



## **Membranes for Viral Clearance**

*Combining High Virus Clearance  
and  
Control of Processing Costs*



**ADEBIOTECH**

**Technologies innovantes en  
séparation industrielle des protéines**

**28,29 et 30 octobre 2013**

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# Membranes for Viral Clearance

## Membrane Chromatography



Direct Flow Filter (DFF)  
Virus Filter



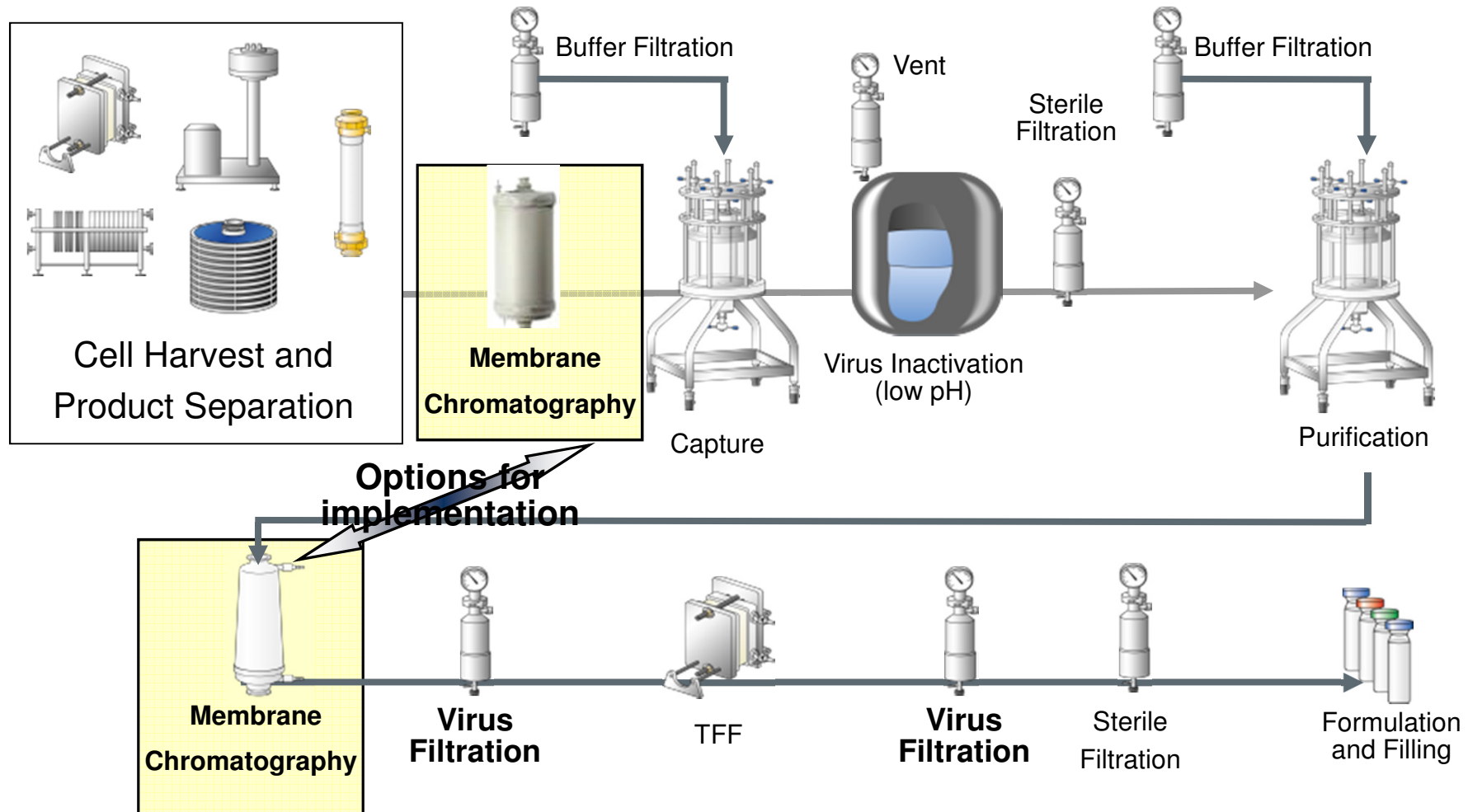
Direct Flow Filter (DFF)  
Air Filter





# Process Implementation

## Downstream Processing





# References

## Column Guard Applications

- Early removal of contaminants – prior to column chromatography
- Enhances performance and lifetime
- Peter Gagnon – Purification Tools for Monoclonal Antibodies  
*“Pre-purification” removal of DNA and endotoxin can only improve the efficiency of the rest of your process for reducing these contaminants to target levels. It’s likely that this treatment supports significant virus removal as well.*
- Clarification of Cell Culture Harvest Utilizing Membrane Chromatography, Joe Lepore et al, Centocor, Poster, Recovery 2008
- Removal of complicating components, prior to Pro-A capture
- Reduced post Pro-A precipitation



# Upstream Process Implementation

## Case Study

- Biopharmaceutical company, Paris, France:



