Continuous Biomanufacturing

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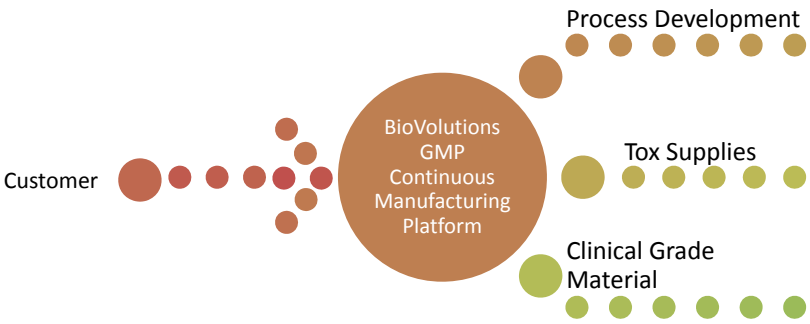
President
bioVolutions Inc.
15 January 2015

Connecting a World of Pharmaceutical Knowledge

Our Capabilities



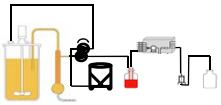
Advantages of Continuous Biomanufacturing

Speed

Quality

Cost

Modular



Continuous Manufacturing of Mabs

Automated processing times with fewer steps

- Accelerated production of antibody
- Increased efficiency
- No manual handling, increased safety

Smaller equipment and facilities

- More flexible operation
- Reduced inventory
- Lower capital costs, less work-in-progress materials
- Smaller ecological footprint

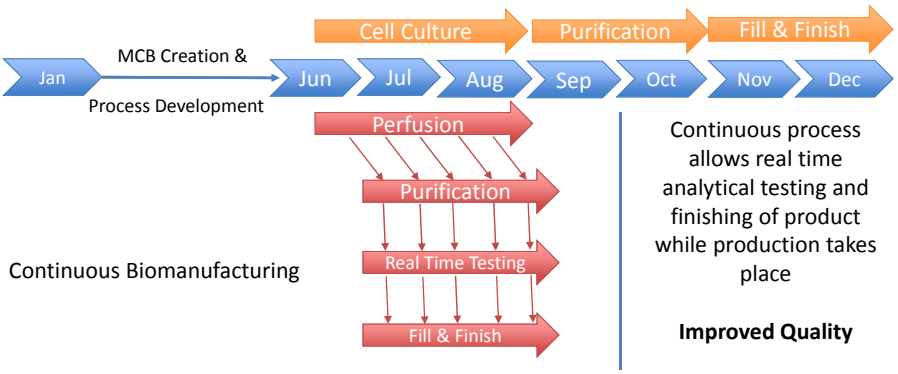
On-line monitoring and control for increased product quality assurance in real-time (PAT)

- Amenable to Real Time Release Testing approaches
- Consistent quality

Accelerated Production of mAbs

Traditional Fed-Batch

Manufacturing time can be cut down from 12 to 8 months



Continuous Biomanufacturing

Continuous process allows real time analytical testing and finishing of product while production takes place

Improved Quality

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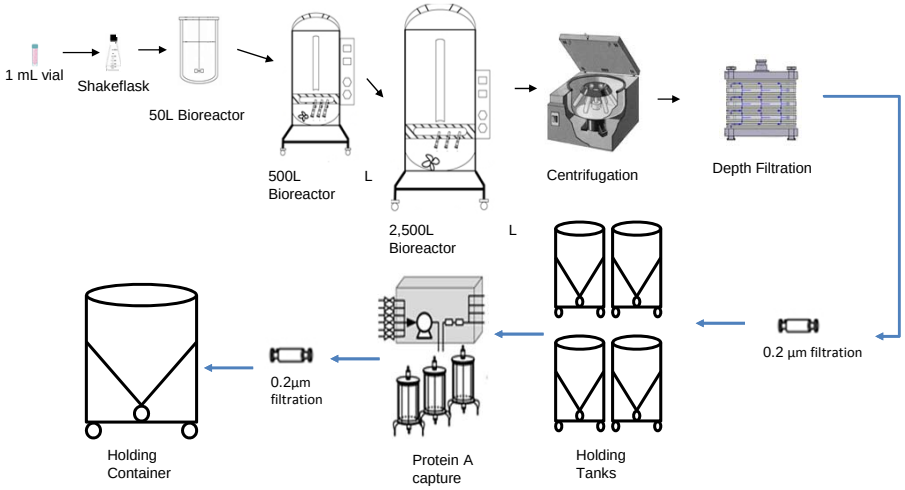
Traditional BioManufacturing Process



