



TRENDS AND TENDENCIES IN
THE SINGLE-USE INDUSTRY

Establishing Continuous Manufacturing in a Relevant Production Scale

Presenter

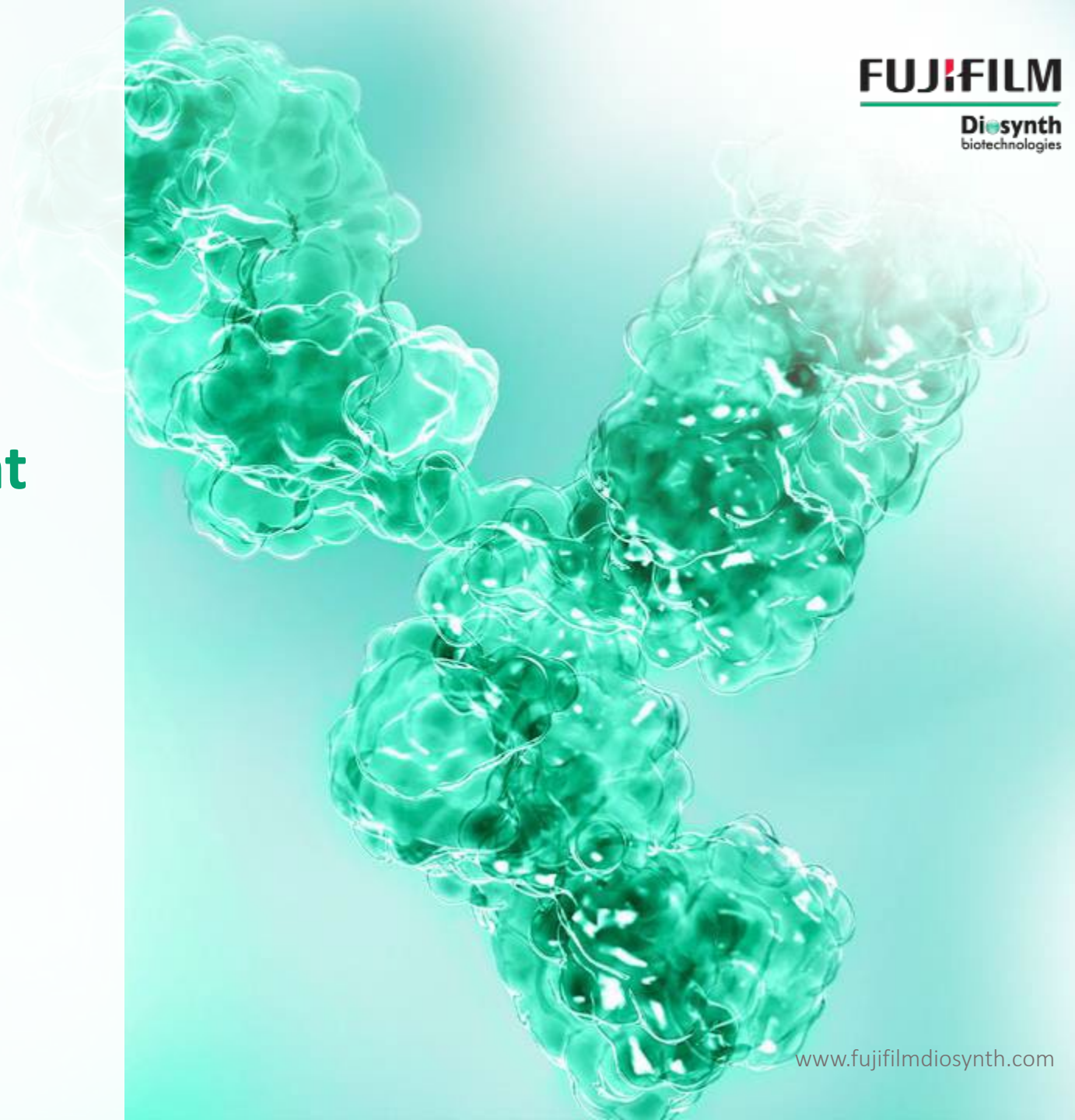
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Hvidovre, 21st September 2023

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Agenda

- Introduction
- PDA TR 66
- CDMO setup
- Why go for Continuous Manufacturing
- Quality advantages of Continuous Manufacturing
- Development of a multi-functional Continuous Manufacturing process system
- Case study - Continuous Monoclonal Antibody Manufacturing
- Optimal column loading case study
- Questions

PDA Technical Report No. 66

Technical Report No. 66

Application of Single-Use Systems in Pharmaceutical Manufacturing

PDA Application of Single-Use Systems in Pharmaceutical Manufacturing Technical Report Team

