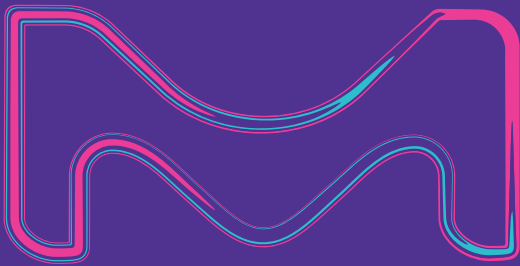


# Continuous Manufacturing - Alignment with Quality Risk Management (QRM) Principles

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The life science business of Merck KGaA,  
Darmstadt, Germany operates as  
MilliporeSigma in the U.S. and Canada.

**Millipore  
Sigma**

# Agenda

Continuous  
manufacturing–  
Alignment with QRM  
Principles

- 1 **Leverage QRM – Take home messages**
- 2 **Regulatory/ Industry QRM Overview**
- 3 **Closed Systems for Continuous Bioprocessing**
- 4 **mAb Production using Advanced Continuous Processing Technologies**
- 5 **Viral Clearance Filtration – QbD overview & continuous process validation approach**
- 6 **Concluding Thoughts – Regulatory Expectations**



# 01

Leverage QRM –  
Take Home messages

## Prior to ICH Q13

# How to leverage a quality risk management approach

### 1 Principles of Practice

Even though continuous bioprocessing is a different manufacturing approach, the same foundation principles can be utilized to manufacture a biologic drug product that is safe and effective.

### 2 Process & Product Understanding

The first recombinant monoclonal antibody (mAb) was approved as a human therapeutic 35 years ago. A templated process has been in place for decades. General industry knowledge is more than sufficient to shift to continuous manufacturing.

### 3 Key Factors to Consider

What are the areas of concern when moving from batch to continuous bioprocessing? It is important to focus and leverage understanding of adventitious agent risk mitigation and overall control strategy.

### 4 Leverage Advanced Design

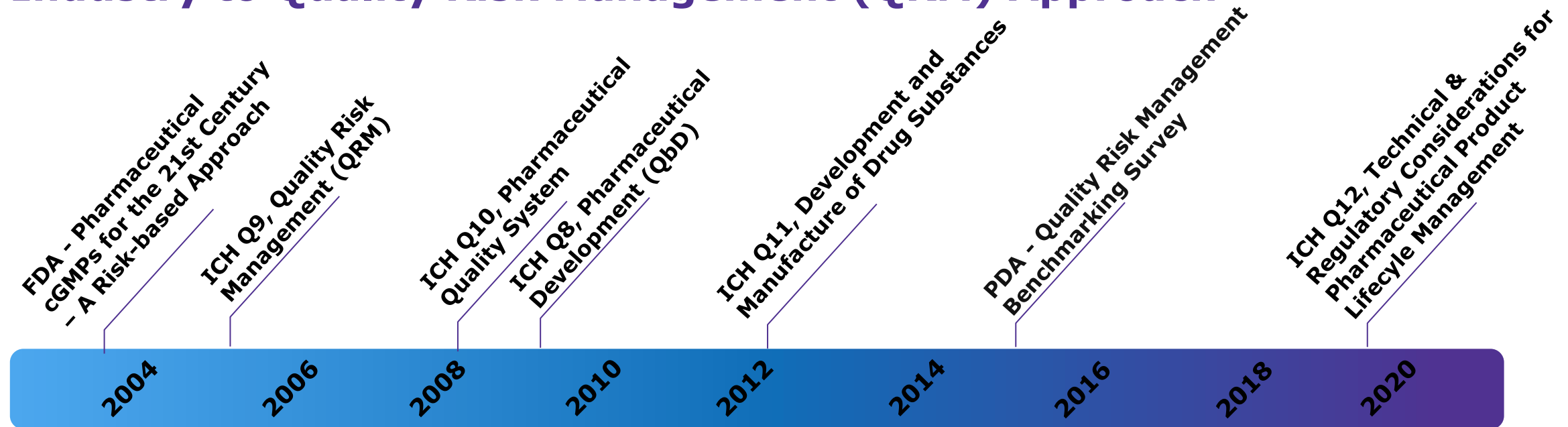
Technologies have advanced both in manufacturing equipment and testing approaches. Let's discuss how single-use, closed systems, and others could mitigate the risk of product quality issues.



# 02

## Regulatory / Industry QRM overview

# Timeline – Regulatory Efforts to Shift Mindset in Pharma/Biopharma Industry to Quality Risk Management (QRM) Approach



**US FDA Warning Letters (2006-2013)** - The majority of citations indicate that there are problems with faulty(20%) or absent (80%) risk assessment.

**2015/2016 - PDA Quality Risk Management Benchmarking Survey** – “the full benefits of QRM have not yet been fully realized”

**Review of QbD dossier submissions in EU\*** - The implementation of QbD for biologics has been quite rare (7% of all QbD dossiers) and virtually all from large multinational companies.

## Legend:

**FDA** – US Food and Drug Administration

**ICH** – International Conference on Harmonization

**QbD** – Quality by Design (not testing!)

**PDA** – Parenteral Drug Association

\* Horst et al., Implementation of Quality by Design (QbD) Principles in Regulatory Dossiers of Medicinal Products in the European Union (EU) Between 2014 and 2019. *Therapeutic Innovation & Regulatory Science* (2021) **55**:583–590.

