SIGNIFICANTES AVANÇOS TECNOLÓGICOS QUE POSSIBILITAM A INTEGRAÇÃO DE BIOPROCESSOS CONTÍNUOS

Farm. Juan M. Centeno Crowley
Scientific & Laboratory Services
Pall Biopharmaceuticals

Juan M. Centeno Crowley
Farmacêutico (Universidad de Buenos Aires)

- **Pall Biopharmaceutical (Actual):** Scientific & Laboratory Services. Senior Technical Support. Project management, upstream/downstream filtration scale-up (Direct Flow Filtration, Tangential Flow Filtration, Chromatography, process validation/support, and product technology transfer).
- **GemaBiotech (2006-2011):** Provide molecular biology support to develop new strategies for cloning and expression of recombinant target proteins in mammalian and bacterial systems. Downstream process.
- **Instituto Fundación Leloir (1999-2006):** Research project entitled "Interaction mechanism of the antibodies binding with its DNA target". I investigated the molecular basis of this interaction, using spectroscopic and biophysical methods to generate and integrate the structural data with a mechanistic analysis.

Vision for Continuous Bioprocessing

Leading provider of integrated platform technologies for continuous manufacturing of biologics

- ***Platform***

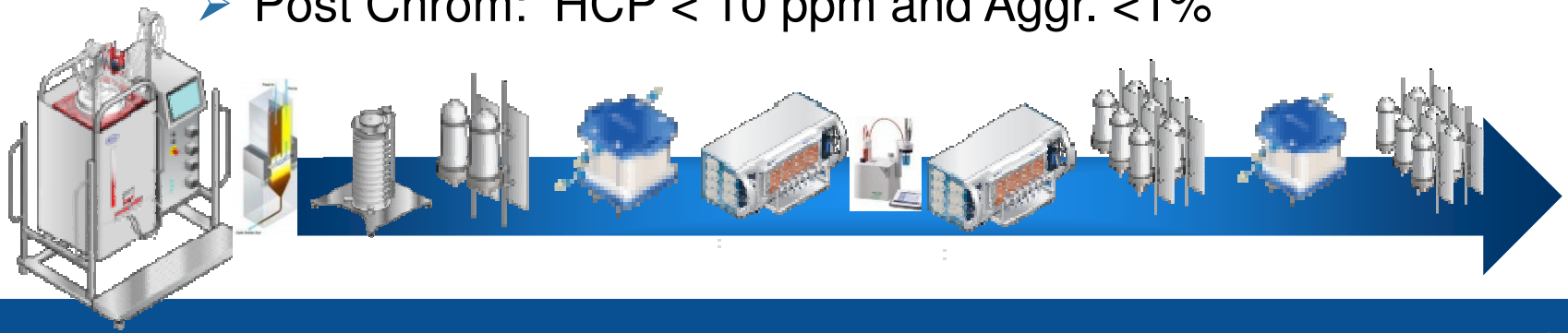
  Robust across multiple molecules (>75%) at multiple scales from PD > Clinical > Commercial Manufacturing

  Ability to complete process development within four weeks

  High overall yield (65%)

  Meets/Exceeds purity requirements

  - Post Chrom: HCP < 10 ppm and Aggr. <1%

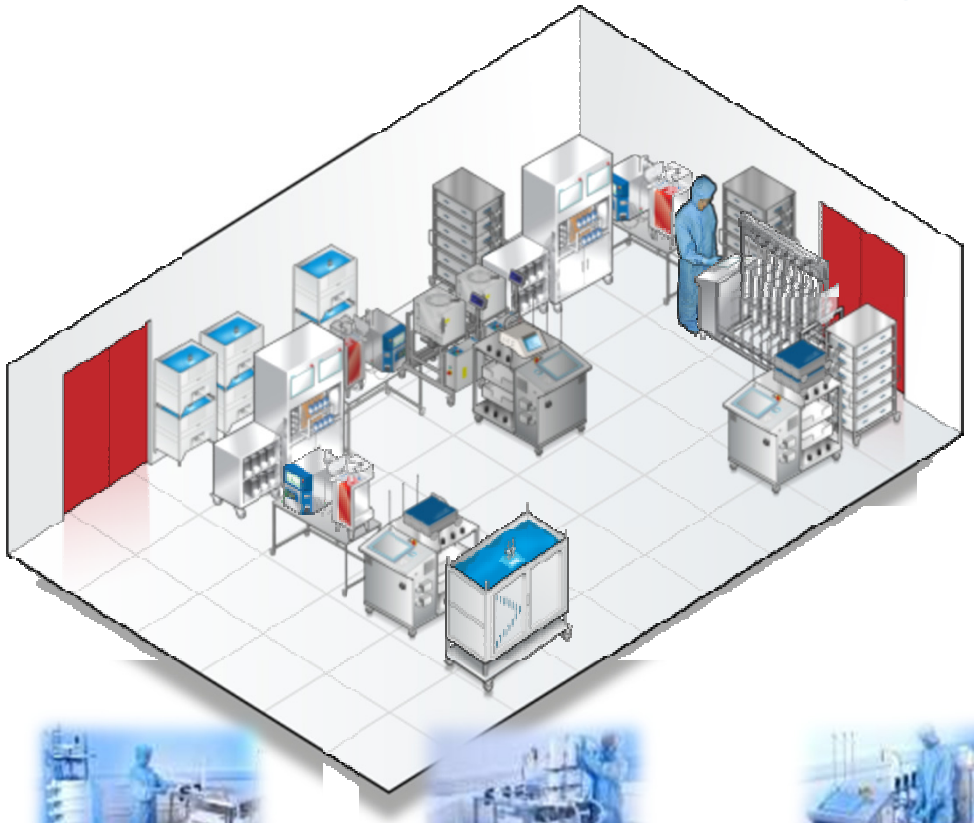


Factory of the Future: What does Continuous Processing enable?

- **Attributes for Next Gen Facilities**
  - Flexibility
  - Designed for smaller batch sizes/ runs
  - Quality built in to process
  - Real time release
  - Localization/in country

- **Fundamental Components Required**
  - Single Use Technology
  - Connected Continuous Downstream Production
  - Modularity in facility design for implementation
  - Possible connection of Upstream and Downstream
  - In-line and at-line analytics

