

Single-use manufacturing design and implementation: from becoming a reality, to paving the way for future growth

GE Single-use Symposium
Boston, Nov 1, 2016

S. McNaull
Fujifilm Diosynth Biotechnologies



One Global Company

3

SITES

*Billingham, UK
College Station, TX
RTP, North Carolina*

6

LICENSES

*For commercial
manufacturing.*

1,100

EMPLOYEES

World Wide

20+

YEARS

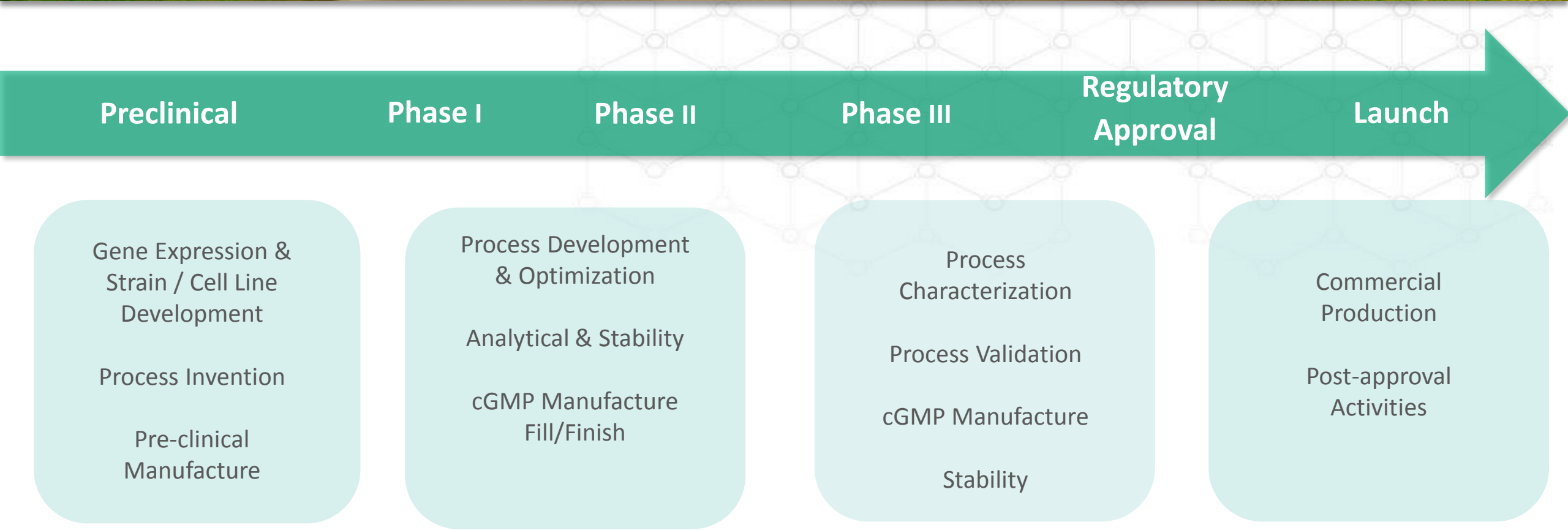
*Of Biologics CDMO
experience.*

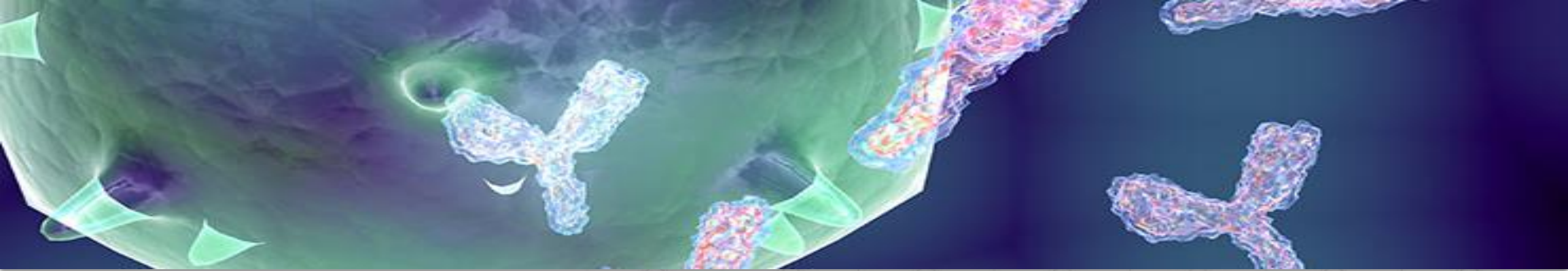
280+

MOLECULES

*In process development and/or
manufacturing.*

With you all along the road To clinical success





Our Cell Culture Experience

60+

mAb, mAb-like and
Ig-fusion molecules

55

CHO Programs

45

MAb Programs

12

Cell Line Development
Programs

29

Programs Completed GMP
Manufacturing

Single-Use Bioprocessing Journey



- The advent of single-use technologies enabled capacity expansions that were previously not realistic
- Our single-use bioprocessing journey started with proof of concept bioreactor evaluations
- Comparability between single-use and stainless steel bioreactors enabled our entry into the GMP manufacturing space
- Knowledge gained as early adopters provides a strong engineering basis that is applied for new equipment design
- Efforts now encompass design of an all single-use manufacturing facility

Single-use Technology Enabled GMP Expansion



Justification:

- Capacity can be increased quickly within existing facilities
 - Implementation in an existing facility in ~12-14 mo. vs. ~24 mo. for stainless steel
 - Capital investment and payback time is significantly less than stainless steel
- Single-use Efficiency and Operational Flexibility Gains

Implementation:

- Single-use Technology Platform Developed
 - SUB technologies evaluated and operating platform developed
 - Purification mAb platform leveraged with SU implementation
- GMP Manufacturing expansions: Existing suite refurb and new facilities
 - First 1000L GMP expansion combined two small scale cell culture GMP suites
 - New all single-use facility in the UK: 1,000L and 2,000L USP and all SU downstream
 - 2,000L expansion in the US within existing suites

Production Bioreactor Selection



➤ Factors Taken into consideration

- Process performance; mixing and mass transfer, sparge flexibility and leveraging Fujifilm platforms
- Speed of implementation and qualification
- Control system capabilities and automation tie-in
- Engineering design and workmanship
- Equipment cost and product support
- Track Record
- In-hand process performance for each vendor

➤ GE (Xcellerex) was chosen as the PD and Manufacturing model

- Process performance and flexibility of design
 - 5:1 turndown, good mixing with sparge design flexibility
- Quality of hardware and ‘software” (bag designs) engineering
- Speed and ease of implementation in manufacturing were key factors

Stainless Steel (SS) vs Single Use Bioreactor (SUB) Comparison:

"The CHO Story"



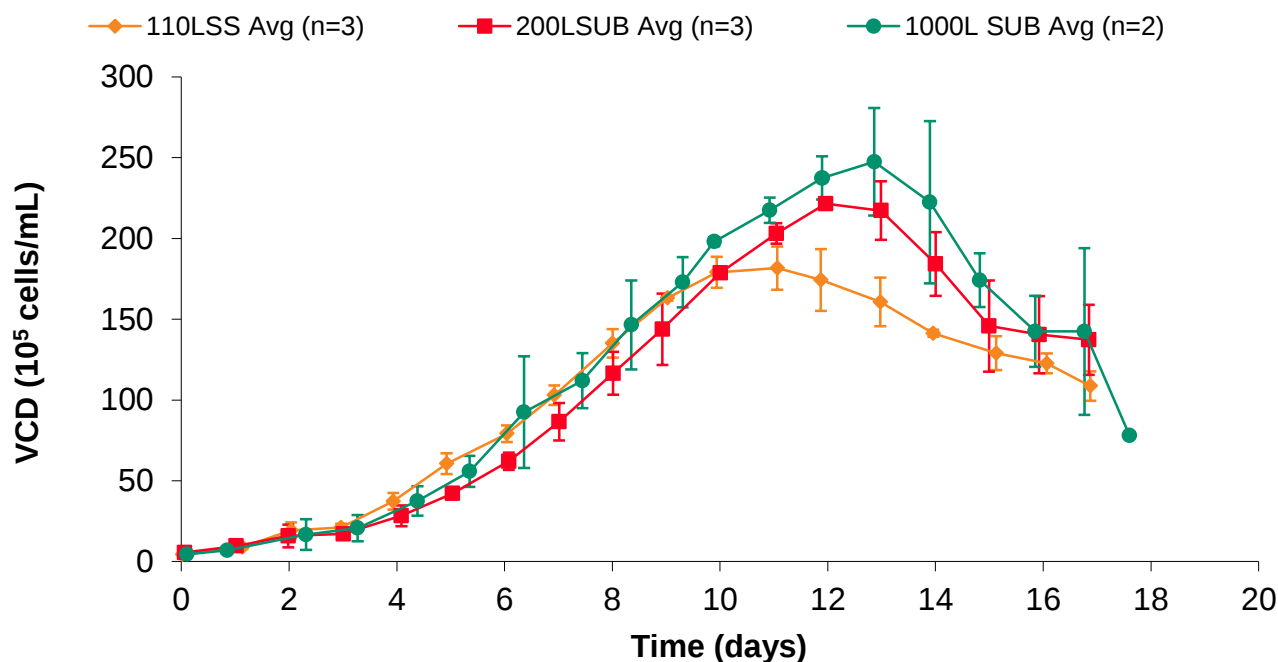
- XDR-200 CHO mAb runs (n=3) were compared directly to 110 L stainless steel reactors (n=3)
- High cell density process (20-25E06 cells/mL)
- FDB stainless steel bioreactor mass transfer and scale up know-how was used as a basis for sparger customization and gassing strategies
- Mixing speed and gas sparger designs were refined to achieve necessary mixing time, O2 mass transfer and CO2 stripping
- Technical learning from 200 L scale was applied to achieve successful scale-up to 1,000 L scale