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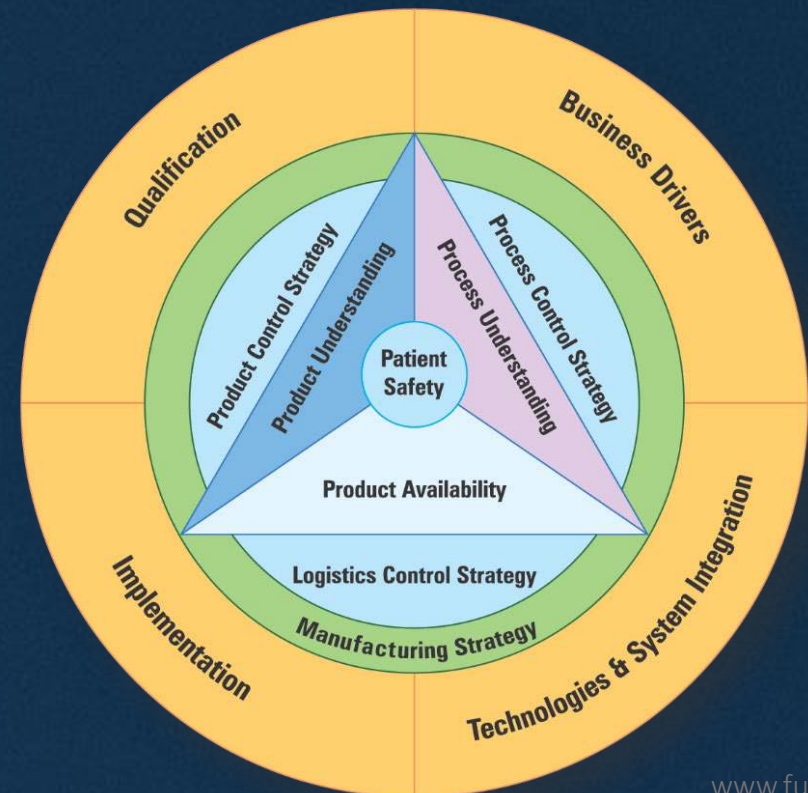
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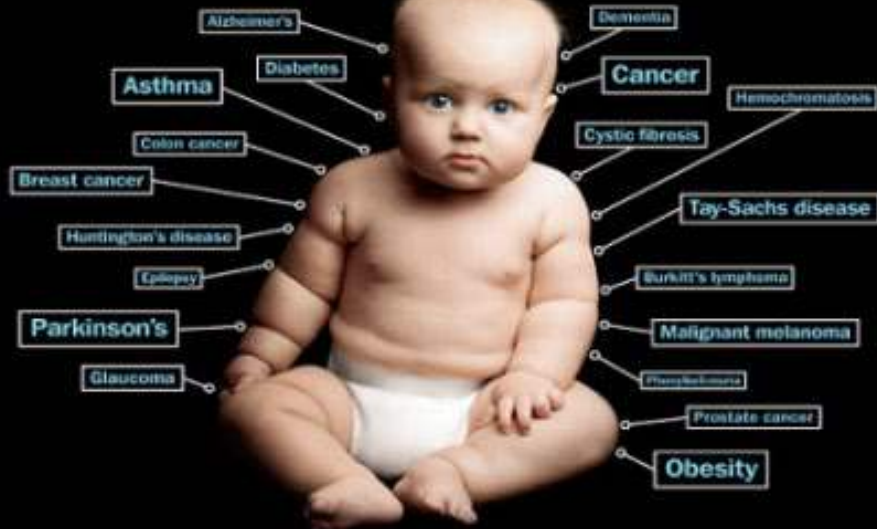


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TIME

Want to Know My Future?



New genetic tests can point to risks — but not always a cure

BY BONNIE ROCHMAN

www.time.com

FUJIFILM

Diosynth
biotechnologies



www.fujifilmdiosynth.com

What is a CDMO – Contract Development Manufacturing Organization

CDMO



Dating



Wedding



Marriage

Sponsor



First F2F



Contract



Project execution



Strategies for supplying market demand



Scale-Up

Multiple 20,000-L bioreactors

Efficiency of scale

Ideal for high-volume products



Scale-Out

Multiple 2,000 L bioreactors
Options for multiplexing (2 x 2000L)

Flexible strategy mitigates risks due to uncertainties in commercial demand

Ideal for lower volume products

Leverages FDB's 'mAb platform' technology



Continuous

Single or multiple 500-L bioreactors or larger

Improved production efficiencies

Flexibility and potential to deliver high-volume

Advantages of Continuous Manufacturing (CM)

- Integrated processing with fewer steps
 - No manual handling, increased safety
 - Shorter processing times
 - Increased efficiency
- Smaller equipment and facilities
 - More flexible operation
 - Reduced inventory
 - Lower capital costs, less work-in-progress materials
 - Smaller ecological footprint
- On-line monitoring and control for increased product quality assurance in real-time
 - Amenable to Real Time Release Testing approaches
 - Consistent quality