Critical Skills for Building the Factory of the Future



System design expertise

Leading edge application understanding for ALL unit operations

Full understanding of regulatory requirements

Depth filtration

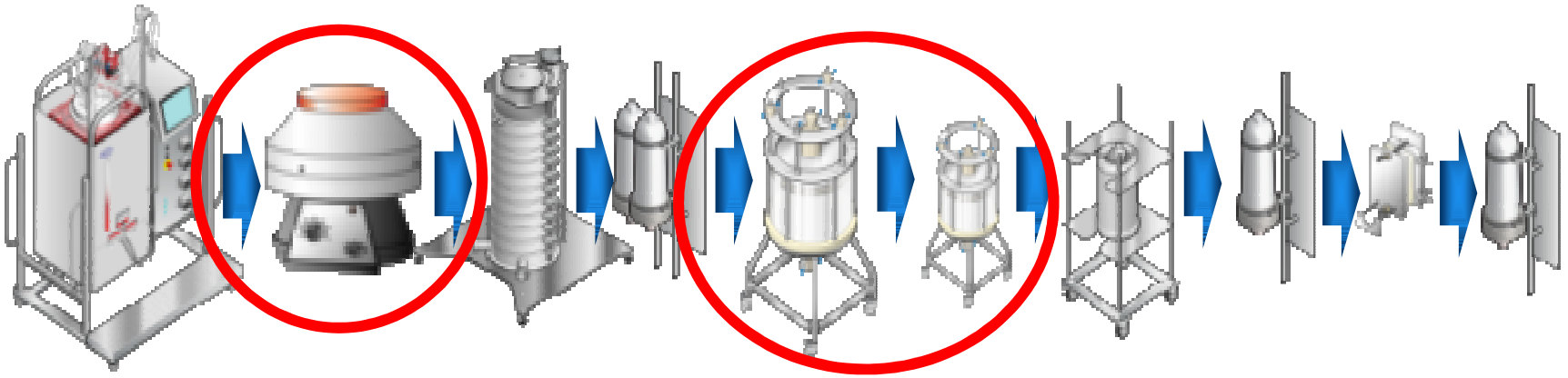
Virus filtration

Virus inactivation

Chromatography & Membranes

Buffer & media prep

Lean Thinking: From Batch to Continuous



Eight Wastes in Production

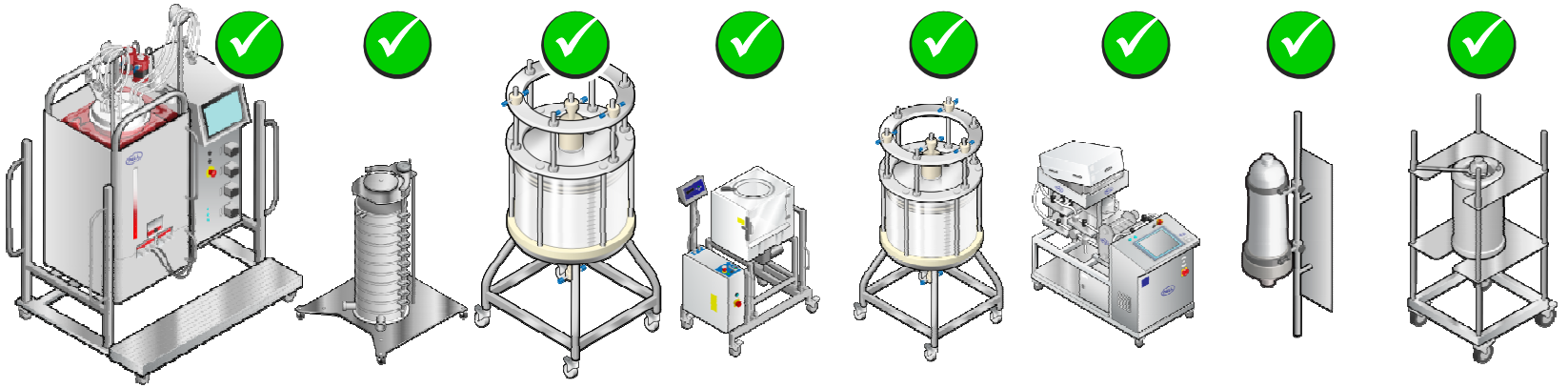
Defects
Overproduction
Non-Utilized Talent
Motion
Transportation
Waiting
Inventory
Extra Processing

Lean ***"One Piece Flow"***

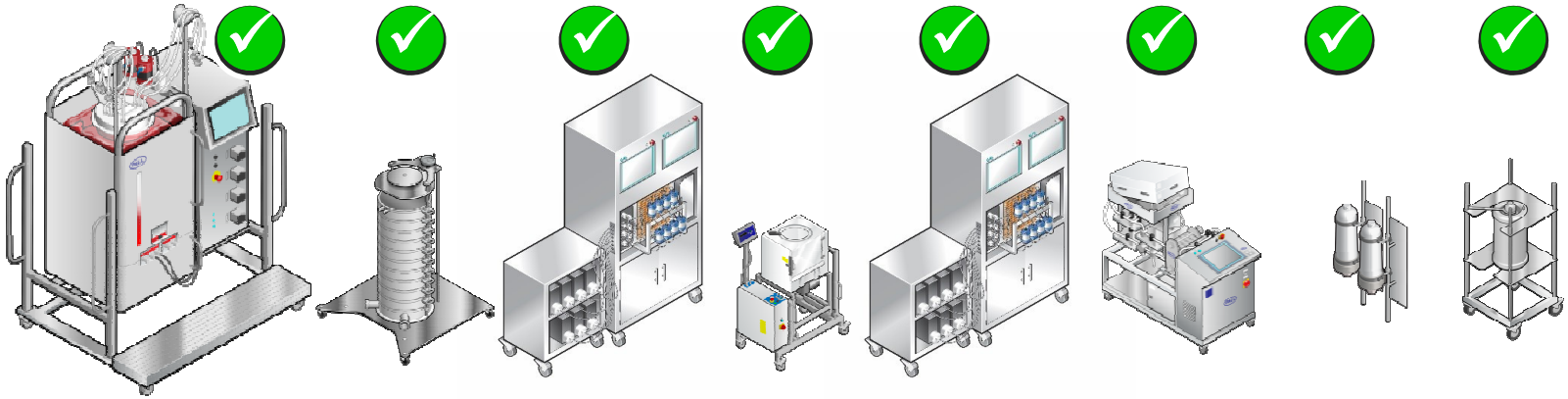
Goal: Higher quality and productivity in a smaller foot print with shorter lead times