## Regulators encourage innovation – Why is the industry not moving?

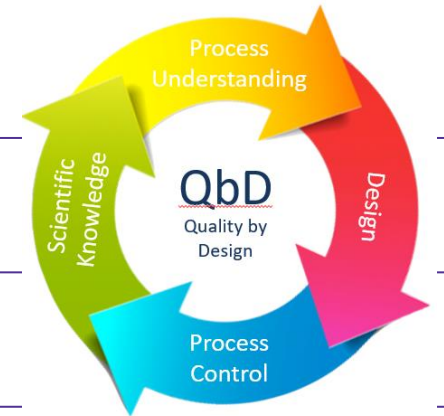
*“Let me just step back another step and say — and this would also disturb some people — that I really think the culture of regulation that we had over the years, [produced] a kind of a **fear relationship**. And I am still told that **industry is in a state of fear, many of them, of FDA**. That kind of a fear relationship is not going to grow a quality culture, because there is a fear of adverse consequences... That is antithetical to the idea of a quality culture, where people own quality and say, ‘we can stand up to the FDA because we make a quality product, and we know it and we monitor it, and we are proud of it. That is our quality culture.’”*

Transcript from April 2015 International Society of Pharmaceutical Engineering (ISPE), quality metrics meeting. Quoted by Dr. Janet Woodcock, currently acting commissioner of the US FDA and head of CDER.

## Regulators Encouragement for...

# A paradigm shift in manufacturing operations regulatory oversight

Rule-Based	Risk-Based Compliance
<ul style="list-style-type: none"> <li>• “Box checking” approach—or dotting i’s and crossing t’s—in order to ensure your organization is obeying prescribed rules and regulations.</li> </ul>	<ul style="list-style-type: none"> <li>• Depends more heavily on analysis in order to circumvent risks or determine risks worth taking</li> </ul>
<ul style="list-style-type: none"> <li>• Quality by “testing”</li> </ul>	<ul style="list-style-type: none"> <li>• Quality by “design”,</li> <li>• based on ICH Q8</li> </ul>
<ul style="list-style-type: none"> <li>• <i>Subscribing</i> to established rules</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Spurring</i> new and innovative processes</li> </ul>
<ul style="list-style-type: none"> <li>• Tactical</li> </ul>	<ul style="list-style-type: none"> <li>• Strategic</li> </ul>
<ul style="list-style-type: none"> <li>• Risk Aversion</li> </ul>	<ul style="list-style-type: none"> <li>• Value Creation</li> </ul>
<ul style="list-style-type: none"> <li>• Driven by a <b>siloed</b> compliance department or <b>siloed</b> initiatives in various departments.</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Integrating</b> departments, technology systems and processes is necessary to determine the <b>overarching</b> risks and how they should be handled—whether it’s to avoid their implications or drive value</li> </ul>





# Make it Easier to Conform with CGMP



**"A number of technologies and resources are available that can facilitate conformance with CGMP and streamline product development, including use of:**

- **Disposable equipment** and process aids to reduce cleaning burden and chances of contamination
- **Commercial, prepackaged materials** (e.g., WFI, pre-sterilized containers and closures) to eliminate the need for additional equipment or for demonstrating CGMP control of existing equipment
- **Closed process equipment** to alleviate the need for stricter room classification for air quality
- **Contract or shared** CGMP manufacturing facilities and testing laboratories (including specialized services). For example, some academic institutions have developed shared manufacturing and testing facilities that can be used by institutional sponsors."

# Monitor and Control Quality via Partnership with Supplier

“Only a partnership with a SUS\* supplier can ensure that quality is as good as, or better than what is achieved with traditional systems.”

Robert Repetto, Pfizer,  
Co-Author PDA Technical  
Report 66.

\*SUS = Single-Use System

## End User

- Process and Manufacturing Knowledge
- System Design and Operation
- Product and Patient Knowledge
- Internal Procedures and Controls
- Risk Tolerance / Past Experience



## Supplier

- Experience across a variety of processes
- Material/Component Knowledge
- Product/Service Technical Expertise, including qualification and design
- Product Manufacturing and Controls
- Product Shipping and Handling Best Practices



# 03

Closed Systems = bioburden  
control

## Why Closed Systems?

Closed-system processing using single-use technology might be an attractive option for a range of biomanufacturers with different motives. These could include:

- **Continuous manufacturers operating processes for many weeks at a time and wanting to avoid a build-up of bioburden within their equipment**
- Reduce Facility Costs
- Scenarios where temporary bioproduction is required.

