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An Update on Significant Technology Advances Enabling Integrated Continuous BioProcessing

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Increasing Use of Innovative Single-Use Technologies



2012: Sterile Disconnectors



2012: Single-use Filling Needles



2013: Single-use Bioreactors



2013: Automated Systems for Single-use Processes



2013: Medistad Acquisition



2014: ATMI LS Acquisition BioReactors & Mixers



2015: BioSMB Acquisition



2015: Acoustic Wave Separation



2001: Capsule Systems



2002: Sterile Connectors



2007: Biocontainers



2009: Single-use Depth Filters



2010: Single-use TFF



1980 – 90s: Single-use Capsule filters



2000: Chromatography Capsules

New Single-Use Technologies



Kleenpak™ Presto Sterile Connector

Performance

- Permanent sterile connection of two fluid streams in large range of applications

Usability

- Sterile connections in three intuitive, simple steps even in unclassified environment without compromising sterility of the fluid paths



Allegro™ STR Single-Use Bioreactors

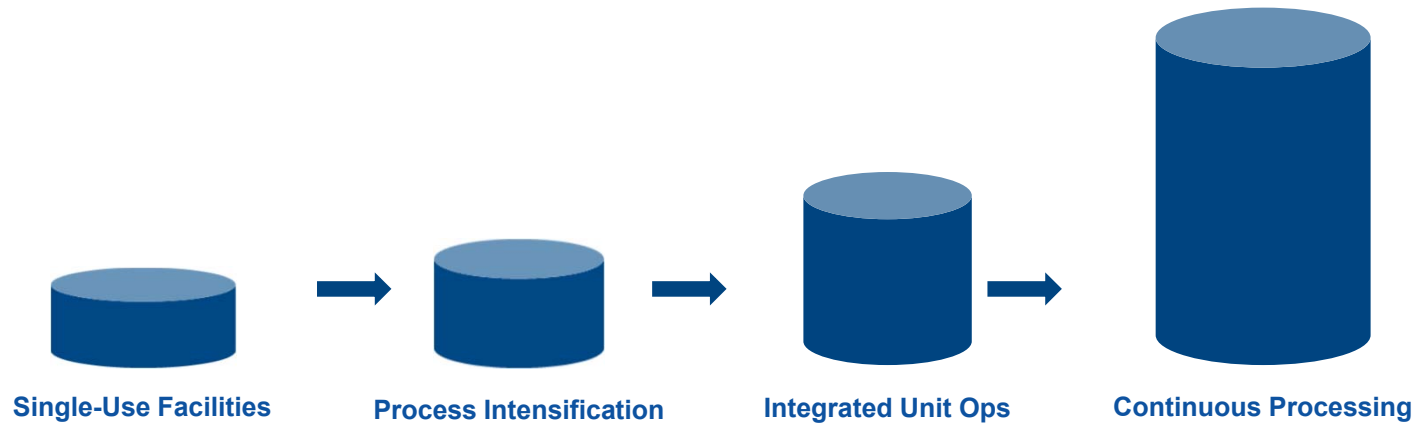
Performance

- Good cell culture performance
- Easy to scale up

Usability

- Quick and easy installation
- Reduced error rate
- Reduced space requirements

Evolution in BioProcessing



Impact

Reduced

- Processing time
- Operating costs
- Footprint
- Capital outlay

Improved


- Facility efficiency
- Manufacturing flexibility

Pall's Continuous BioProcessing Lab




100+ g mAb produced in 24 hrs

Regulatory Push Towards Continuous Manufacturing (CM)

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Advantages of Continuous Manufacturing

- Smaller equipment and facilities
 - Lower capital, operational and environmental costs
 - Increased safety
 - Potential for modular units
- Integrated processing with fewer steps
 - Total processing times shorter; faster product release
 - Simplified scale-up
- More flexible operation
 - Adjust production to meet demand, emergencies, etc.
- Benefits to both patients and industry



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- **Adjust production to meet demand, emergencies etc.**

Benefits to both patients and industry

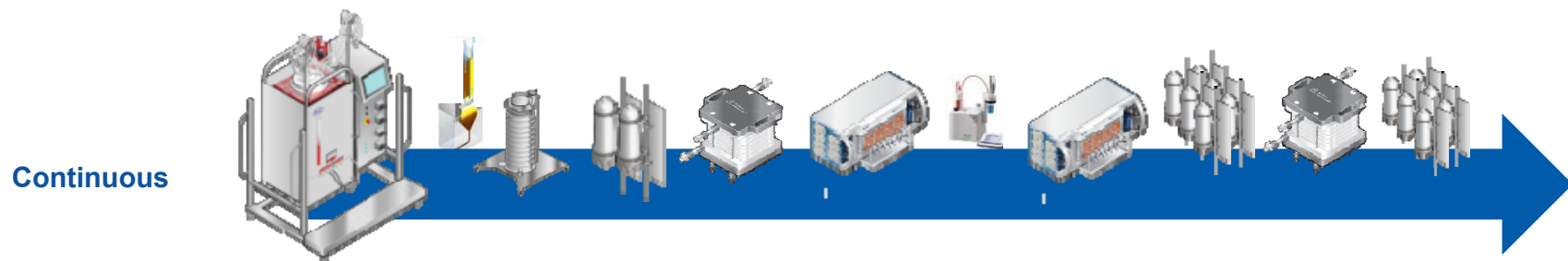
Source: Modernizing Pharmaceutical Manufacturing: from Batch to Continuous.
Thomas O'Connor, Ph.D., Science Staff US FDA CDER, Presentation ISPE, Singapore, August 2016

