Quality By Design (QbD) Approach to Virus Filtration Operations

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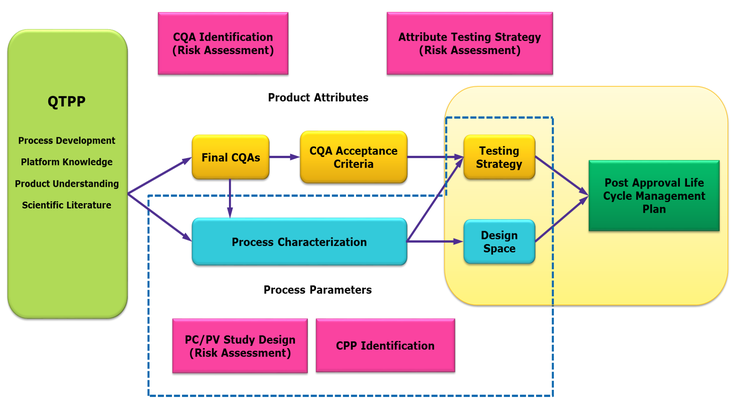
Introduction

Quality by design (QbD) is a scientific approach to formalize the quality of manufactured products. It ensures quality of products by identifying critical process parameters (CPP) that impact critical quality attributes (CQA) of the product. For the virus filtration operation, virus retention performance of filters can be considered a CQA. Understanding the impact of system, operating and process parameters on virus retention performance helps rank risks and identify control strategies to assure consistent performance of this dedicated virus reduction step in biomanufacturing processes, Figure 1.

Figure 1. QbD Concept to Advance Product and Process Quality[1, 2]

Quality Target Product Profile (QTPP)

Process Characterization/Process Validation (PC/PV)



The development, characterization and validation of a virus filtration operation depends on sound science and the principles of quality risk management. This poster summarizes results of process characterization studies with Viresolve® Pro Devices. These testing ranges correspond the area indicated by the blue dashed line in Figure 1, and the output of studies is discussed in the context of the CQA for virus filters, virus retention performance.

Parameters that could impact virus filter clearance performance can be grouped into three categories:

- Feed parameters
- Process parameters
- Virus filter characteristics

Table 1. Process Parameters
Values are for illustrative purposes only.

Category	Process Parameter	Example Template Mfg. Range	Variation Causes
Feed	Protein concentration	0.5-25g/L	Titer, flushes, chromatography cuts
	Conductivity	0.5-25 mS/cm	Buffer variability, dilution variations batch-to-batch, pH adjustment
	pH	4.5-8.0	Feed variability, pH adjustment
	Temperature	10-30°C	Environmental controls HVAC, cleaning water temperature
	Aggregates	0-2%	Hold time, harvest variability, chromatography cuts
	Protein pI	6-9	Amino acid content
	Buffer species	Acetate, Phosphate, MES, Citrate, Histidine	Protein specific
Process	Constant flow or pressure operation	Constant pressure or flow	Plant preference
	Pressure	20-50 psig	Gauge error
	Processing endpoint: % flow decay L/m^2 throughput Kg/m^2 mass throughput	0-75% 400-2000L/m^2 1-10 kg/m^2	Batch variability
	Process Interruption	0-5 hours	Batch variability
	Recovery flush	0-100L/m^2	Batch variability
	Pre-use caustic flush	0-50 L/m^2	Plant decision
	Shelf time	0-1 yr	Scheduling & demand
Virus Filter	Device lots	Magnus 2.2 lot	Batch variability
	Integrity test value	0.5-0.784 sccm/m^2-psi	Batch variability, temperature, wetting

Results

Small-scale, replicated one or two parameter studies were performed with Viresolve® Pro Micro Devices to assess the impact of different process parameters on virus retention. Results are summarized below.

Feed Parameters

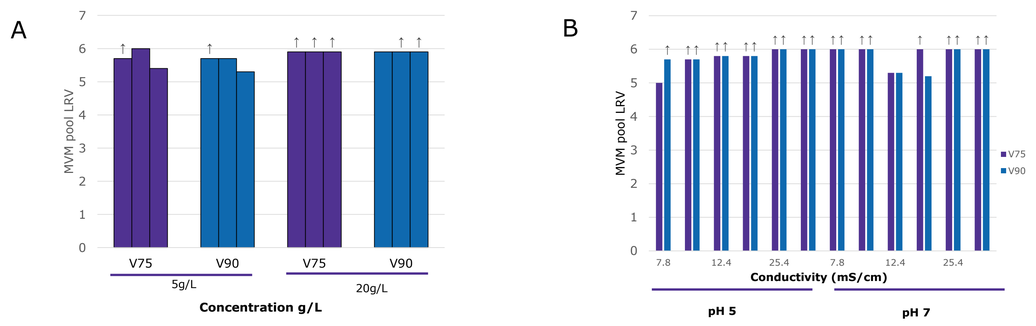


Figure 2: Result of studies evaluating virus filter feed parameters on Minute Virus of Mice (MVM) retention
(A) Protein concentration at 75% and 90% flux decay (V75 / V90)
(B) Feed conductivity and pH at 75% and 90% flux decay (V75 / V90)
Arrows indicate values were at assay limit.