### Advantages:

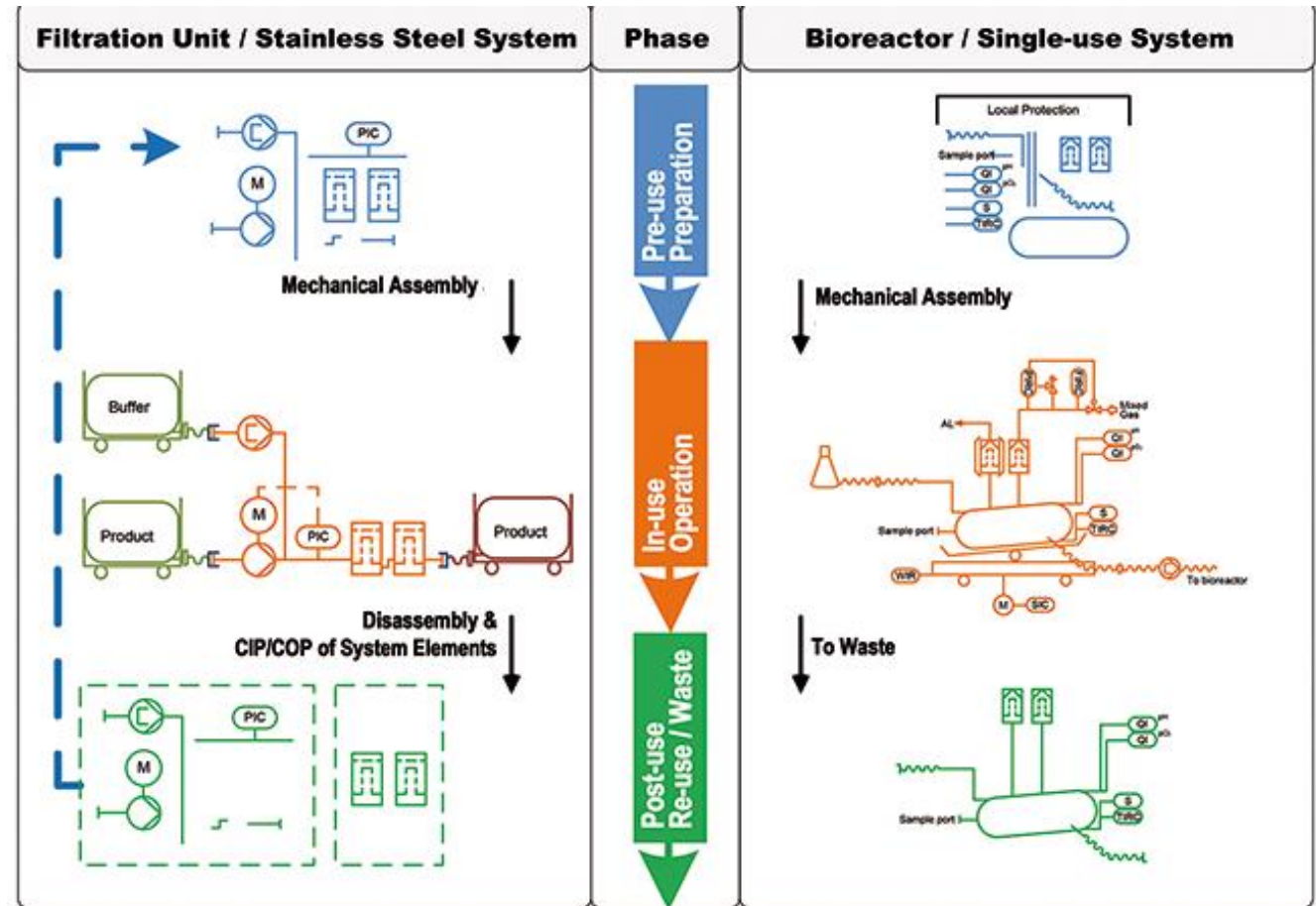
- The risk of contamination is greatly reduced, due to the **physical barriers** protecting the product from human contact.
- Closed systems **reduce operating time** by relying less on operator handling and more on pre-assembled components.
- Operations can be **performed in lower classification cleanrooms** reducing the costs

# Closed system life cycle – emphasis on bioburden control

**Pre-use:** System is prepared to the required level of **integrity, cleanliness, and bioburden**.

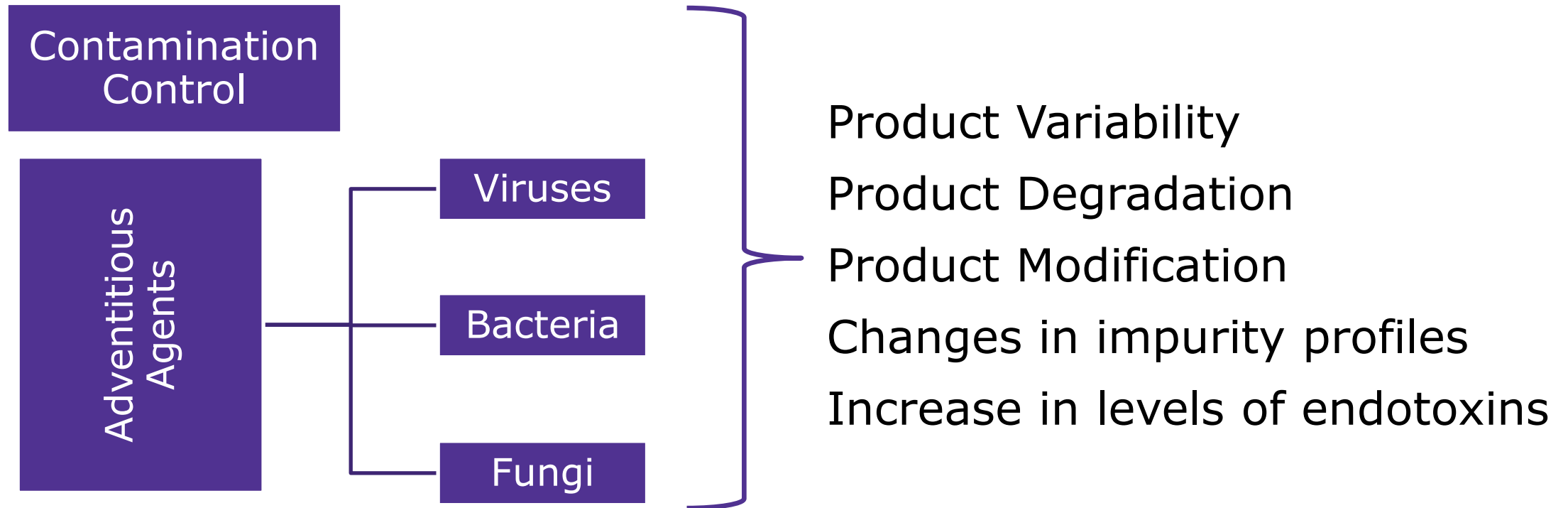
**In use:** The closed system is in production, known as “**closed processing**.” Connections and disconnections are critical in the design to maintain closure; mitigate risk with sterilizing grade filters

**Post-use:** Measurements should verify that closure was maintained during processing. If the system or its components are cleaned and sanitized, storage and/or transport should protect their closure.