FDA Perspective on Continuous Manufacturing

IFPAC Annual Meeting
Baltimore, January , 2012

Sharmista Chatterjee, Ph.D.
CMC Lead for QbD
ONDQA/CDER/FDA

Potential for reduced cost

8

Meeting Product Demand Challenge



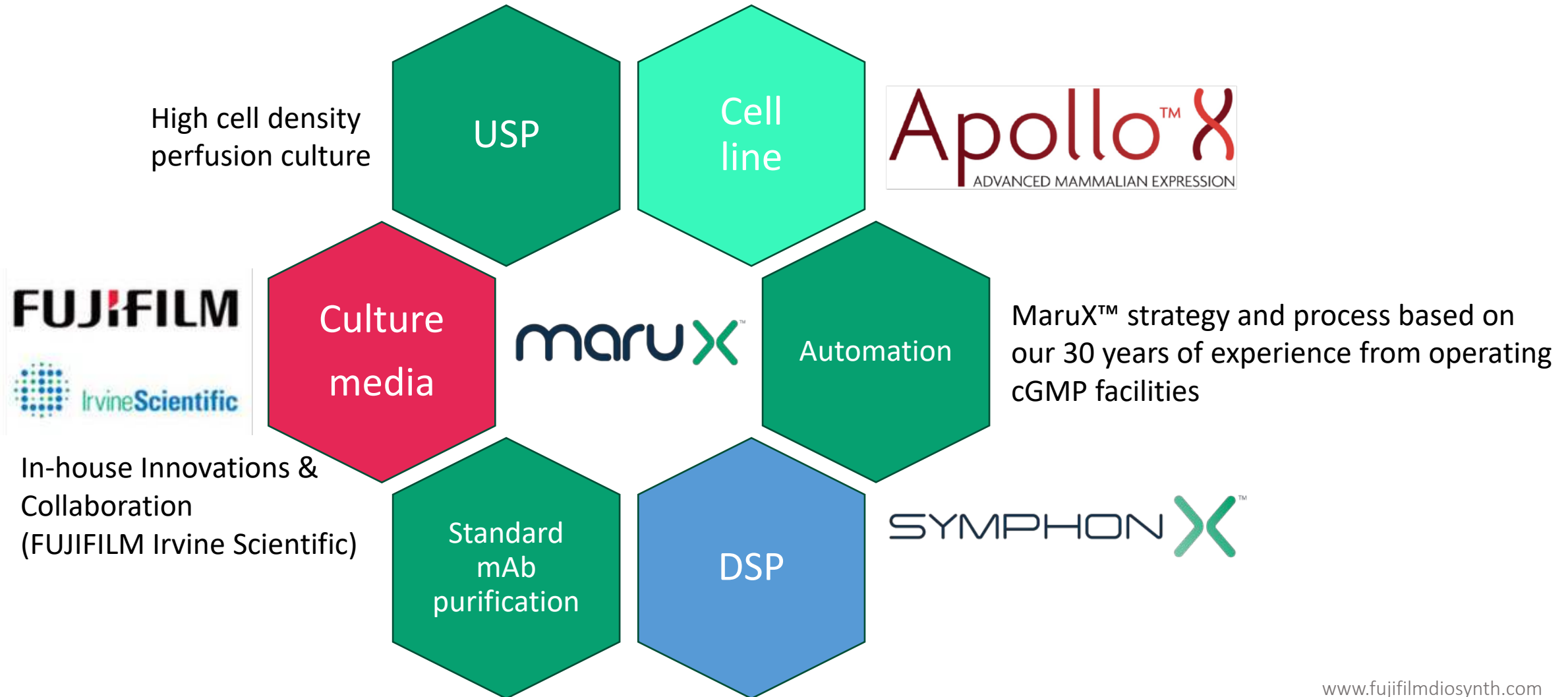
This when you need to build the facility, knowing that the product has a 90% chance of falling

What is currently holding back implementation of CBP?

- Precedence - someone else needs get it through the FDA/EMA first
- Robust PAT tools, defined regulatory path, robust single use technology
- Comfort level and lack of PAT and control tools
- CBP doesn't easily fit into existing infrastructure / facilities / Quality systems
- Economic justification and adaptation of current Quality/Regulatory programs
- Unit operations not fully developed for continuous processing; not a standard platform

**Lack of experience and concern
of authorities point of view**

MaruX™ - end-to-end automated and integrated upstream and downstream processing



SymphonX™: in-house DSP technology platform



Multi-functional

Disposable Flowpath

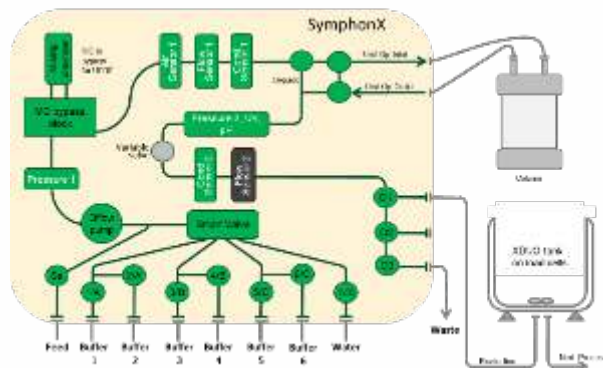
Buffer Management

Automation Software

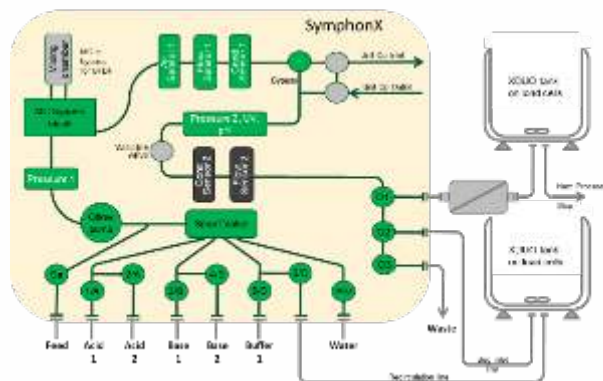
- All standard purification steps
- Simplifies and de-risks operations
- Irradiated, functionally closed USP Class VI compliant flow path
- Chemical compatibility & mechanical robustness
- In-line point-of-use dilution, conditioning or blending
- Isocratic and gradient mixing
- CFR21 Part 11 and GAMP5 compliant
- Data Integrity
- Networked/integrated

