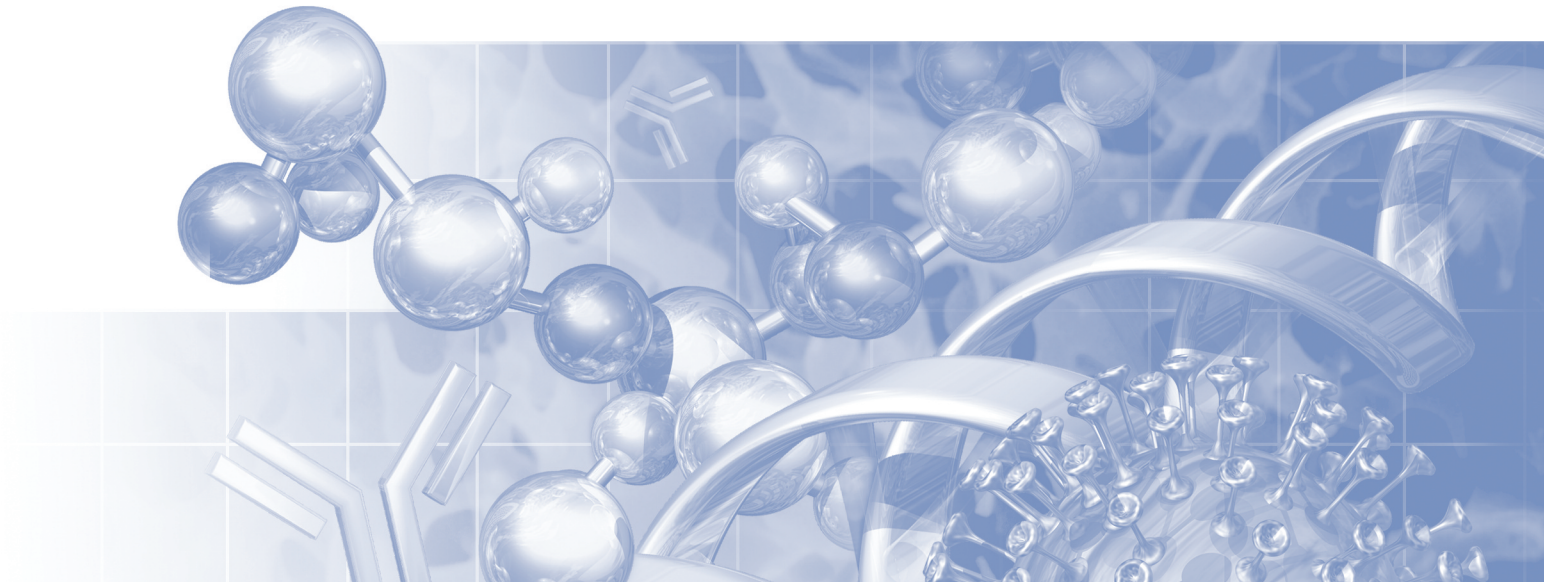
PALL Life Sciences

Application Note

USD 2997

Pressure Interruptions (Stop/Start) During Virus Filtration: Assuring Safety Using Robust Process Technology and An Appropriate Risk Mitigation Strategy

Oliver Triebsch and Nigel Jackson, Ph.D.



*Filtration. Separation. Solution.*SM

Introduction

Virus filtration is a robust technique which is a vital part of the overall viral clearance strategy (inactivation and removal). Filtration's size exclusion mechanism complements other inactivation or removal techniques by targeting the physical dimensions of the virus. Its proven efficacy for both small 'non-enveloped' parvoviruses and larger retroviruses enables process designs based on orthogonal methods to achieve a high degree of virus safety.

Recent expert conference reports suggest that flow pausing and/or filtration pressure interruption during virus filtration is associated with virus passage. Process interruption can sometimes occur in clinical or commercial scale manufacturing due to risk factors including:

Common Risk Factors

- Feed vessel switching
  - For product recovery buffer flush added to the product pool at the end of filtration
  - When multiple bags and storage tanks are used due to transportation requirements
  - When batch volume is larger than vessel size (capacity limitations)
- Unlikely Risk Factors
- Power outages
  - Many manufacturing facilities have the necessary electrical infrastructure to prevent minor power outages. Electrical outage can cause the virus filtration feed pump to stop, which could result in the lowering of filtration inlet pressure
- Mechanical failures
  - Leaks or failures in pumps, valves etc
- Scheduling of personnel/shift-breaks

1. Cause/Mechanism

The loss of virus removal performance in some small virus retentive filters when the process is interrupted appears primarily to be due to diffusion. While size-exclusion is the primary retention mechanism for virus retentive filters, since the viruses are not permanently adsorbed there is always a small chance that viruses can diffuse from fully-retentive areas of the membrane matrix to areas along a lower-retention flowpath. The much greater convective flow during normal processing will counter the diffusive flow to minimize this effect. However, where the convective flow is reduced or eliminated by pressure interruption, then a small number of viruses may be able to diffuse to a position where they could pass through the membrane.