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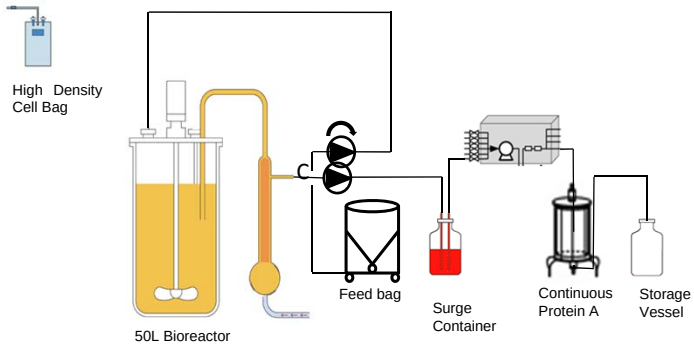
BioVolutions' Continuous Manufacturing



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Our Continuous Biomanufacturing Pilot Plant

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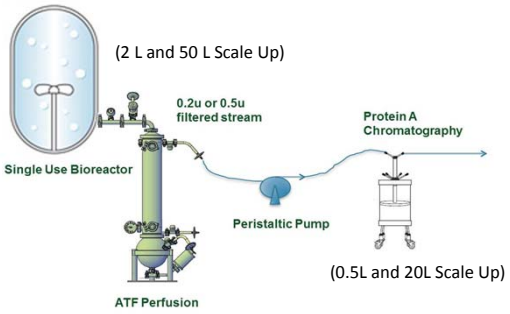
Modular Facility

Case Study of a Monoclonal Antibody (A-mAb)

Pilot Study

- Monoclonal Antibody – A-mAb
- 2L-50L HyClone SUB
- RefineTech ATF Perfusion
- Delta V Control Tower
- 30 day continuous run



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CQAs (eg. Glycosylation, HCP, DNA, Aggregation)

- **Product Variants (eg. galactosylation, afucosylation)**

IgG1	% HighMan	% G0	% G1	% G2	% Sialic acid	% Gal Alpha	% Core Fucose
A-Mab	7±5	71±10	19±10	3±10	1±5	0±5	91±20
B-Mab	1±5	78±10	17±10	4±10	2±5	0±5	94±20
R-Mab	2±5	46±10	40±10	12±10	3±5	0±5	95±20

Process CQA	Acceptable Ranges
HCP	0-100ng/mg
DNA	$<10^{-3}$ ng/dose
Aggregates	0-5%

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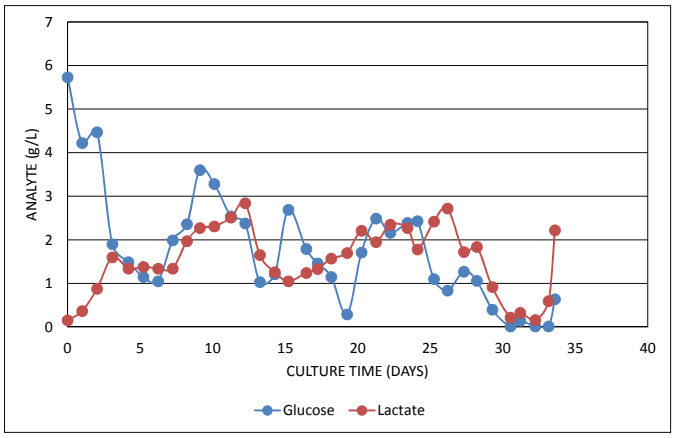
QbD: Risk Assessment Mitigation Matrix (RAMM) for selecting CPPs