Same flow path different unit operations

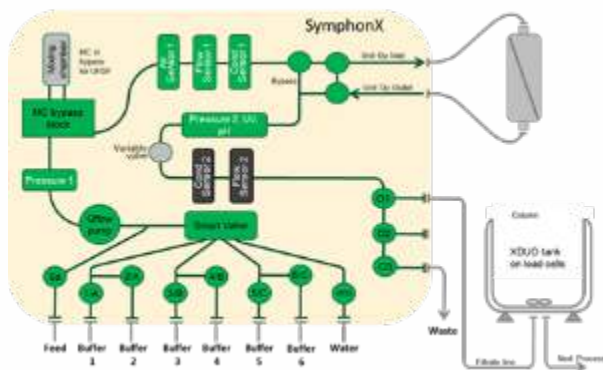
- Chromatography



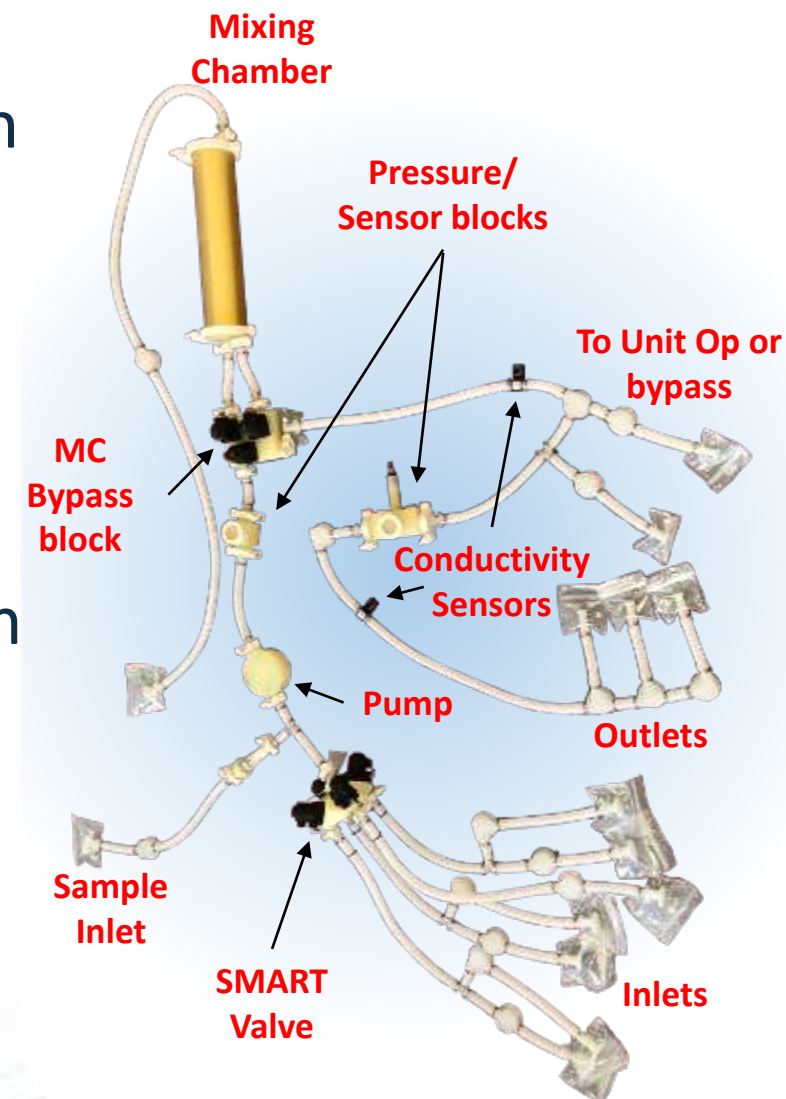
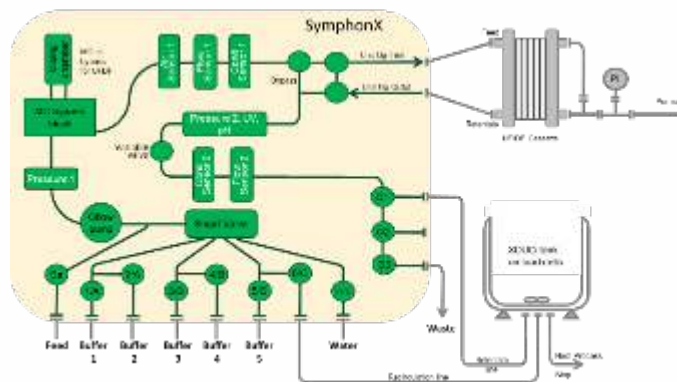
- Titration/Viral Inactivation