## Closed bioprocess

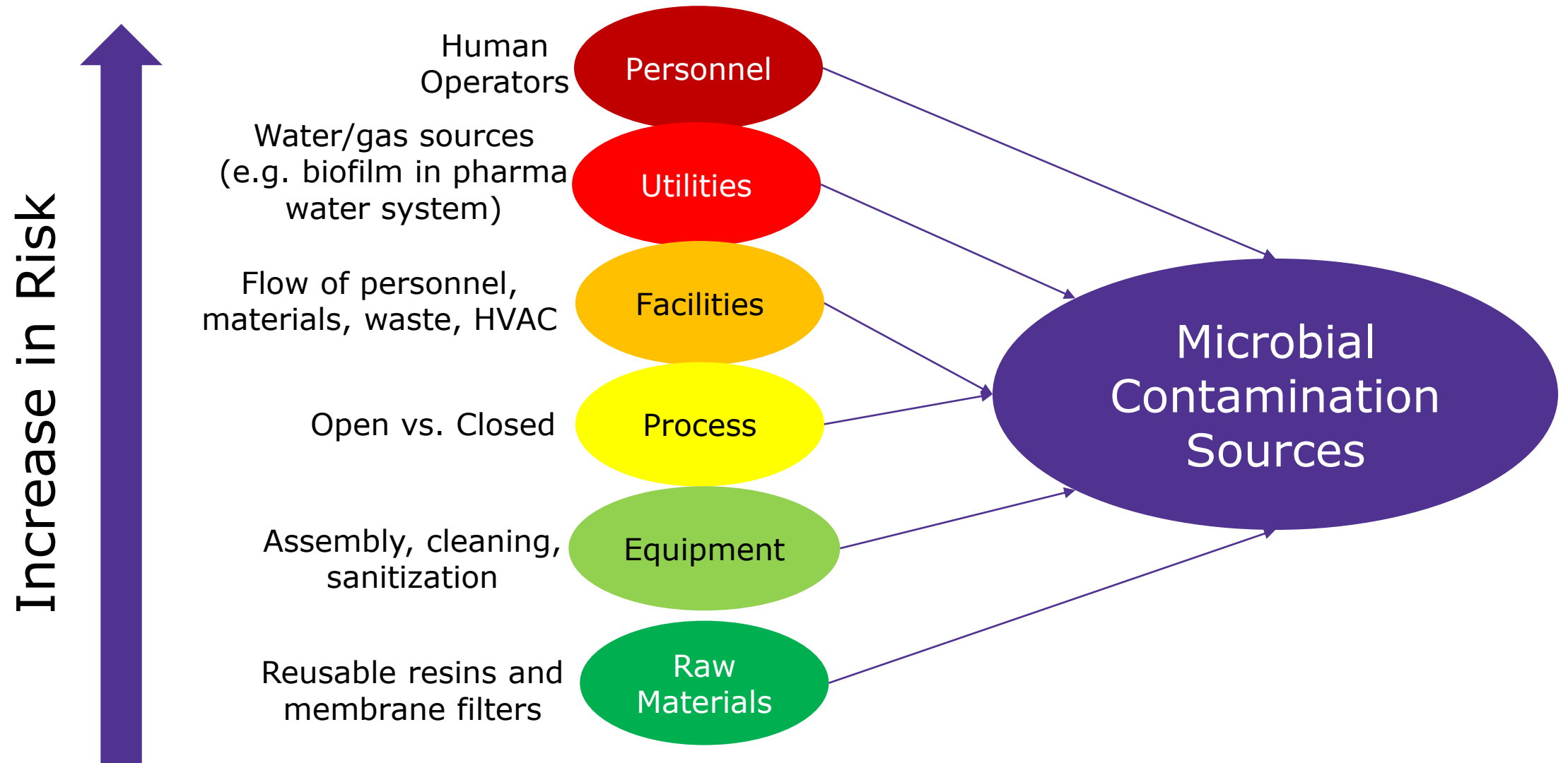
### Regulators highlight contamination control strategy\*...



- \* (1) Perform risk assessments on a periodic basis and (2) Continuous improvement in quality risk management

[Source: Case Studies of Microbial Contamination in Biologic Product Manufacturing | American Pharmaceutical Review - The Review of American Pharmaceutical Business & Technology](#)

# Risk Factor Hierarchy for Microbial Contamination



Source: Case Studies of Microbial Contamination in Biologic Product Manufacturing | American Pharmaceutical Review - The Review of American Pharmaceutical Business & Technology

# Bioburden control

## What regulatory findings have happened historically?

Upstream	
Issue	Corrective Action
Problems with the sampling devices	Replacement of a membrane valve in the sampling device
Addition valve issues	A preventive maintenance plan for valves was instituted.
Incorrectly fitted components	Installation SOPs were updated with pictures/figures.
Missing O-rings	Replacement of O-rings
Incorrect installation and deformation of an air filter after sterilization	All installation SOPs were updated and employees were trained on the revised versions.
Inadequate slope of a condensate line	SOPs were updated to check for slope of condensate line

Downstream	
Issue	Corrective Action
High bioburden counts in several batches - development of biofilm and inadequate contamination control procedures for the UF/DF steps.	Cleaning, storage and reuse of UF/ DF systems
	Assessment of the water for injection (WFI) system and transfer lines
	Revisions to bioburden limits based on process capability
	Sanitization of buffer tanks
	Validation of hold times and storage conditions of process intermediates
	Introduction of in-process bioburden reducing filters (in cases where there were no filters before the UF/DF steps)

The minimum current good manufacturing practice (CGMP) requirements for preparation of finished human drug products are described in 21CFR 211. These include the use of suitable protective apparel (21CFR 211.28), appropriate facility design and placement of equipment (21CFR 211.42), equipment cleaning and maintenance (21CFR 211.67), and production and process controls (21CFR 211.100).



# Closed Bioprocess and Bioburden control

## General Comments

General	Specific & Relevant
Understand the microbial entry points	Closed systems “block” microbial entry
Appropriate design of facility and equipment	Single-use systems and automation offer flexibility to facility design with ballroom concept, eliminating risks of contamination from personnel, material, waste handling
Validated cleaning and sterilization cycles for equipment	Single-use systems eliminate this requirement. Sterilization is only necessary for high-risk operations, such as at and post final sterilizing grade filter.
Measures to reduce bioburden and bacterial endotoxins at appropriate steps in the process	Bioburden and endotoxin controls for raw materials and equipment. Principles of practice are the same for single-use, closed and continuous processes.
Routine monitoring of these process steps for bioburden and endotoxin with defined alert and action limits.	Same principles of practice

[Source: Case Studies of Microbial Contamination in Biologic Product Manufacturing | American Pharmaceutical Review - The Review of American Pharmaceutical Business & Technology](#)

# Closed bioprocess and Bioburden Control

## Focus on Chromatography – Questions/Answers

**Q:** What about chromatography columns, in terms of microbial contamination?

**A:** The columns, once packed, are closed. Storage and sanitization solutions which mitigate microbial contamination have been well-studied and implemented for years.