Development of Fujifilm single-use platform



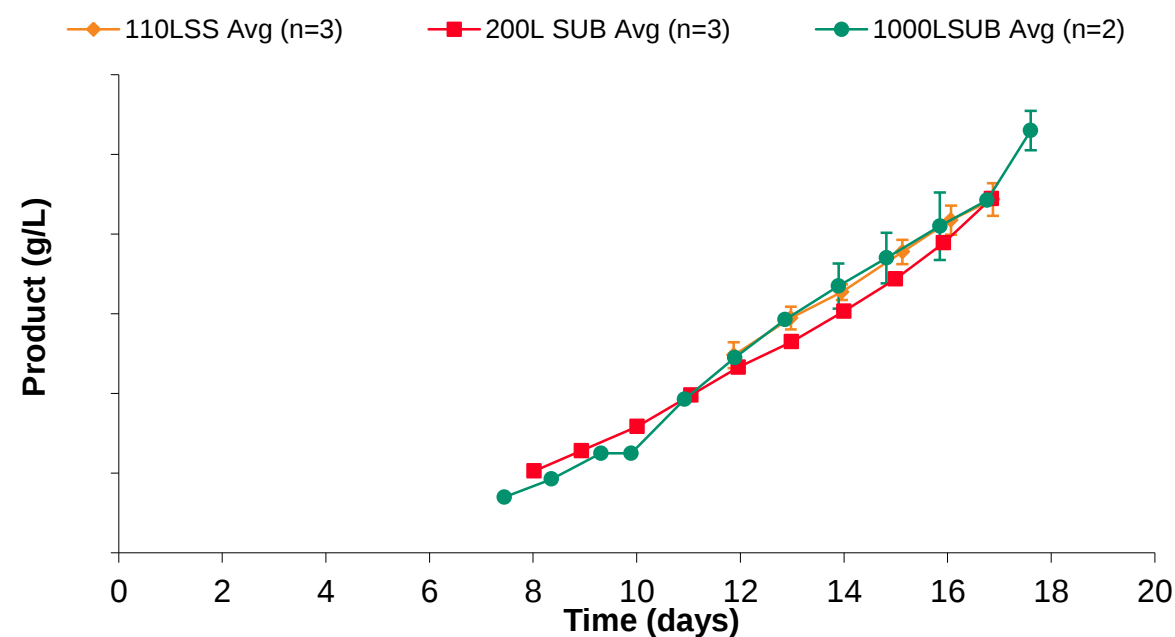
- Fujifilm experience with stainless steel (SS) reactors used as SUB design basis for mixing and mass transfer
- 200L SUB high density CHO runs were used to optimize parameters
- 200L and 1000L SUB growth and productivity were $\geq$ 110L SS
- Manufacturing success with over 20 GMP batches produced

CHO Growth



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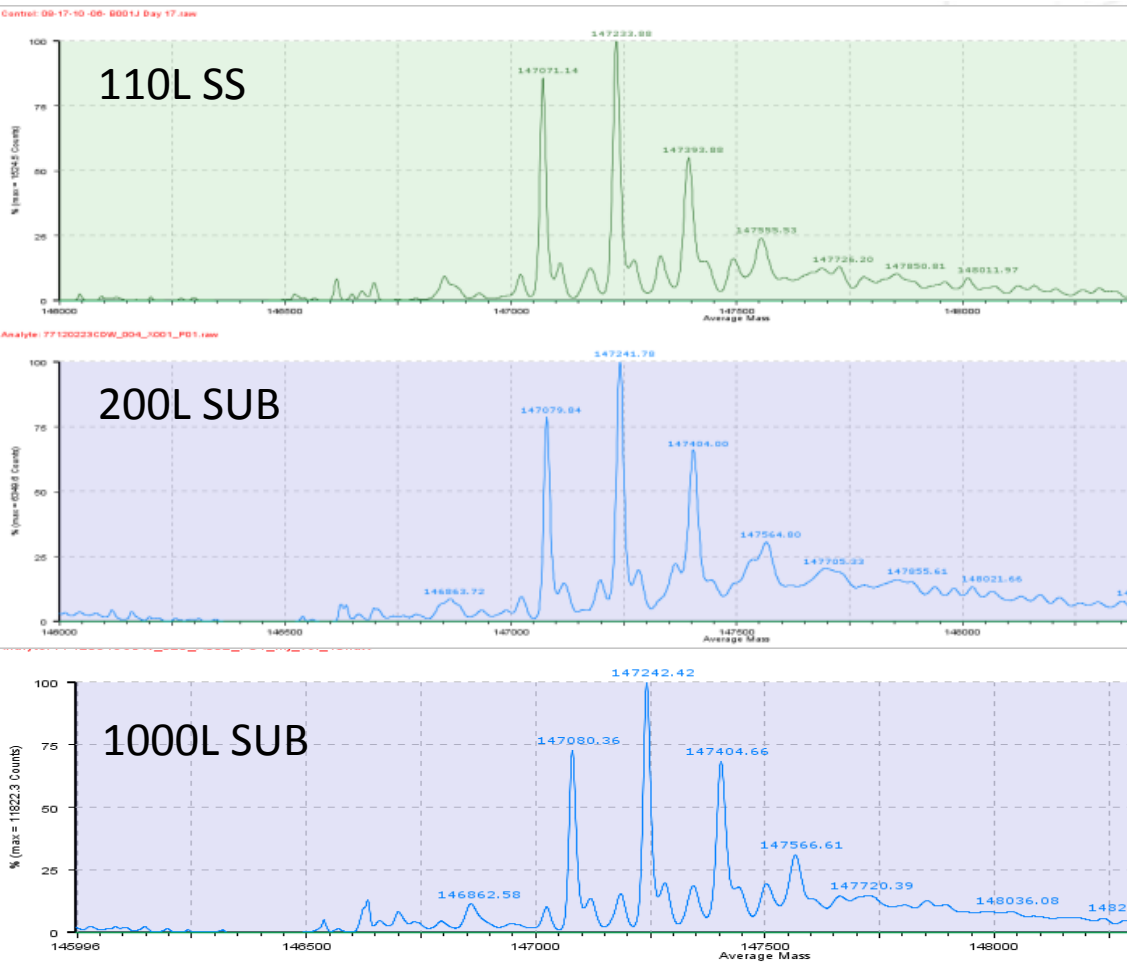
Product Titer



