Virus Filtration for Biosimilars : From needs to Solutions

3rd International Conference and Exhibition on Biowaivers, Biologics and Biosimilars - Hyderabad

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Layout of Presentation

1. Virus Filtration
2. Virus Validation
3. Q & A

Virus Filtration



Virus Safety Issue

Virus	Year	Company	Reported By
EHDV	1988	Bioferon GmbH	Bioferon
MMV	1993	Genentech	Genentech
MMV	1994	Genentech	Genentech
Reovirus	1999	Abbott Labs	FDA
Cache Valley	2000	?	BioReliance
Vesivirus 2117	2003	Boehringer-Ingelheim	BI
Cache Valley	2004	?	BioReliance
Human Adeno	?	Eli Lilly	Eli Lilly
Vesivirus 2117	2008	Genzyme, Belgium	Genzyme
Vesivirus 2117	2008	Genzyme, USA	Genzyme
Vesivirus 2117	2009	Genzyme, USA	Genzyme
PCV 1	2010	GlaxoSmithKline	GSK
PCV 1&2	2010	Merck	Merck

US '96	**MVM**	**Media**	**High Costs Incurred**

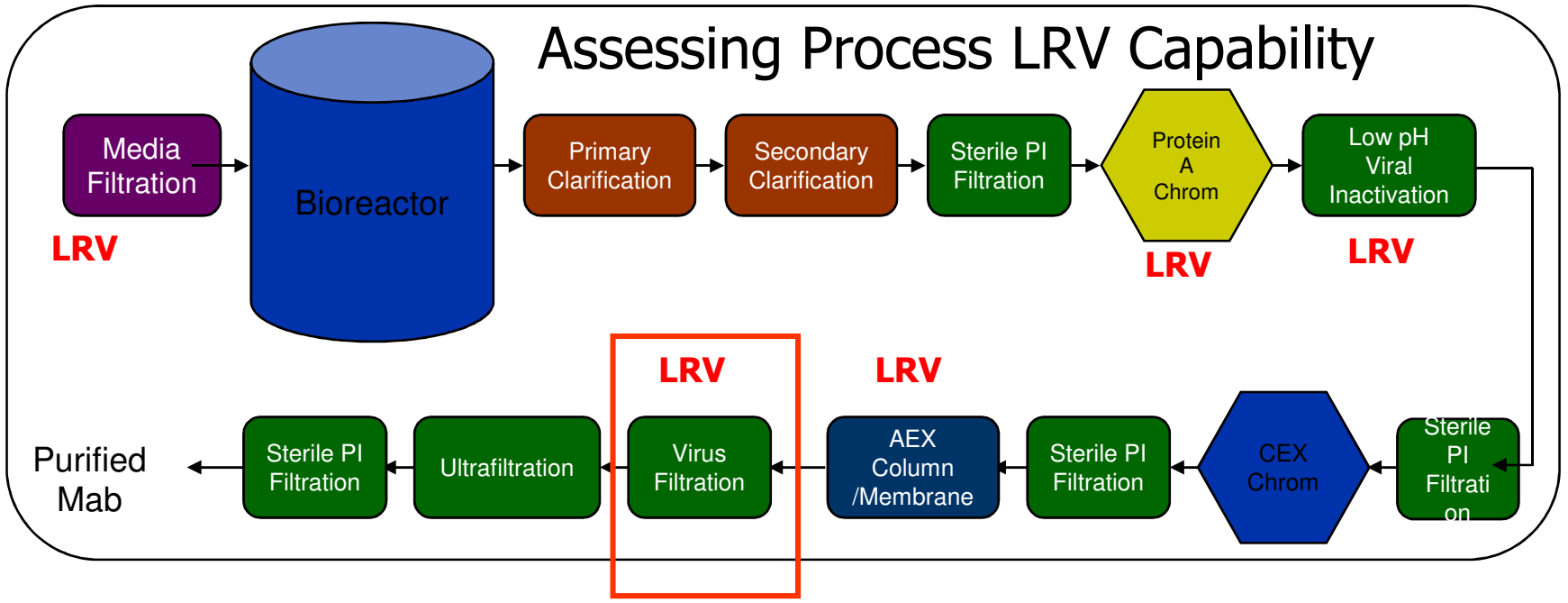
Raw Materials (Selection/Testing)