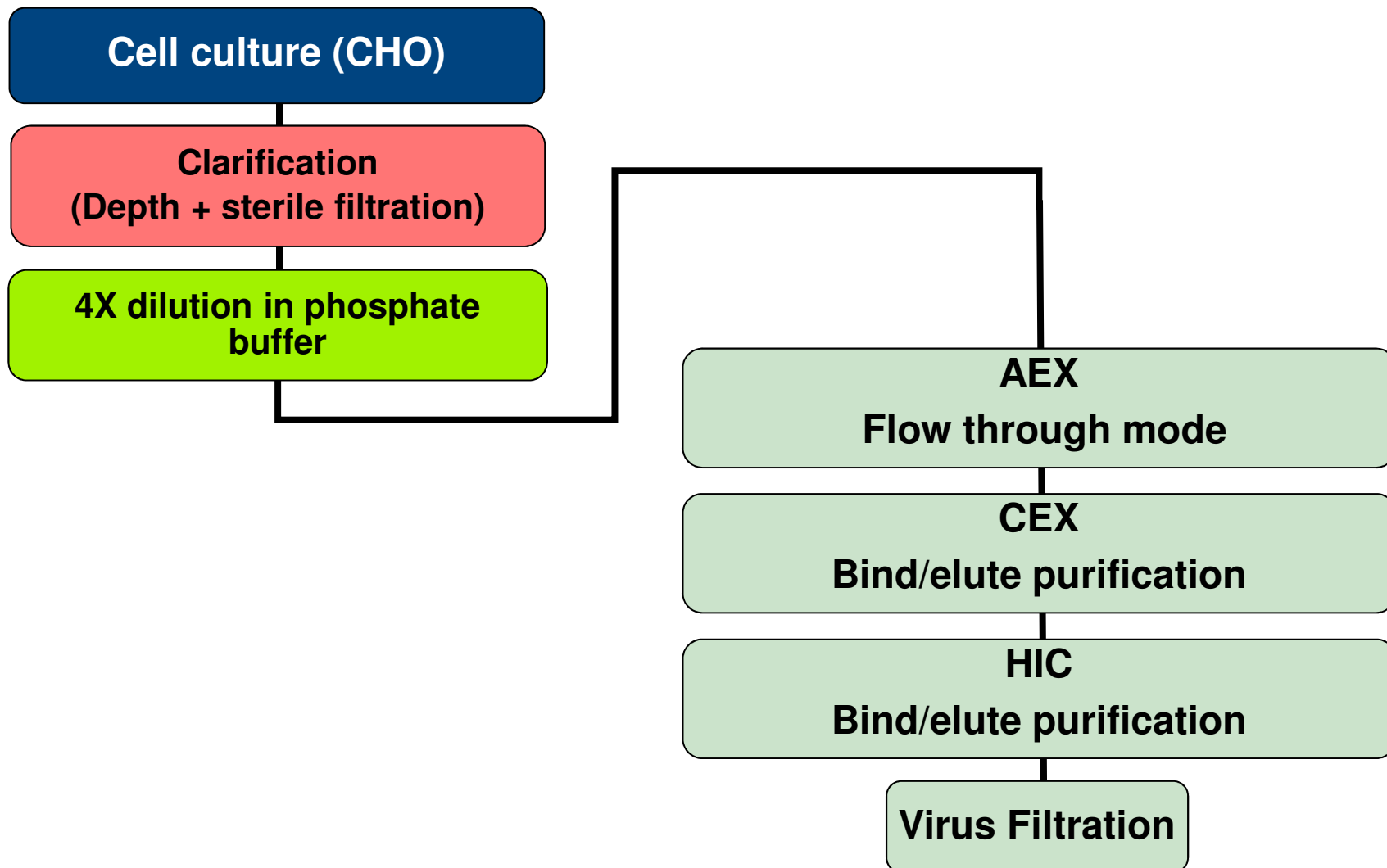
[www.cytheris.com](http://www.cytheris.com)

- Development of a recombinant human Interleukin 7 (rhIL7) as a new therapeutic candidate for use in immune modulation
- Process development from CHO cells, 600L scale GMP production for **Phase IIa/IIb** clinical trials (9 countries)



# Initial Process

## rhIL7 at Cytheris





# Virus removal

## in initial Process

Initial Process	AEx	CEx	HIC	Virus Filtration	Total LRV
<b>MLV</b>	Run A = 2.55 Run B = 2.39	Run A = 0.72 Run B = 1.16	Run A > 4.28 Run B > 4.06	Run A > 4.10 Run B > 4.11	<b>11.65</b> <b>11.72</b>
<b>Reo3</b>	Run A = 2.07 Run B = 3.52	Run A = 1.72 Run B = 1.55	Run A > 4.58 Run B > 4.97	Run A > 4.38 Run B > 4.26	<b>12.75</b> <b>14.30</b>
<b>MVM</b>	Run A $\approx$ 0 Run B = 0.98	Run A $\approx$ 0 Run B $\approx$ 0	Run A = 2.90 Run B = 2.53	Run A = 4.74 Run B = 4.56	<b>7.64</b> <b>8.07</b>

