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Virus Filtration in Continuous Bioprocessing – Considerations for Filter Design Space and Validation Strategies

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INTRODUCTION

Continuous bioprocessing of biopharmaceuticals can offer many benefits such as more agile manufacturing with a reduced footprint. Chromatography and virus inactivation are often implemented as continuous unit operations, and viral clearance is validated by similar strategies to a batch process. However, most end-users have leaned towards batch-mode implementation of virus filters, even in a continuous process, by repeatedly storing product in a tank, prior to passing through a virus filter, and consequently batch-mode virus filter validation.

However, to fully realize the benefits of continuous bioprocessing, it is desirable to fully integrate virus filtration into continuous bioprocessing applications. Pall have applied the principles of Quality by Design (QbD) to assess the different design spaces for batch vs. continuous bioprocessing and identify potential risks. By analyzing both supplier and end-user data, we have developed technical solutions and are proposing three different strategies that can be used to overcome some of the complexities associated with validating virus filtration in a fully integrated continuous bioprocess.

INTEGRATION OF VIRUS FILTRATION (VF) INTO CONTINUOUS BIOPROCESSING – ASSESSMENT OF DESIGN SPACE

Figure 1

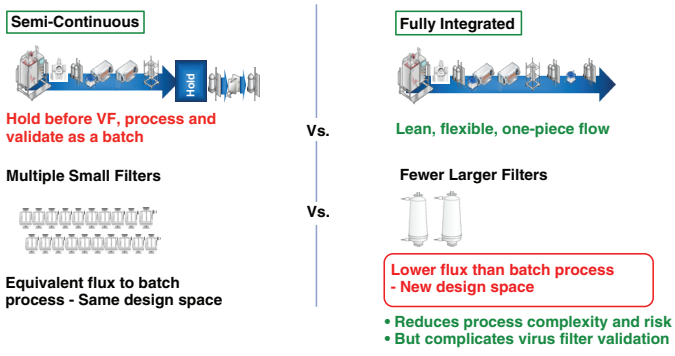
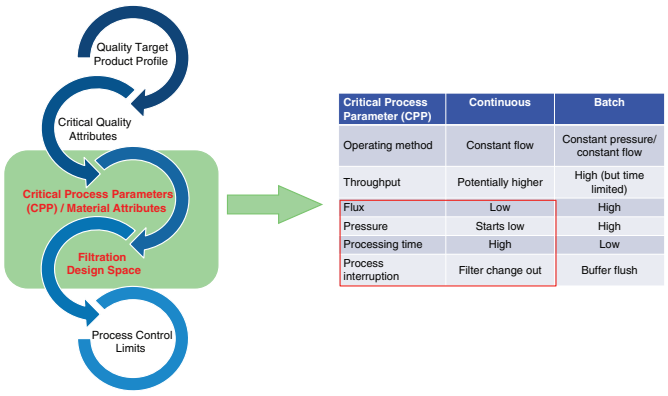


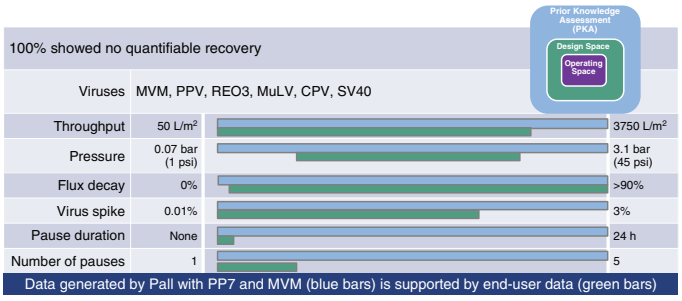
Figure 2



Critical Process Parameter (CPP)	Continuous	Batch
Operating method	Constant flow	Constant pressure/ constant flow
Throughput	Potentially higher	High (but time limited)
Flux	Low	High
Pressure	Starts low	High
Processing time	High	Low
Process interruption	Filter change out	Buffer flush

Figure 3

Compilation of Pall and >50 end-user virus validation results supports robust performance of Pegasus™ Prime virus filters in continuous bioprocessing design space



Through regulatory engagement and prior knowledge assessments, low flux, extended filtration times and process interruptions are considered CPPs for integrating virus filtration into continuous bioprocessing applications. However, multiple studies have demonstrated robust performance of Pegasus Prime virus filters at the extremes of these CPPs.

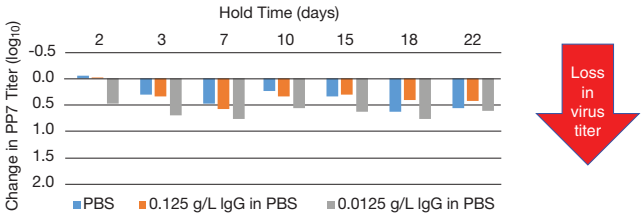
This novel design space presents additional complexities for validation of virus filtration into a fully integrated continuous bioprocess. Therefore, Pall have developed solutions to overcome some of these perceived barriers, and can offer strategies to address different technical challenges.