Relative Importance of Output on CQA	9	1	1	9	3	3	3	3	3	3			
Process Parameters	pH	CO2	VCD	Viability	Bioburden	Endotoxin	Titer	Mycoplasm	In Vitro viral	MMV PCR	Tot	Impacts	Proc
Perfusion Rate	1	1	9	9	1	1	1	1	1	1	118	Quality & Growth	WC-CPP
Sparge Oxygen Flowrate	1	9	1	1	1	1	1	1	1	1	46		
Agitation 110-125 RPM	3	9	3	3	1	1	3	1	1	1	90	Gas Evolution Rate	GCP
pH	0	3	3	9	1	1	3	1	1	1	111	Quality & Growth	CPP
DO (>40%)	1	1	3	3	1	1	3	1	1	1	64	Titer	
Seed Density (0.5 x 10E6)	1	1	3	3	1	1	3	1	1	1	64	Cell Growth	WC-CPP
N-1 Inoculum Volume	1	1	1	1	1	1	1	1	1	1	38		
Temperature	1	1	3	9	1	1	9	1	1	1	136	Quality &Growth	CPP
Duration of Perfusion	1	1	1	3	1	1	1	1	1	1	56		
Glucose Control	1	1	9	9	1	1	9	1	1	1	142	Quality & Growth	CPP
Lactate Control	1	1	9	9	1	1	9	1	1	1	142	Quality & Growth	CPP
Anti-Foam Control	3	1	1	1	1	1	1	1	1	1	56		
Protein Load Protein A	1	1	1	1	3	3	9	3	1	1	80	Quality & Titer	CPP
Elution pH Protein A	1	1	1	1	3	3	9	3	1	1	80	Quality & Titer	CPP
Totals	17	32	48	62	18	18	62	18	14	14			

QbD: Design of Experiments (DoE) (Taguchi L9)

Experiment/ Pattern	Temperature (ºC)	pH	Glucose (g/L)
1 / −−−	36.5	7.2	0
2 / −00	36.5	7	1
3 / −++	36.5	6.8	3
4 / 0−0	36.0	7.2	1
5 / 00+	36.0	7	3
6 / 0+−	36.0	6.8	0
7 / +−+	35.5	7.2	3
8 / +0−	35.5	7	0
9 / ++0	35.5	6.8	1

Glucose and Lactate Control



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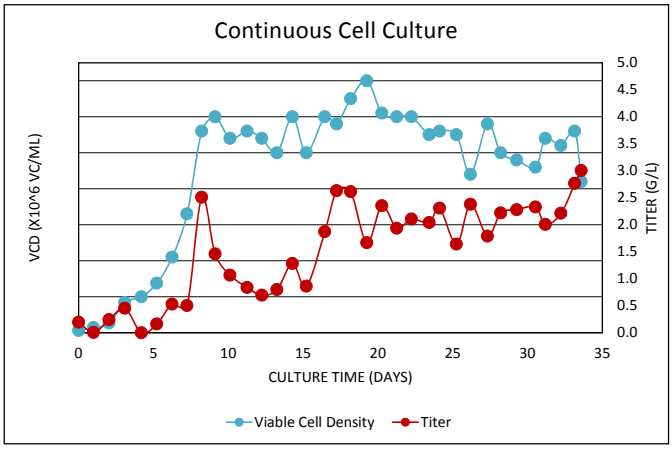
Upstream Titers



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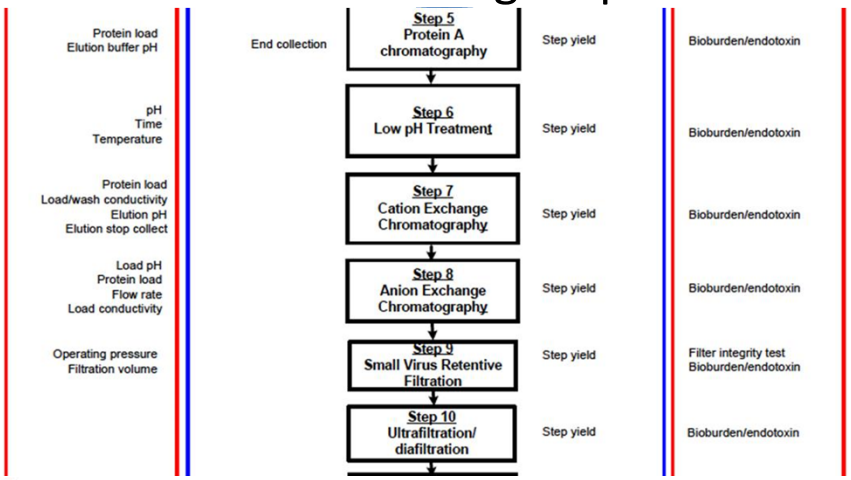
Upstream Overview

