GMP–
PHARMA
CONGRESS

#sharing challenges
and solutions in practice

FUJIFILM Diosynth Biotechnologies CDMO: Multifunctional Single-Use Purification System for connected and integrated Continuous Processing

Facility & Technology Projects

Part of PharmaCongress – Düsseldorf/Neuss, 31 May - 1 June 2022

SYMPHONX™

Single Use Technology collaboration case study

Development and use of a multi-functional purification skid

FUJIFILM Diosynth Biotechnologies
Gemü GmbH

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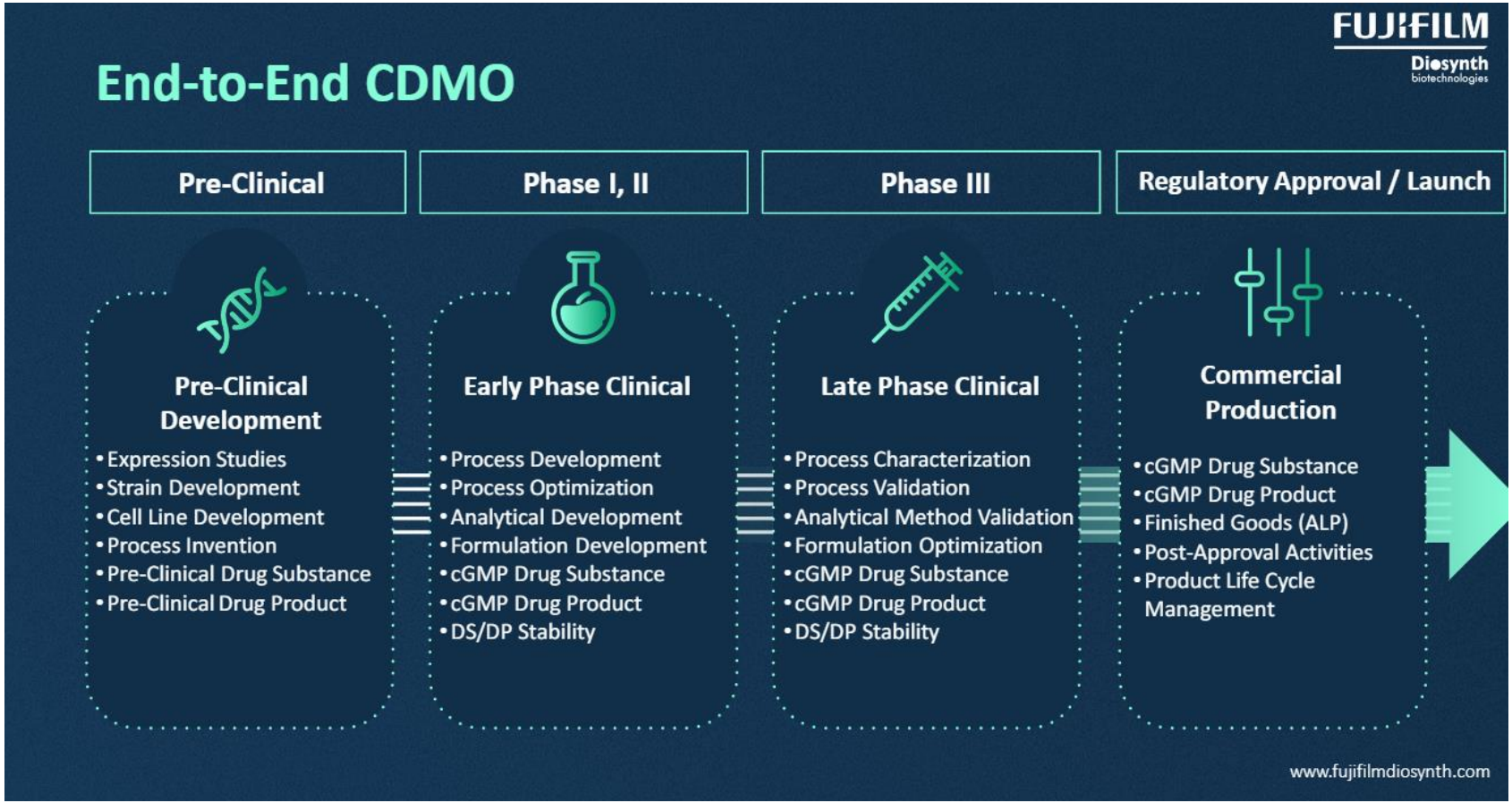