**Q:** What about sterilizing pre-packed chromatography columns by irradiation (e.g. gamma, X-ray, ebeam)?

**A:** Avoid manipulations that will cause chemical damage to the column, which has the potential to negatively impact the function of the column separation. I would track all specifications and be wary of any changes, even within acceptable ranges.

**Q:** What about gamma irradiation of single-use systems?

**A:** These polymeric materials have been studied more extensively by the medical device industry and their function may not be correlated to chemical properties but more physical characteristics. Even in the medical device industry, incidents regarding needle bonding adhesives and PVC material chemical changes have been detrimental.

### PROPOSAL:

Avoid irradiation exposure for all chromatography resins and membranes.

- Risk of affecting chemistries and affinity ligands far outweigh benefits of sterilization.
- Experts highlight that "principles of practice" for chromatography bioburden controls have not changed.

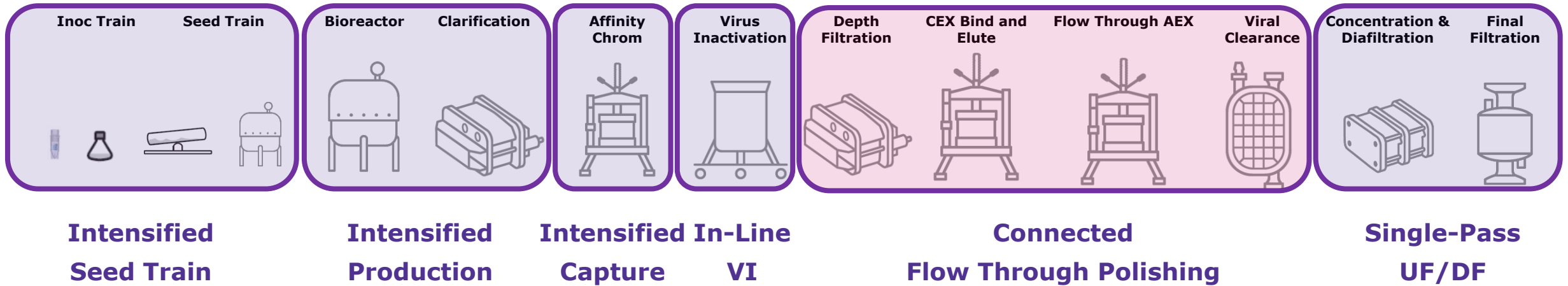


# 04

## mAb continuous processing technologies

# Next Generation Processing

## Evolution: Batch → Intensified → Continuous



Product  
Manager –  
Cindy Delagree



MCC



iVI

### Operating Scale

- 2,000 L SUB operated in fed-batch mode
  - Single harvest with 2.5 day batch cycle
- 1,000 – 2,000 L SUB operated in perfusion mode
  - Continuous harvest for 20-30 days
  - Target flowrate of 1,000- 2,000 L/day

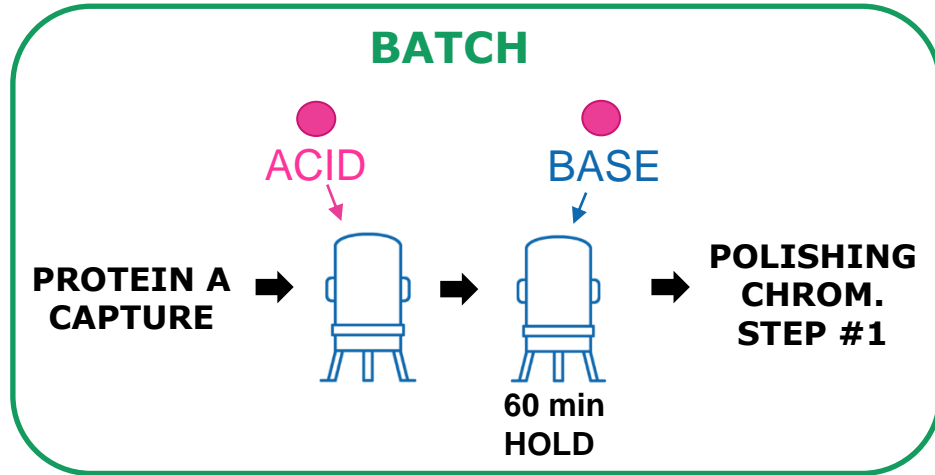
# Risk Mitigation through Design – Focus on Bioburden