- Filtration



- Ultrafiltration/Diafiltration

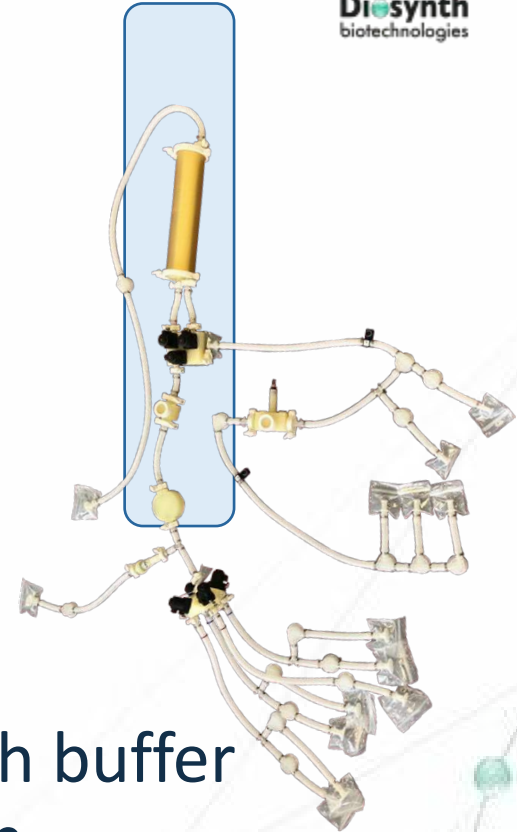


Delivery of Advanced Buffer Management

FUJIFILM

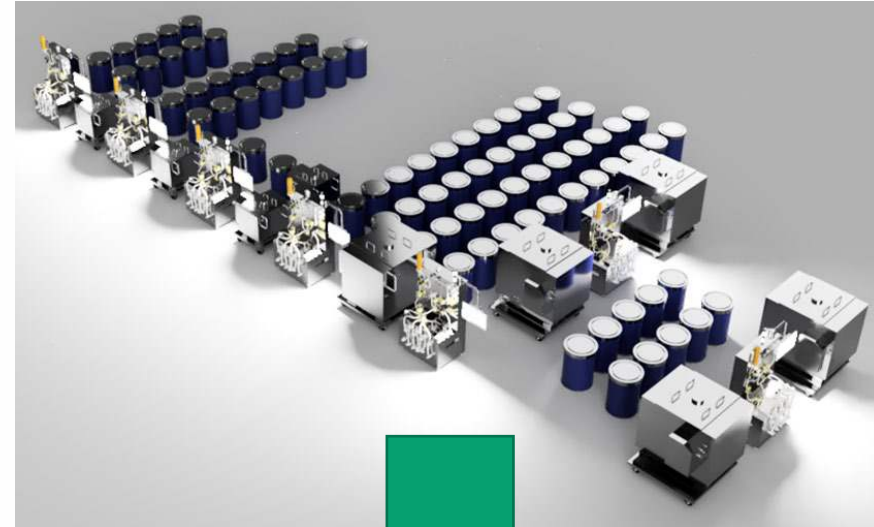
Diosynth
biotechnologies

- 4-way SMART valve block upstream of a single pump with proprietary static mixing chamber downstream of pump
- SMART Valves either open or closed
 - Only one valve open at a time
- Buffer dilution or blending of stock solutions to generate isocratic buffers or buffer gradients
- Mixing chamber converts the time separated aliquots of each buffer into a homogeneous buffer for supply into the unit operation



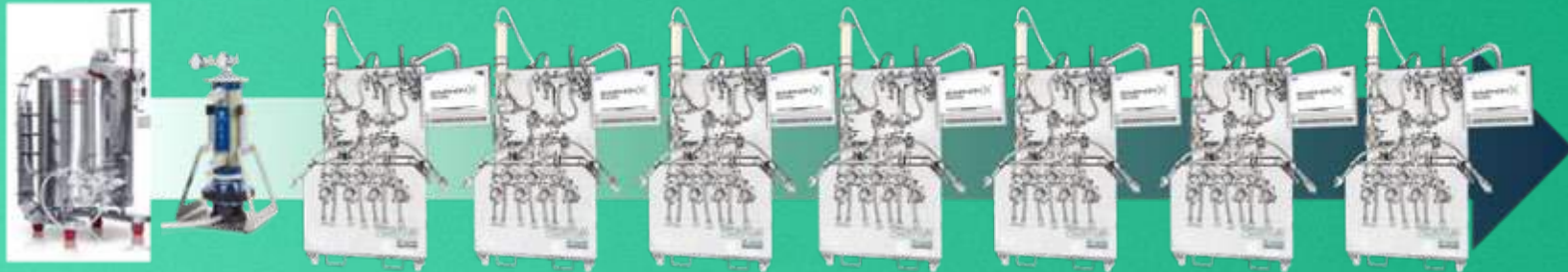
Buffer Management

- Point-of-use in-line dilution using SymphonX™
- Buffer Strategy
 - 5x buffer concentrates for buffers on all 7 unit operations
 - 4x buffer stock for high salt and formulation buffer
 - 1x buffers used for CIEX gradient
 - All pre-made and 0.2 µm filtered
- 1,600 L 5x buffer conc / week
- 800 L 4x buffer conc / week
- (~13,500 L 1x buffer / week)



maruX™

Continuous Monoclonal Antibody Manufacturing: IgG1 (lambda) case study



maruX™ Continuous mAb production facility

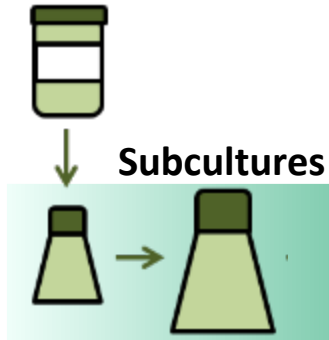
- 400 m² non-GMP suite (Billingham, UK)
- Functionally closed end-to-end disposable flow path
- Semi-continuous operation
 - Upstream: 500 L Perfusion bioreactor and ATF cell retention device using ApolloX™ perfusion cell line and FUJIFILM Irvine Scientific media
 - Downstream: intensified batch processing with SymphonX™
 - Intermediate break bags on load cells
 - Viral clearance and analytics are aligned with current fed-batch processes



Integrated USP and DSP generates >15kg purified mAb in 30 days



Perfusion ready
CHO cell line



Subcultures



WAVE25™
(perfusion)