Strategies for Supplying Market Demand

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

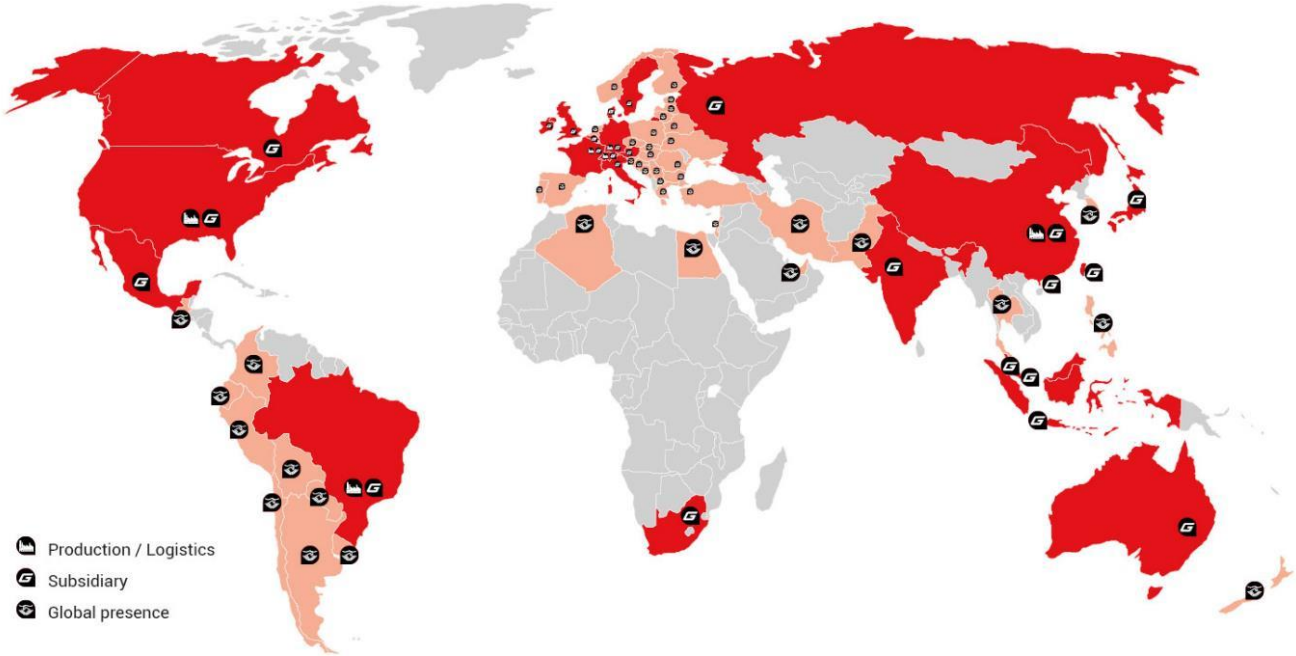
Improved production efficiencies

Flexibility and potential to deliver high-volume

Made by GEMÜ

Our quality promise

- Manufacturing in accordance with internationally recognised **production and security standards**
- **A consistently high level of quality all over the world** – irrespective of the manufacturing site



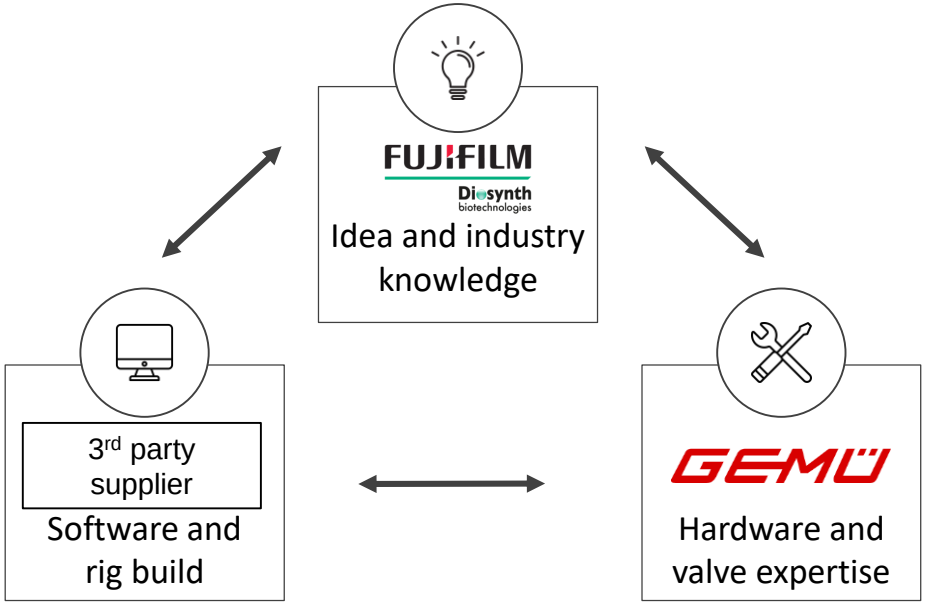
Why SymphonX™?

Normally in the DSP several units are needed for different processing steps:

- Tangential flow filtration
- Protein A affinity chromatography
- Viral Inactivation
- Cation and anion exchange chromatography
- Viral Filtration
- Ultrafiltration/diafiltration

This requires a lot of equipment types and various training needs!

