    - Differential pressure will decrease to zero immediately (no flow).
    - During 'off' phase filter will be exposed to no dp.

Figure 6

Filtration driven by pump- upstream of filter

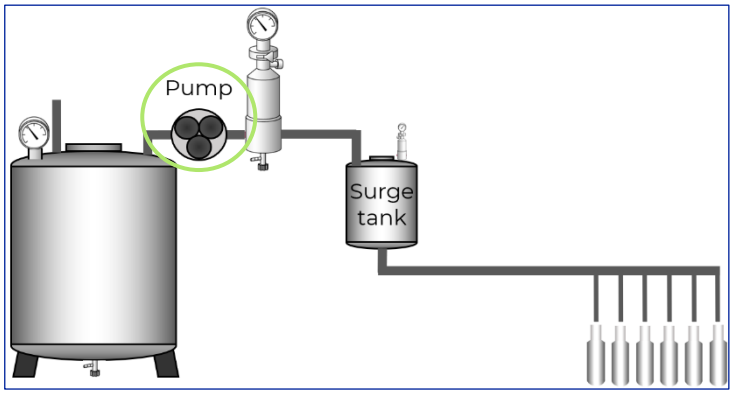
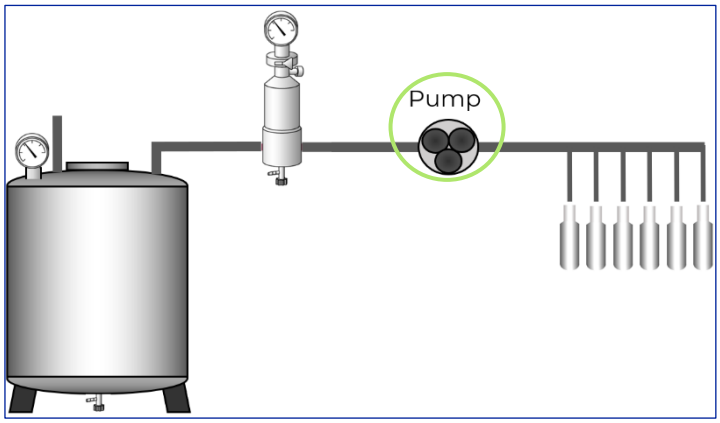


Figure 7

Filtration driven by pump-downstream of filter



5.2 Method of Simulation of Intermittent Cycles in the Laboratory Configuration

The simulation of intermittent cycles in the laboratory configuration for a bacterial retention test needs some attention. The challenge phase of a bacterial retention test always requires a second filter (recovery filter) downstream of the test filter which changes the pressure conditions of the line. Only during pre-conditioning phases when no bacteria are applied is the recovery filter not installed.

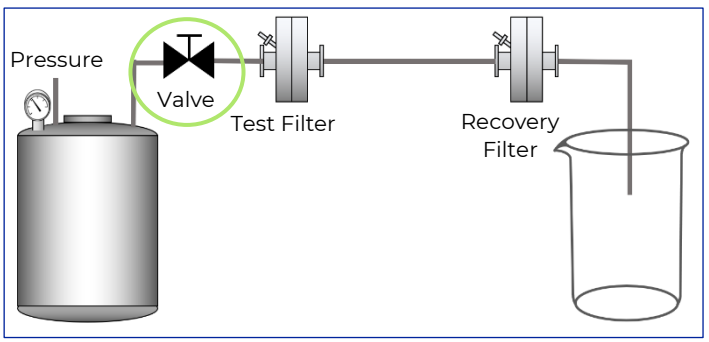
- **Filtration driven by pressurization of pressure vessel:**
  - Valve upstream of test filter (see Figure 8)

    Stop of flow ('off'):

    - Upstream pressure on the test filter decreases slowly – depending on the flow of the remaining liquid to the downstream side.
    - During 'off' phase the test filter will be exposed to no dp at zero system pressure.

Figure 8

Filtration driven by pressurization of pressure vessel – valve upstream of test filter



Start of flow ('on'):

- Upstream pressure is present immediately.
- Differential pressure levels to flow related dp a short time later.

- Valve downstream of test filter (see Figure 9)

  Stop of flow ('off'):

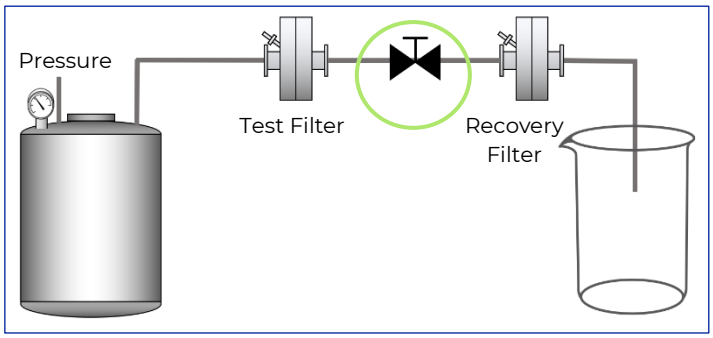
  - Downstream pressure increases to upstream pressure immediately.
  - During 'off' phase the test filter will have no dp at full system (upstream) pressure on the test filter.

  Start of flow ('on'):

  - Flow starts immediately at full system pressure.
  - Differential pressure levels to flow related dp again.