Pall's Vision for a Platform for Continuous BioProcessing

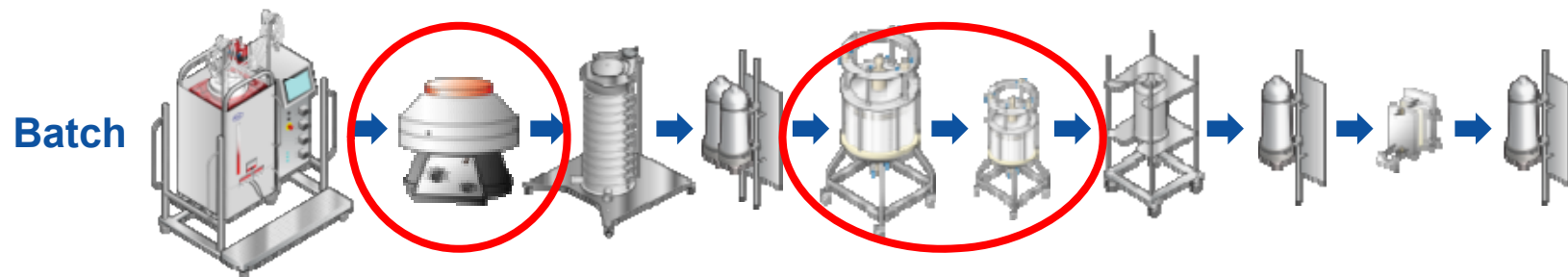
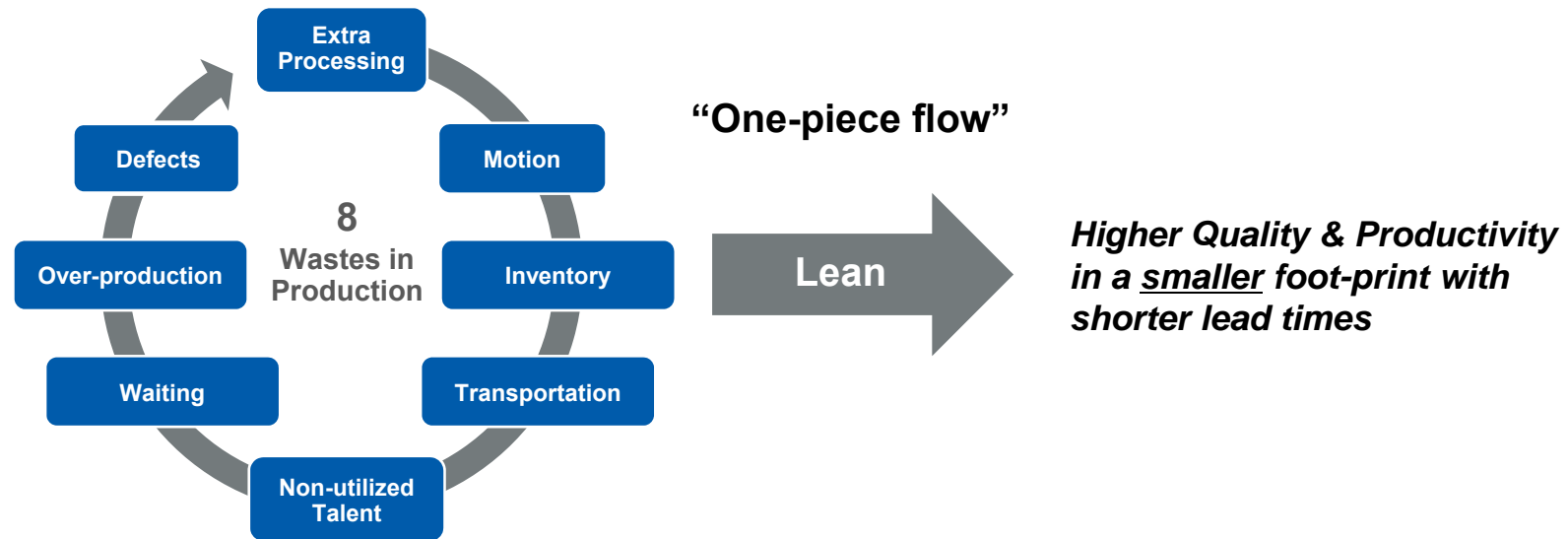
Leading provider of integrated platform technologies for continuous manufacturing of biologics