Successful Collaboration



Description

SymphonX™

- Purification platform system
- Integrated buffer dilution system
- Single flow path for multiple use
- Versatile modular system
- Scalable system 6 – 740 L/hr

Key Features

SymphonX™

- Single-use flow path with disposable pump head, valve bodies and sensor probes
- Flexible software interface
- Automation friendly process control
- Developed and validated for use in GMP
- Successfully deployed for
  - GMP batch manufacturing
  - non-GMP continuous mAb production

Main Advantages

SymphonX™

- Multiple application capabilities within the same skid i. e. one skid can cover the whole Bio purification train
- Automated system
- Ease of training (one skid as opposed to many)
- Tech transfer between locations and facilities
- Improved forecastable supply chain
- Embedding sustainability principles into Single-Use Technology through robust flow path design

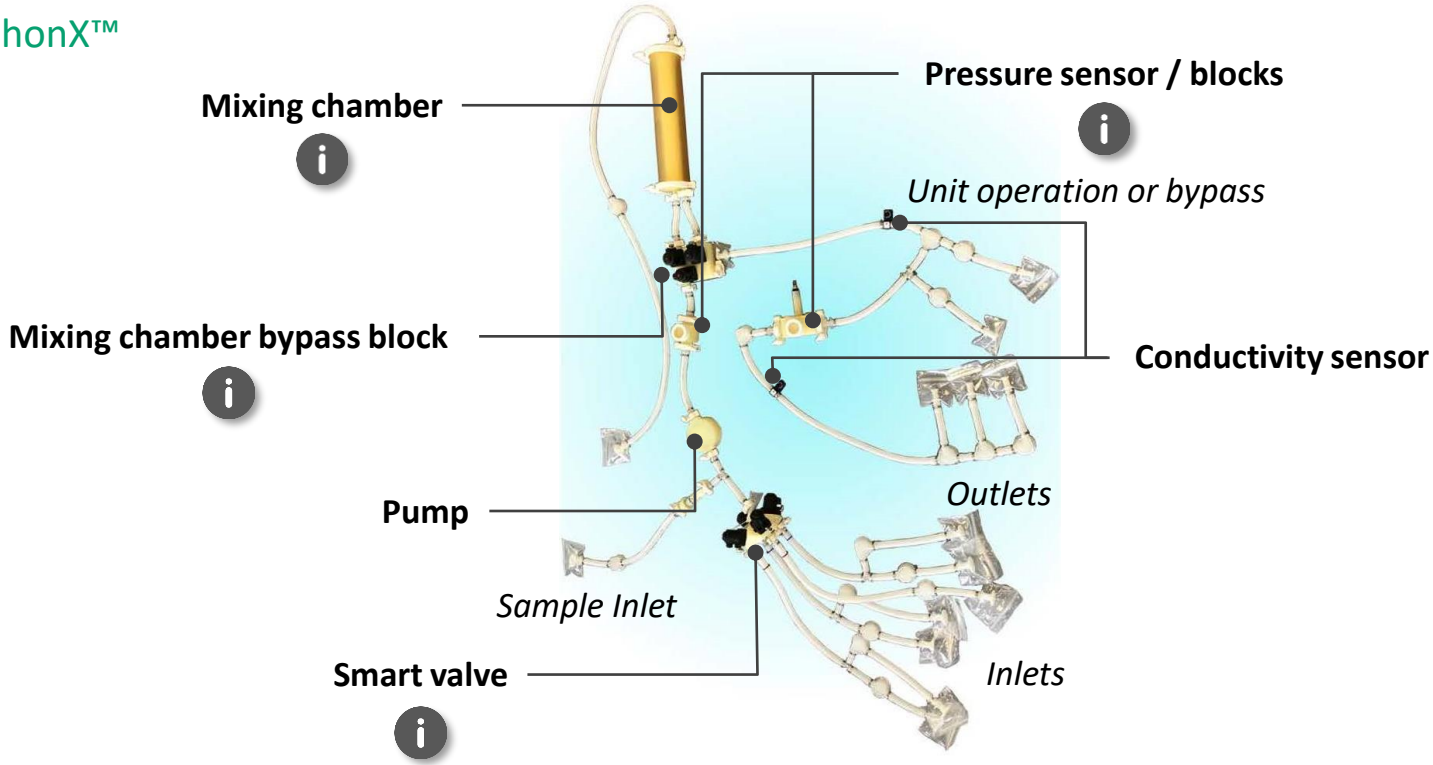
User Requirement Specification

SymphonX™

- Sustaining a linear flow within a range of 6 – 740 L/hr
- Internal diameter of all flow path components is ½”
- Materials PP, EPDM, PEEK, Silicon, TPE or PSU
- Operating temperatures: 4 – 40 °C
- Ends sealed with blanking caps, bags or aseptic connectors
- Assembled under ISO Class 8 conditions
- Assemblies to withstand gamma, X-ray or equivalent irradiation of 25 kGy (maximum 45kGy)
- Shelf life to be 12 – 24 months