Process Parameters

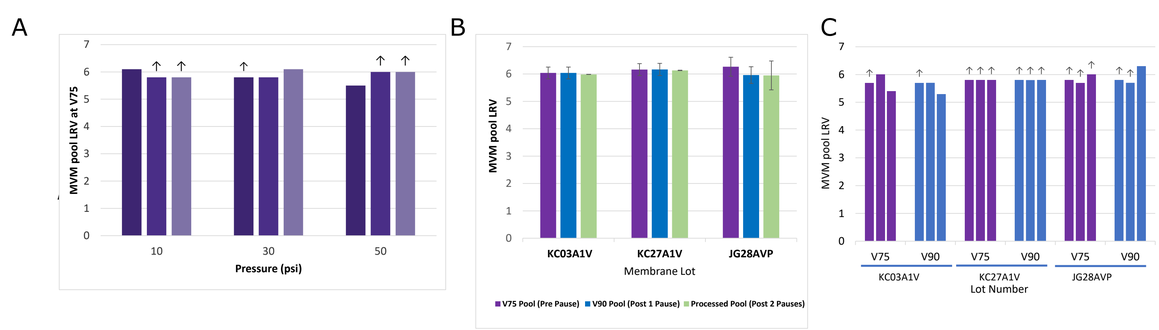


Figure 3: Result of studies evaluating filter operating parameters on MVM retention
(A) Operating pressure
(B) One or two process pauses of 30 mins duration with different membrane lots (mean of 3 replicate Devices)
(C) Flux decay processing endpoint (V75 / V90) with different membrane lots
Arrows indicate values were at assay limit.

Virus Filter Characteristics

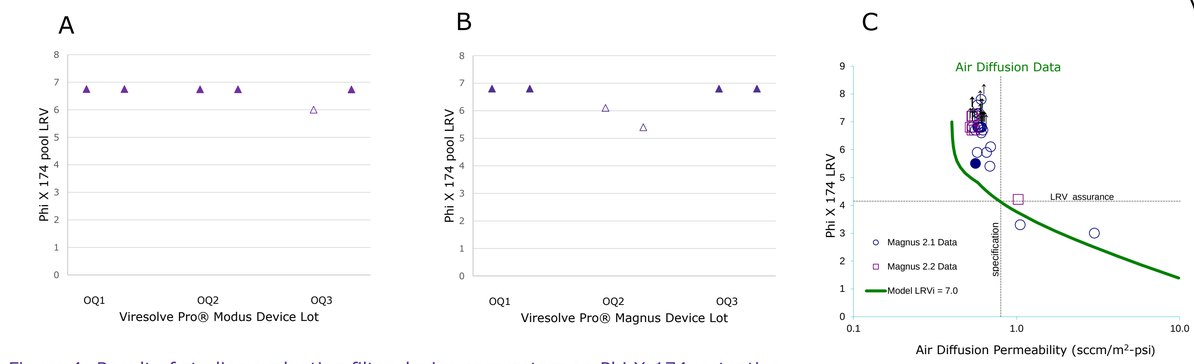


Figure 4: Result of studies evaluating filter device parameters on Phi X-174 retention.
(A) Modus Device lots
(B) Magnus Device lots
(C) Pre-use air diffusion value and Phi X-174 retention
Filled shapes indicate samples were at assay limit.

Summary

Results demonstrate that under all conditions tested, Viresolve® Pro Devices exceeded the retention claim of ≥4.0 log reduction value (LRV).

Viresolve® Pro Devices appear relatively insensitive to many feed/process parameters and filter attributes, indicating that the Device can be expected to provide robust virus retention under a broad range of conditions. No critical process parameters that compromised virus retention were identified for filtration operations using Viresolve® Pro Devices.

Virus retention occurs predominantly by the mechanism of size-exclusion where virus size and membrane pore size distribution are the only significant variables determining retention levels. Air water diffusion testing provides reliable assurance of performance, with values higher than the specification indicating the presence of defects in the device which could lower retention. This test is an important element of any control strategy to assure reliable performance of the Viresolve® Pro Device.

We strive to help biologics manufacturers simplify risk assessments and streamline clearance evaluations for filtration operations and are continually developing standard-setting products that minimize risk, improve reliability and ensure reproducibility.

References
[1]Hakemeyer et *al*., Biologicals 44 (2016): 306-318
[2]International Conference on Harmonization, ICH Topic Q8, Pharmaceutical Development", 2009