Platform

- Robust across multiple molecules 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%



Lean Thinking From Batch to Continuous BioProcessing



Cadence Acoustic Separator*

Continuous Clarification

- Acoustophoretic separation for continuous removal of cells and cell debris
- > 85% clarification efficiency
- Reduces depth filtration area by 4X
- Greatly reduces buffer volume and increased yield
- Robust clarification platform process

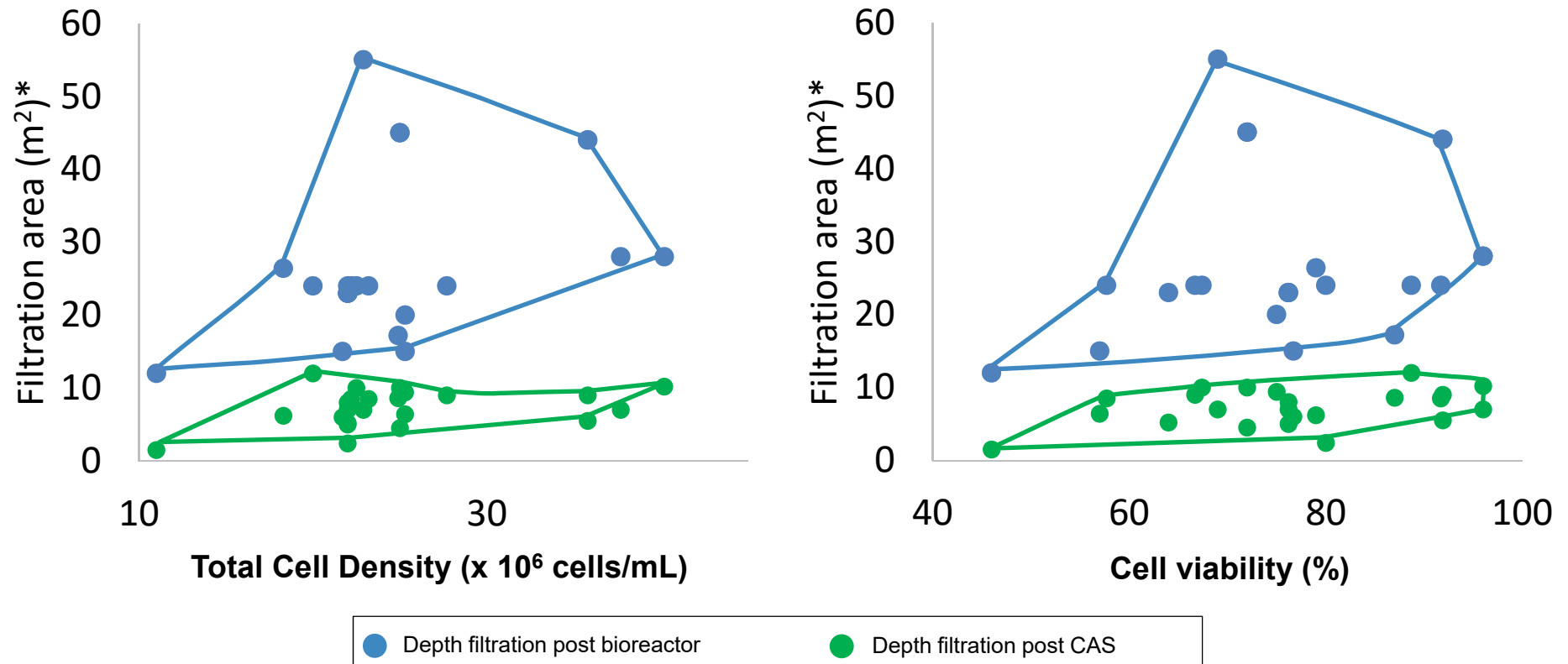
**Continuous process with
minimal temperature rise and
no impact on protein quality**

* On June 15, 2015, Pall announced the exclusive licensing agreement with FloDesign Sonics (FDS) for acoustic wave separation (AWS) in Bioprocessing