Flow Path

SymphonX™



Competences

GEMÜ

Quality management systems

- Manufactured in compliance with GMP
- Compliance with ISO 9001
- Manufacturing site registered with the FDA
- TSE/BSE-compliant manufacture
- Transport validation as per ASTM
- Cleanroom manufacturing and assembly in cleanroom class 8 according to EN ISO 14644-1

Product requirements

- ISO 10993 compatibility
- USP/EP-compliant purity
- Use of FDA-compliant plastics
- Radiation sterilization by X-ray

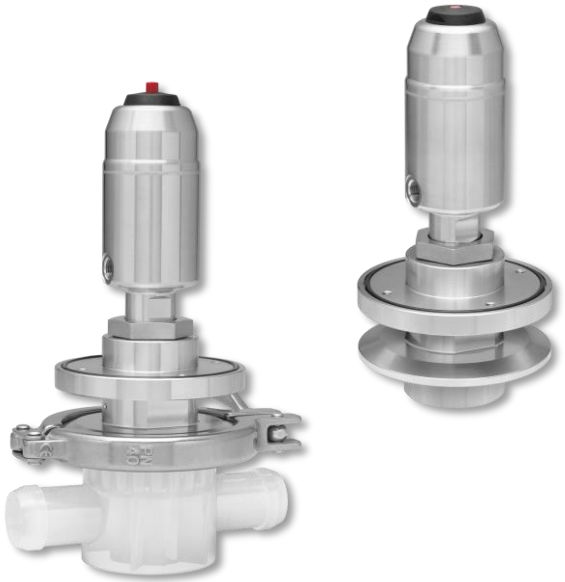
Design and production of individual products and solutions

Single-Use Diaphragm Valve

GEMÜ SU40 SUMONDO

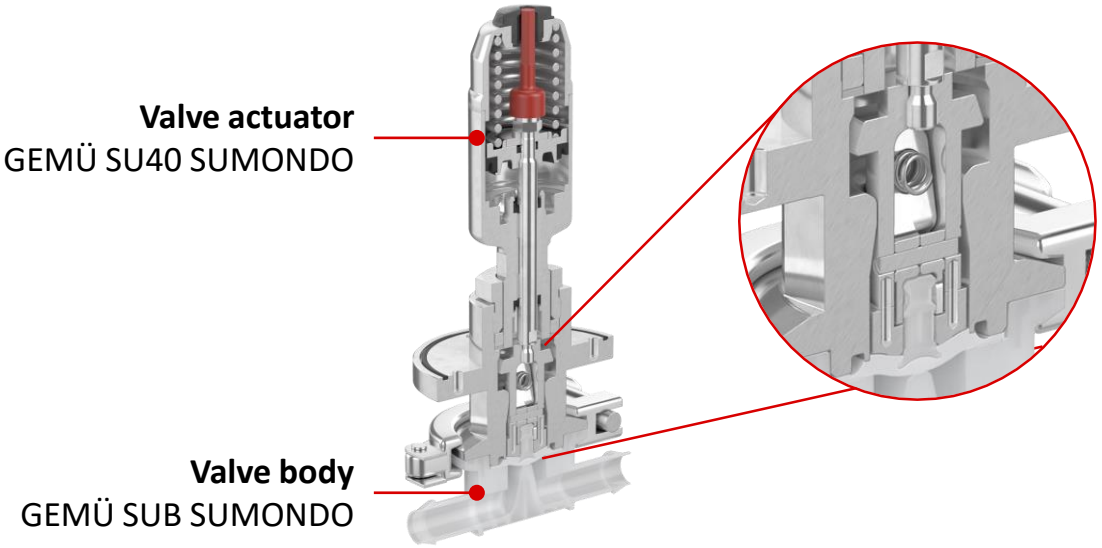
Features

- Easy, application-friendly valve body assembly
- Impact-resistant and corrosion-resistant
- Integral optical position indicator
- Simplified installation thanks to the fastening clamp
- Optimized body replacement time



Single-Use Diaphragm Valve

GEMÜ SU40 SUMONDO | connection principle



Single-Use Diaphragm Valve

GEMÜ SU60 SUMONDO

Features

- Hermetic separation between medium and actuator
- Optimized assembly options
- Open/close function, positioner and process controller
- Force and speed are variably adjustable
- Optimized body replacement time
- Can be operated via eSy-Web or Modbus TCP web interface

maruX™

Continuous Monoclonal Antibody Manufacturing

Connected SymphonX™ case study

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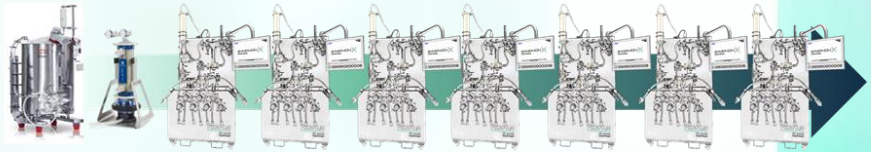