- Produces High Titers (~2 g/L)
- Reduce Media Volumes by minimizing the Perfusion Rate
- Glucose and Lactate Control the Perfusion Rate

Results: Upstream Design Space (DS) based on Glycosylation CQA

IgG1	% HighMan	% G0	% G1	% G2	% Sialic acid	% Gal Alpha	% Core Fucose
A-Mab (Test Article)	0	54	39	7	2	0	97
A-Mab (Reference)	7±5	71±10	19±10	3±10	1±5	0±5	91±20
B-Mab (Test Article)	0	85	15	1	0	0	96
B-Mab (Reference)	1±5	78±10	17±10	4±10	2±5	0±5	94±20

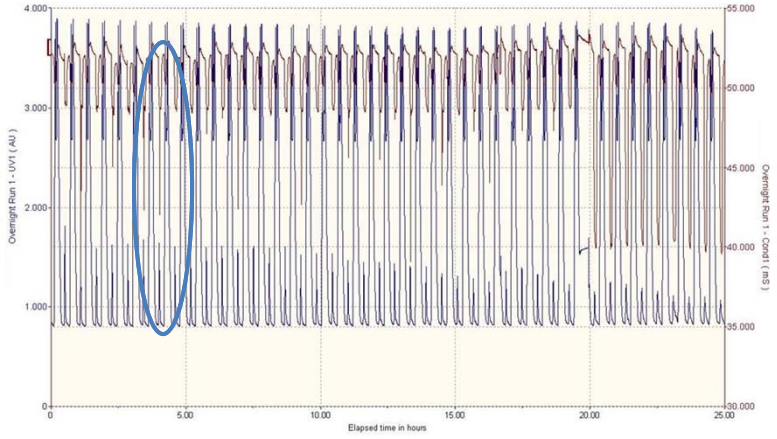
Overview of Downstream Manufacturing Steps



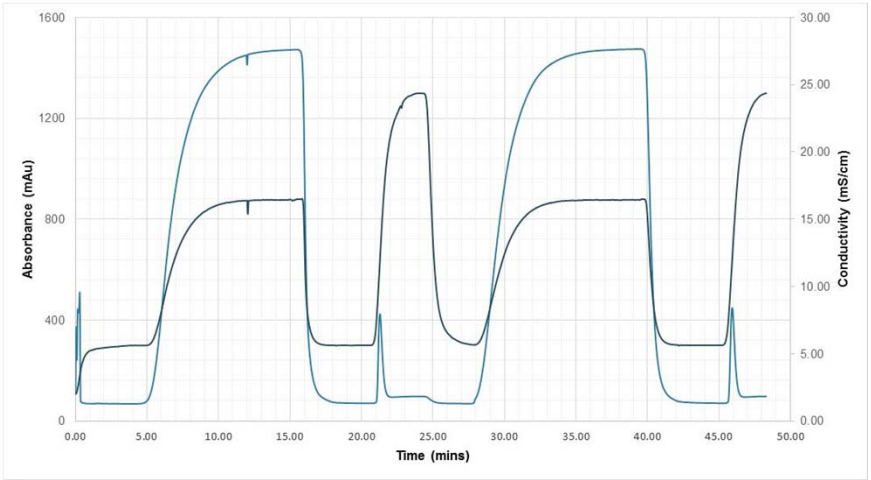
Downstream Strategy

- Replace interim holding tanks with peristaltic pumps to perform continuous downstream purification
- Load perfusate onto Single Protein A column
- Synchronize the purification cycle (Load, Wash, Elute, Regenerate) with the upstream rate of perfusion

Continuous Purification of A-Mab



Continuous Purification of A-Mab



Continuous Purification

- Produces purified antibody continuously
- Reduce the amount of Protein A resin by ~ 20-fold
- The cycle time controls the rate of purification
- HCP < 7 PPM which simplifies the downstream processing