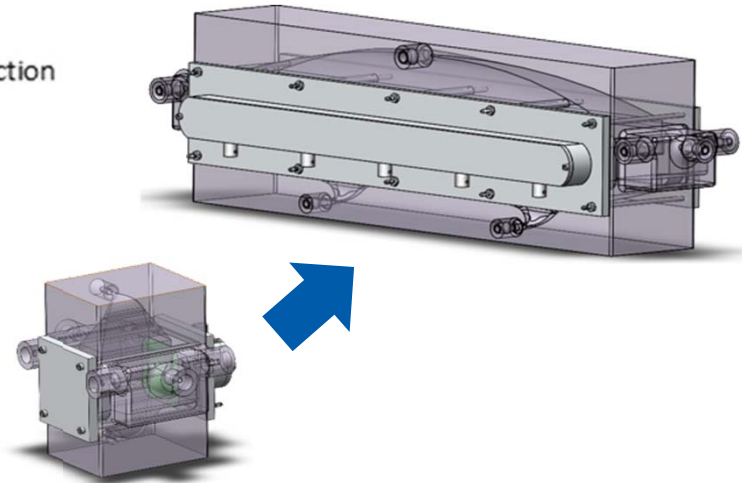
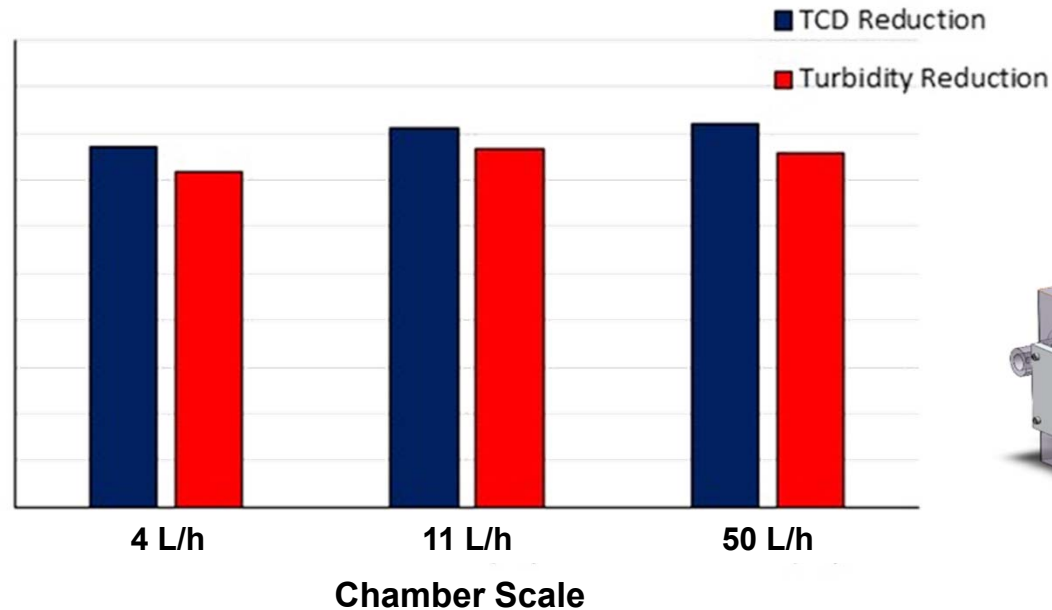


Towards a Robust Platform Process

Continuous Clarification Platform CAS / Depth / Sterile



Scalable Clarification



Consistent performance at multiple scales* via novel flow chamber and component design strategies

*Scale-up runs were conducted using single-stage chambers

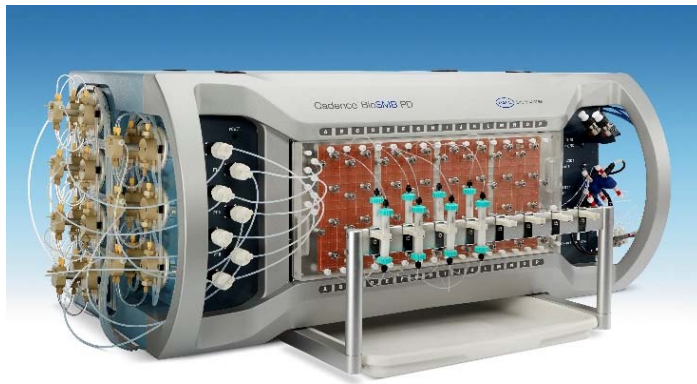
Pall's Continuous BioProcessing Lab



100+ g mAb produced in 24 hrs

BioSMB Technology*

- System for continuous chromatography
- Cassette** can handle up to 16 column/capsule positions
- Single use with simple flow path



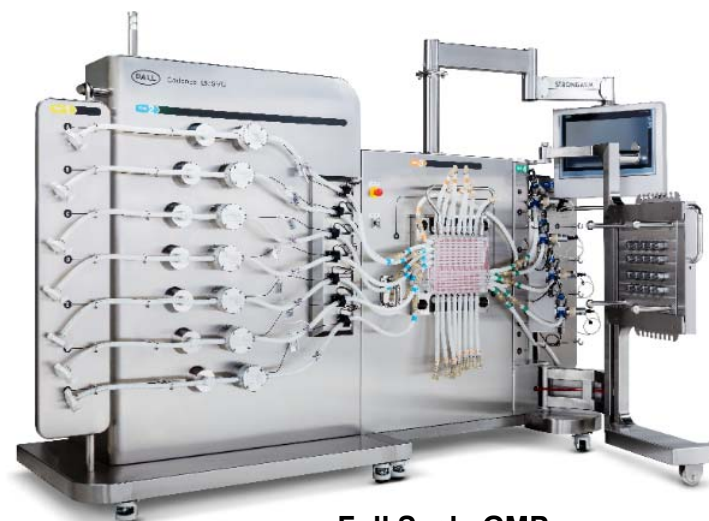
* Pall Announced the acquisition the BioSMB technology platform from Tarpon Biosystems on March 31, 2015.