Integrated Continuous Bioprocessing

Fed Batch USP + Batch DSP

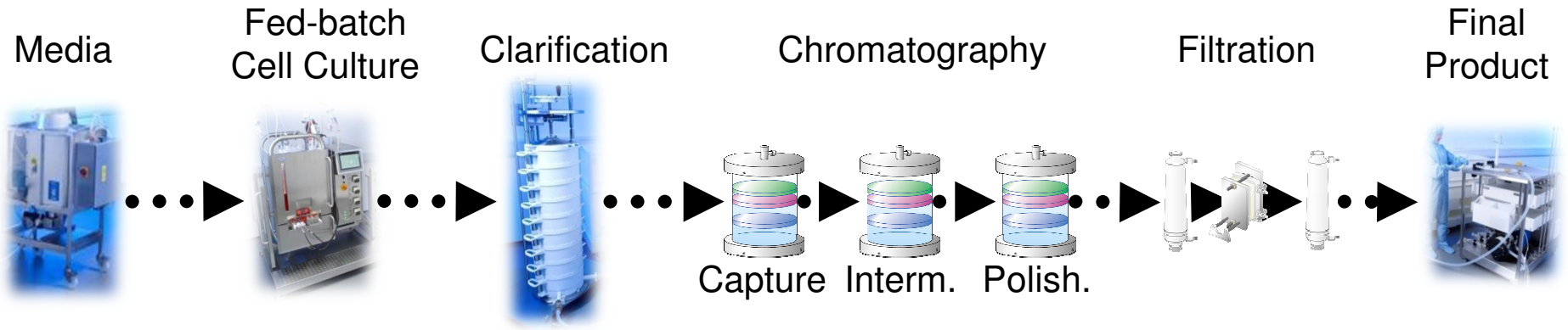


Fed Batch USP + Continuous DSP



The Journey from Batch to Continuous Bioprocessing

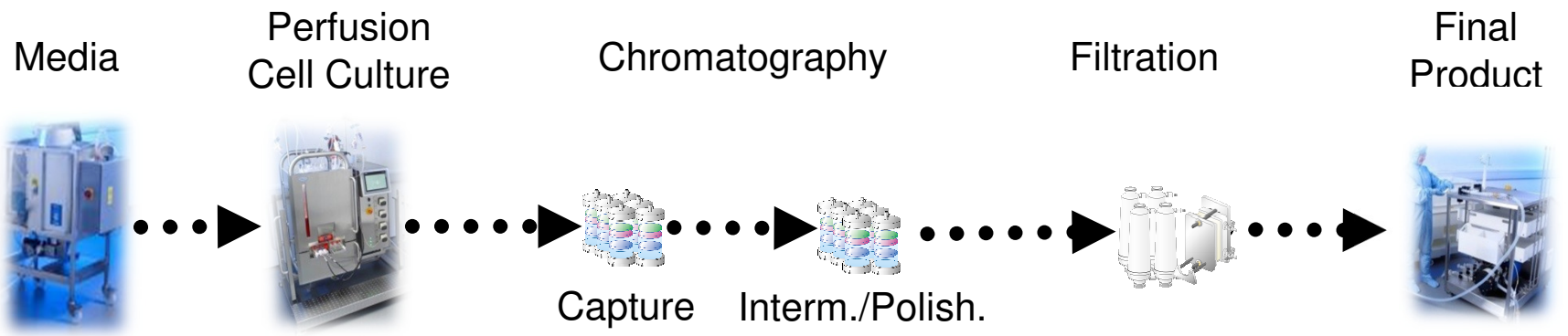
Batch Bioprocess

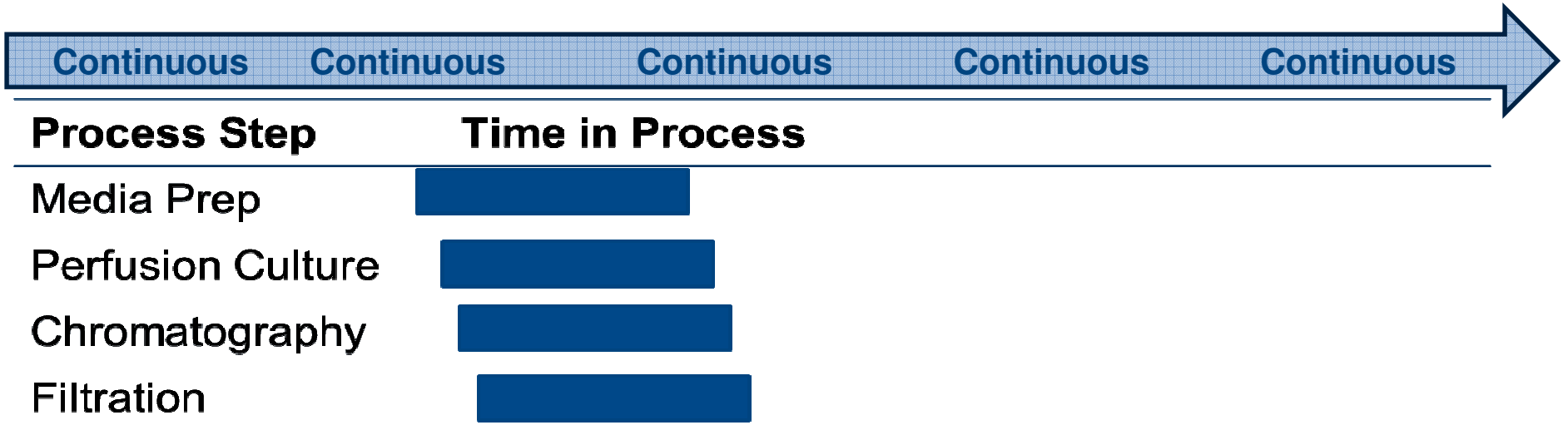


Process step	Time in Process
Media Prep	
Fed-batch Cell Cult.	
Clarification	
Chromatography	
Filtration	