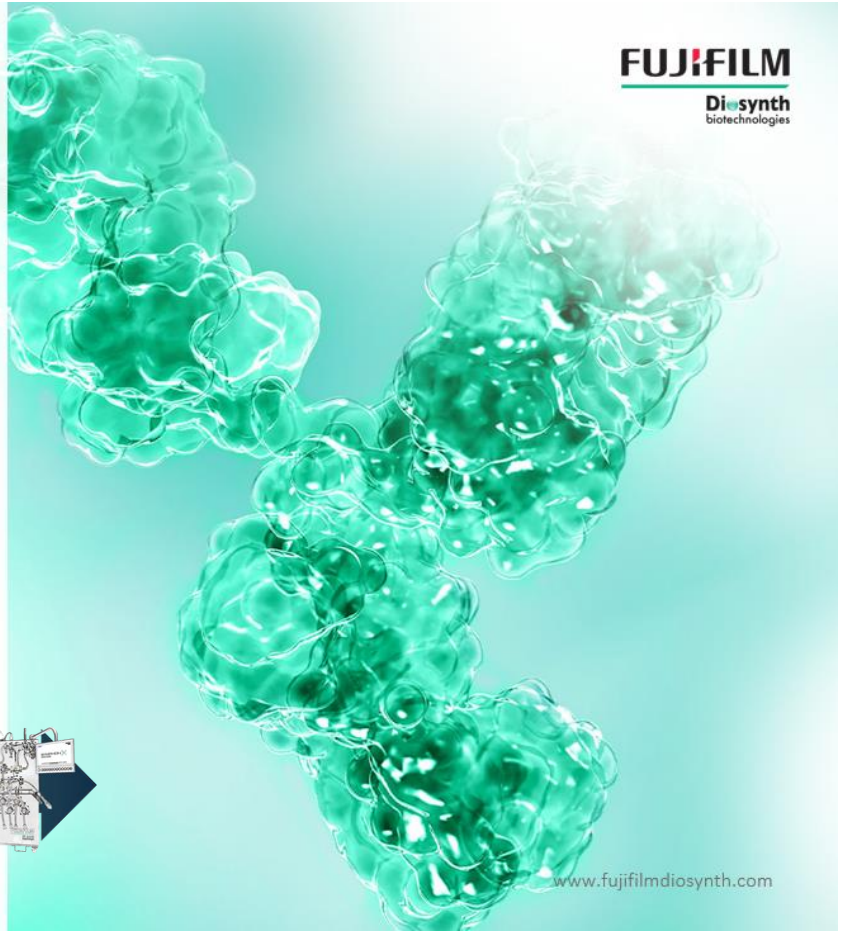

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Continuous mAb Production Facility

- 400 m^2 non-GMP suite (Billingham, UK)
- Functionally closed end-to-end disposable flow path
- Semi-continuous operation
  - Upstream: 500L Perfusion bioreactor and ATF cell retention device using Apollo™X 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
  - Minimising 'Cost of Quality' and perceived Regulatory risk

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

Process Overview non-GMP

FUJIFILM Diosynth biotechnologies

Continuous

Apollo™ ADVANCED MAMMALIAN EXPRESSION

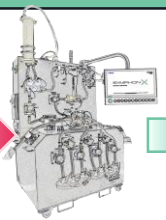
Perfusion ready CHO cell line

FUJIFILM IrvineScientific

Feed

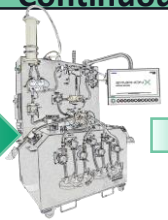
USP

500 L Bioreactor
2x 6 day DSP supply
120x 10^6 cells/mL
2x 10 m^2 ATF devices
1.8 g/L/day mAb



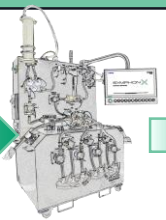
USP-DSP

Load conditioning
30 kDa hollow fibres
2x 3 days



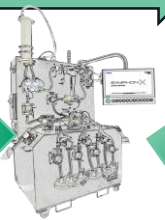
DSP (1)

Protein A column
3.1 L CV Praesto
1. 22 cycles
2. 27 cycles



DSP (2)

Viral Inactivation
2 tank low pH hold
1. 10 cycles
2. 14 cycles



DSP (3)

CIEX column
3.1 L CV Poros XS
1. 27 cycles
2. 41 cycles

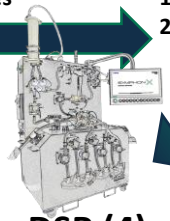
SYMPHONX™

Purification skid

Hold Bag

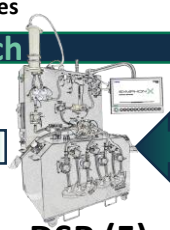
Eluate pooled (6 days per lot)

Batch



DSP (4)

AIEX membrane
1.2 L Sartobind Q
1 cycle



DSP (5)

Viral Filtration
4 m^2 Planova BioEx
1 cycle

DSP (6)