** = Cassette: US Patent: US8920645 B2

Scalable Continuous Chromatography



Process Development



Full Scale GMP

Attribute	BioSMB PD Only multicolumn chromatography system that makes 24-hour process development a reality	BioSMB Process Production time of 6 h for a 2000 L bioreactor with a single use flow path that can be set up in 30 minutes or less
Patented Valve Cassette Design	✓	✓
Flexibility in Column arrangement (series or parallel)	✓	✓
Number of Columns	3 – 16 *	3 – 8
Flow Rates	0.6 - 3 L/h	30 – 350 L/h

* for ease of integration development

Cadence BioSMB Process – Evaluation

**Feedstream: 400 L harvested
CHO cell culture fluid**

mAb titer: 5.8 g/L

**5 Capture Columns: OPUS*
prepacked columns
(14 cm i.d. x 5 cm; 0.77L)
containing KANEKA KanCap A**

Flow rate: 37 L/h

Residence time during load: 2 min 36 sec

No. of cycles: 13

Operating binding capacity: 46.4 g/L

Dynamic binding capacity: 45 g/L (6 min RT)

Total sorbent volume: 3.85L

Data courtesy of Nuno Pinto and Mark Brower



* OPUS is a trademark of Repligen Corporation

Scalability Data

	Batch Reference	Cadence BioSMB PD*	Cadence BioSMB Process**
Feed titer	5.8 g/L	5.8 g/L	5.8 g/L
Elution titer.	9.54 g/L	13.84 g/L	13.85 g/L
Product yield	98%	97%	97%
Aggregate	0.45%.	0.72%	0.65%
LRV DNA	n.a.	4.16	5.02
LRV HCP	2.4	2.61	2.51

* 5 x 5 mL KANEKA KanCapA columns (0.025 L at 0.24 L/h)

** 5 x 0.77 L KANEKA KanCapA columns (3.85 L at 37 L/h)

Cadence BioSMB Process Scalability

- A total of 2.3 kg mAb (400 L at 5.8 g/L) was purified in 12 hours
- Only 3.85 L of Protein A sorbent was required (KANEKA KanCapA)
- 5 columns was the optimal configuration
- The batch process was transferred to continuous and scaled up within 4 weeks
- The BioSMB PD process was successfully scaled up >150-fold

BioSMB Chromatography Platform

1. KANEKA KanCap A* Capture Column
2. Viral Inactivation
3. SupraCap™ KS50 Depth filter
4. Mustang® Q XT5 Capsule
5. CMM HyperCel™ Column

- No buffer adjustment for linked process
- Four steps running on 2 Cadence BioSMB PD systems
- Scale up from 5 to 50 mL columns
- Process up to 200 L bioreactor feed in 24h



	5 mL columns	50 mL columns
Throughput (g/h)	2	10**
HCP (log reduction)	4.7	4.3
Aggregate content	1-2%	1-2%