Cells
- MCB
- WCB

Media
serum→serum-free

Other additives:
- B-Trypsin
- B-Insulin
- BSA
- B-Transferrin
- Pluronic F68
- antifoams

→ animal free



Unprocessed Bulk

Final Product

Testing Products

Regulatory Documents – Viral Safety

ICH Q5A(R1) – 1997:

- "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (1997)" Also under EMEA – CPMP/ICH/295/95
- Provide a general framework for virus testing experiments for the evaluation of virus clearance and the design of viral tests and clearance evaluation studies

Points to Consider – CBER (1997)

- "in the Manufacture and Testing of Monoclonal Antibody Products for Human Use"
- General recommendations around "virus clearance" for inclusion in IND or BLA
  - One or more steps known to *remove or inactivate viruses*
    - At least two orthogonal robust steps e.g. low pH viral inactivation, filtration
  - Demonstration of the ability of a purification scheme to remove adventitious agents & other contaminants by means of a *clearance study*

When is Virus Clearance Data Required?

Clinical Development

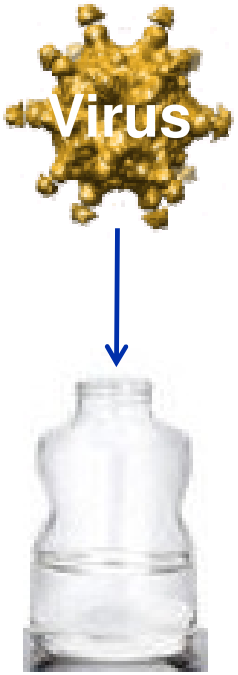


	Phase 1	Phase 3
Viral Validation Requirements	Demonstrate Viral Clearance with: 1) One **Small** Model Virus, and 2) One **Large** Endogenous Virus	Demonstrate **Robustness** with a wide spectrum of viruses of different structure and genome types
Virus Type	MMV (Small Parvovirus) X-MuLV (Large Retrovirus)	MMV (Small, ss DNA, ne) Reo 3 (Large, ds RNA, ne) X-MuLV (Larger, ss RNA, e) PRV (Still Larger, ds DNA, e)

Virus Filter Validation

Best Practices for Success at the Validation Lab

Virus Filtration Challenge Testing



Unspiked Feed

1. Spike Virus



2. Microfiltration
(0.1, 0.22, 0.45)



3. Virus Filter

4. Assay and calculate LRV

$$LRV = LOG\left(\frac{C_{vf}\,V_f}{C_{vp}\,V_p}\right)$$

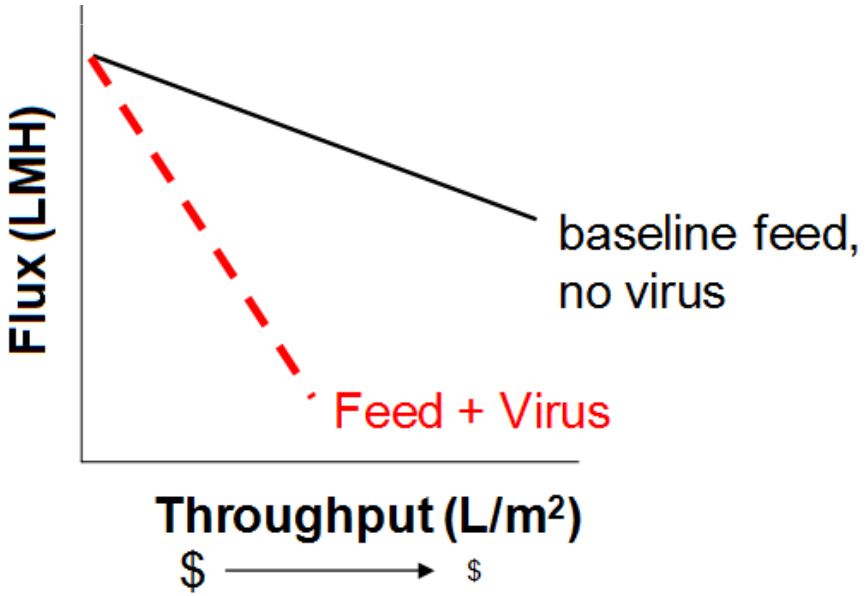
Virus Filter Validation – Challenges

Manufacturing-scale filtration area is based on the achieved spiked throughput of small scale devices.

Throughput reduction could be due to artifacts of the experimental system, such as addition of virus spike.