The Journey from Batch to Continuous Bioprocessing

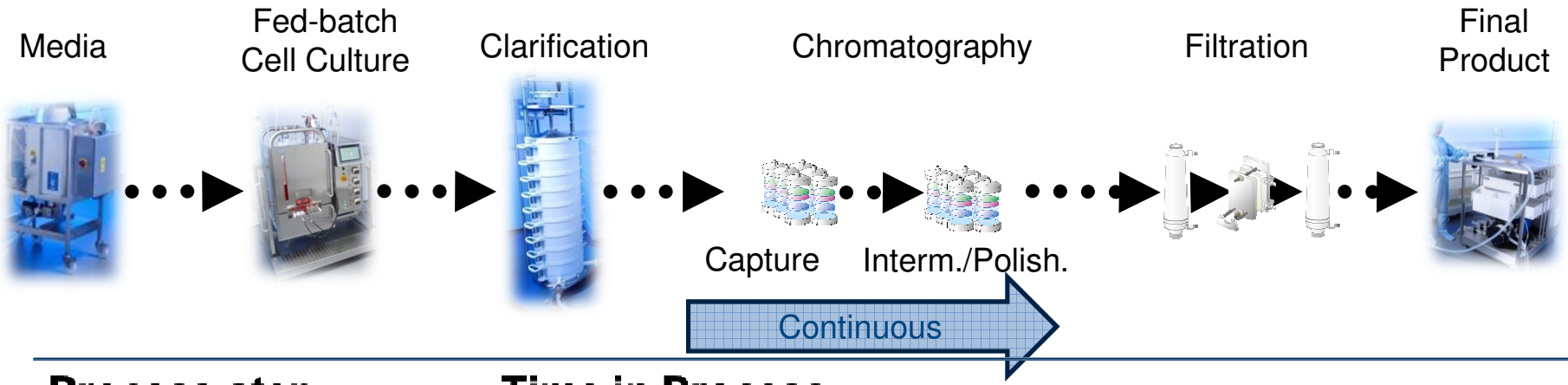
Continuous Bioprocess



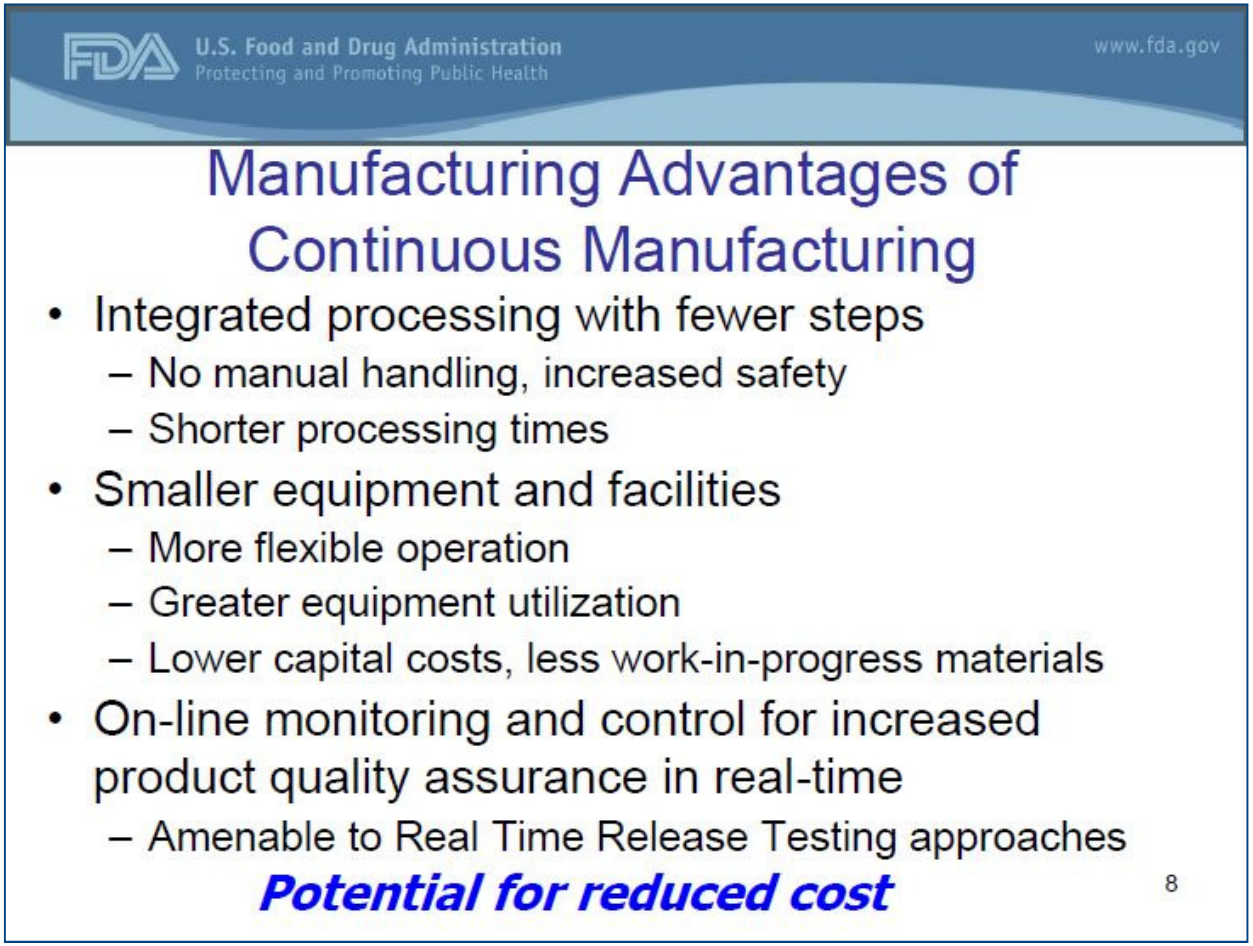


The Journey from Batch to Continuous Bioprocessing

Hybrid Batch/Continuous Bioprocess



FDA on Continuous Processing

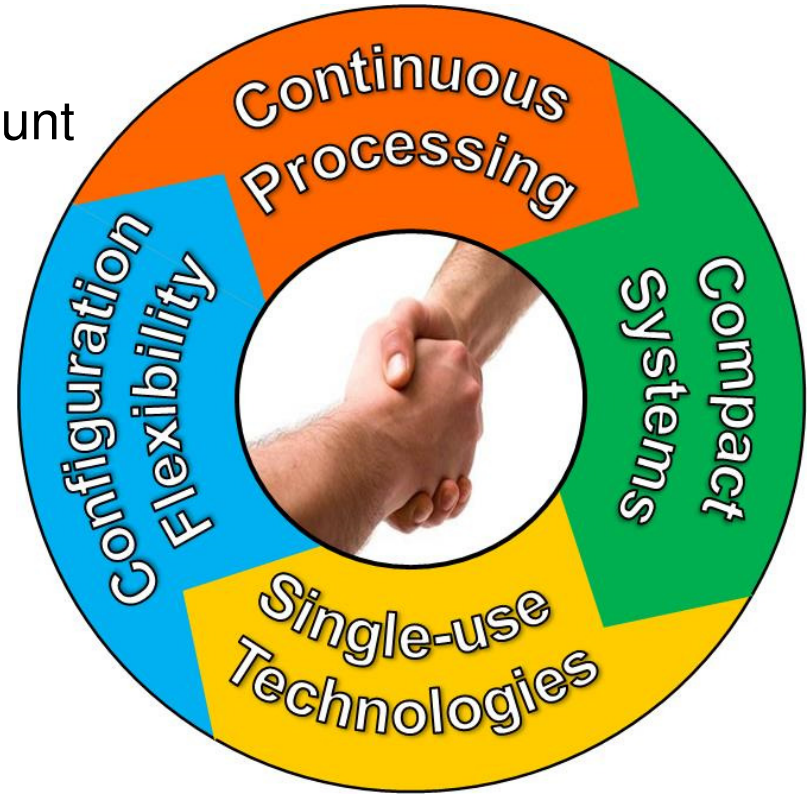


Janet Woodcock, CDER, FDA, "Modernizing Pharmaceutical Manufactruing – Continuous Manufacturing as a Key Enabler", p 33, MIT-CMAC International Symposium on Continuous Manufacturing of Pharmaceuticals, May 2014

Continuous and Single-Use

Continuous Technologies:

- Driven by volume instead of product amount
- More compact process equipment
- Eliminates interstage tanking



Disposable Technologies:

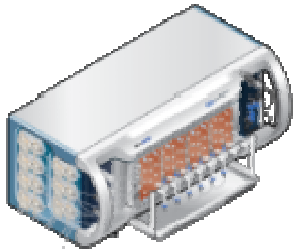
- Increased flexibility
- Fast turn around time
- Risk reduction

Enabling Technologies for Continuous Processing

Acoustic Wave Separation (AWS)

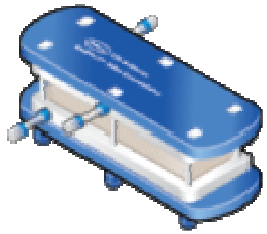
Cell Clarification and Perfusion

Continuous Chromatography



Continuous Multi-column Chromatography

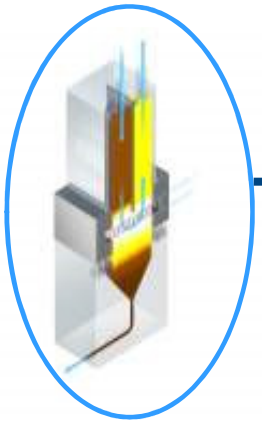
In-Line Concentration (ILC)