UFDF
5 m^2 30kDa cassettes
3 cycles

BDS

3.25 kg mAb/Lot
0.54 kg mAb/day
1.08 g/L/day mAb

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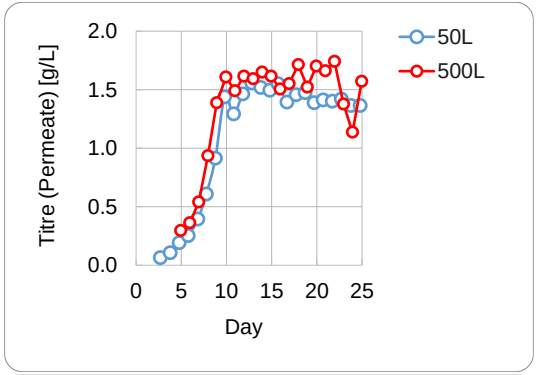
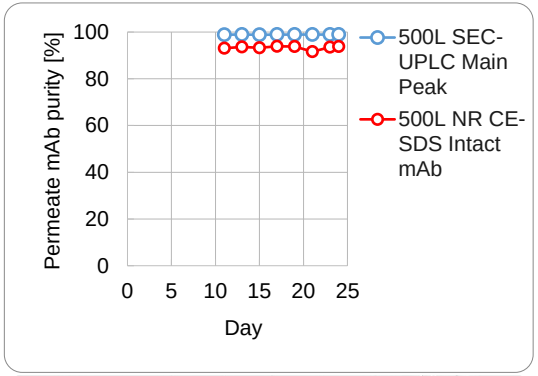
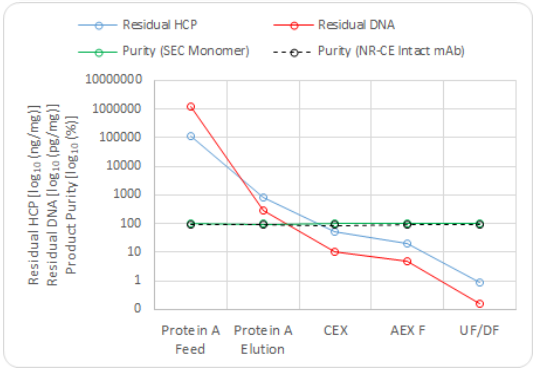
maruX Process Performance

FUJIFILM Diosynth biotechnologies

- Highly productive perfusion process
  - Cell density 120x10^6 cells/mL ±10%
  - Viability >90 %
  - Consistent product quality
- Robust semi-continuous downstream purification process
  - Expected clearance of residuals
  - Consistent product quality







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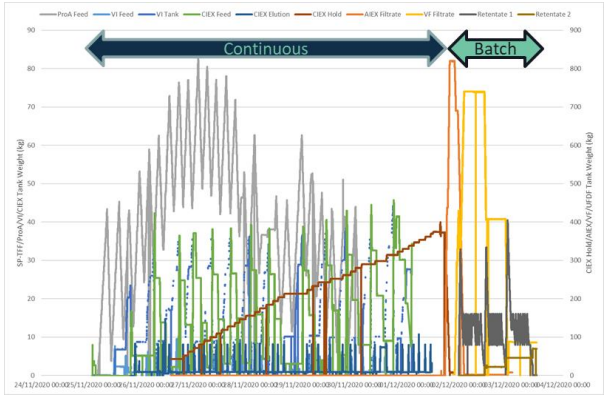
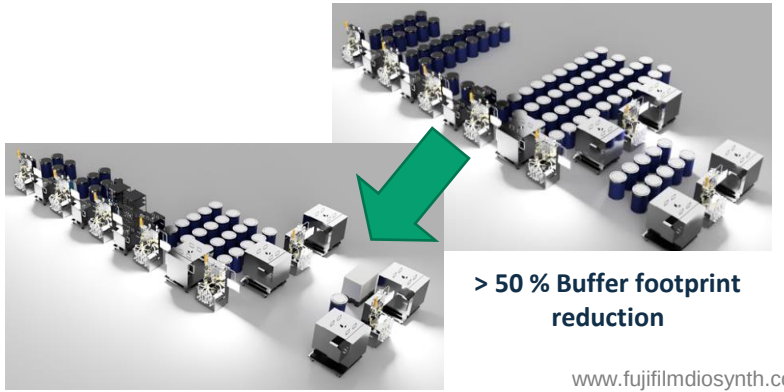
maruX™ Buffer Management

FUJIFILM Diosynth biotechnologies

- 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 mm filtered
- ~14,500 L liquid / week
  - 10,000 L Water
  - 1,600 L 5x buffer conc / week
  - 800 L 4x buffer conc / week
  - 2,100 L 1x buffer /week