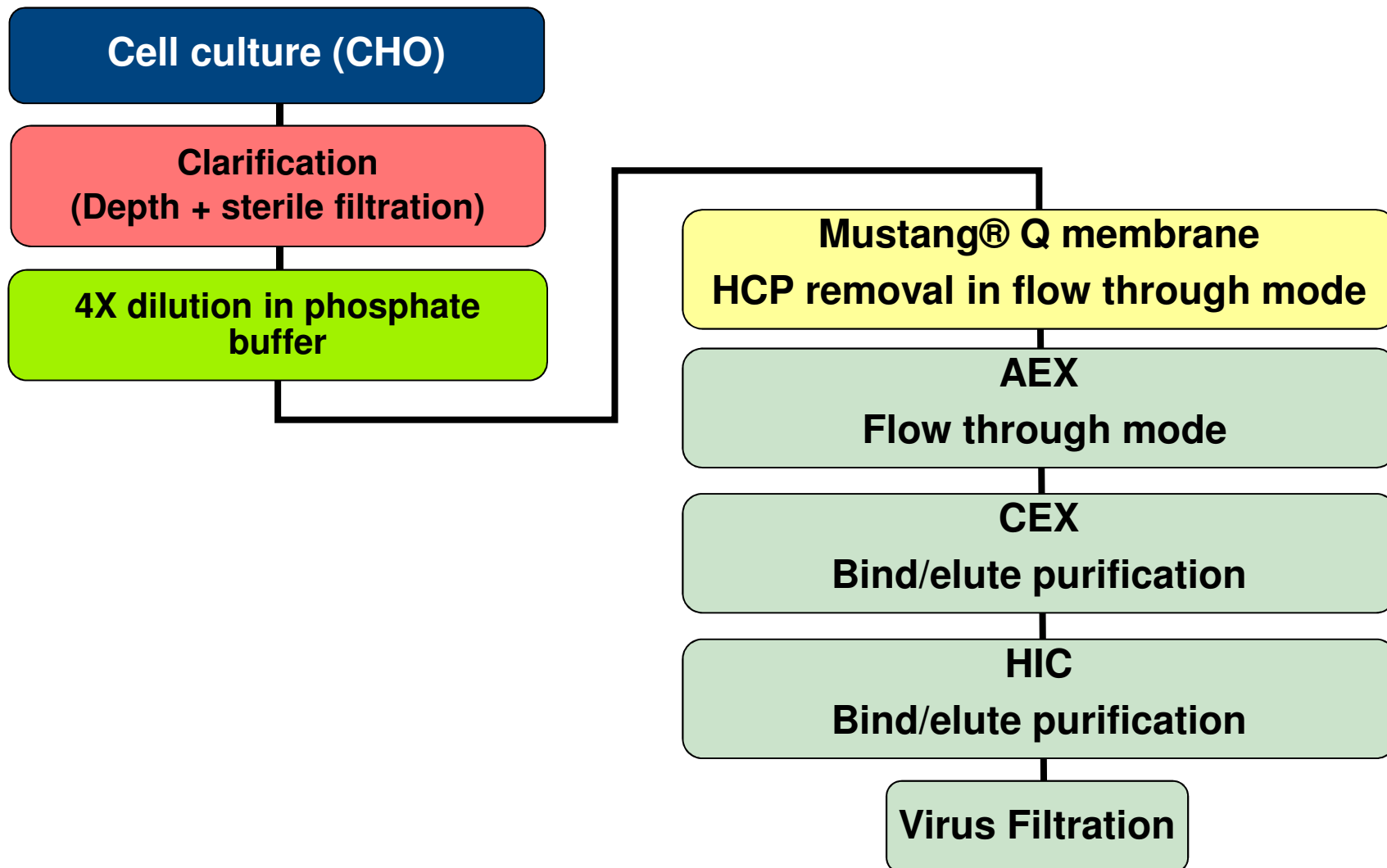
\* LRV: log reduction value





# Optimized Process

## rhIL7 at Cytheris







# Virus removal in optimized Process

New Optimized Process	Mustang Q	AEx	CEx	HIC	Virus Filtration	Total LRV
MLV	Run A > 4.52 Run B > 4.57	Run A > 4.12 Run B > 4.05	Run A = 1.01 Run B = 1.30	Run A > 4.74 Run B > 4.96	Run A > 4.06 Run B > 4.05	18.45 (+6.80) 18.93 (+7.21)
Reo3	Run A > 4.78 Run B > 5.13	Run A > 5.6 Run B > 5.7	Run A = 1.49 Run B = 1.39	Run A > 4.3 Run B > 4.3	Run A > 4.16 Run B > 4.22	20.33 (+7.58) 20.68 (+6.38)
MVM	Run A > 4.81 Run B > 5.17	Run A > 5.99 Run B > 6.23	Run A ≈ 0 Run B ≈ 0	Run A = 4.76 Run B = 5.46	Run A > 5.15 Run B > 5.50	20.71 (+13.07) 22.36 (+14.29)

Optimized Process Using:  
Mustang® Q XT5 Capsule (XT5000 in process, flow-through mode)



# Scale Down Process

at Cytheris using Mustang Q XT



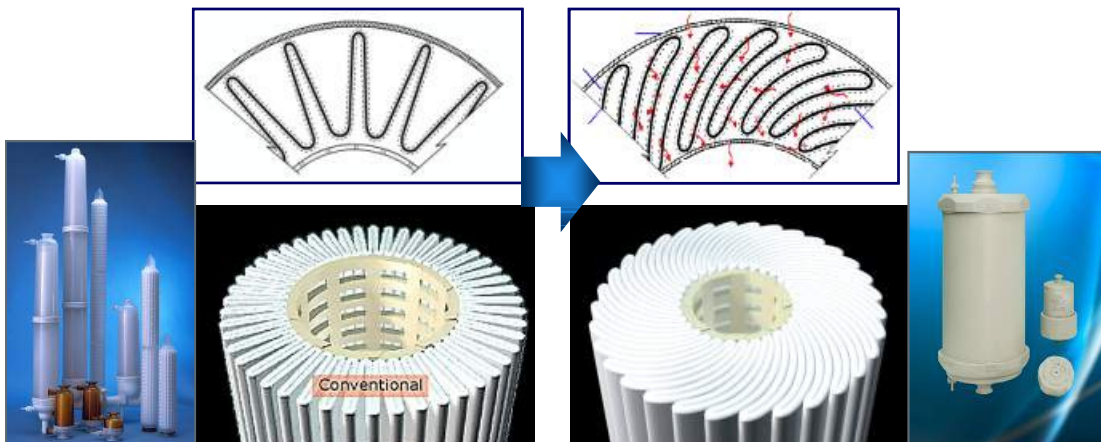
Mustang Q Capsules + Allegro™ System + PK System



# Current scale Process

at Cytheris using Mustang Q XT5000

- Current scale 600L GMP
- Guard column position
  - Need capacity and flow performance
- Scale down indicated 20L membrane volume needed
  - 25 Mustang NP8 capsules (780mL each)
  - 4 Mustang XT5000 units (5L each)
- Process configuration chosen as 2 x 2