Development of Fujifilm single-use platform



Product Quality: Glycosylation patterns



Successful SUB Performance

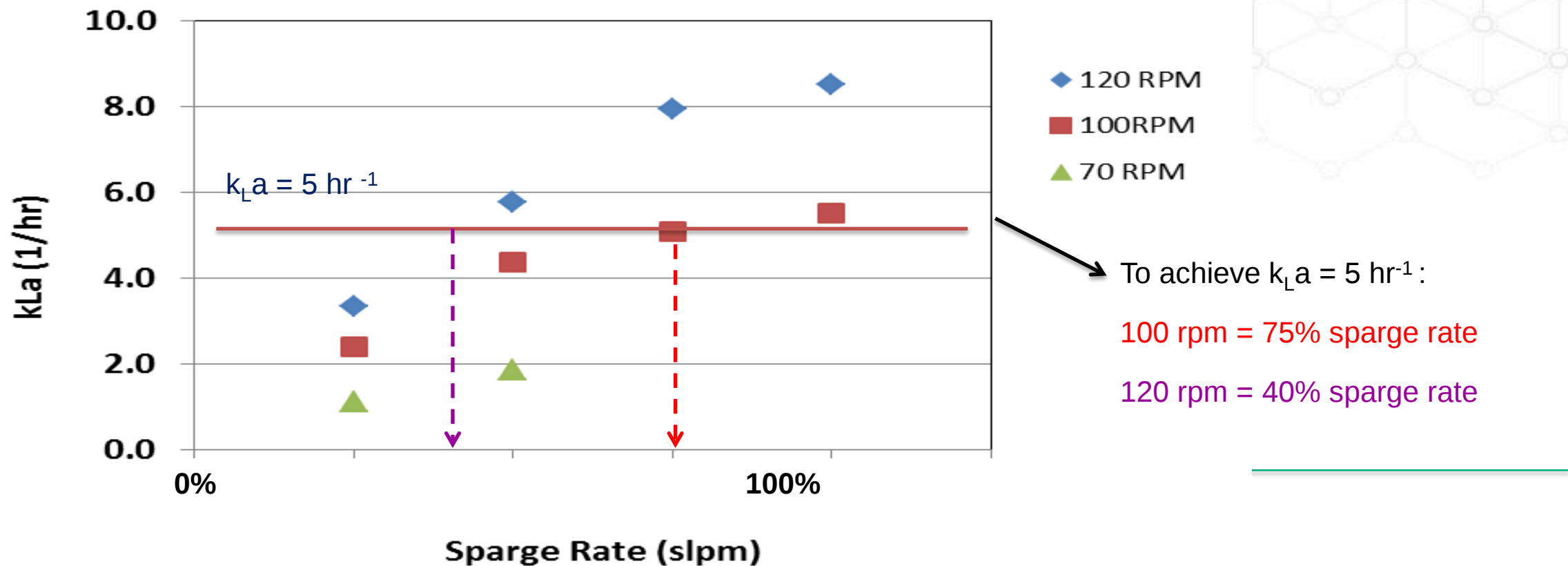
	CHO mAb		BEVS	
	SS	SUB	SS	SUB
Cell growth	✓	✓+	✓	✓
Product titer	✓	✓	✓	✓
Product quality	✓	✓	✓	✓
SUB control	✓	✓+	✓	✓+

► 1000L SUB process transferred from RTP to UK Manufacturing facility with matching results

Bioreactor Scale Up by Mass Transfer



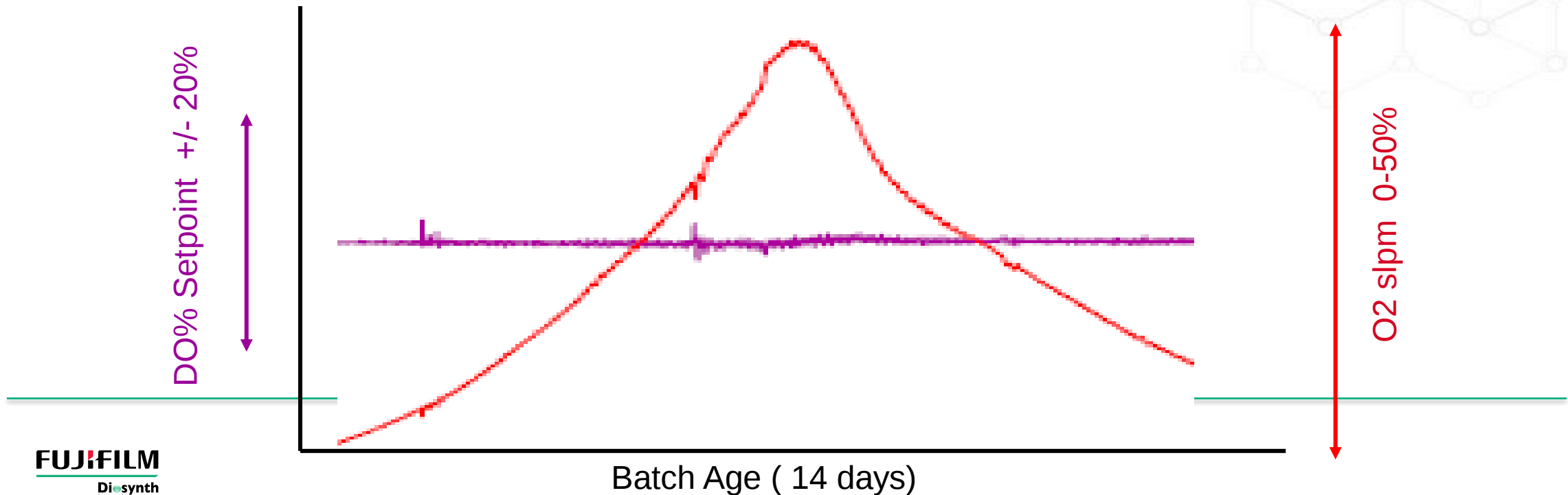
- 1) determine (peak) k_La at lab scale
- 2) choose mfg scale agitation rate to achieve peak k_La
- 3) agitation speed will affect sparge on demand (impacts stripping)