> 50 % Buffer footprint reduction

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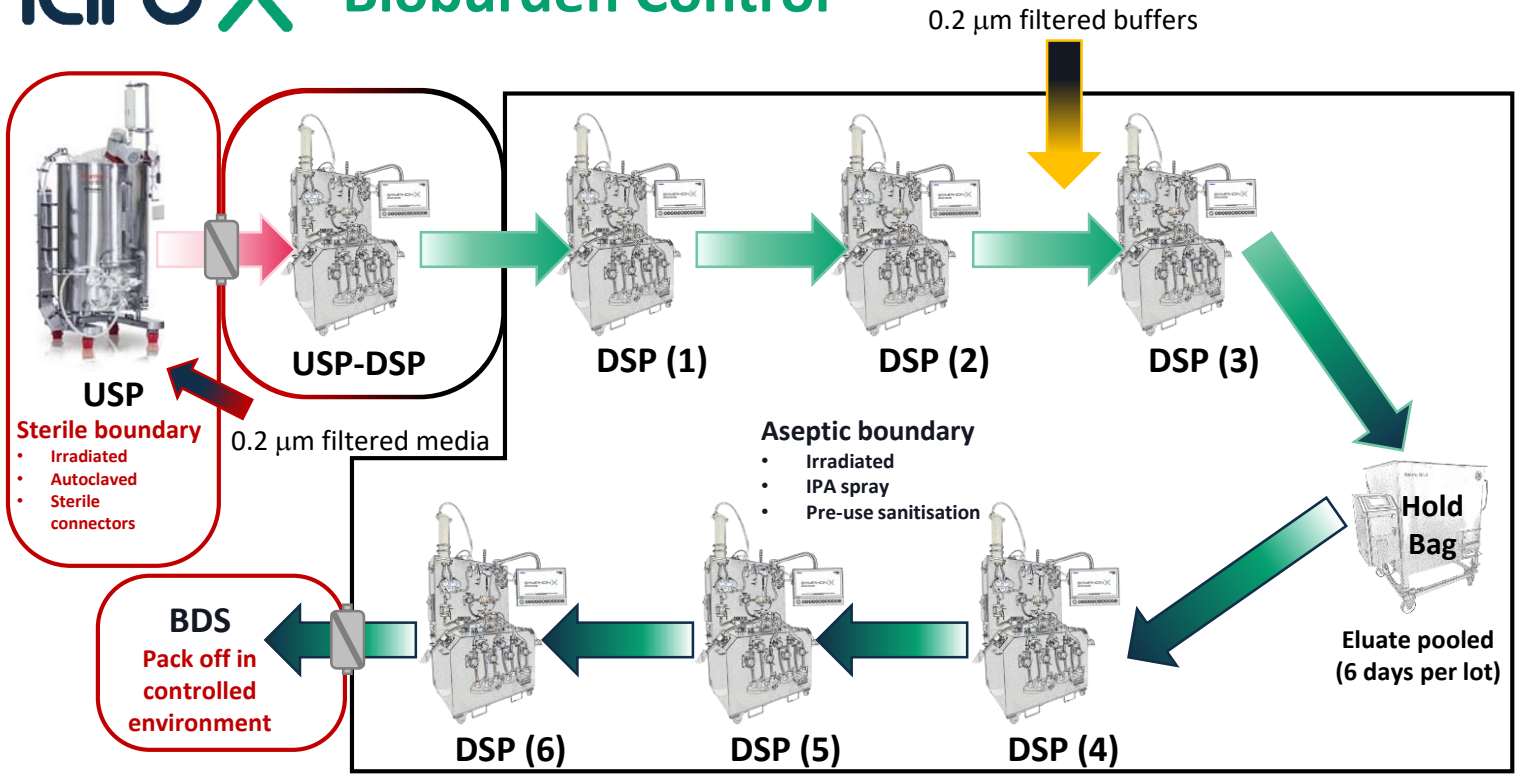
maruX™ Bioburden Control

FUJIFILM Diosynth biotechnologies



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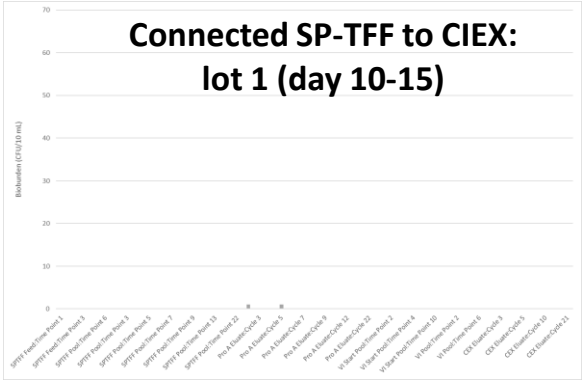
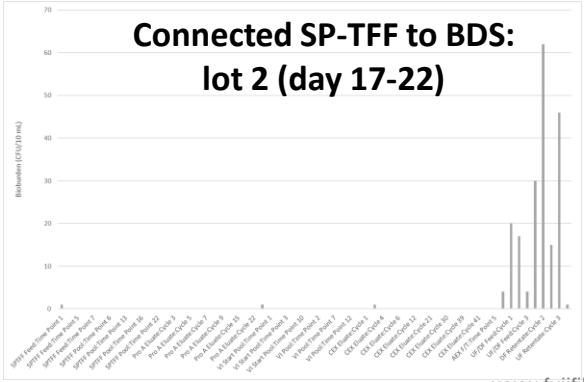
Bioburden Control