Artifacts therefore lead to costly oversizing of virus filtration devices and/or failure to meet validation targets.

Artifacts may cause dramatic reduction in throughput

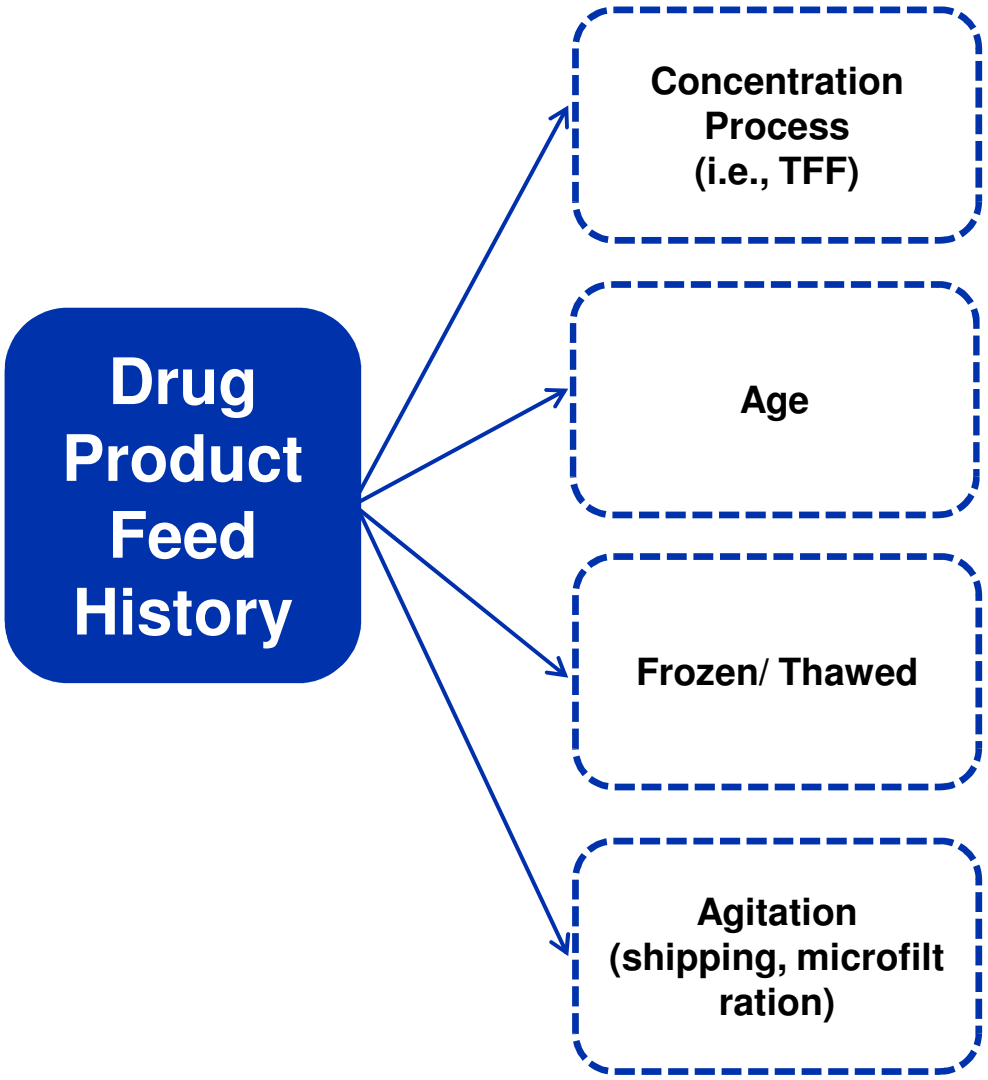


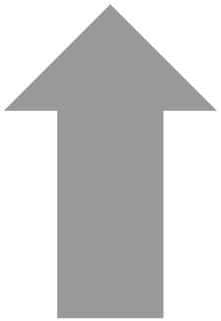
Artifacts of Virus Filter Validations

Non-Representative Feed

Addition of Virus Spike

Non-Representative Feed





Increase in drug product aggregate

Achieving optimal performance is necessary to demonstrate the scale down model of the manufacturing process.