## Mobius® Multi Column Capture System

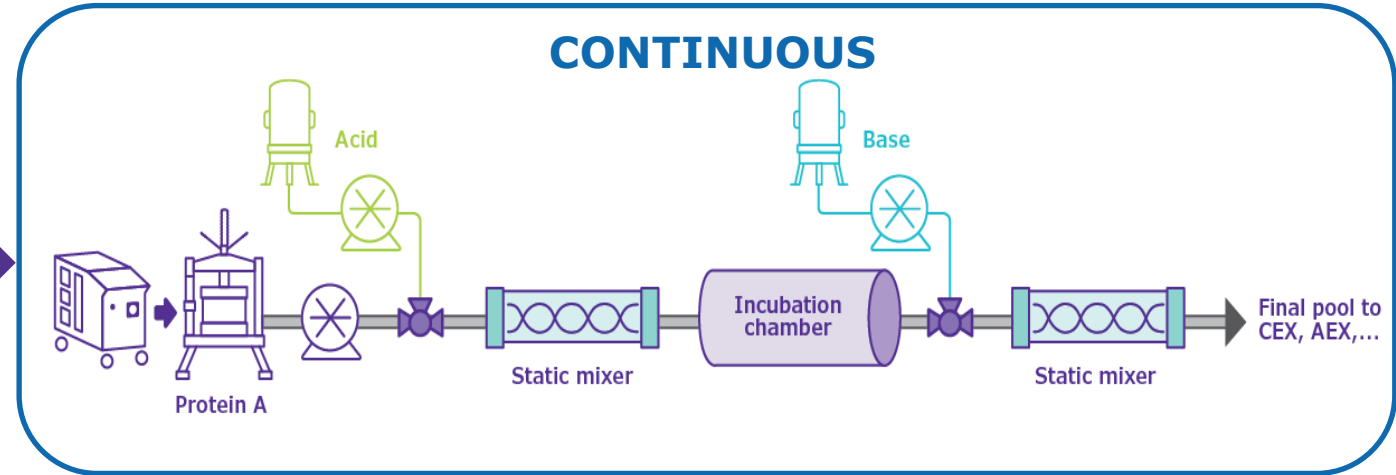


Risks	Mitigation
<b>Static</b> – the fluid flows (i.e. flushes) slowly or does not flow in sections of the system (i.e. dead leg)	<b>Design system to be dynamic</b> with fluid continually flowing, especially around valve junctions. Test for flow flush timing and worst-case conditions.
<b>Bioburden generated during process itself</b> , based on risk of upstream impact of cell culture media and host cell artifacts.	<b>Bioburden reduction filter</b> (0.2 um) to mitigate microbial entry point from upstream. Additional filters may be added within system, but not necessary.
<b>Bioburden results from non-sterilized chromatography columns run for 20-30 days</b>	<b>Bind/elute</b> (Protein A affinity chromatography) mitigates risk versus flow through. Chromatography columns undergo <b>sanitization</b> cycles.
<b>Bioburden present in single-use system components</b>	<b>Pre-gamma irradiated</b>
<b>Human operator errors</b>	<b>Automated system</b>

# Continuous In-Line Virus Inactivation



**Industry standard: 60 minute hold**  
**Robust inactivation > 4 LRV**  
**2 holding tanks required**  
**Manual process**



**Continuous pH adjustment with dynamic hold**  
**Eliminates large holding tanks**  
**Automated**  
**Enables continuous operation**



**Applicability dependent upon:**

- Residence Time
- Virus inactivation kinetics
- Efficient incubation chamber design

# Risk Mitigation through Design – Focus on Bioburden

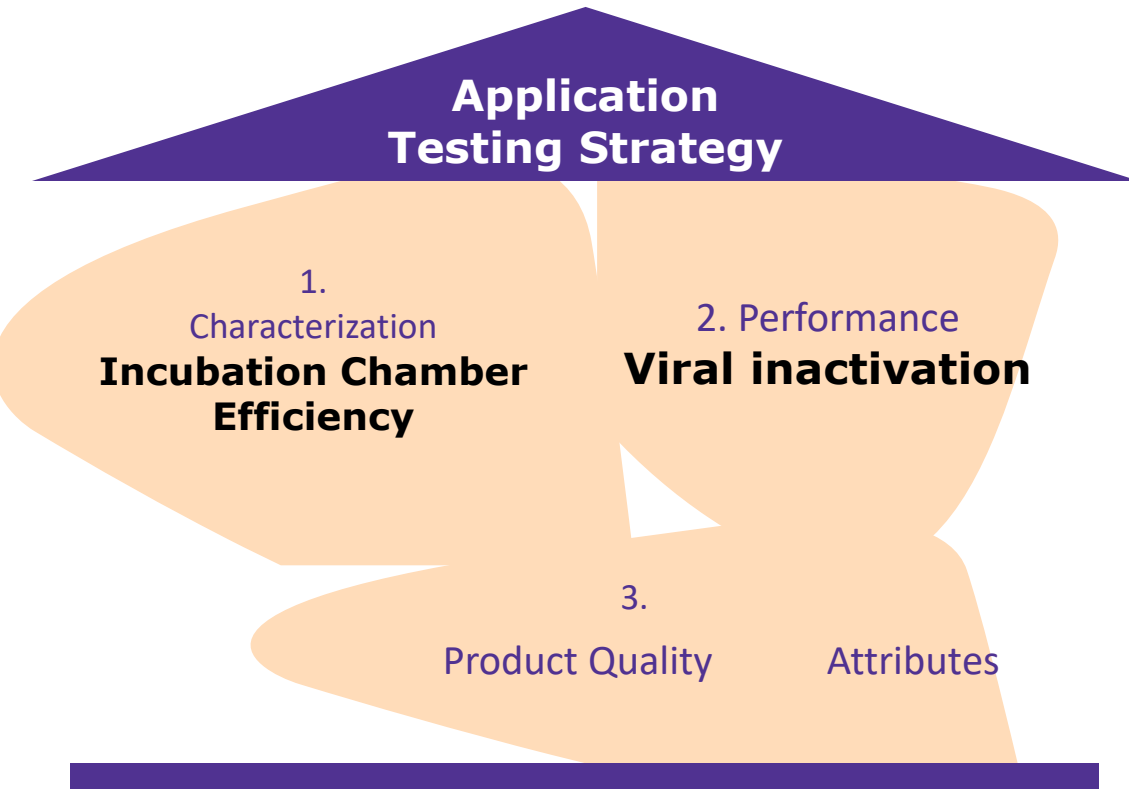
## Mobius® inline Virus Inactivation



Risks	Mitigation
<b>Static</b> – the fluid flows (i.e., flushes) slowly or does not flow in sections of the system (i.e., dead leg)	<b>Design system to be dynamic</b> with fluid continually flowing, especially around valve junctions. Test for flow flush timing and worst-case conditions.
<b>Bioburden generated during process itself</b>	<b>Limited Risk</b> – further downstream, low pH conditions
<b>Bioburden present in single-use system components</b>	<b>Pre-gamma irradiated</b>
<b>Human operator errors</b>	<b>Training and instructions</b> for specific inputs, along with <b>automated system</b> controls