High cell density
inoculation



Feed

Automated
cell bleed

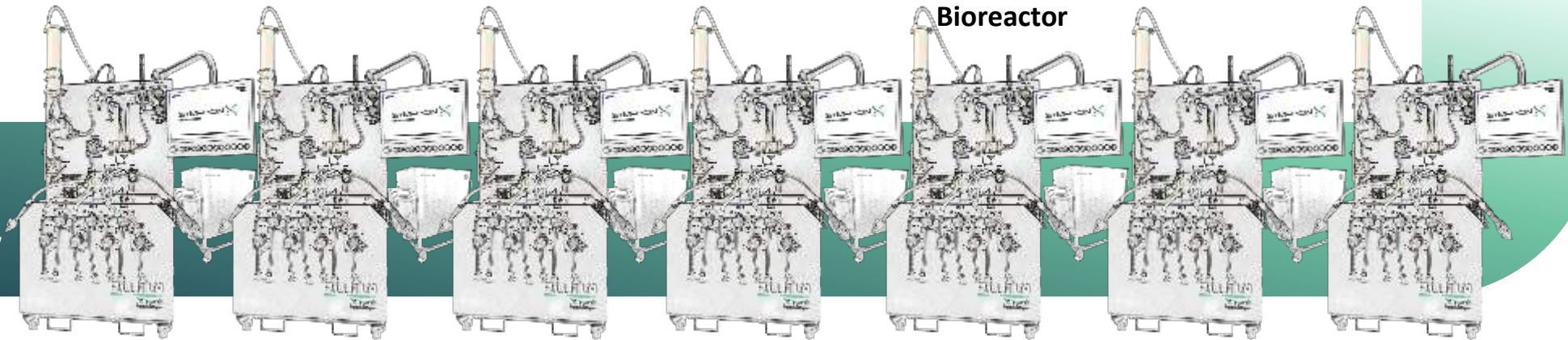


500 L Perfusion
Bioreactor

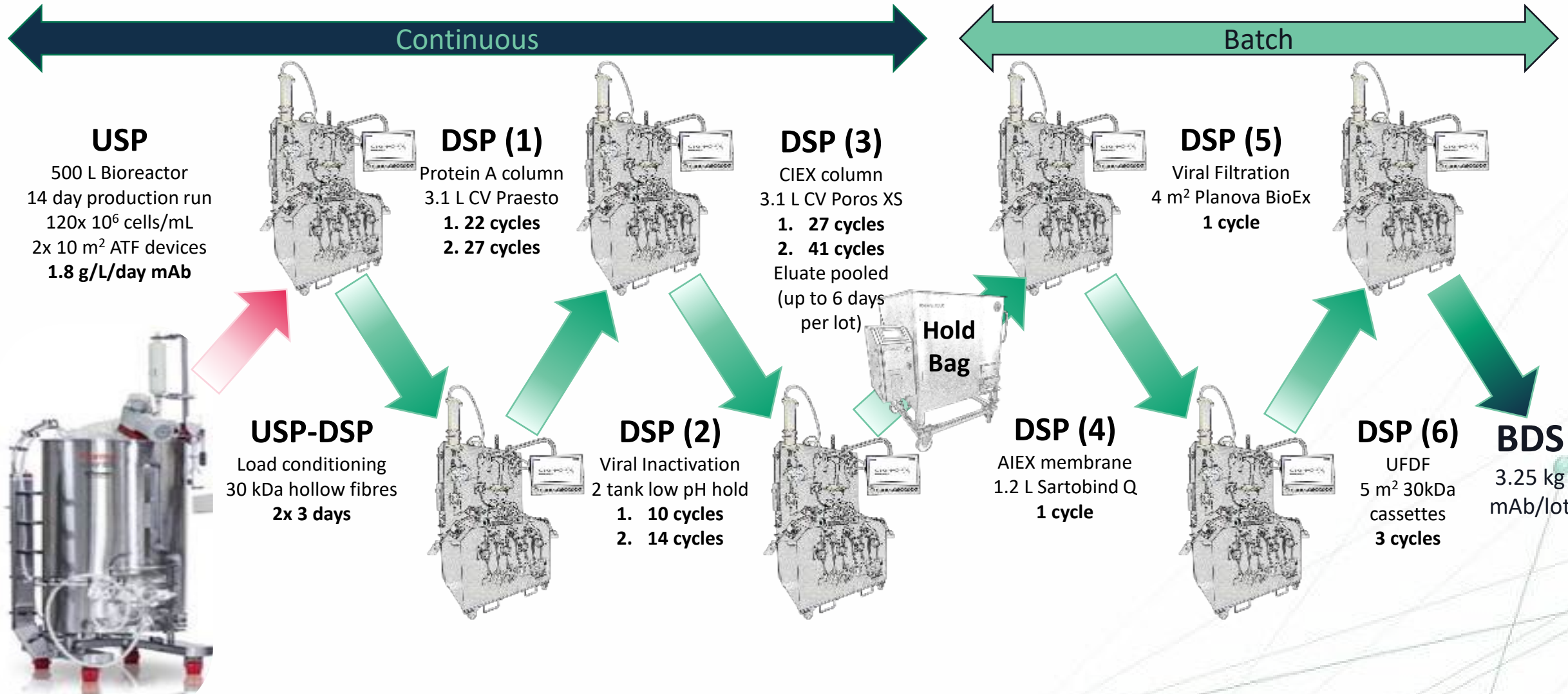


ATF10

Purified
Antibody



Process Overview



- Production bioreactor

- 24 day run
- 1.2 vvd (600 L perfusate)

- Very high cell density

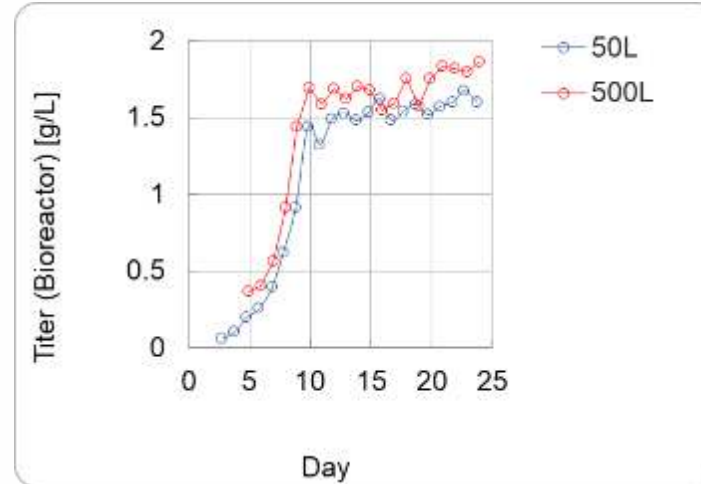
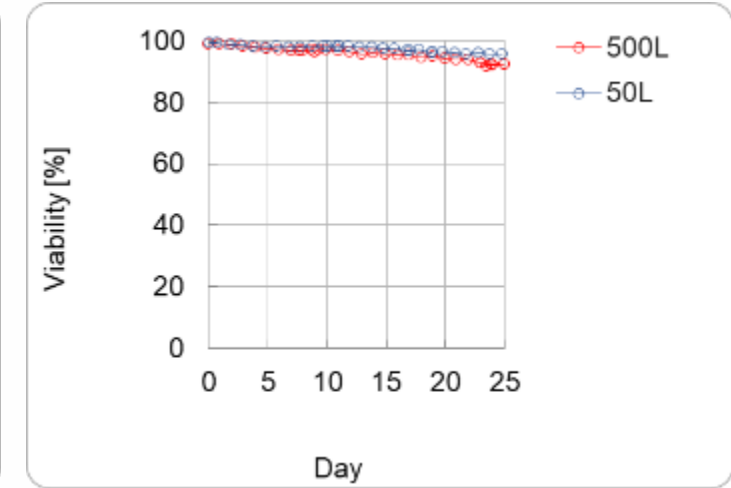
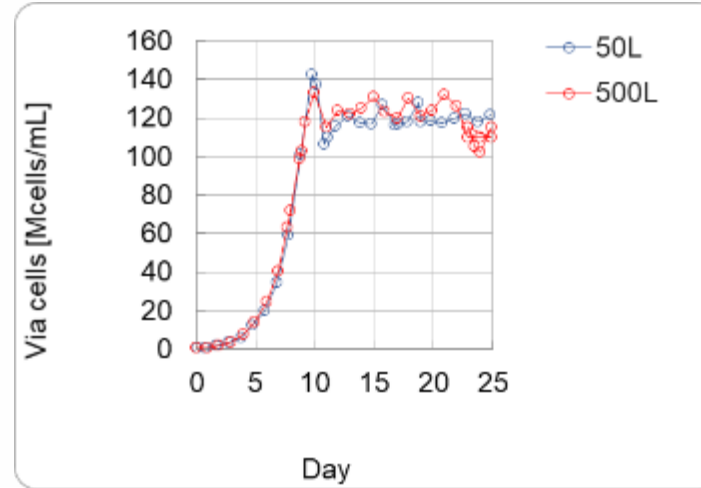
- 120×10^6 cells/mL $\pm 10\%$
- Viability >90 %