- Functionally closed processing in non-classified room showed good bioburden control
  - No contamination of USP
  - No bioburden detected in 1st five continuously operating and connected DSP unit operations over 12 days of operation including flow path change out
    - ≤1 cfu/10 mL with two different end-to-end flow path sets
  - Pre-sanitisation failure demonstrated no transmission of bioburden contamination to upstream process steps
  - Bioburden cleared by final filter (≤1 cfu/10ml)





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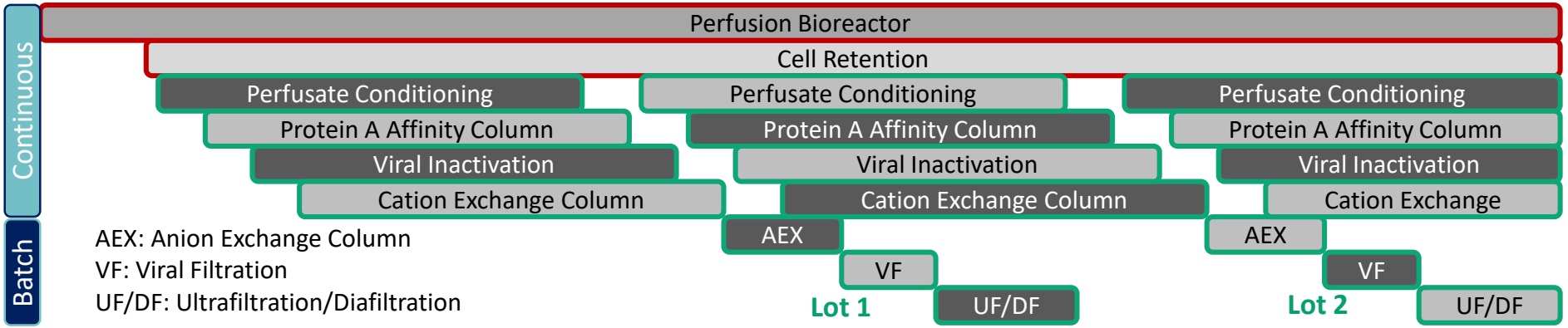
Comparable Drug Substance to Batch process

Drug Substance Quality Attribute		Target	Batch Process	Continuous Process
Concentration	(g/L)	35 – 45	37.2	39.5
SEC: Monomer peak	(%)	>87.5	97.3	98.4
Non Reduced CE-SDS	(%)	78.6 – 96.0	90.6	91.1
Reduced CE-SDS: Heavy Chain	(%)	58.5 – 71.5	65.0	64.2
Reduced CE-SDS: Light Chain	(%)	29.3 – 35.9	32.6	32.3
cIEF: pI		8.50 – 9.40	8.95	8.97
cIEF: Neutral peak	(%)	47.3 – 57.8	48.9	56.9
N-Glycan: G0F	(%)	65.8 – 80.4	73.1	74.8
Residual DNA	(pg/mg)	<100	2.09	<0.16
Residual HCP	(ng/mg)	<100	2.2	0.9
Residual Protein A	(ng/mg)	<20	Not determined	4.0

maruX Next step: Proposed GMP Operation

FUJIFILM Diosynth biotechnologies

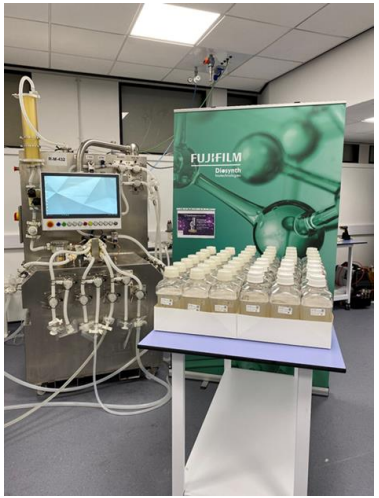
- **500 L perfusion bioreactor**
  - Constant feed into downstream ≥25 days
  - Residence time distribution mapping
- **Integrated downstream purification**
  - Flow path change out brackets lot
  - Traceability equivalent to current batch strategy
  - Viral clearance equivalent to current batch strategy



AEX: Anion Exchange Column
VF: Viral Filtration
UF/DF: Ultrafiltration/Diafiltration

Collaboration enabled advancement of technology platform

- Development of SymphonX™ through collaborative relationship with suppliers
  - Co-development of components
  - Delivery of system fit for purpose
- Successful demonstration of 500 L manufacturing scale continuous mAb production in a non-GMP facility
- Single-use mammalian GMP facility under construction in the UK for 2024 operations with 500 L GMP MaruX platform



Thank you for your attention

QUESTIONS?