PROPOSED VIRUS FILTER VALIDATION STRATEGIES FOR INTEGRATED CONTINUOUS BIOPROCESSING APPLICATIONS

Figure 4

PP7 titer is maintained in different fluids for up to 22 days

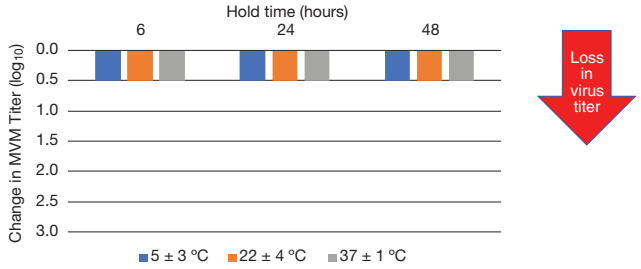
$$\text{Titer Change } (\log_{10}) = (\log_{10}) \frac{\text{PP7 Titer (T=1 minute)}}{\text{PP7 Titer (at relevant timepoint)}}$$



All data are mean values of duplicate samples

Figure 5

MVM titers in cell culture media are not impacted at any temperature tested for 48 hours

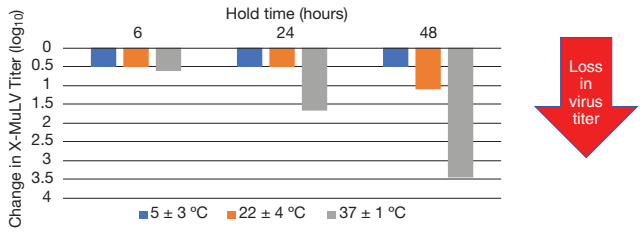


All data are mean values of duplicate runs

No change in titer detected from initial spike (< 0.5 log $_{10}$)

Figure 6

X-MuLV titers in cell culture media are negatively impacted by time and temperature



All data are mean values of duplicate runs

At 5 °C, X-MuLV showed no change in titer compared to the initial spike (< 0.5 log$_{10}$)

Figure 7

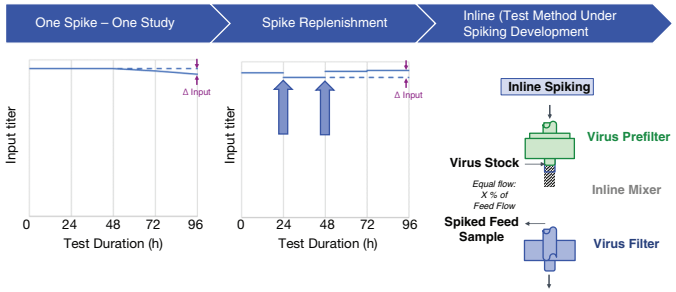


Figure 8

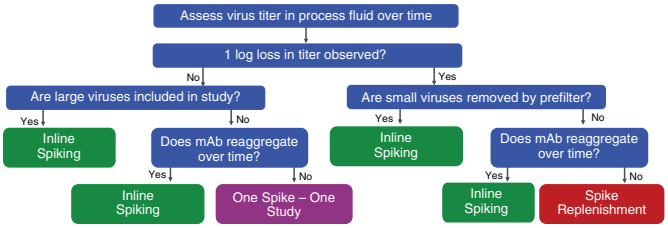
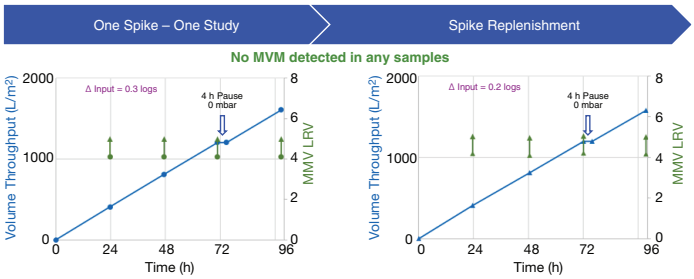
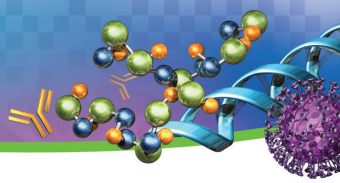


Figure 9



- Pre-testing is recommended to verify specific virus titer in product over time prior to performing virus filtration studies
- Pall have proposed three different validation strategies for integration of virus filtration into continuous bioprocessing
  - **One Spike – One Study** – can be used if test virus maintains titer over test duration. Most simplistic virus filter validation strategy.
  - **Spike Replenishment** – spike and process fluid are changed at pre-determined frequencies. Requires additional sampling and adds complexity to determine overall virus clearance.
  - **Inline Spiking** – consider for situations when viruses are removed by the prefilter and/or the mAb reaggregates after prefiltration. Requires careful consideration of flow dynamics to ensure adequate mixing of the virus under low flow conditions.



CONCLUSIONS

- Technical complexities associated with complete integration of virus filtration into continuous bioprocessing can be perceived as a barrier to implementation
- Pall have demonstrated that by following QbD principles to assess CPPs, alternative validation strategies are required
- Next generation filters such as the Pegasus Prime virus filter, show robust performance in the unique design space required for continuous bioprocessing
- Determining a suitable virus filter validation strategy requires careful consideration of virus and product stability, but Pall have developed three methods to address different scenarios
- Alternative validation strategies were based on regulatory input for integrated continuous bioprocessing
- Pall is available for further technical assistance with all virus filtration applications

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