Key parameters that can affect this phenomenon include:

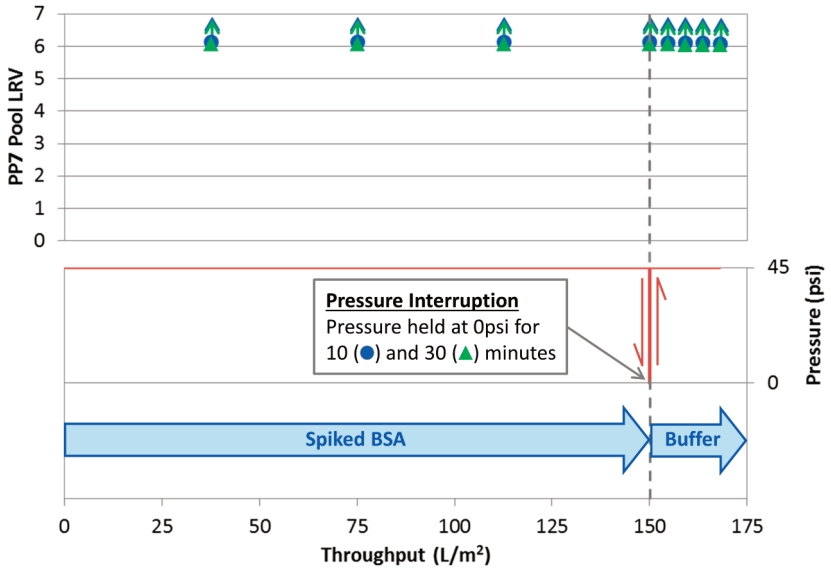
Fixed Parameters	Virus Size	• Fixed by membrane choice and virus type
	Membrane Pore Size/Distribution	
Low-Impact Parameters	Feed Viscosity	• Minimal variation possible within a given process
	Process Temperature	
	Virus Input Concentration	• Affects both input viral load and number of diffusing viruses - low impact on process titer reduction
	Throughput	
High-Impact Parameters	Time (duration of flow pause or pressure interruption)	• Potential to vary by orders of magnitude for a given process
	Magnitude of Pressure Reduction (reduction in convective flow)	• Can be reduced to minimize pressure interruption using proper process controls (see Pall's position and risk mitigation strategy) see section 2

Recent expert conference reports have reported the following observations:

- Multiple virus filters demonstrate changes in performance after pressure interruptions
- The effects of pressure interruption vary, depending on the specific protein solution tested
- Virus passage is strongly dependent on the duration of pressure interruption, supporting the theory of diffusion-related passage
- Results are comparable between bacteriophage PP7 and mouse minute virus (MMV)
- Reduced pressure differential reduces convective flow, leading to lower retention
- Higher feed-viscosity limits virus breakthrough during pressure interruption, consistent with a reduced rate of diffusion

Figure 1

Pegasus™ Grade SV4 Virus Removal Filters: Pall pressure interruption study. Tests carried out in triplicate for each pressure interruption time. All pool concentrations were below the limit of detection. Note: data is illustrative of performance under the specific protein (bovine serum albumin in phosphate buffered saline) and test conditions.



2. Recommended Risk Mitigation Strategy

Everything should be done to minimize or avoid pressure interruption during process development and process scale. Best practice is to use state-of-the-art automated virus filter systems which can significantly reduce the impact or prevent the occurrence of pressure interruption where possible

- Pressure interruption steps should be included in the overall virus validation where required (see also the three-step approach described in Section 3)
- No virus filter can claim to be completely immune to this effect, but second generation small virus-retentive filters such as Pegasus grade SV4 are more robust against pressure drop effects (Figure 1)
- Process control of pressure interruptions is recommended in process systems for all virus filters
- The pressure differential control limits should be kept within a tight range throughout the collection of any portion of the filtrate pool
- Pressure traces should be recorded in batch records

- Implement automated feed vessel switching (e.g. for product to buffer flush transition) with smooth pressure transition through the use of automated process-scale virus filtration systems