Figure 9

Filtration driven by pressurization of pressure vessel – valve downstream of test filter



- **Filtration driven by pump:**

  - Pump upstream of test filter (see Figure 10)

    Stop of flow ('off'):

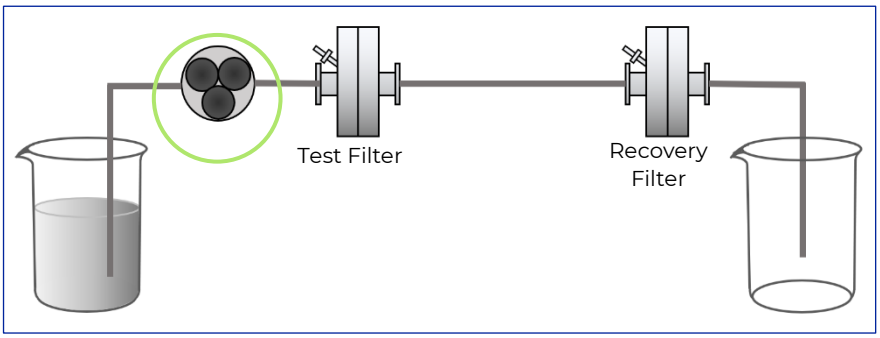
    - Upstream pressure on the test filter decreases slowly (through test and recovery filter, if installed).
    - During 'off' phase the test filter will be exposed to no dp at zero system pressure on the test filter.

    Start of flow ('on'):

    - Upstream pressure increases slowly.
    - Differential pressure increases slowly.

Figure 10

Filtration driven by pump – upstream of filter



5.3 Numbers and Duration of Intermittent Cycles

Dependent on the configuration of the filling machine in commercial manufacturing processes, the intermittent cycles are executed differently. In case a surge tank is installed and needs to be filled between minimum and maximum level, the 'off' times (no flow) and the 'on' times (flow) are longer than if the liquid is filled directly into vials. In such cases the 'off' and 'on' times are very short. Longer 'off' and 'on' times might also result in fewer cycles than the short 'off' and 'on' times.

As consideration of the filter user's process is required for filter validation it is good practice to include intermittent cycles to simulate the full-scale process as closely as possible. That also includes the number of cycles and the cycle times.

However, the details of the intermittent filling process are not always provided in the required way to set up the test sufficiently. A short proposal for the filter user to calculate the intermittent cycles might then help to receive useful information:

Number of cycles = Total volume [mL] / Volume filled at a time (either surge tank or vials) [mL]

The time required to fill the single volume may also be provided.

Often very short cycle times are provided (only a few seconds) as 'off' and 'on' times, resulting in a huge number of cycles. This is mainly due to processes filling into low volume vials.

5.4 Realization of Intermittent Cycles During Bacterial Retention Testing

As previously mentioned, it is good practice to simulate the intermittent cycles of the commercial manufacturing process. However, it may not always be possible to achieve an exact simulation in a scaled down laboratory test. Appropriate automated laboratory equipment to switch short intervals will be required.

Physically, intervals from 1 second 'off'/1 second 'on' upwards will be possible if a suitable programmable interrupter is available and used.

However, these very short cycle intervals provide some disadvantages for the performance of the test. They will not allow the differential pressure (or the flow rate) to decrease completely and to increase again for such a short cycle time. Thus, it will not be possible to meet the specified process parameters of differential pressure (or flow rate). Additionally, the actual differential pressure and the actual flow rate cannot be measured precisely at any time of the cycle. Only a measurement of an average differential pressure or flow rate over the time will be possible.

Therefore, because of the disadvantages of very short cycle intervals, minimum cycle intervals have been defined for bacterial retention tests:

- 1 minute 'off'/1 minute 'on' or
- 30 seconds 'off'/30 seconds 'on'

The equipment and the product liquid characteristics determine which of the cycle intervals from above are used.

During these intervals the differential pressure and flow rate may decrease to zero and then increase again to the specified parameters. Additionally, the actual differential pressure and the actual flow rate can be measured.

Although these defined minimum cycle Intervals allow specified parameters to be reached and sufficient measurements to be taken, compromises may still need to be made. Very short cycle intervals such as these cannot be simulated, and the requested number of cycles may not be able to be met.

Thus, the compromise here would be meeting the more important specified process parameters such as differential pressure or flow rate and waiving the simulation of intermittent cycle numbers.

6 Conclusion

Aseptic pharmaceutical manufacturing processes typically require a final sterile filtration step prior to the final filling. The filling machines fill the drug product liquid into the vials and require a non-continuous flow to allow for the change of vials. Thus, the sterile filtration step will be non-continuous or intermittent.

As this intermittent filtration is part of the manufacturing process it is good practice to consider it in product and process specific filter validation.

The character of an intermittent filtration is alternation between flow and no flow accompanied by differential pressure and no differential pressure. This alternation could potentially impact the retention properties of a filter. Various effects may be responsible for filter performance.

Thus, consideration of intermittent filtration cycles is required during bacterial retention testing and may also be of interest for adsorption of product components on the filter membrane, while all other investigations performed during filter validation are not impacted.

Intermittent cycles impact the important process parameters—differential pressure and flow rate. Differential pressure and flow rate are both considered during all bacterial retention test phases, both the pre-conditioning and challenge phase. Hence, intermittent filtration should be simulated during all phases of the bacterial retention test.

The configuration of the bacterial retention test rig to simulate intermittent cycles depends on individual requirements of the process (flow rate or differential pressure as the driving parameter), and characteristics of the liquid etc. Thus, the decision of using a pump or a pressure vessel and the position of a valve has to be taken individually.

Additionally, it might not be meaningful to meet very short cycle intervals during simulation, if at the same time the important parameters—differential pressure and flow rate—cannot be achieved or measured. Thus, minimum intermittent cycles times of 1 minute ‘off’/1 minute ‘on’ or 30 seconds ‘off’/30 seconds ‘on’ have been defined to ensure meeting other relevant process parameters whilst accepting this may not meet the exact cycle parameters.

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