* KANEKA KanCapA is a trademark of KANEKA Corporation

** throughput limited by incoming titre

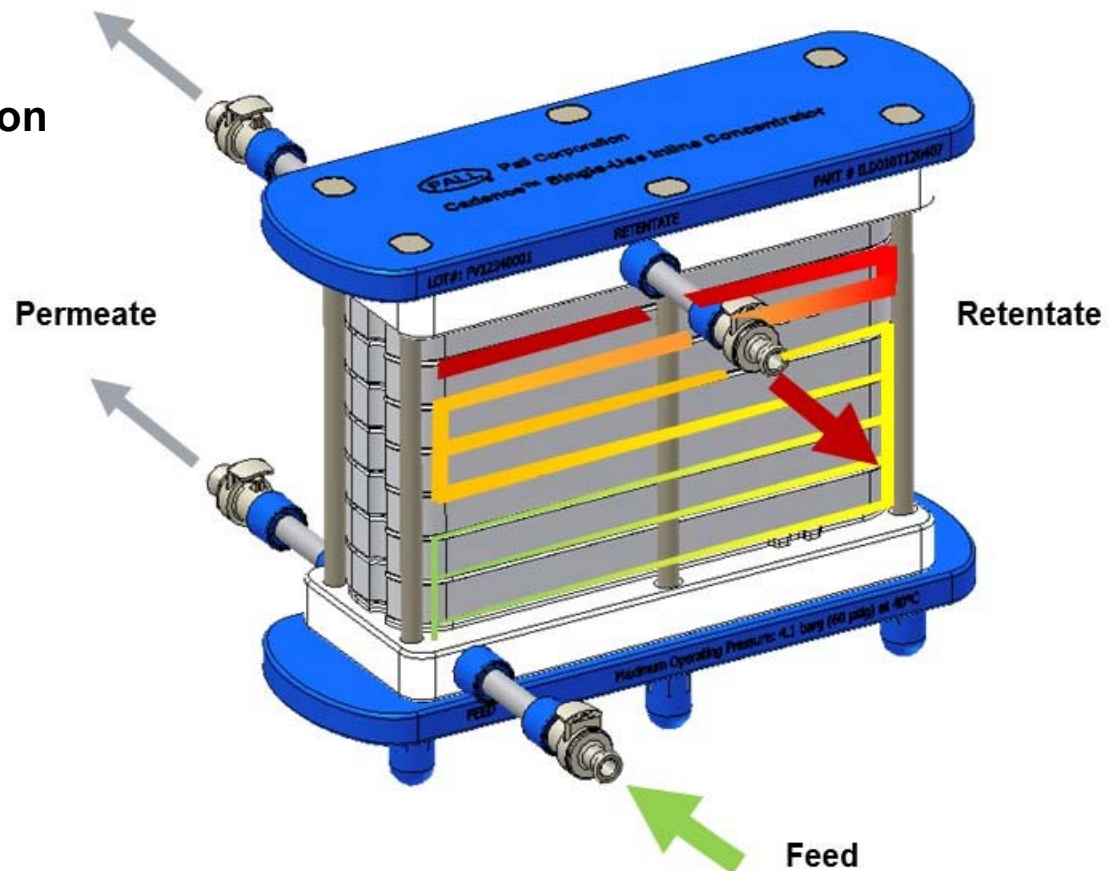
Cadence ILC Single-Pass TFF*

Performance of TFF with the simplicity of direct-flow filtration



Benefits

- Stable performance for 2 – 4 X concentration (up to 100 g/L)
- Continuous processing, with shorter process time by process coupling
- No recirculation
- Low shear exposure
- Low hold-up volume
- Easy module installation, plug and play
- No foaming or mixing issues

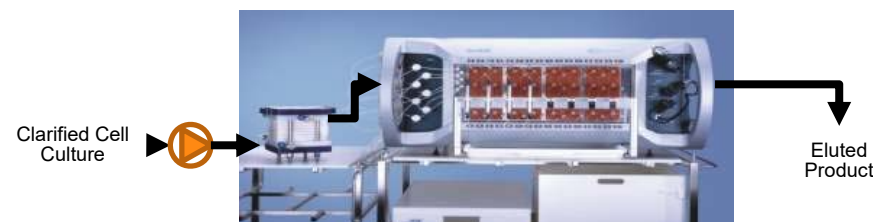


* US Patents: 7,384,549B2; 7,682,511B2; 7,967,987B2; 8,157,999B2 Note: These SPF™ Technology patents are owned by SPF Innovations LLC. In 2009, Pall Corporation acquired an exclusive license from SPF Innovations LLC to manufacture, market and sell SPF Technology for biopharmaceutical applications.

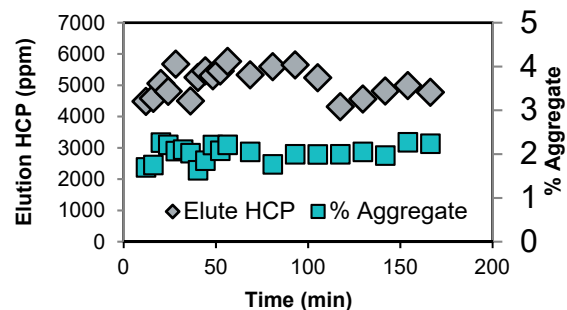
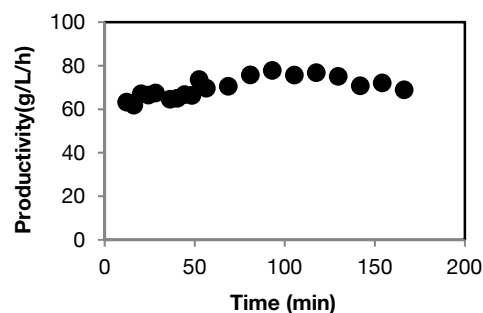
Process Integration– ILC + BioSMB System