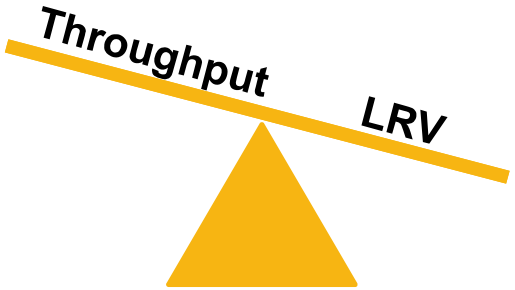
Controlling changes to aggregate levels is the key to optimizing virus filter performance!

Addition of Virus Spike

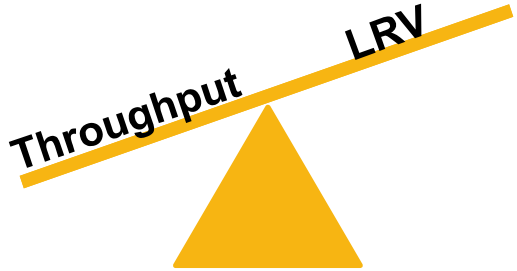
Virus Spike Percentage

Virus Preparation Purity

Virus Spike Percentage: Choosing the Optimal

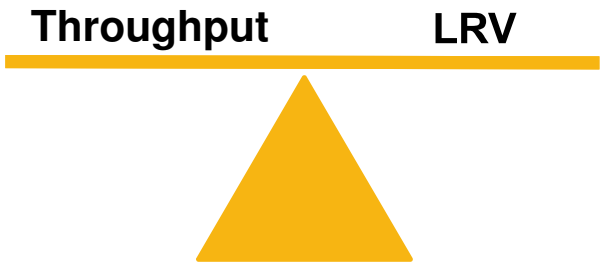


Spike too high, achieve LRV but sacrifice throughput



Spike too low, achieve throughput but sacrifice LRV

Optimal spike percentage dependent on: *spike titer, prep purity, target LRV*



Optimal spike to achieve throughput *and* LRV

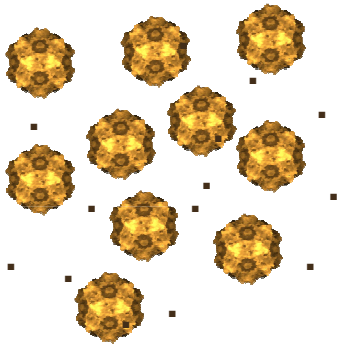
The Trouble with Virus Spikes

Typical "purified" virus preparation



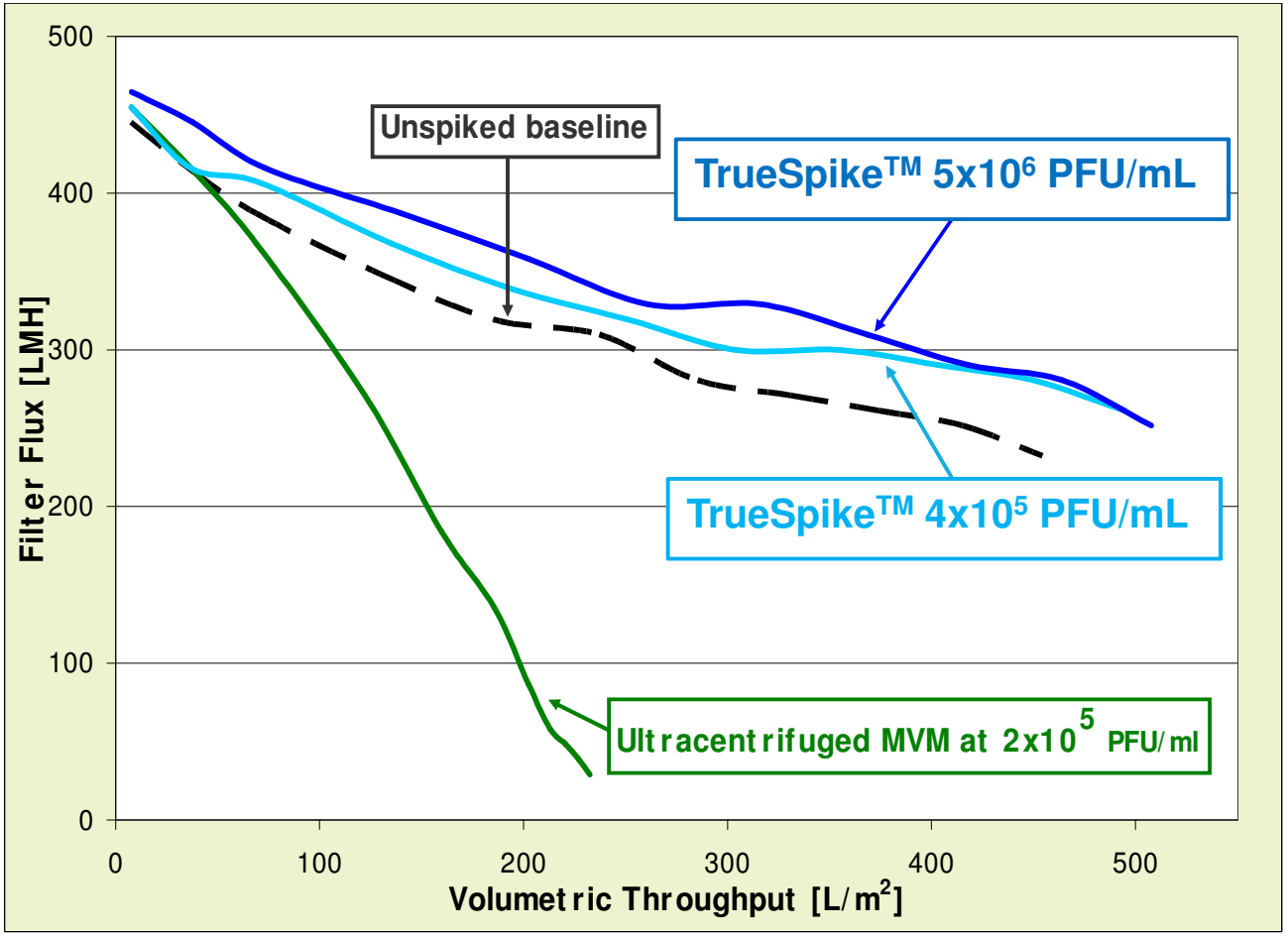
- Contains mostly **non-viral substances**
- Impurities are largely **uncharacterized**
- Virus stocks vary from lot to lot, leading to **unpredictable filtration results**