- Productivity

- 1.8 g/L/day $\pm 10\%$
- 15.4 pg mAb/cell $\pm 10\%$

- mAb supply to downstream

- 0.96 kg mAb/day



• Product Quality

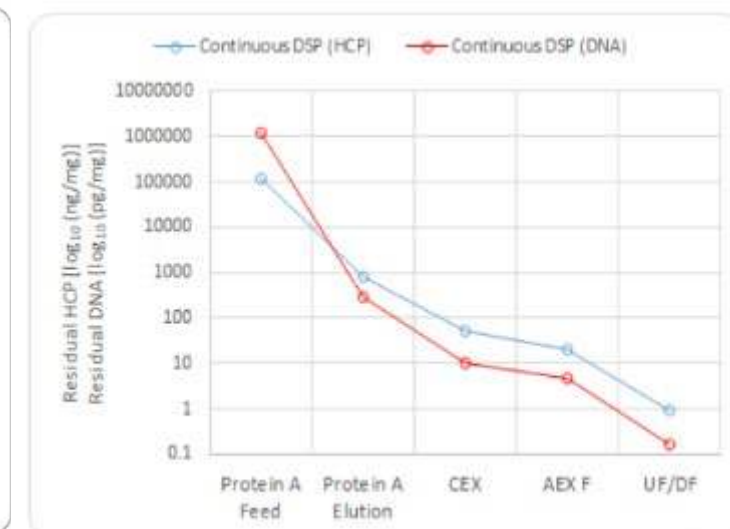
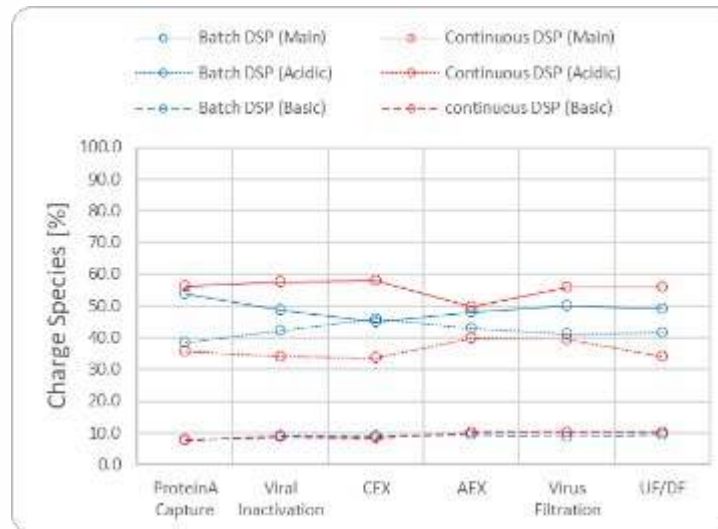
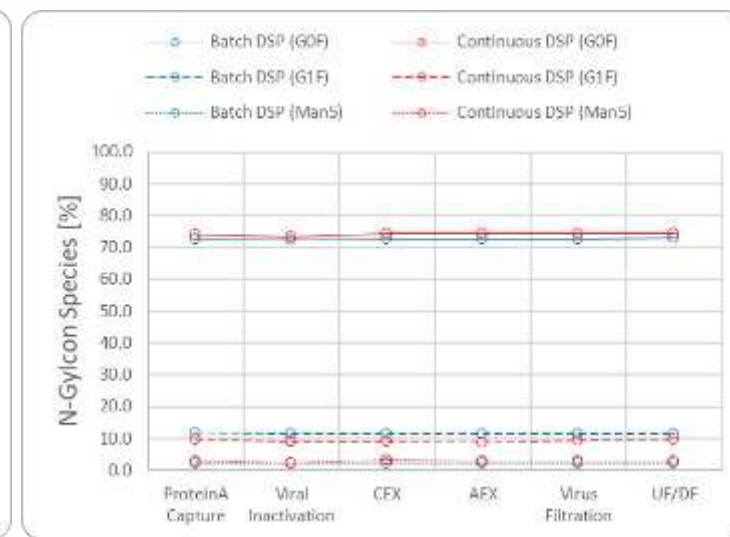
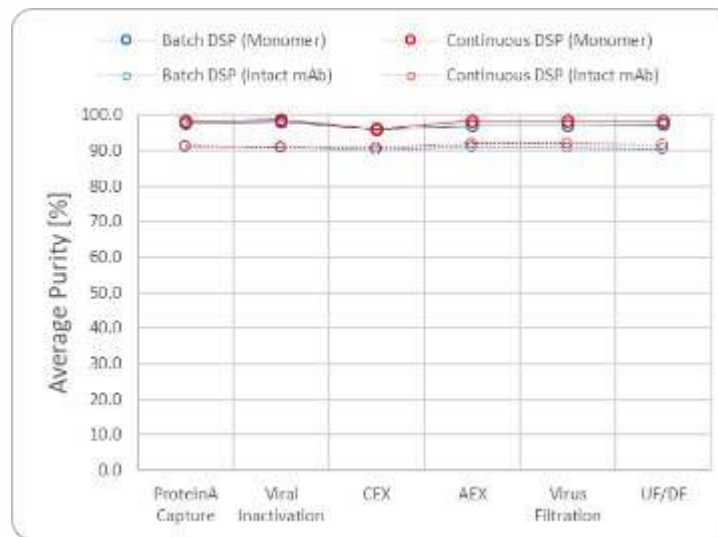
- Comparable quality between batch and continuous purification process
- Consistent quality attributes across purification process