Integration of enabling technologies
for continuous bioprocessing

Protein A mAb capture performance using Conventional, BioSMB and ILC-BioSMB



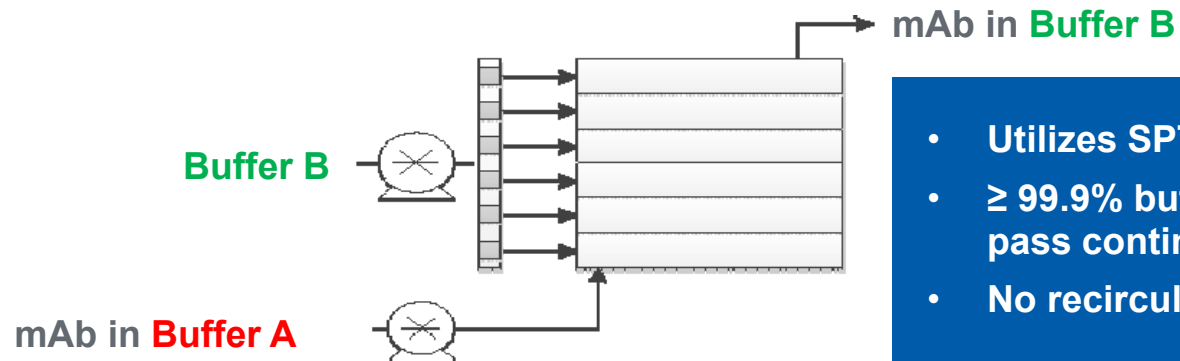
Process	Number of Columns	Binding Capacity (mg/mL)	Residence Time (min)	Initial mAb titer (mg/mL)	SPTFF VCF (fold)	Post ILC mAb conc. (mg/mL)	Cycle Time (min)	Specific Productivity (g/L/h)	HCP (Log red.)	Aggregate (%)
Conventional	1	26.0	4.5	2.0	N/A	N/A	150	10	2.46	2.0
BioSMB	4	29.1	0.6	2.0	N/A	N/A	39	45	2.44	2.1
ILC-BioSMB	7	36.0	0.6	2.0	3.4	7.0	33	67	2.29	2.0



**35 mL Resin
(7x5 mL columns)
yields 2+ g mAb/h**

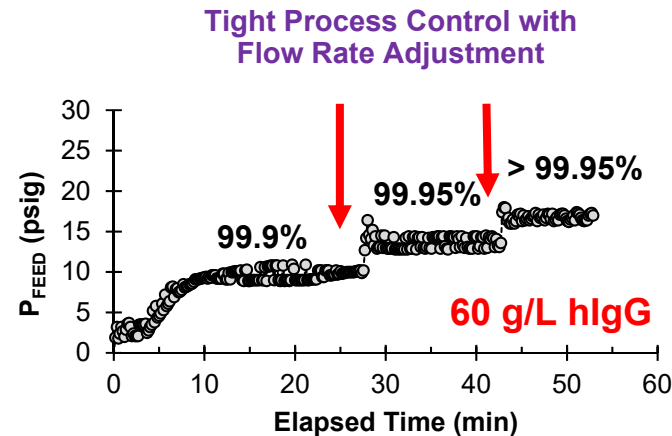
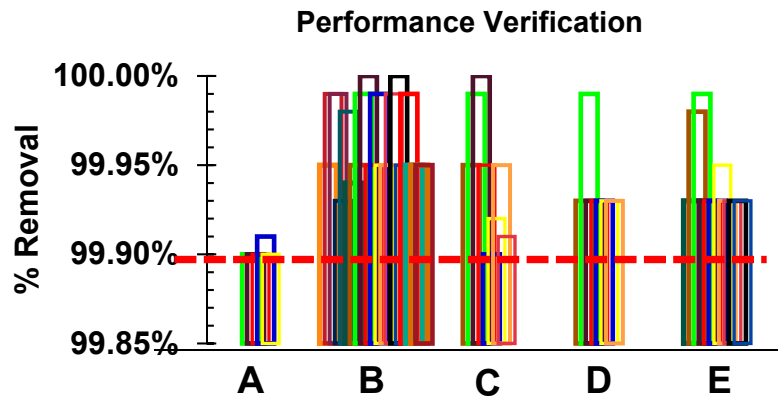
Process Development in 24 hours:
Journal of Chrom A, 2015 Oct
16:1416:38-46 Pall Application Note:
USD3002

Redefining Continuous Final Formulation



- Utilizes SPTFF design principles
- ≥ 99.9% buffer exchange in single pass continuous mode
- No recirculation

Inline Diafiltration (ILDF) leveraging Cadence Single-Pass TFF Technology



- End-user tested, robust, scalable & reproducible performance
- Successfully tested with 20 molecules and 12 buffer systems
 - $\geq 99.9\%$ (or ≥ 3 -log) removal efficiency
 - Steady flow and pressure profiles over 2-75 g/L concentration range
- “Set it and forget it” operation





Integrated Continuous BioProcessing @ 100 g/day

24h Run in Progress...