# Regulatory Acceptance

## Application Testing Strategy – 3 Pillars



### ❖ Viral Inactivation Performance

- In-line performance robustly meets ASTM 2888 Standard (30-60 min residence time)
- Inactivation kinetic studies to support short duration hold (~10 min)
- Comparability of batch and in-line kinetics (batch performance predictive of in-line) + product quality attributes

### ❖ Incubation Chamber Efficiency

- Chamber design for robust, reproducible, and predictable performance
- Safety factor analysis to “guarantee” 5+ LRV
- Scalability from bench to commercial scale to support validation studies





# 05

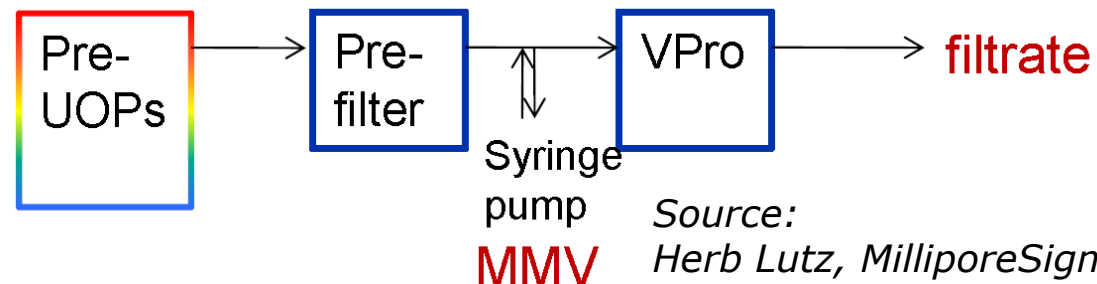
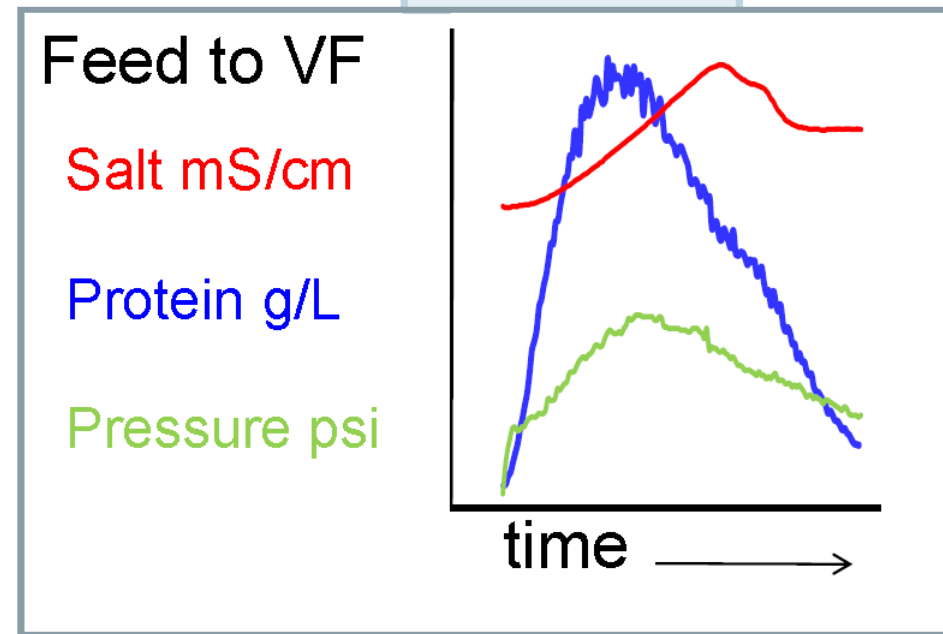
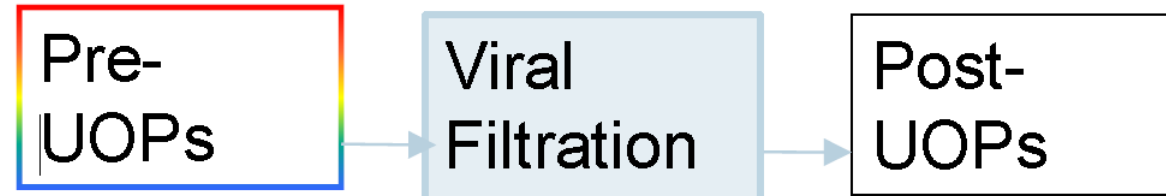
## Viral clearance filtration – QbD and Validation

# In-Line Spiking: Viral Clearance Validation for Continuous Processing

## Key considerations -

- Sequential unit operations are started before the previous steps are completed.
- Virus filter or other clearance step sees variable operating feed parameters.

*ICH Q5A - Measure virus removal using scaled down models that mirror large scale production to ensure that the virus removal results can be translated to the biotherapeutic product.*