1000L SUB Modeling results



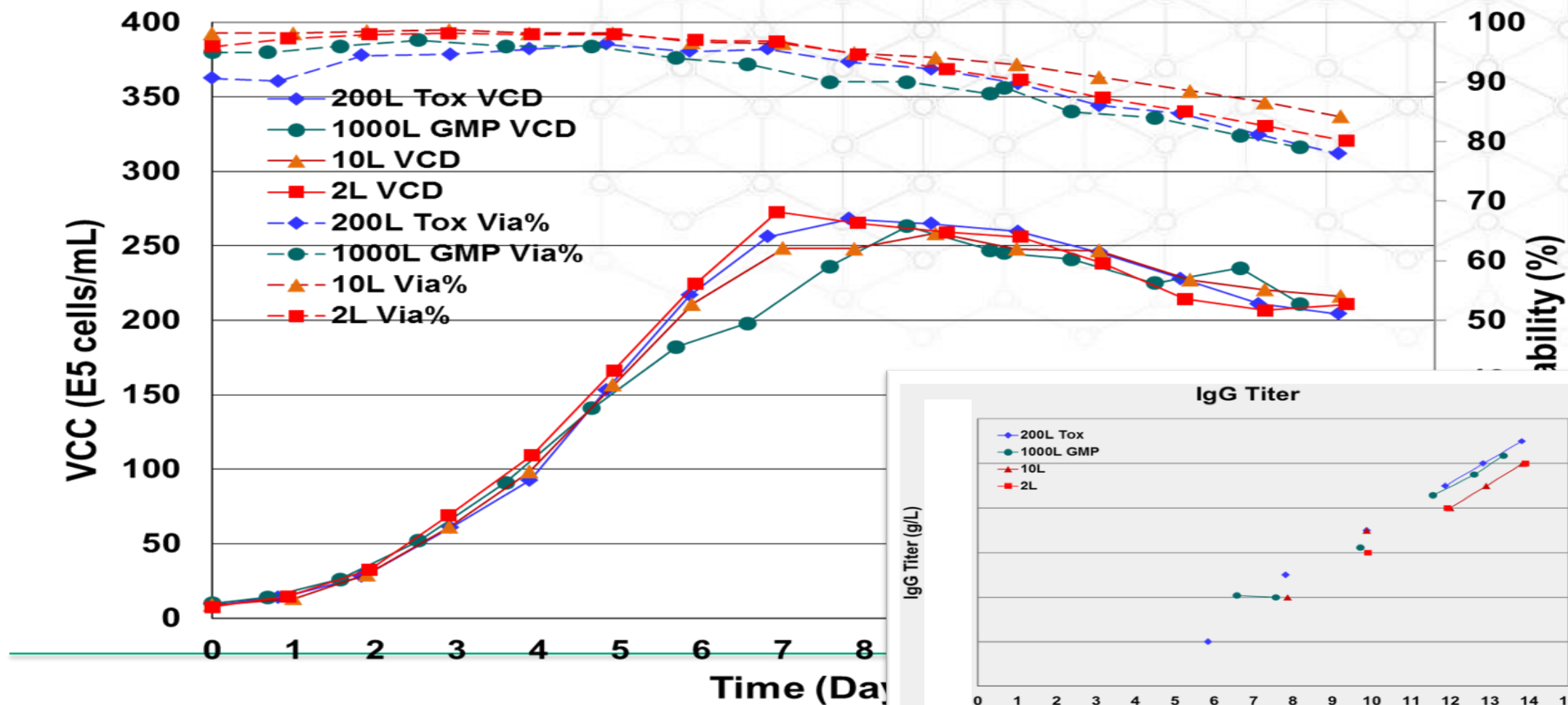
- Example below shows the SUB O₂ sparge rate and resulting DO control for a 14 day CHO cell culture batch at ~30E06cells/mL
- O₂ sparge rate reached 50% of max and provided CO₂ levels that were comparable to lab scale (not shown)
- DO% control was within approximately $\pm 5\%$



FDB SUB Scale Up Performance



Cell Growth



Upstream Learning from Early Adoption



➤ Design

Well designed connectivity to minimize number of sterile connections

- Design of feed bags with on board filters and tubing to match SUB
- Standard connectors and tubing sizes for welding/sterile connectors
- Use liquid media and many pre-made solutions (feeds, antifoam, etc.). Weigh gains vs. COGs.