Cost Analysis of Continuous Manufacturing

Assumptions used for COGS model

Parameter	FB	CM
Seed Train	20L, 80L, 400L, 2,000L	500mL, 20L, 100L
Production Bioreactor	Up to 10,000L	Up to 1,000L
Product Titre	2.5 g/L	0.8 g/L
Growth & Production Phases	3 days per seed 13 days in production	3 days per seed 32 days in production
Media Consumption	Up to 10,000L	1.8 vvd
Media Cost	$20/L	$5/L
Protein A Consumption	300L ($3.6M)	20L ($240K)

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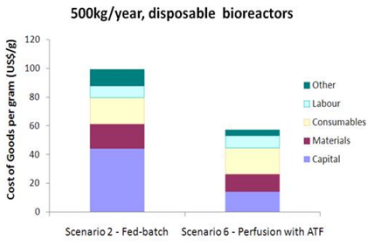
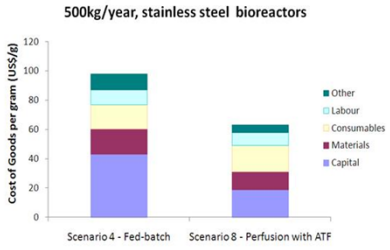
Results at 500Kg / year

- A comparison of fed-batch to perfusion with the ATF System at "large" scale:
  - Perfusion utilizes a smaller footprint and
  - Lower capital investment costs
  - And has lower operating costs
- The advantage of disposable bioreactors reduces with increasing bioreactor size, as required





Capital (US$)	106.7M	33.1M
Floor Area (m^2)	4,012	2,447

Capital (US$)	103.9M	44.1M
Floor Area (m^2)	5,096	3,152

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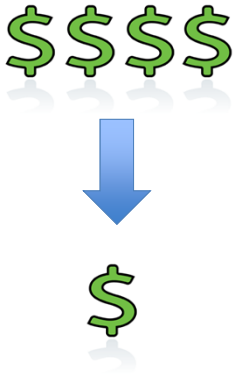
Summary of COGs Model

- A ~$30m capital budget could give you a facility that annually produces:
  - 50Kg of antibody in FB mode in stainless steel tanks
  - 500Kg of antibody in perfusion mode in disposables.
- If you had 10 products to manufacture, and need 50Kg of each per year:
  - $100m capital is required for a fed-batch facility, with no spare capacity
  - $30m capital is required for the perfusion facility, with 20% spare capacity



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Summary

Perfusion will be adopted where flexibility, lower capital investment and facility costs, and operating at smaller scales are primary decision-driving factors

-Eric Langer, Pharmaceutical Processing, 2014

- Continuous Biomanufacturing of Monoclonal Antibodies produces high titers and good quality product in line with QbD principles
- Equipment is utilized more efficiently and the equipment footprint is much smaller
- Faster production of mAbs compared to Fed-Batch, reduces manufacturing time by 4 months
- The Capex for a new facility is significantly lower than conventional batch facilities

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Acknowledgements

The Team:

Dr. Remco Spanjaard, Chief Scientific Officer

Dr. Snehal Padhye, Director Analytical Services

Mark Henry Kamga, MSc., Technical Supervisor

Jine-Jine Li, MSc., Analytical Supervisor

Tom Roper, BSc., Technical Operator

Dr. Myron Dittmer, Chief Quality and Regulatory Officer

Ciro Whooley, MBA, Chief Financial Officer

bioVolutions' Services

Partnered CRO

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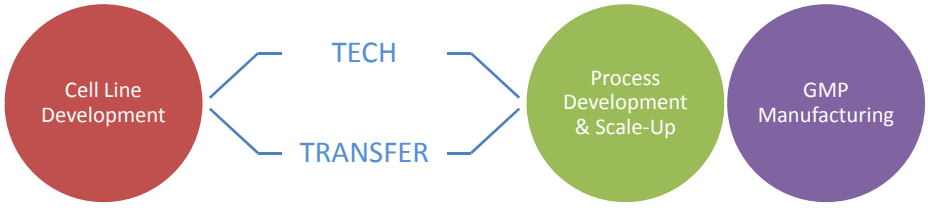

- One-stop shop
- Smaller companies – easier communication
- Cost effective