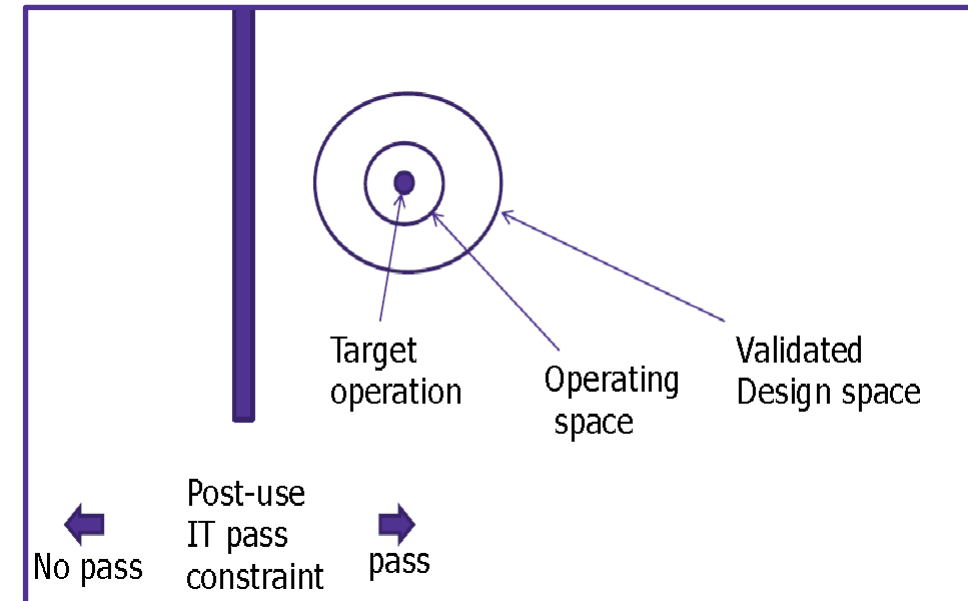
Source:  
Herb Lutz, MilliporeSigma

Millipore  
Sigma

# MilliporeSigma and MedImmune

## QbD collaboration – viral clearance filtration (Viresolve Pro)

- Resulted in the production of a knowledge package under QbD principles
  - Can be adopted by different users of Viresolve Pro and for different molecules
  - Addresses a previous gap in scientific understanding for regulatory filings
- In-house and vendor data can work synergistically to inform
  - Risk Assessments
  - Process characterization plans
  - Control strategy
- Cumulative (load volume and recovery flush) was identified as the only CPP for viral filtration – *conservative approach*
  - Based on mode of action
  - Need for additional project specific data to determine impact of amount load
  - Possibly downgraded after additional studies
- Knowledge package is very useful but does not preclude the implementation of in-house studies



Source:  
Herb Lutz, MilliporeSigma



# 06

## Concluding Thoughts

## Concluding Thoughts

### Regulatory agencies...

- Are supportive of **innovative biopharmaceutical manufacturing**, including continuous manufacturing (CM). However, there is a lack of experience.
- Encourage the implementation of continuous manufacturing using a **science and risk-based (QRM) approach**.
- Recommend **early and frequent discussions with Agency** before implementation to ensure there is a mutual understanding.
- Highlight that current regulatory framework is adequate to allow CM (ICH Q7, Q8, Q9, Q10, Q11, etc). ICH Q13 will harmonize definitions and make things more efficient, but **existing guidelines are supportive**.
- Expect a level of detail and understanding **about control strategy** based on the risk.



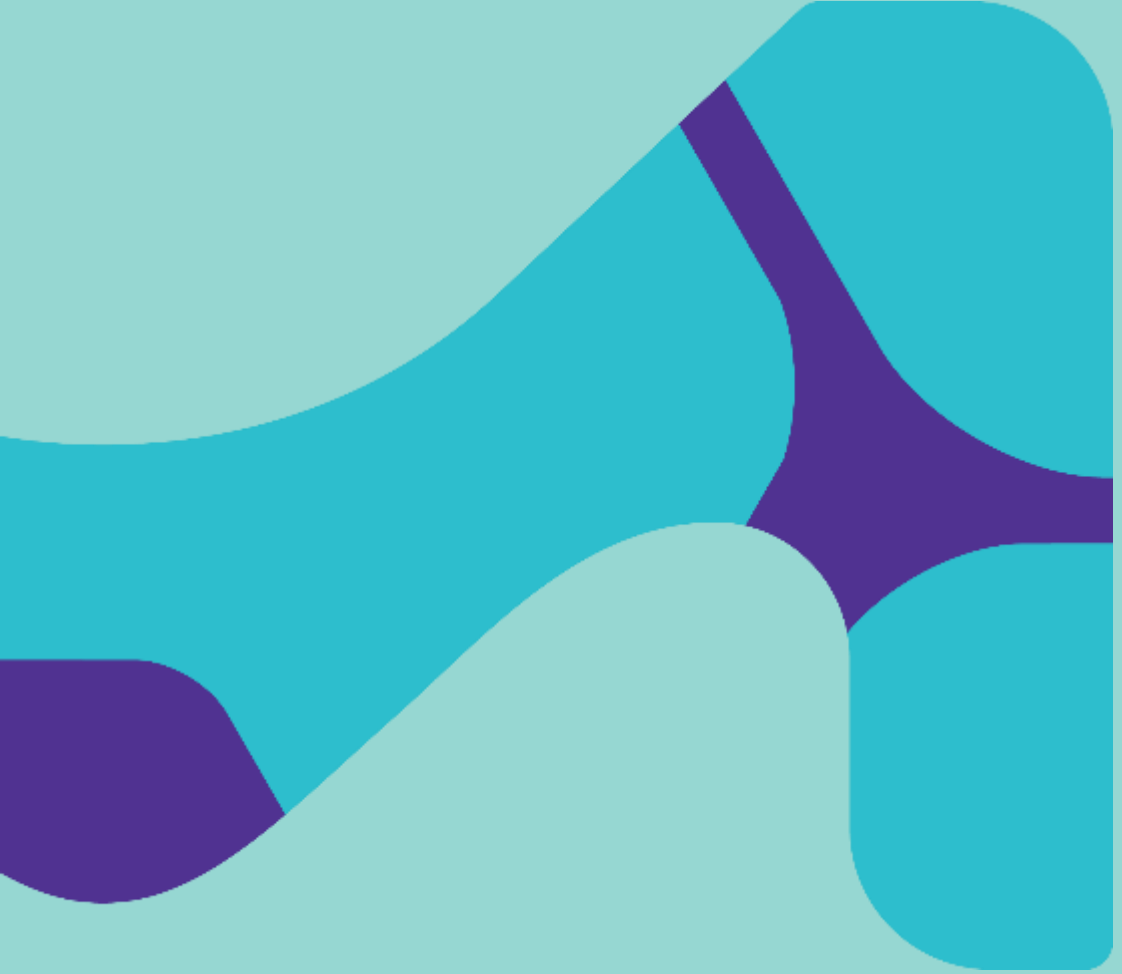
# Acknowledgements

MilliporeSigma Colleagues:

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Herb Lutz – Thought Leader Expert

Cindy Delagree – Product Manager



Thank  
You