# Membranes for Viral Clearance

## Membrane Chromatography



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Virus Filter

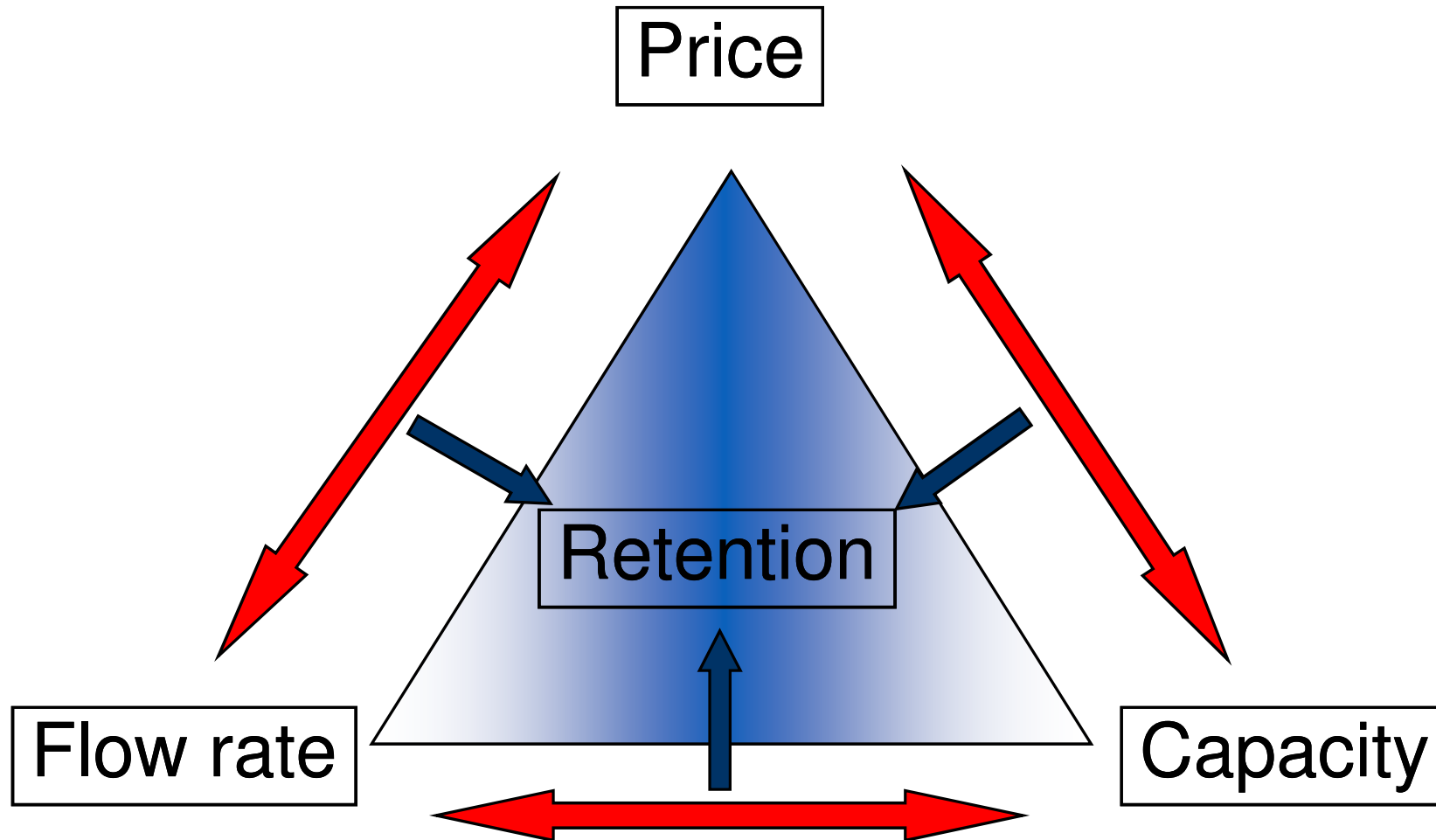


Direct Flow Filter (DFF)  
Air Filter





# Performance of Virus Safety Step

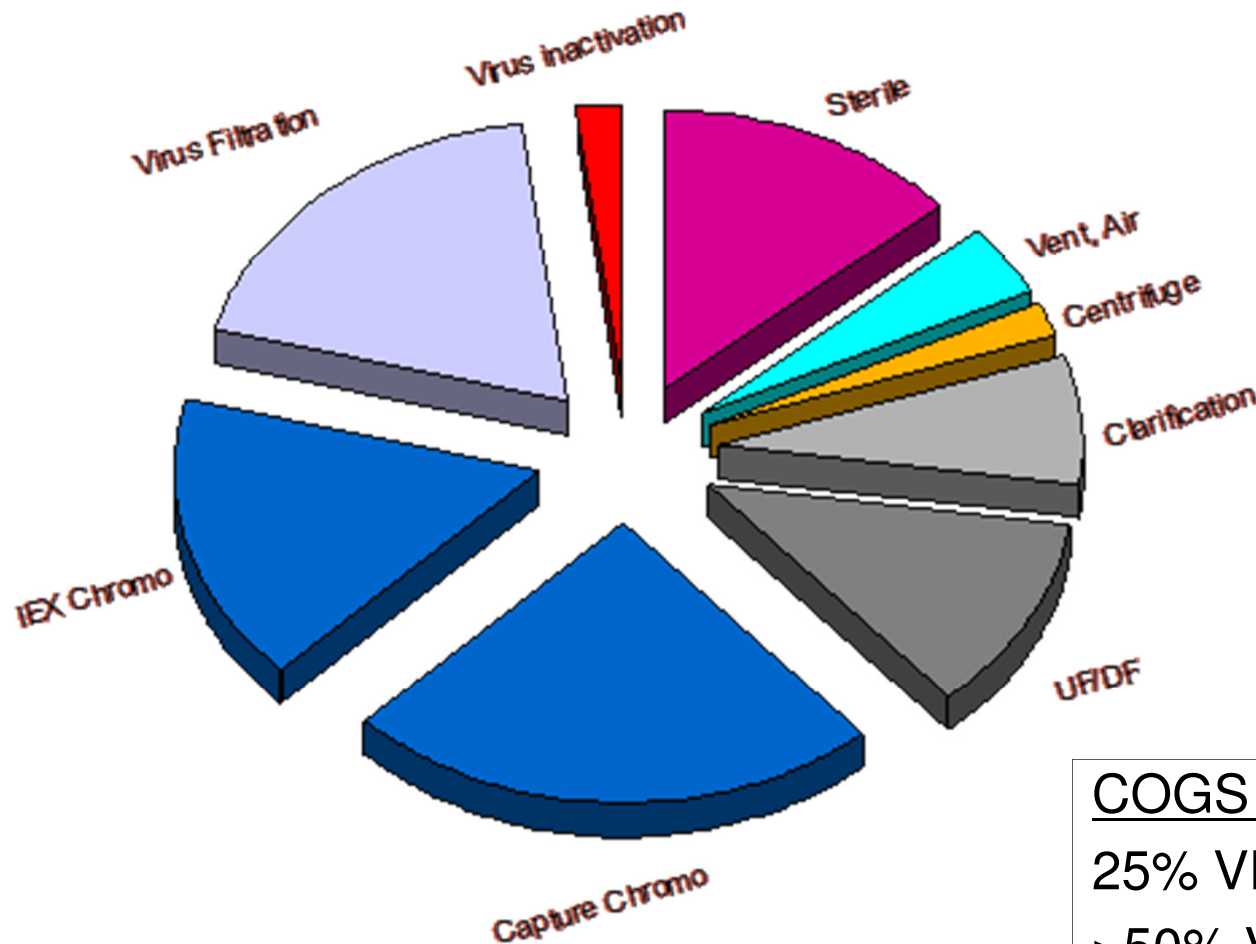






# COGS Consumables

Biotech Market, Pall estimate



Cost Categories & Detail

1	Capital	Capital Charge
2	Materials	Media
		Buffer
		Bought WFI
		CIP
		QC tests
3	Consumables	Resins/MA
		Bags
		Filters
4	Labour	Process
		Quality
		Indirect
5	Other	Insurance & other
		Waste management
		Maintenance
		Utilities