Bag design details

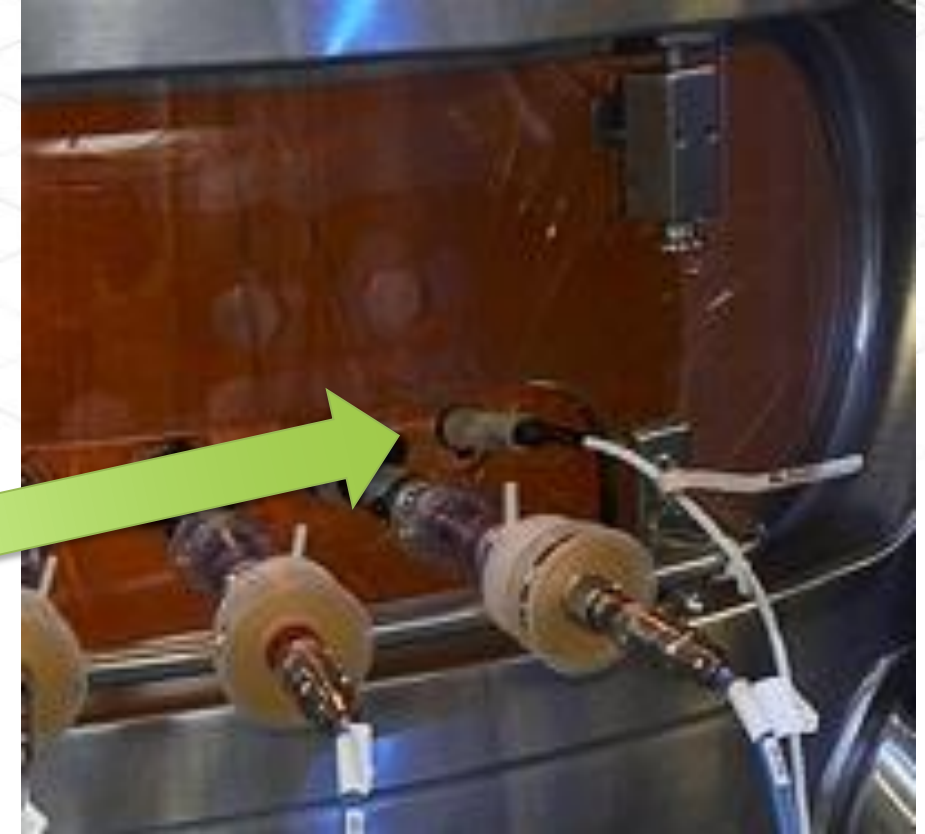
- Ensure tubing is long enough for connections to media and other equipment
- Alignment of software (bags and connectors) and hardware (equipment).
 - Example: tubing diameters are appropriate for pump heads to avoid wear, etc.

In-Use Experience

- Bag installation, choice of connections, etc.
- The “Devil is in the details”....

Upstream Learning as Early Adopters

- Example of the Devil in the details...



Downstream Learning from Early Adoption



➤ Design Limitations

- Skid limitations in terms of sizes, flow rate, mixing, temp control, pressure transfer
- Mab throughput limitations (low chrom skid flow-rates, low TFF membrane capacity, etc.)
- Heating or cooling of large (>1000L) process volumes can be difficult

➤ Instrumentation Limitations

- Sensors (P, T, UV, flow, cond) lack precision and accuracy
- In some cases traditional probes are used (e.g. pH probes)

➤ Installation

- Installation of manifolds can be “cumbersome”
- Cross connectivity issues due to lack of manifold labeling
- Operator standardization of instruments as part of self check
- Standard manifold tubing sizes may require different connectors

Creating biomanufacturing capacity

A global partnership



Driven by the industry need for cGMP mammalian cell culture biomanufacturing capacity

Four successful capacity expansion projects on two continents

Creating the UK's first fully single-use biomanufacturing facility



1000 L project

- Single-use WAVE Bioreactor™ systems
- Xcellerex™ XDR cell culture suite
- ÄKTA™ready and ReadyToProcess™ prepacked columns

Billingham, UK

2013



1000 L project

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- Xcellerex XDR cell culture suite
- ÄKTAready purification system

Research Triangle Park, US

2012

2014

2000 L project

- Xcellerex XDR 2000L bioreactor added

Research Triangle Park, US



2015

2000 L project

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Billingham, UK



Ongoing partnership

2017

2018

2019



Fujifilm Single-use mAb Facility Design



- All single-use equipment
- Production Reactors: 3 x 2,000L SUBs with standard seed train
 - Assumed titers ranging from 2 to 8 g/L
 - One batch per week
- Downstream
 - Smaller pre-packed columns with up to 10 cycles to reduce RM costs
 - Use of one set of three Single-use chromatography skids to run industry standard mAb platform
 - TFF systems must have at least 10m² membrane area capacity
 - Goal of small, medium and large downstream bill of materials
- Defined allowable process duration for each unit operation
- Output Goals: operational standardization, reduce consumables/RM costs, facility fit process