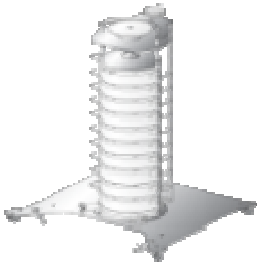
Single Pass TFF Protein Concentration

Acoustic Wave Separator

Up to 2000 L Bioreactor

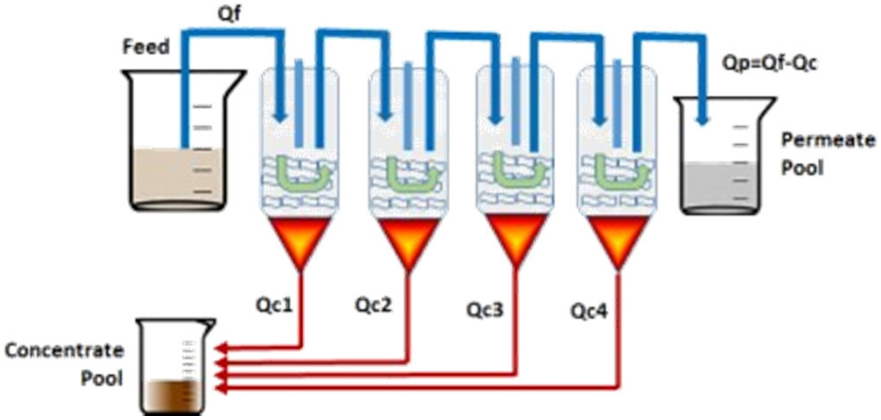


AWS

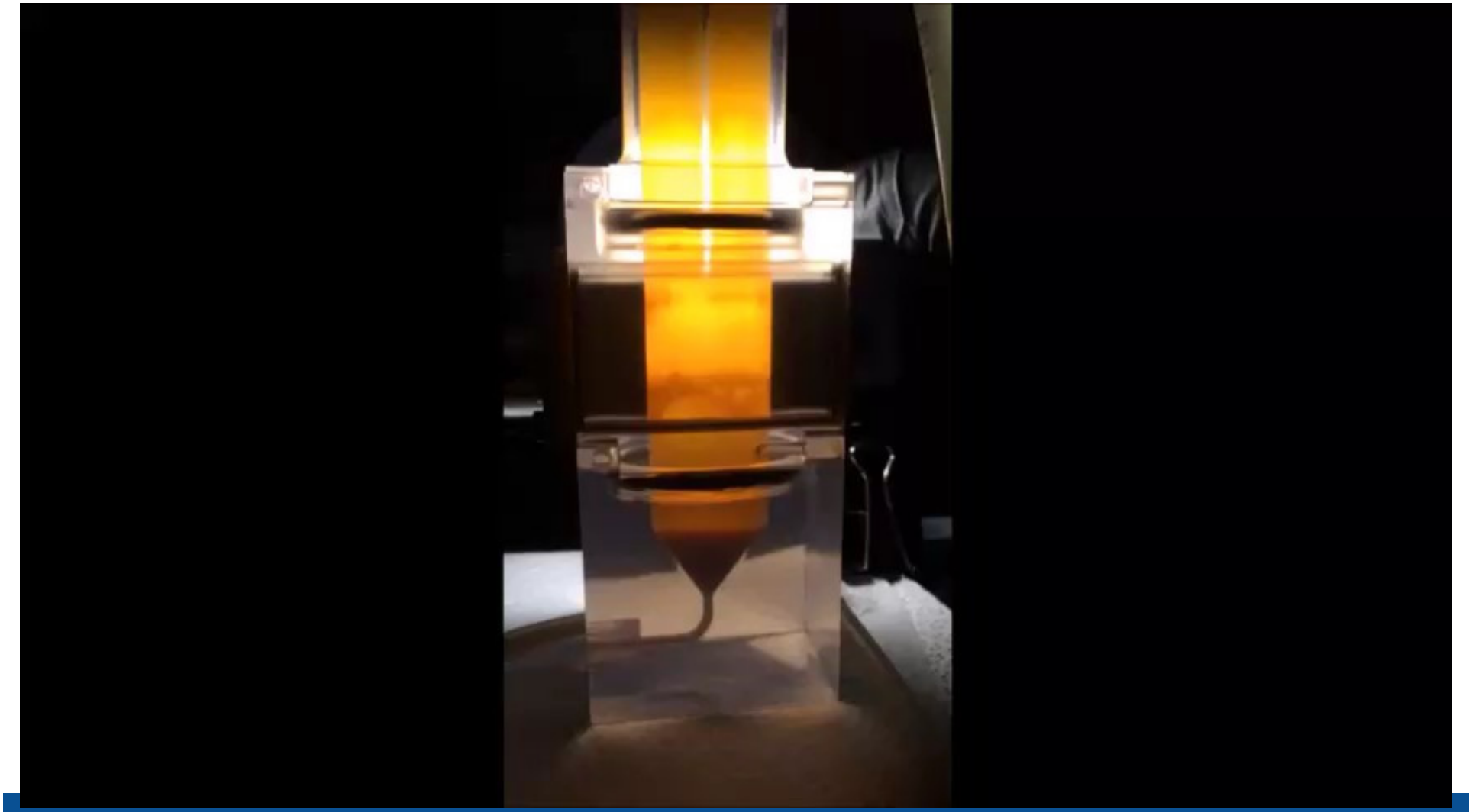


Depth Filtration

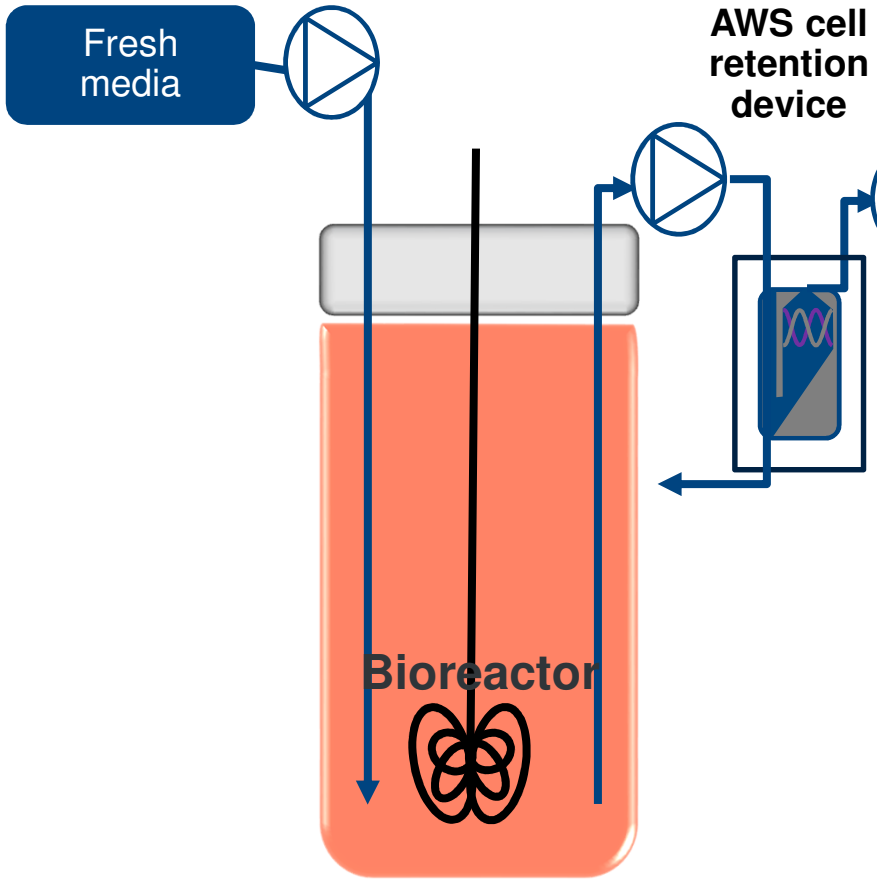
Sterile Filtration



Acoustic Wave Separation



Acoustic Separator Perfusion Cell Culture

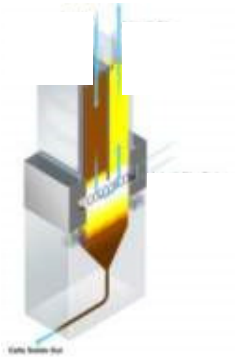


Requirements:

- **Gamma sterilized**
- **No fouling and therefore no loss of product transmission**
- **No impact on cell culture performance and product quality (product related impurities, contaminant content)**
- **Stable performance up to 90 days**
- **Fully disposable**

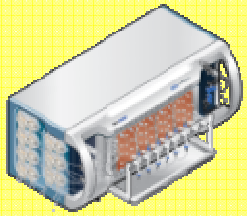
Enabling Technologies for Continuous Processing

Acoustic Wave Separation (AWS)



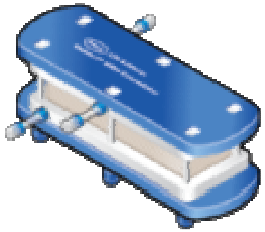
Cell Clarification and Perfusion

Continuous Chromatography



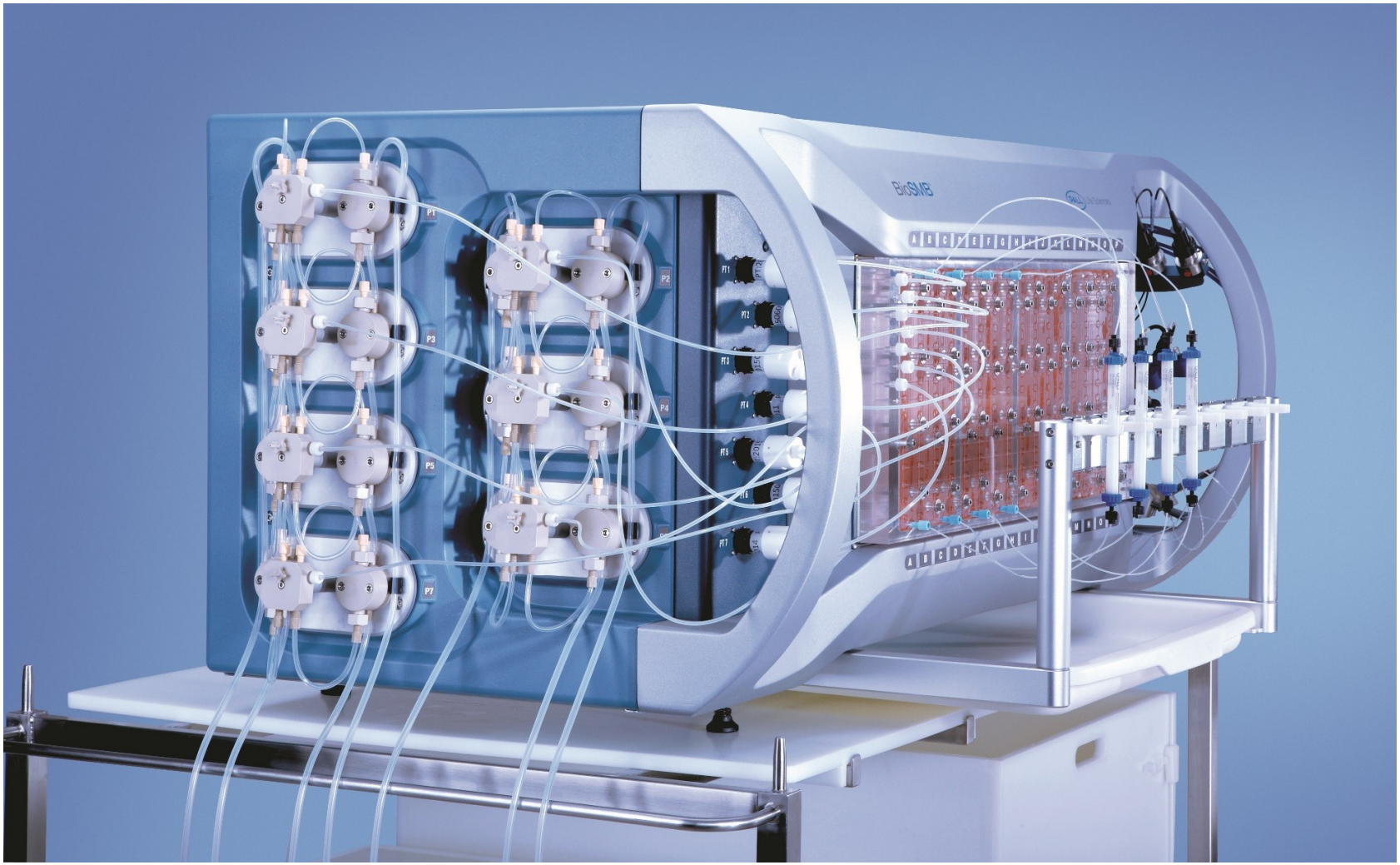
Continuous Multi-column Chromatography

In-Line Concentration (ILC)