Advanced approaches to virus prep purification



- Contains **mostly virus**
- **Highly characterized**
- Consistent virus stocks, enabling **reliable filtration performance.**

TrueSpike™ MVM Hydraulic Performance



genzyme | EMD MILLIPORE

Lancaster Laboratories

BioProcess INTERNATIONAL

BioProcess TECHNICAL

Predicting Virus Filtration Performance with Virus Spike Characterization

Damon R. Asher, Ashley L. Slocum, Katherine F. Bergmann, Paul Genest, Amanda B. Katz, Jason J. Morais, Catherine M. Lawrence, and Patricia Greenhalgh

9 g/L mAb feed
(sensitive to virus spike)

Viresolve Pro Devices

Virus Validation – Summary

Prior to the validation study, ensure the artifacts that are inherent do not negate the scale down model.

Mitigating scale-down model artifacts + **High quality virus spikes** + **Optimized virus spike percent**

=

SUCCESS!
(achieve target LRV and target filter throughput)

Summary

Virus filtration is a robust unit operation to ensure product safety used in most bioprocesses

Spiking studies are needed to demonstrate virus clearance capability

Considerable importance should be given to PD & spiking studies to leverage a high throughput at manufacturing.

MM has products, processes & expertise to support our customers in successful PD, spiking support and scaleup implementation of Vpro.

Viresolve Pro: Device Range

Micro Device



- PD Kit – 9 devices
- Validation Kit – 9 devices, 100% integrity tested
- Vent prevents air locking
- Device area and typical volumes*:

  ~3.1 cm² (~0.15 to 0.3 L)

Modus Devices



- Convenient, self-contained disposable format
- 100% air/diffusion and Binary Gas tested by Millipore
- End-user integrity test: air/water diffusion
- Range of devices for small to mid-volume batches*:

  0.017 m² (7.5 to 15 L)
  0.07 m² (30 to 60 L)
  0.2 2m² (~100 to 200 L)

Magnus Devices



- Convenient, stackable format—up to 10m² per holder
- Disposable flow path
- 100% air/diffusion and Binary Gas tested by Millipore
- End-user integrity test: air/water diffusion test
- Range of devices for large batches*:

  0.51 m² (250 to 500 L)
  1.53 m² (750 to 1500 L)

* - Assumes throughput of 500 - 1000 L/m² @ 5 to 10 g/L MAb concentration

Thank You!

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