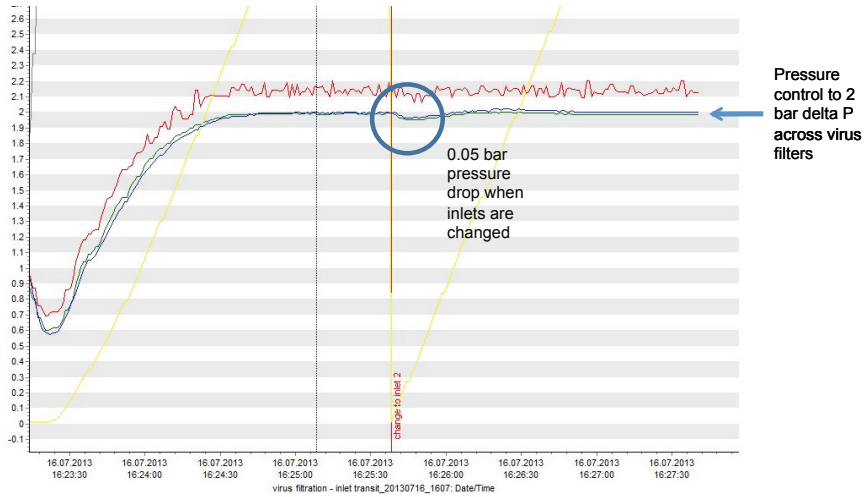
  Example:
  – Automatic transition based on weight input limits
  – Operator prompt for manual transition to buffer flush
- Prevent or mitigate the possibility of power outages
  – Secure the power supply using isolated power supply generators for key equipment
  – Use an automated system capable of quickly rebooting and restarting flow
- Mitigate the possibility of equipment failure
- Purchase robust equipment and ensure proper equipment maintenance
- Schedule personnel to allow appropriate monitoring and control of the virus filtration process at all times

Figure 2

Process-Scale Virus Filtration: Allegro™ MVP System with Pegasus SV4 Virus Removal Filter Capsules

Figure 3

Virus filter inlet curve during fluid vessel switch



3. Recommended Approach for Pressure Interruption Studies with Pegasus Grade SV4 Virus Removal Filters

Step 1 Evaluate the possible risks in your process-scale virus filtration for pressure interruption (see Introduction)

Step 2 Mitigate or eliminate the pressure interruption risks. Everything possible should be done to minimize or avoid pressure interruption at process scale through process control. Best practice is to use state-of-the-art automated virus filter systems which can significantly reduce or prevent the impact of pressure. Contact your local Pall representative to discuss the best technical solution with our systems engineering experts.

Step 3 Based on the process control limits implemented in step 2, a risk-based approach should be taken in selecting the parameters which need to be validated in the Pegasus SV4 virus filter down-scale model.

3.1 Parameters for Pall Minidisc Capsules with Pegasus SV4 Virus Removal Filter Membrane

Virus Spike Level

Pall's recommended approach is to use a spike level that achieves a 10^6 mL^{-1} input titer.[1]

Pressure

Pall recommends that small-scale filterability tests and virus validation studies are carried out at constant pressure. Pall therefore recommends using an operating pressure of 3.1 bar (45 psi) to achieve the maximum flux performance.[1]

Recovery Buffer Flush

If a product recovery buffer flush sample is required Pall recommends priming the upstream volume with buffer and flushing through 3 mL of buffer per Minidisc capsule, or another appropriate amount as determined by protein transmission studies.[1]

Duration of flow pause or pressure excursion

Based on the risk assessment carried out in step 3, an appropriate worst-case duration for pressure excursion should be chosen. Typically this will be the maximum excursion allowed by the process control limits. If an Allegro MVP Single-Use System for virus clearance is used in commercial scale manufacturing allowing fluid transition in less than 30 seconds at not more than 0.05 bar pressure drop when inlets are changed, then a duration of pressure interruption of at least 1 minute and a pressure drop of at least 0.5 bar is recommended. This gives a safety margin and less complicated implementation in the down-scale model.

1 For more details see: Pall publication USD 2778: 'Filterability Testing and Virus Challenge of Pall Minidisc Capsules with Pegasus SV4 Virus Removal Filter Membrane'

PALL Life Sciences

Corporate Headquarters
Port Washington, NY, USA
+1.800.717.7255 toll free (USA)
+1.516.484.5400 phone
biopharm@pall.com e-mail

European Headquarters
Fribourg, Switzerland
+41 (0)26 350 53 00 phone
LifeSciences.EU@pall.com e-mail

Asia-Pacific Headquarters
Singapore
+65 6389 6500 phone
sgcustomerservice@pall.com e-mail

Visit us on the Web at www.pall.com

E-mail us at biopharm@pall.com

International Offices
Pall Corporation has offices and plants throughout the world in locations such as: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, India, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Poland, Puerto Rico, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, the United Kingdom, the United States, and Venezuela. Distributors in all major industrial areas of the world. To locate the Pall office or distributor nearest you, visit **www.pall.com/contact**.

Filtration. Separation. Solution.SM

3/15, PDF, GN14.6021 USD2997