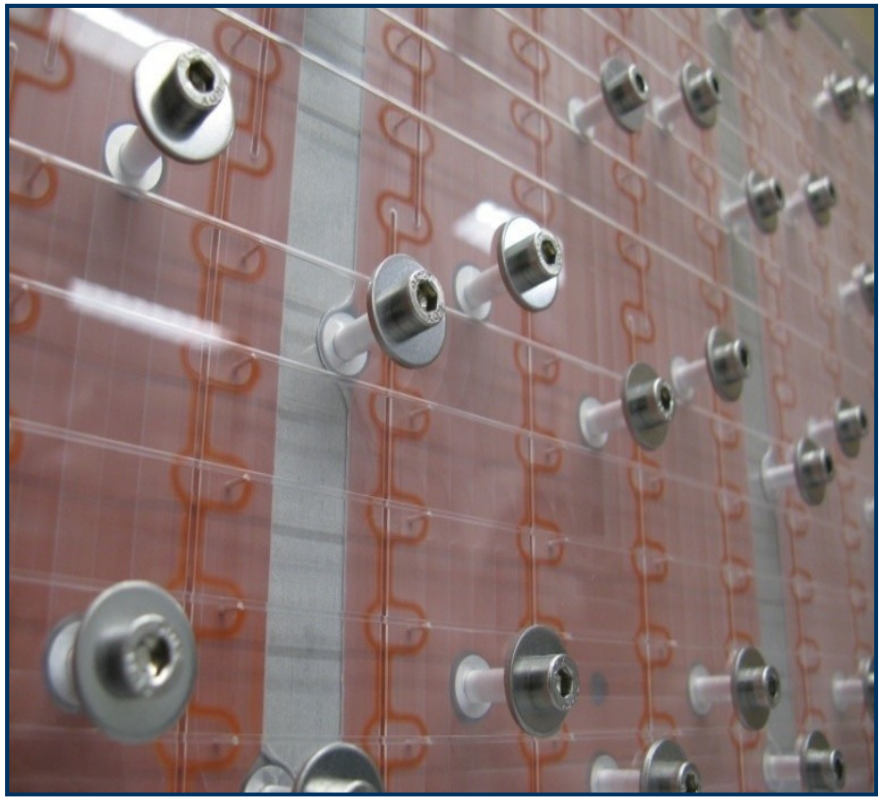
Single Pass TFF Protein Concentration

Process Development System



BioSMB: Patented Valve Technology

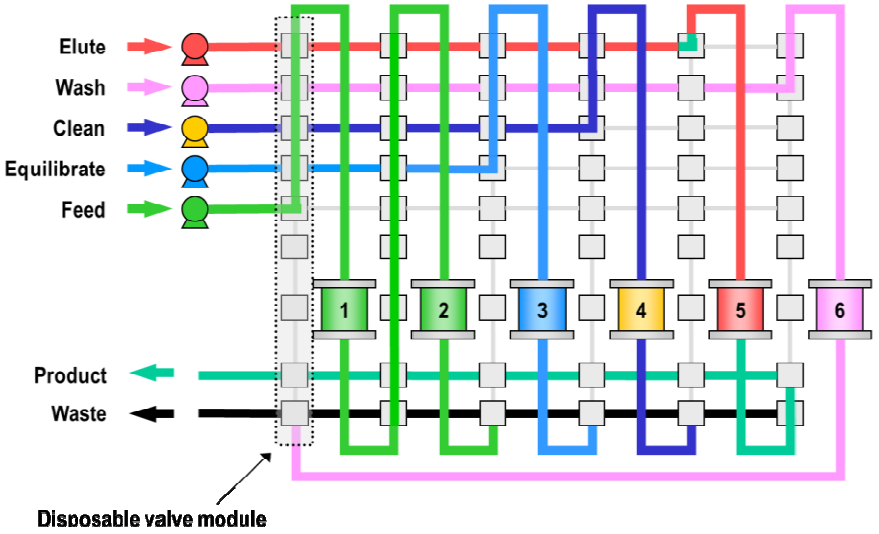
- Integrated Valve Cassette
  - 240 membrane valves & flow path in one acrylic block
- Comprises all valves needed to handle up to 16 columns or membrane devices
- Currently in 1mm and 3 mm bore
  - Larger bore for production system
- Can be used in specific fluid control applications

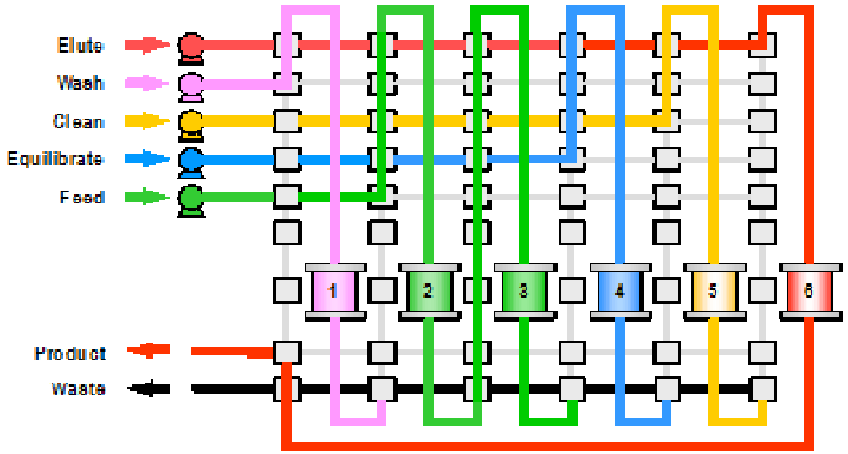


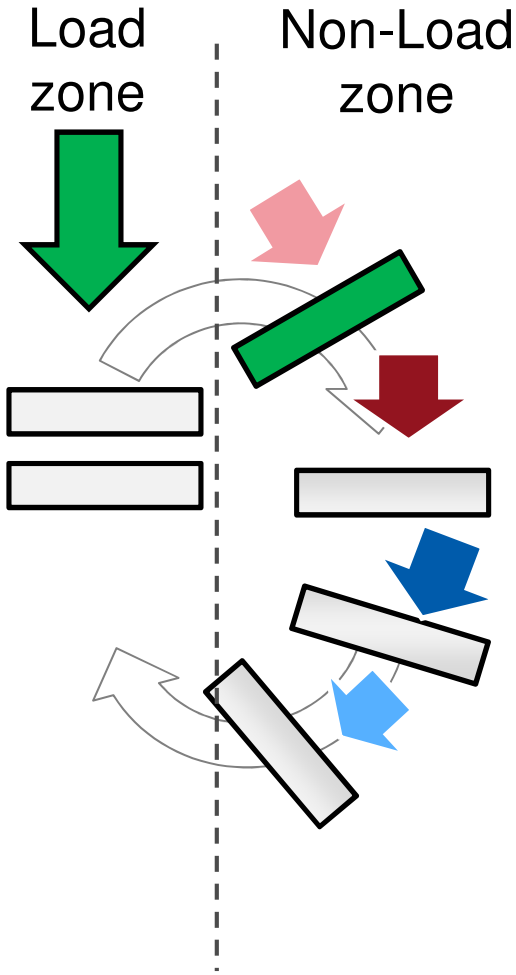
Combines Flexibility with Simplicity & Scalability

Patent EP 1775001 A1, Patent US20100144028 A1

Continuous Chromatography

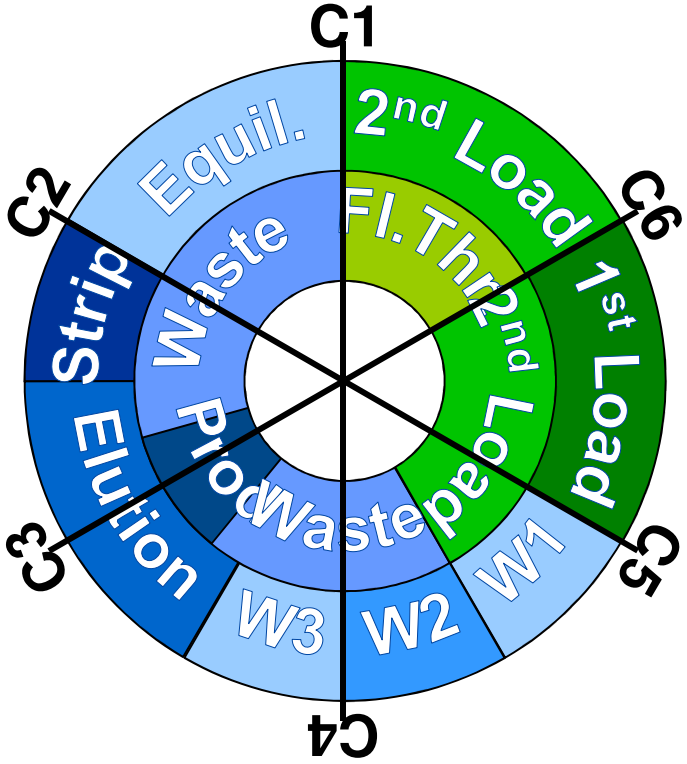






Continuos Circular Chronogram

- Visualizes current state of the process
- Columns travel through the process (or actually vice versa)
- Each column results in one elution peak every cycle



UV Absorbance in Product Outlet

Case Study: Clinical & Commercial Mnf

- Processing volume: 2000 L in 8 hr (3 gm/L)
- Blockbuster: optimize for capacity utilization
- Niche/Clinical: optimize specific productivity