## COGS reported:

25% VF in low fouling fluids

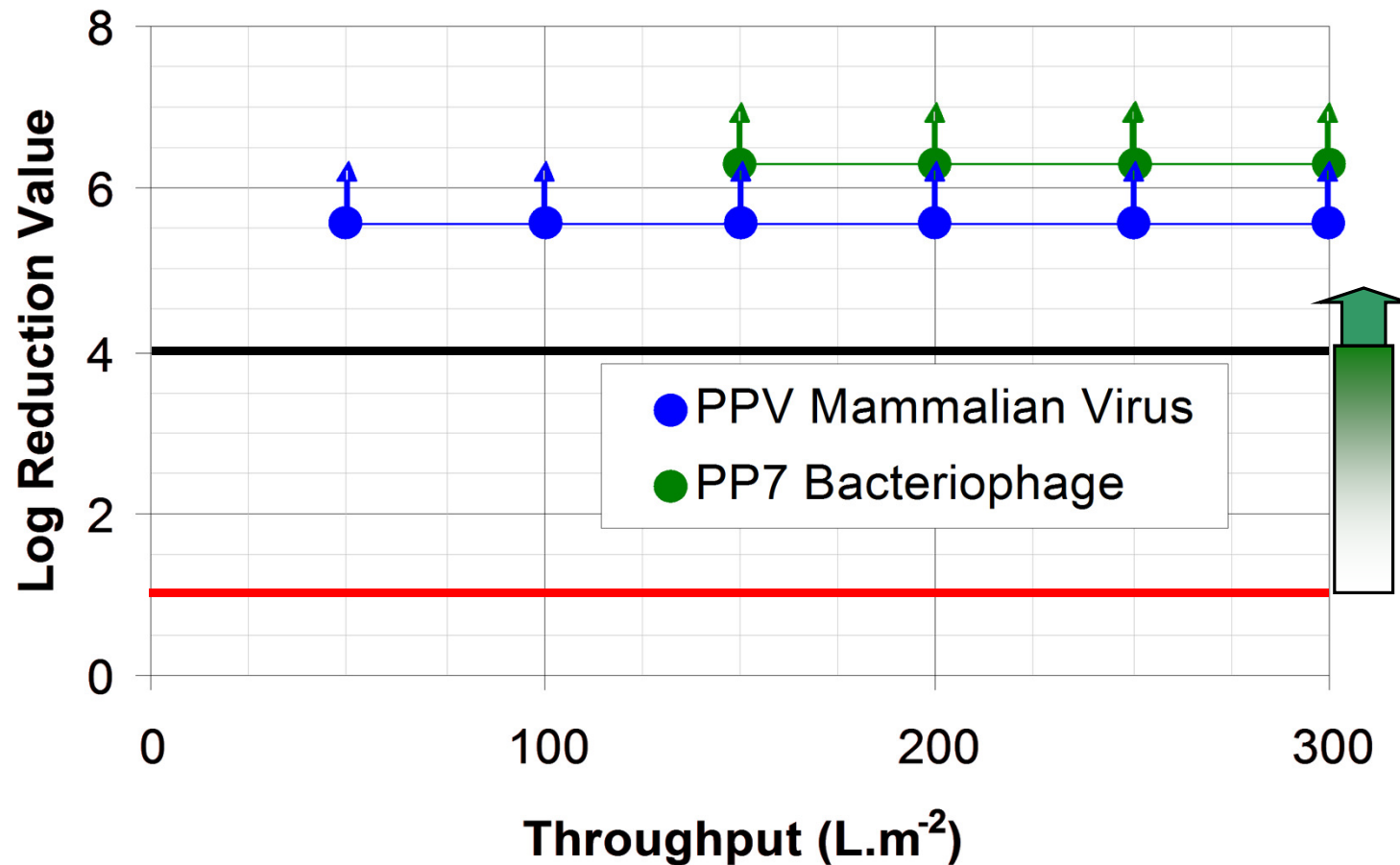
>50% VF in high fouling fluids

PDA Virus safety congress 2011, Spain



# Small Virus Reduction

in 0.1 % BSA by Pegasus SV4 membrane

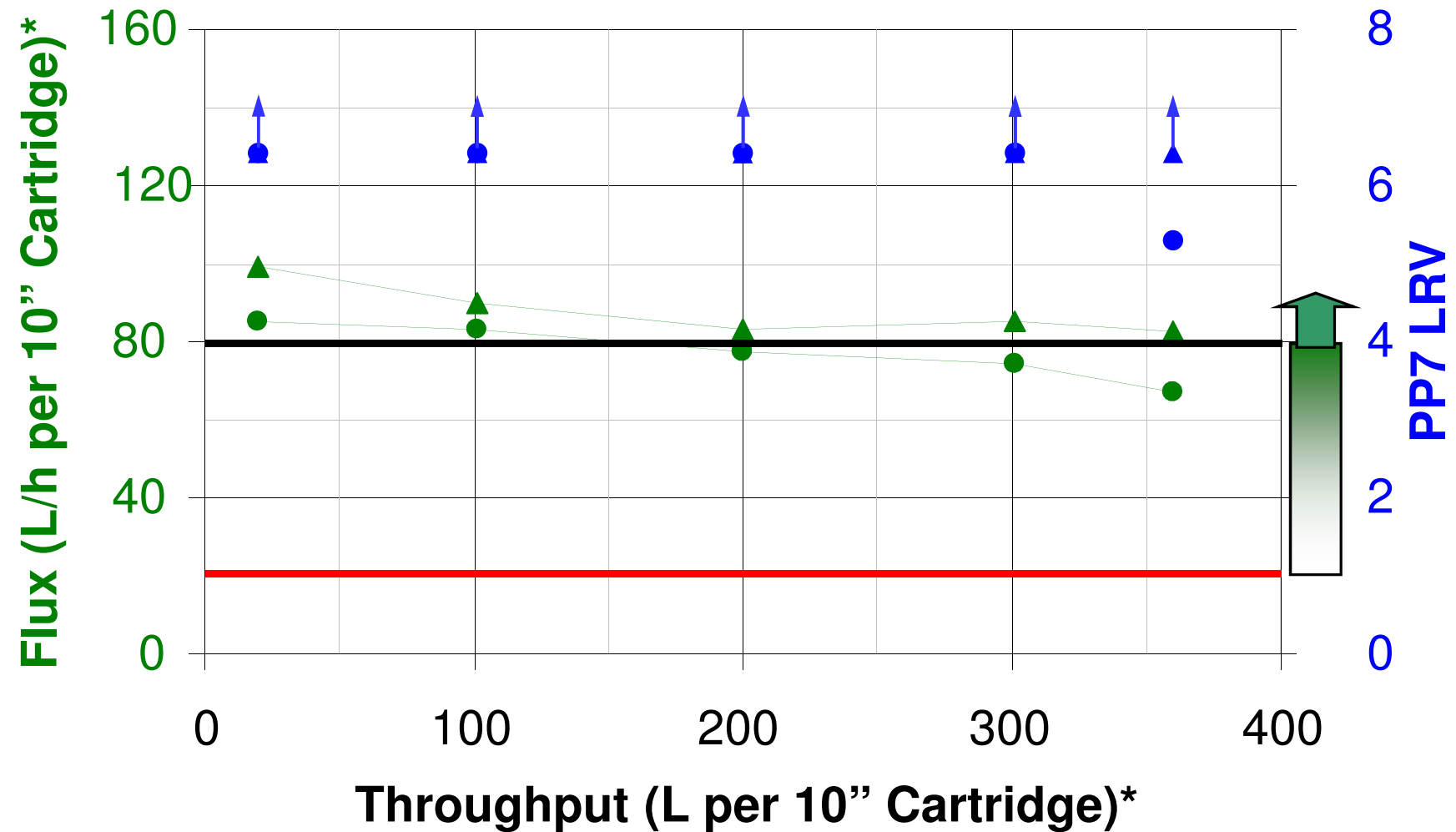






# Small Virus Reduction

in 10 g/L IgG by Pegasus SV4 membrane

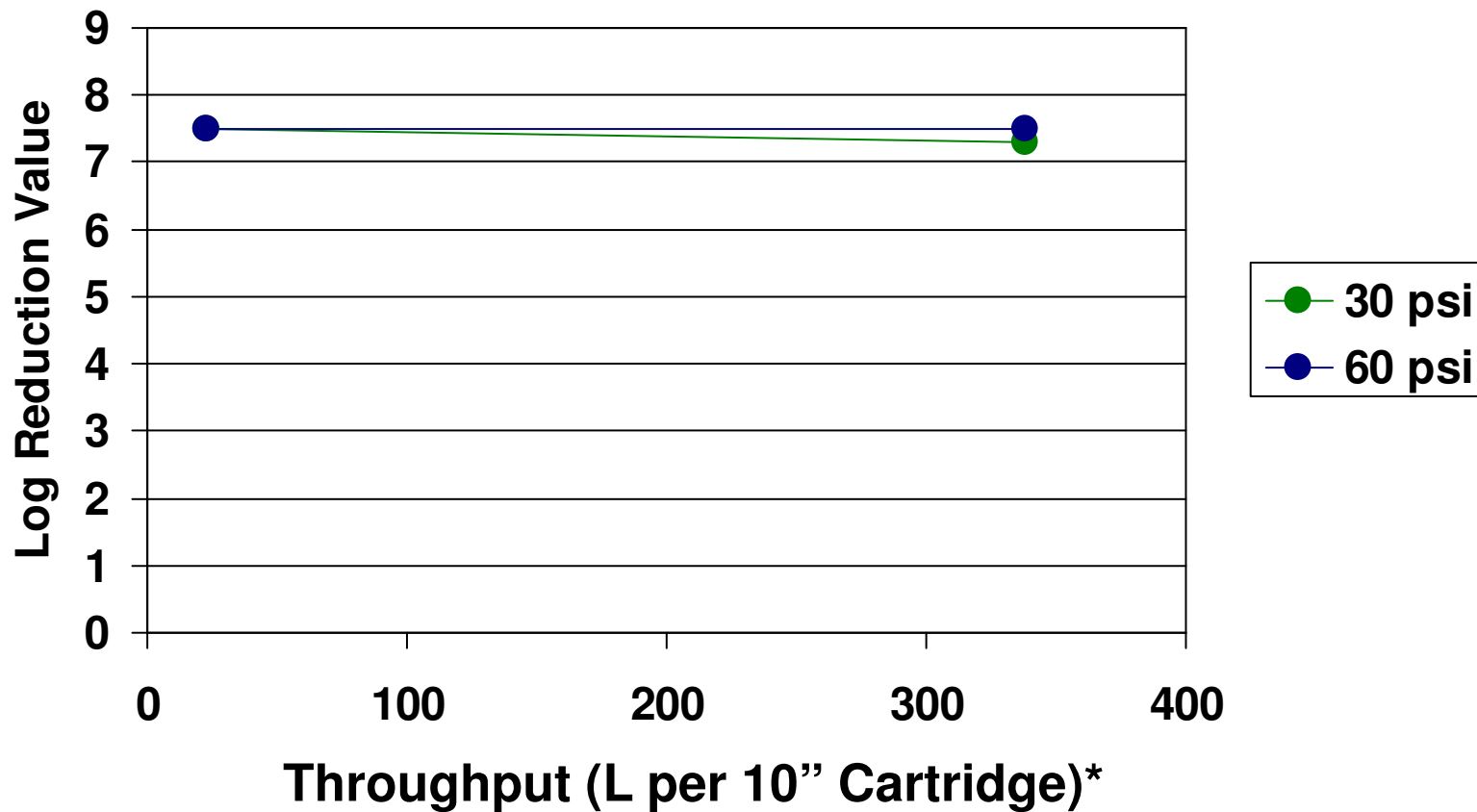