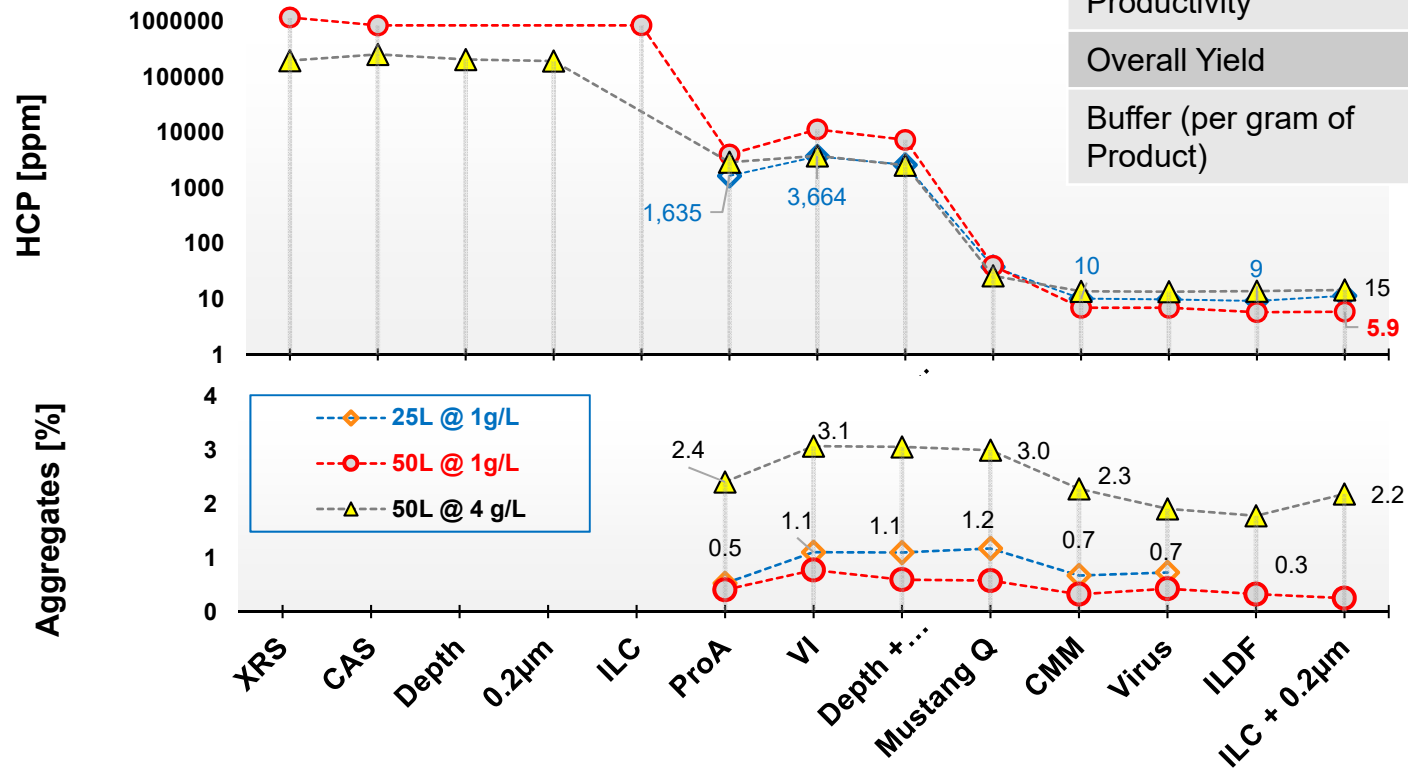


High value & productivity delivered by PD scale equipment and consumables

Unit Op	Sizing used @ 100 g/day
CAS / Depth/0.2µm	4 – 10 L/h / 0.25 m ² / 0.023 m ²
ILC	0.065 - 0.7 m ² (Optional)
BioSMB Capture	8x50 mL KANEKA KanCapA Columns
VI + Depth/0.2µm	0.0088 m ² / 0.002 m ²
BioSMB Polishing Mustang Q (FT) / CMM (B&E)	3x5mL XT Capsules / 6x50 mL Columns
Virus	0.0204 m ² Pegasus™ Prime Virus Removal Filter
ILDF/ ILC / 0.2µm	1.2 m ² / 0.065 m ² / 0.0011 m ²

100 g/day CQA Trends

mAb IN	54L, ~190 g
mAb OUT	1.79L, ~107.2 g
Process Total	20.67 hours
Productivity	~124 g/day
Overall Yield	~56%
Buffer (per gram of Product)	4.9 L/g



Stable Process with HCP < 10 - 20 ppm, Aggr. < 1 - 2%

Availability

Now



Cadence Acoustic Separator

Ideal for process characterization and optimization studies with a process flow of ~4 L/h

Now



Cadence BioSMB PD System

Optimization of continuous chromatography in 24 h

Now



Pegasus Prime Virus filter

Reliability, simplicity & economy

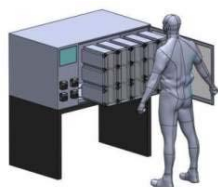
Now



Cadence ILC

Performance of TFF with the simplicity of direct-flow filtration

2017



CAS Full Scale GMP System

Modular design for clarification up to 2000 L bioreactor (250 – 500 L/h)

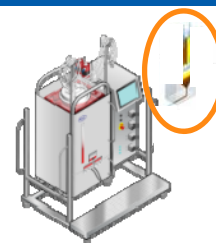
Now



Cadence BioSMB Process GMP System

Design for purification of clinical material from bioreactors of up to 2000 L volume

2017



AWS Benchtop for Perfusion

Ideal for process characterization and optimization studies.

2017



Cadence ILDF

>99.9% continuous buffer exchange without the requirement for recirculation used in conventional UDF



Thank you