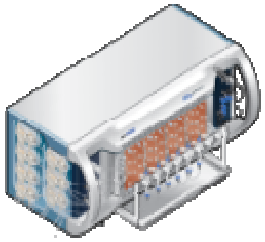
Scenario	Batch	C. Chrom *Commercial*	C. Chrom *Clinical*
Load capacity	30 gm/L	55 gm/L	32 gm/L
Contact time	4 min	3 min	1 min
Specific productivity	14 gm/L/hr	32 gm/L/hr	65 gm/L/hr
PrA media volume	100 L	20 L	11 L
Column dimensions	80 cm ID 20 cm H (2 cycles)	20 cm ID 9 cm H (8 cols)	20 cm ID 5 cm H (6 cols)

Enabling Technologies for Continuous Processing

Acoustic Wave Separation (AWS)

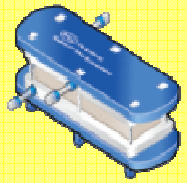
Cell Clarification and Perfusion

Continuous Chromatography



Continuous Multi-column Chromatography

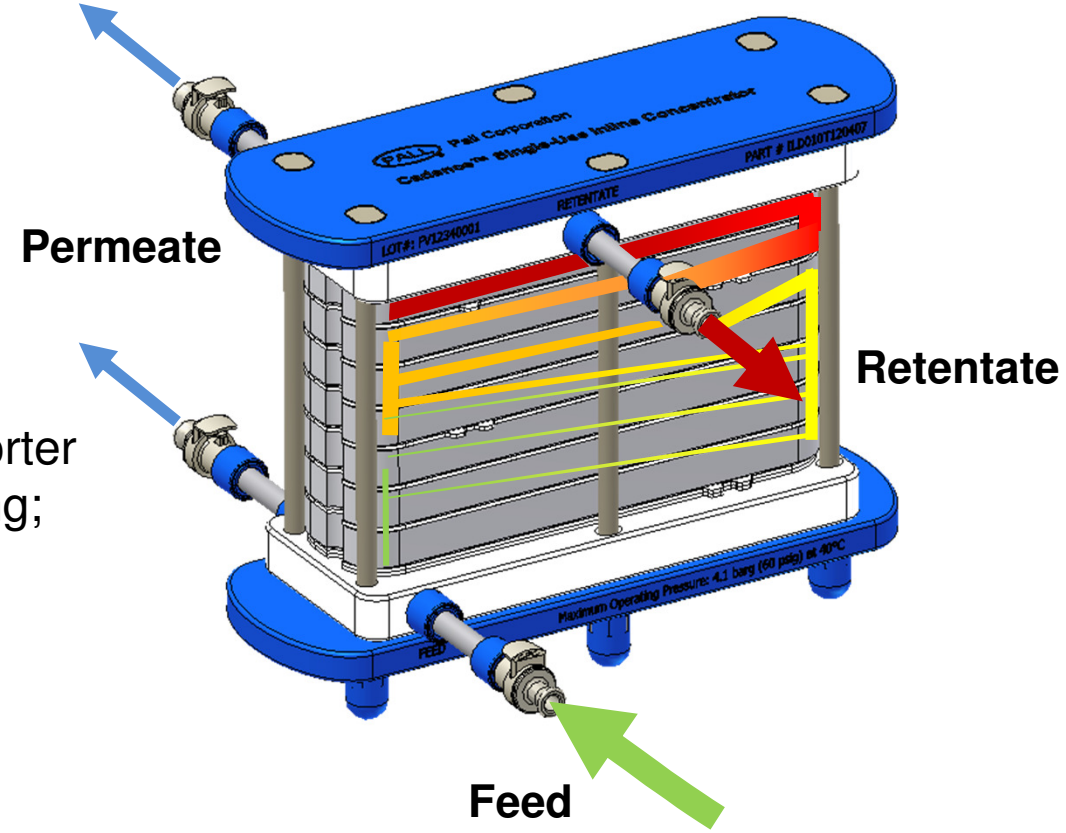
In-Line Concentration (ILC)



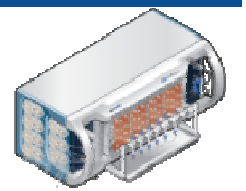
Single Pass TFF Protein Concentration

ILC Single-Pass TFF
Performance of TFF with the simplicity of direct-flow filtration

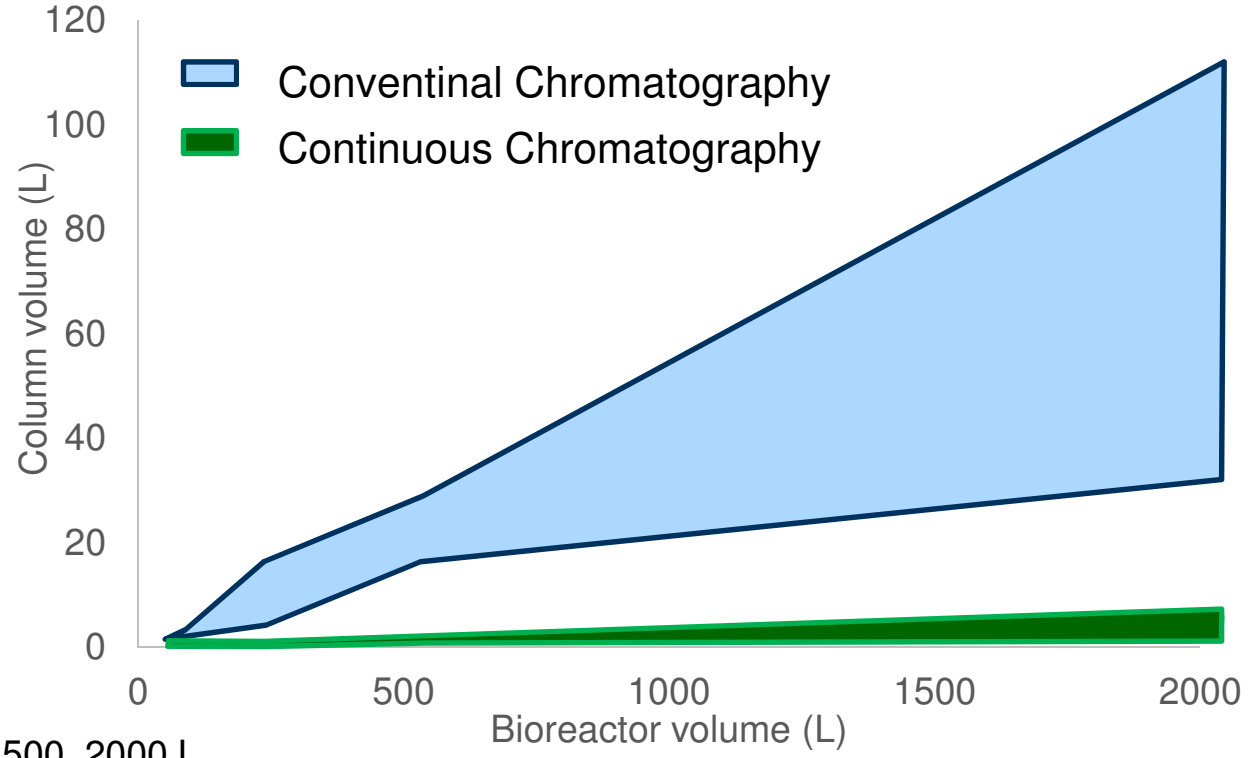
- Continuous processing, with shorter process time by process coupling;
- No recirculation;
- Low shear exposure;
- No foaming or mixing issues;



ILC + Continuous Chromatography:



Highly Flexible Capture Platform Technology

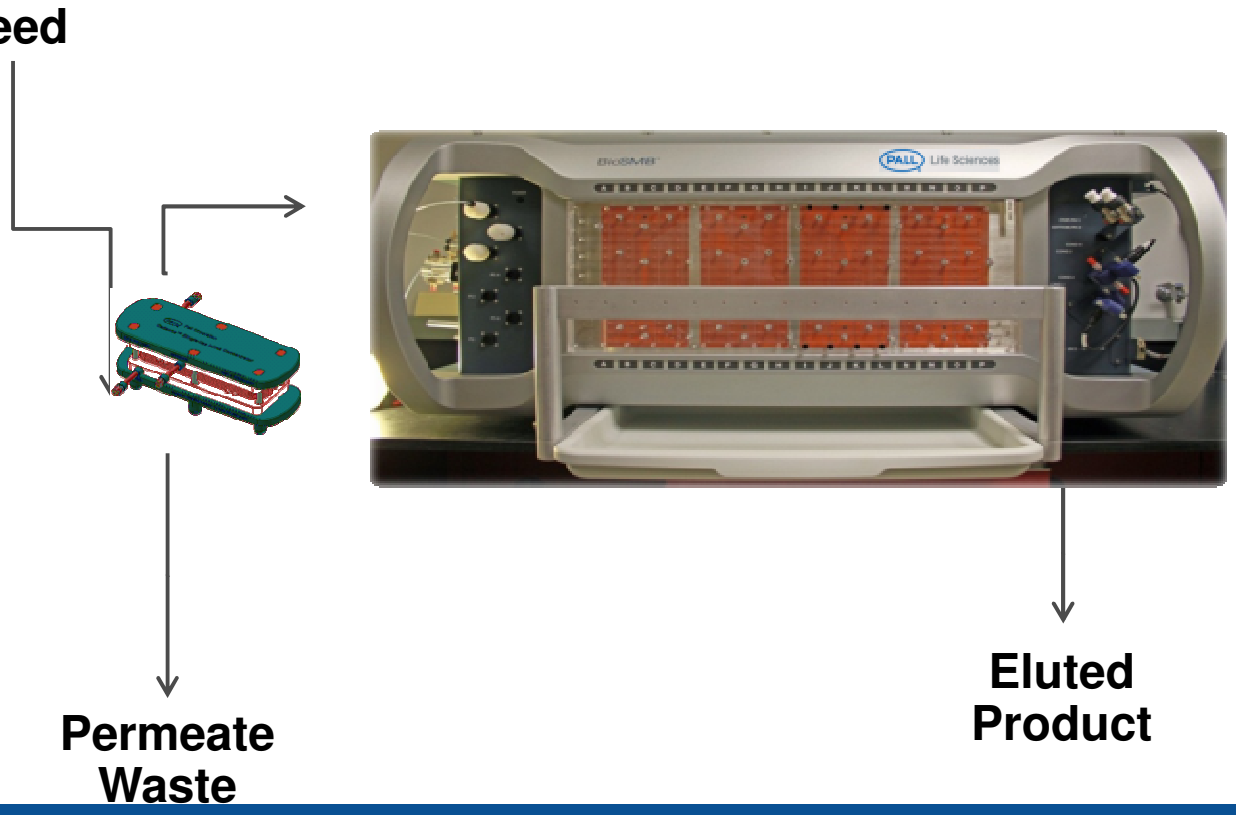


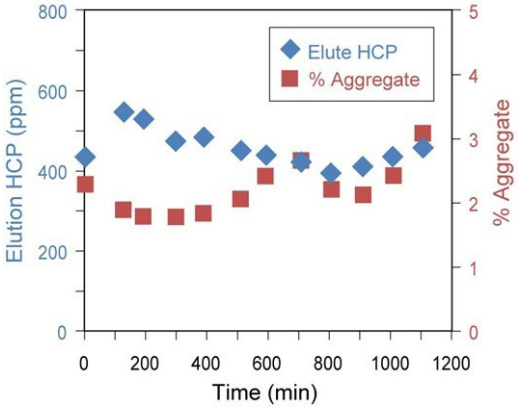
Process scenarios:

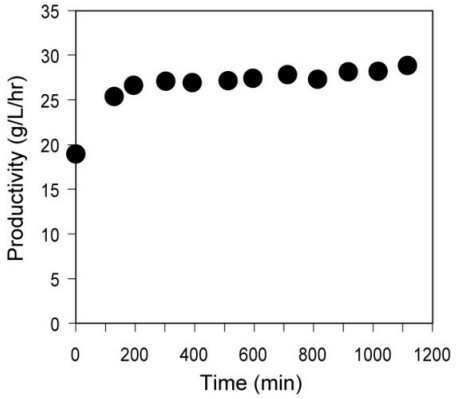
- Bioreactor volume: 20, 50, 200, 500, 2000 L
- mAb titer: 1, 3, 5 g/L
- Process time: 24 h
- ILC VCF: 2, 4

Process Integration On and Around the Continuous Chromatography Systems

The integration of SPTFF and Continuous Chromatography has been operated over extended period of time



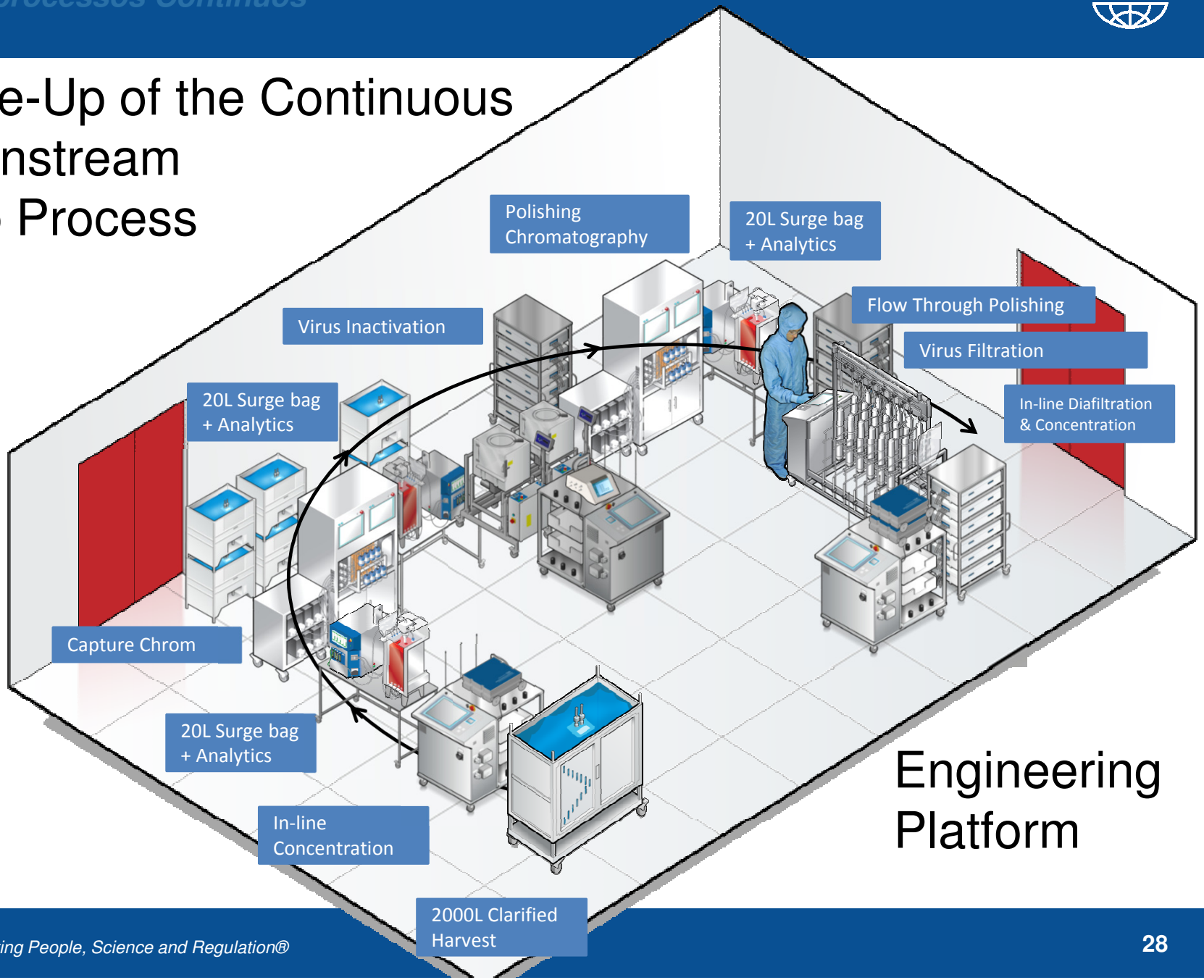




Continuous Laboratory

Ability to produce >> 2 g/h of pure mAb
6 m x 6 m Lab

Scale-Up of the Continuous Downstream MAb Process



Engineering Platform

Continuous Bioprocess: What is Next?

- Process Monitoring and Control
- Automation
- Validation and Regulatory
- Additional Enabling Technologies
  - Viral Inactivation
  - Virus Filtration
  - In-Line Diafiltration

Muito Obrigado!

Discussão e Perguntas