Process Evaluations for Facility Design



1. Process Platform Scaling by mAb Throughput (kg)

- Media and buffer volumes, resin and filter sizing for 2g/L, 5g/L and 8g/L scenarios
- Platform scaling and operational strategies

2. Single-Use DSP Equipment Evaluations

- SU Chromatography and TFF equipment, pre-packed columns-
- Risk Assessment from FDB experience and next generation vendor offerings

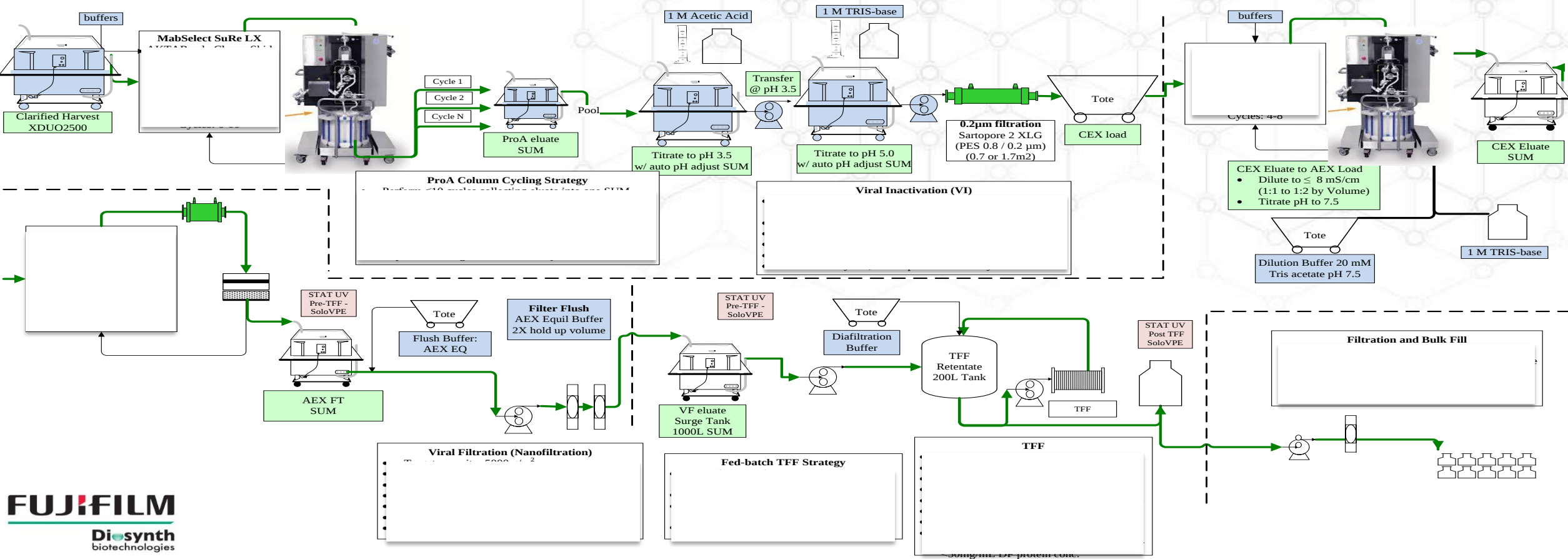
3. Facility Design Implications

- Finalize placement of unit operations for optimal suite scheduling and process flow

4. Closure Assessment

- Define closed processing needs, equipment and consumables capabilities for closed processing

Single-use DSP Process Flow Diagram



Initial (May) Saturn DSP Platform Scaling



- DSP platform scaled by mAb kg throughput (2, 5 and 8 g/L titer scenarios)
- Column size + cycles, platform buffer volumes and filter areas estimated
- RM and consumable costs were estimated using calculator (~\$1M/batch @ 5g/L)

Process Scaling				
BRX Titer (g/L)		2 g/L	5 g/L	8 g/L
ProA Resin Binding Capacity		45	45	45
ProA Column Size (L)		10	20	32
ProA Cycles		8	10	10
ProA Skid Flow Rate (LPH)		147	297	477
Net ProA Process Time (hr)		34	31	26
CEX Column Size (L)		10	20	32
CEX Cycles		6	7	7
CEX Skid Flow Rate (LPH)		147	297	477
Net CEX Process Time (hr)		22	21	20
Q Membrane Size (cm2)		9,747	24,368	38,988
Flow Rate (L/min)		8	20	33
Nanofilter Size (m2)		0.5	1.5	2.0
Flow Rate (L/min)		3	9	12
Net Q Membrane + Nanofilter Time (hr)		5	7	10
UF Membrane Area*		5	10	12*
UF Skid Crossflow rate (L/min)		40	40	48
Net UF Process Time (hr)		5	5	7
Total Buffer Volume (L)		7,406	14,478	21,433

Super Pro Modeling



- Goal was to better quantify process volumes, durations and consumables costs to better define operational aspects...
- Created a simulation to scale the FDB mAb platform over a range of 2g/L to 8g/L
- Inputs: 2000L harvest, flux for filters, resin capacities and yields
- Outputs: Batch duration, size of columns and number of cycles, filter sizes, buffer volumes, SUM sizes
- Stretch Objective: To define small, medium and large purification streams (equipment, column size/cycles, SUMs, BOM)