• Residual Clearance

- Expected clearance of residuals through process

• 3.25 kg BDS from 6 day production “lot”

- 56 % Process Yield (without process optimisation)



Theoretical Example

Yield variation impact on column loading

- Column loading impact on:
 - Residence time
 - Pool volume
 - Processing time
 - Resolution ?
 - Total yield ?
 - Impact on CQAs ??
- Typical solution – run a number of cycles on each column
 - How many cycles (sub- batches)
 - Longer hold time before loading and after pooling – impact on CQAs ?
 - Criteria for pooling sub-batches



Theoretical Example

Yield variation impact on column loading

Process step	Yield Range	Amount of Product (Gram)	Column loading range (g/L resin)
500L Cell Culture yield	2.7 – 3.3 g/L	1.350 – 1.650	
Harvest	80 – 90 %	1.080 – 1.485	
Prot A	75 – 85 %	810 – 1.262	16.2 – 25.2 (50 L)
CIEX	85 – 95 %	689 – 1.119	6.89 – 11.2 (100 L)
AIEX	80 – 90 %	551 – 1.079	5.51 – 10.8 (100 L)

Theoretical typical standard MAB process. One cycle per column

Theoretical Example

Yield variation impact on column loading

Process step	Yield Range	Amount of Product (Gram)	Number of runs on a 2 L column	Column loading range (g/L resin)
500L Cell Culture yield	2.7 – 3.3 g/L	1.350 – 1.650		
Harvest	80 – 90 %	1.080 – 1.485		
Prot A	75 – 85 %	810 – 1.262	20 – 32	20
CIEX	85 – 95 %	689 – 1.119	35 – 60	10
AIEX	80 – 90 %	551 – 1.079	34 – 68	8

Theoretical MAB process. Running the column steps in a continuous mode

Summary

- Successful demonstration of 500L manufacturing scale continuous mAb production in a non-GMP facility
 - End-to-end functionally closed disposable flow path
 - Data supports moving to 2000 L scale
 - Data supports using N-1 in 20,000 L scale
- USP Highlights
 - High cell density: 120×10^6 cells/mL
 - mAb productivity: 15.4 pg/cell equivalent to 1.8 g/L/day
- DSP Highlights
 - Just-in-time in-line buffer concentrate dilution strategy
 - Generated 0.54 kg/day purified mAb



THANK YOU

“ The secret of getting ahead is getting started. The secret of getting started is breaking your complex overwhelming tasks into small manageable tasks, and starting on the first one.”

Mark Twain



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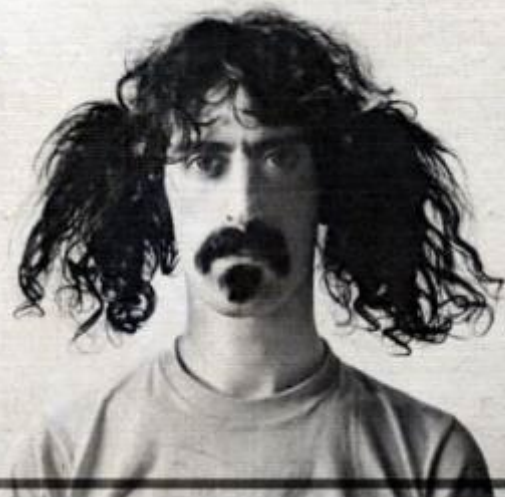
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Without deviation
from **the norm**,
progress is not possible.

-Frank Zappa



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Questions?

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GET COURSE INFO

COURSE CALENDAR FOR: 30. OCT - 14. NOV 2023

30 Oct 2023 9:00-16:45

DAY 1: ARTIFICIAL INTELLIGENCE

- AI and the technologies importance for production.
- The authorities perspectives on the importance of AI Technologies for the GMP environment
- Machine Learning

31 Oct 2023 9:00-16:45

DAY 2: DATA AND DATA ANALYSIS

- Industry (I 4.0) and data understanding (Why and what - Data science projects and processes)
- Effective use of different data sources to solve problems in production
- Data analytics - methods and tools

13 Nov 2023 9:00-16:45

DAY 3: IOT AND XR

- Operational Performance Support through digitalization, Fuji Film
- Internet of things - the technological possibilities and limitations
- Xtended Reality - In the field between available hardware and solving difficult technical problems

14 Nov 2023 9:00-16:45

DAY 4: DESIGN THINKING AND USER EXPERIENCE

- User Interfaces – A UX approach to better technologies
- Operational Performance Support through Augmented Instructions
- Cyber Security Awarenes – challenges and handling