\* Performance predicted from 47mm disc tests.



# PP7 Reduction

in 1% BSA by Pegasus SV4 membrane



2% PP7 Spike, Triplicate Tests

\* Performance predicted from 47mm disc tests.



# Pressure Interruptions (Stop / Start) during Virus Filtration

Can occur during feed vessel switching and product recovery buffer flush

Batch volume is larger than vessel size (capacity limitations)

Buffer flush post wash

## Virus Breakthrough after Pressure Release during Virus Retentive Filtration

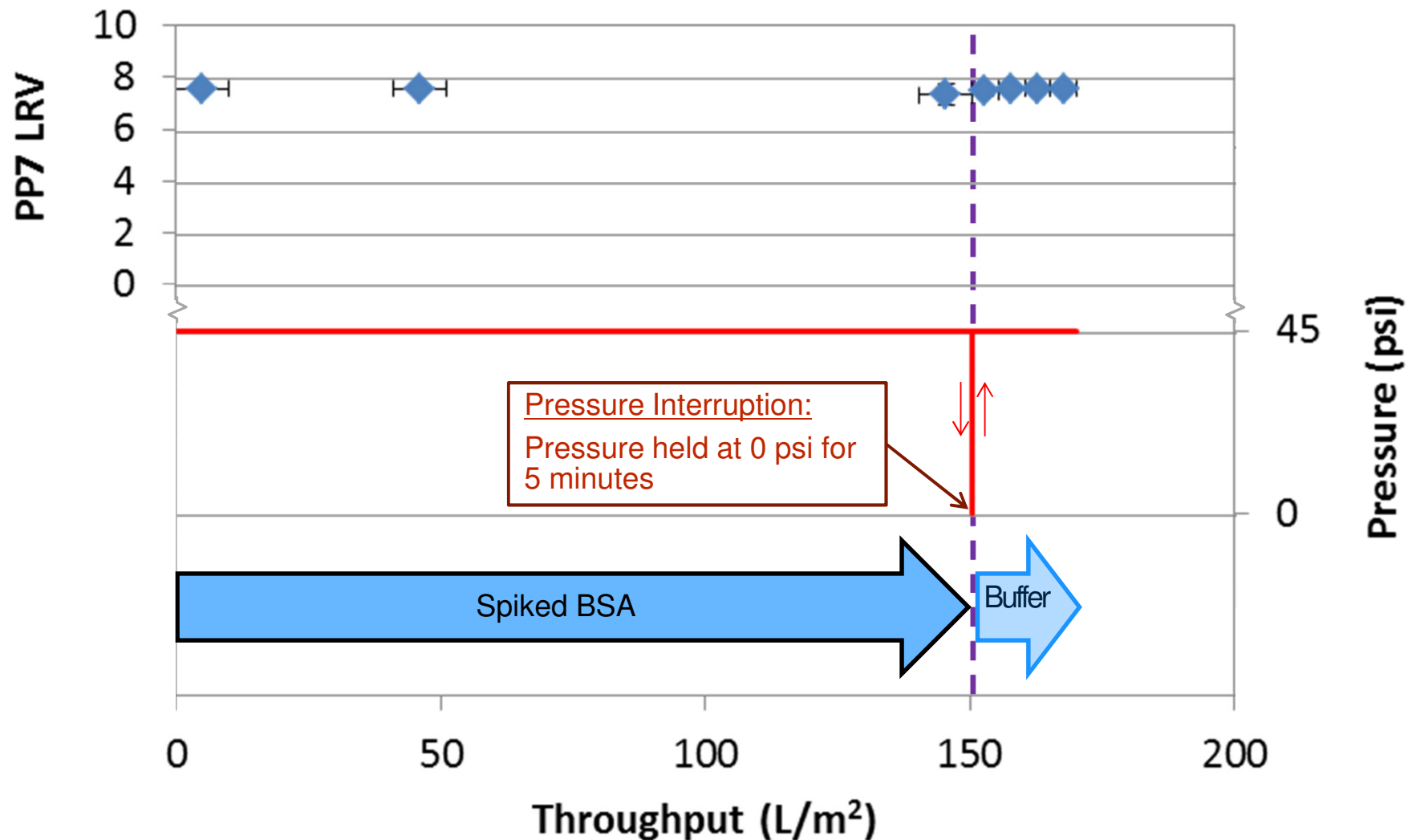
28-June-2012 Informa, Cologne  
Marcel Asper, PhD

charles river

- 1<sup>st</sup> generation parvovirus filters demonstrate variable effects of pressure interruptions (stop / start)
- 2<sup>nd</sup> generation parvovirus filters show more robustness to pressure drop