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SuperPro Results



- 2000L
 - 2.5CV ProA Elution
 - Raw materials (RM) \$ per gram is for one run

	Protein Titer	Process Time	Protein A Size	ProA Cycles	CEX Size	CEX Cycles	kg of Buffer	SUM A	SUM B	SUM C	SUM D1	SUM D2	SUM E
Small	2.0-3.0	98h - 125h	10L	8-12	10L	7-9	6,322-9,203	2500L	500L	500L	1000L	1000L	1000L
Medium	3.0-5.0	76h - 106h	20L	6-10	20L	5-8	9,143-15,023	2500L	500L	1000L	2500L	2500L	2500L
Large	5.0-8.0	86h - 110h	32L	7-10	32L	5-8	17,113-23,534	2500L	1000L	1000L	2500L	2500L	2500L

FDB Modeling Outputs: Process Volume



- SuperPro model provides process volumes for given mAb throughput
- Process volumes drive mixer sizes and PFD defines options needed (cooling, pH control etc)

Titer (g/L)	SUM A	SUM B	SUM C	SUM D	SUM E	SUM F	DS Fill Tank
2	2500	200	200	1000	1000	1000	200L
2.5	2500	200	200	1000	1000	1000	200L
3	2500	500	500	1000*	1000*	1000	200L
3.5	2500	500	500	1000*	1000*	1000	200L
4	2500	500	500	1000*	1000*	1000	200L
4.5	2500	500	500	1000*	1000*	1000	200L
5	2500	1000	1000	2500	2500	1000	200L
6	2500	1000	1000	2500	2500	1000	200L
7	2500	1000	1000	2500	2500	1000	200L
8	2500	1000	1000	2500	2500	1000	200L

SUM A – Harvest Collection

SUM B – 1st SUM in Viral Inactivation

SUM C – 2nd SUM in Viral Inactivation

Note: Use 500L tote(s) to collect VI filtrate/CEX load

SUM D – CEX Eluate/AEX Load

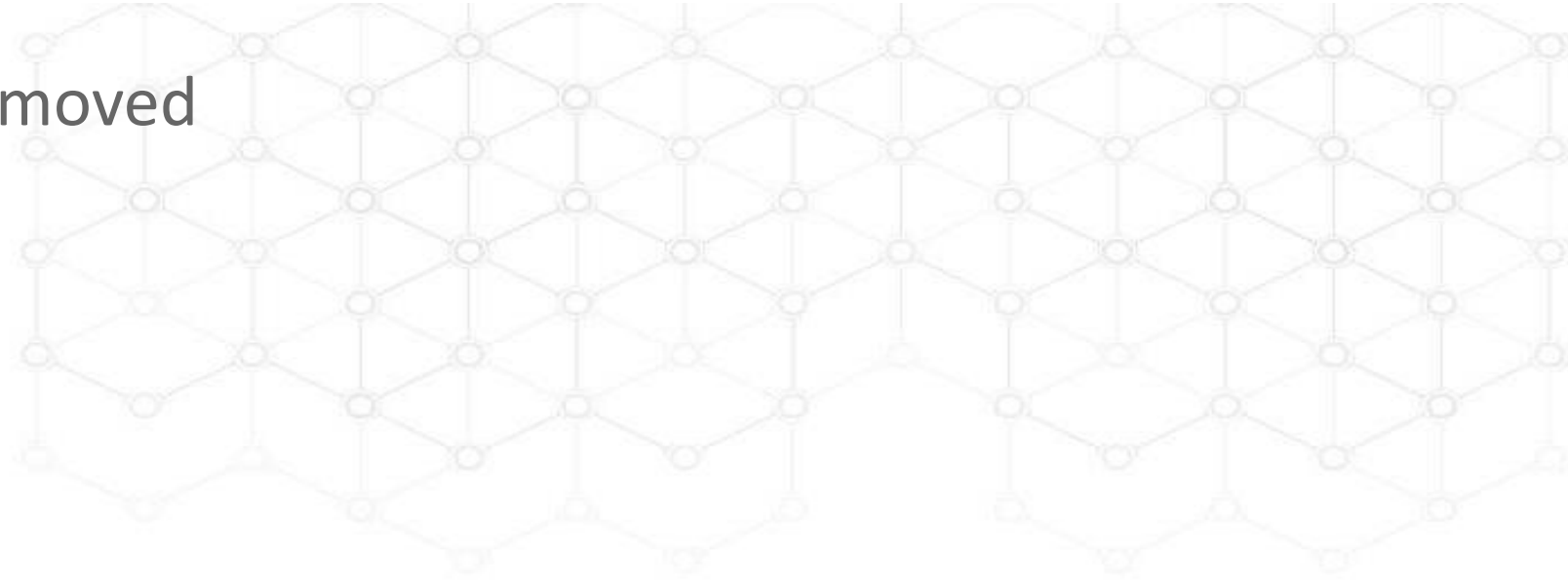
SUM E – AEX Eluate

SUM F – TFF load surge tank

Raw Materials Cost per Gram



- Preliminary data plot removed



Process Design Results



- Created a simulation of the mAb platform over a range of 2g/L to 8g/L
- This model facilitated equipment definition and allowed operational strategies and process schedules to be defined
- This model is used to quickly fit processes coming from internal Process Development, or transferred in from sponsors
- We are achieving our dream of standard small, medium and large downstream BOMs

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Diosynth
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*Your **Biologics and Vaccines** Partner of Choice*