# Small Virus Reduction in BSA by Pegasus SV4 membrane





# Process Scale

## virus filtration systems

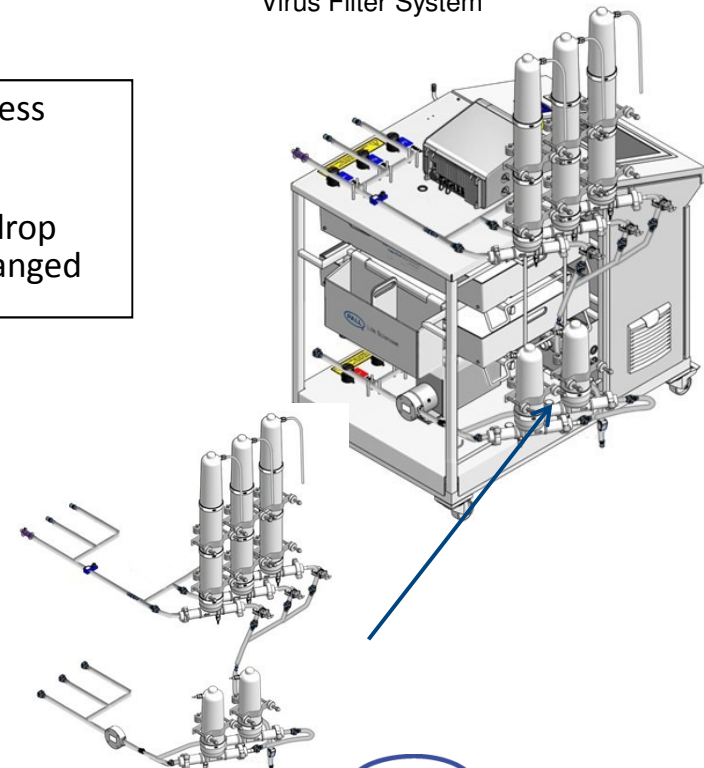
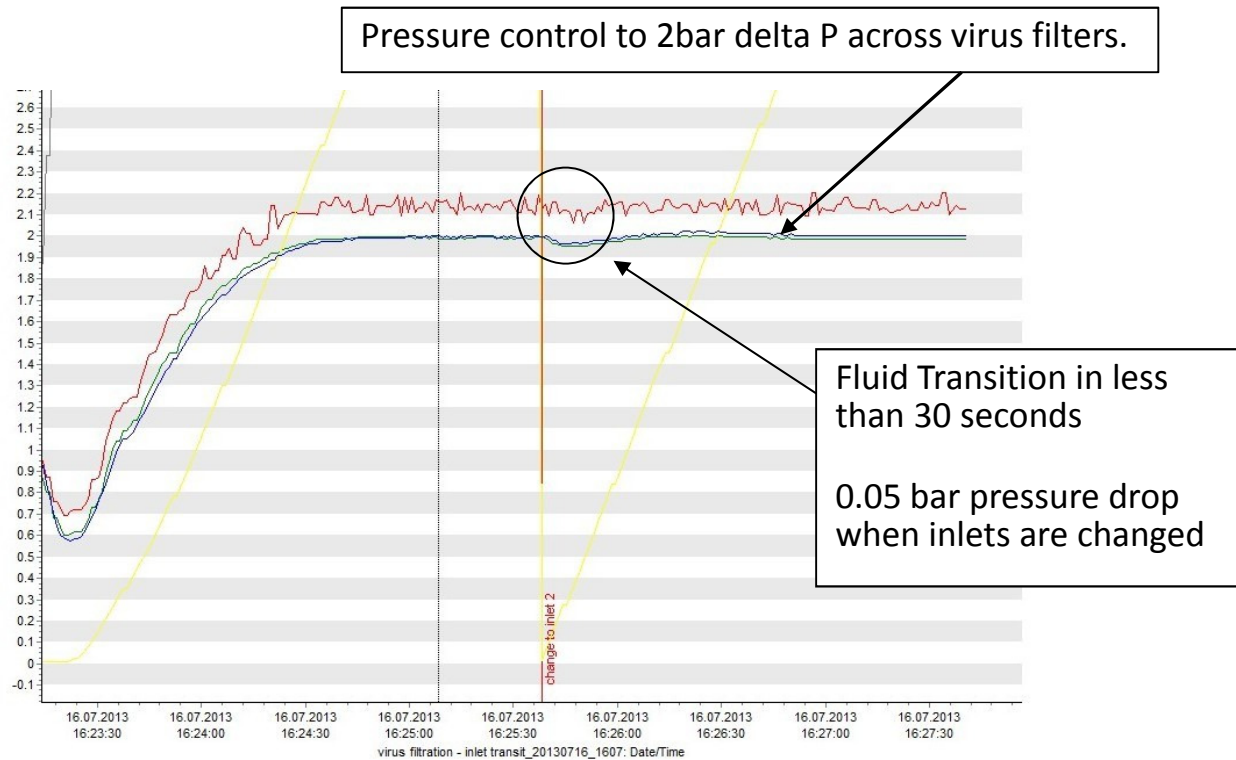
- Control of pressure drop recommended in process systems for all virus filters
- Product to Buffer Flush Transition
  - Automatic transition based on weight input limits.
  - Operator prompt for manual transition to buffer flush.



# Process scale virus filtration systems\*



(\*e.g. MVP Allegro Pegasus SV4  
Virus Filter System







ERROR: stackunderflow  
OFFENDING COMMAND: ~  
STACK: