Opportunities, challenges, and economic drivers for start-to-finish continuous biomanufacturing

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Opportunities, challenges, and economic drivers for start-to-finish continuous biomanufacturing

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Introduction

Biomanufacturing today is informed by our past and considers our current state

Continuous unit operations have been used successfully in manufacturing of several approved products with a collective revenue of $25 billion annually. Many large biopharmaceutical organizations are exploring potential solutions to drive continuous operations on the manufacturing floor. Continuous biomanufacturing carries the hope for achieving the next level of efficiency through significant increases in productivity, floor space reduction, and lower capital cost for manufacturing facilities as well as lower overall production costs. Combining many innovative, promising unit operation technologies with single-use equipment can offer significant economic advantages over batch processing in traditional stainless steel installations.

Adopting advanced process design will need an accurate business case and risk profile for implementation. Within the risk profile, assurance of patient safety and supply through product quality demonstration will be critical. Optimizing the operating space of an entire process, versus a unit operation, will call for thoughtful automation and control strategies. Simplification of equipment design and operator interface points will also be key to success.

This poster will highlight trade-offs and benefits associated with the adoptions of connected and continuous manufacturing.

One of the first challenges to recognize is that decision making and cost analyses combine multiple sources of savings (Fig 1), and often complicate the view of each one or combination of them.

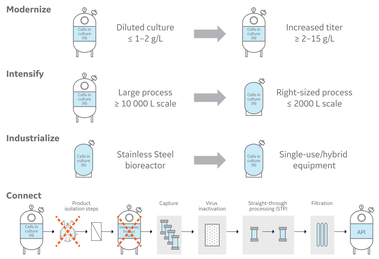

Fig 1. Example sources of savings.

Benefits and challenges

Examples will be highlighted for the following continuous and connected biomanufacturing steps:

- High cell density WCBs
- N-1 and N perfusion
- Protein A fibro units
- Continuous chromatography
- Automation and controls
- CAPEX strategies

Cell culture

Modernize processes by implementing high cell density WCBs and intensify N-1 through perfusion (1)

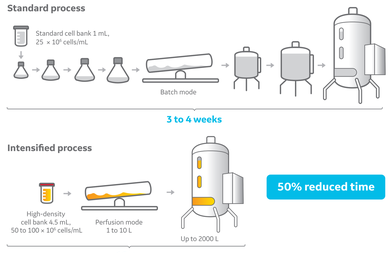

Fig 2. Reduction of time visualized high cell density WCB and perfusion N-1.

There are benefits related to operations time reduction (Fig 2), but there are challenges to processing the increased output. How can continuous biomanufacturing address this?

Continuous unit operations help offset cost implication of adopting modern manufacturing practices

Assumptions:

- 6 × 2000 L at 10 g/L and 3 × 500 L at 6 g/L/d, adjusted for similar annual product output of ~ 1340 kg mAb product
- 1.1 reactor volumes of media in batch mode, two reactor volumes of media per day in perfusion, 10% bleed
- Similar culture media composition and cost/L

The cost of increased titer or output can be balanced with the savings of a continuous operating mode (Fig 3) as long as media costs are managed (2) (Fig 4).

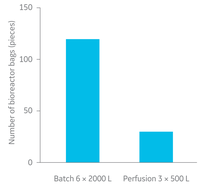

Fig 3. Number of single-use bioreactor bags for batch process vs perfusion process.

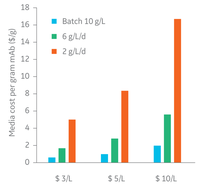

Fig 4. Cost of media per gram mAb for batch vs perfusion process.

mAb capture

Protein A fibro units can operate in batch mode connected to upstream and purify the product within 24 h

Immediate mass transfer enables high productivity (Fig 5 and 6). By operating Protein A fibro units in batch mode connected to upstream you can purify the product within 24 h.

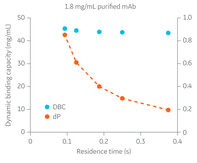

Fig 5. Dynamic binding capacity and pressure drop.

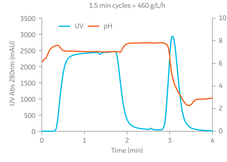

Fig 6. An industrial collaborator achieved 460 g/L/h productivity purifying 40 g mAb with equivalent product quality with a 10 mL unit in one day.

Process productivity and flexibility improved because:

- Process performance is independent of flow rate and tolerant of process variation.
- Technology supports connected manufacturing and scale-out.

Continuous chromatography

For some scales and campaign approaches, continuous chromatography offers value in purification resin savings (Table 1).

Table 1. Manufacturing scenarios with process modes and example resin costs

Manufacturing scenarios	One-time campaigns	Medium length campaigns	All-day/all-year operations
	500 g to 10 kg	10 to 500 kg/yr	200 to 10 000 kg/yr
Batch mode	Resin cost: depends on scale and output	Resin cost: $6–8/g Define process for best capacity and maximum resin utilization.	Resin cost: $3–6/g
Batch + continuous modes	–	Resin cost: ~ $3/g	Resin cost: $2–3/g
	Optimize number of runs with respect to best capacity resin		
Continuous mode	–	Resin cost: $2–3/g	Resin cost: ~ $2/g
	Overcome time-based lifetime (or run/cycle-based lifetime) constraint with PCC		Optimize capacity with PCC

Acronyms

API	active pharmaceutical ingredient
CAPEX	capital expenditure
EMA	European Medicines Agency
FDA	the US Food and Drug Administration
GMP	good manufacturing practice
HVAC	heating, ventilation, and air conditioning
OPEX	operating expenditure
PAT	process analytical technology
PCC	periodic counter-current chromatography
PD	process development
ROI	return on investment
WCD	working cell bank

Operations

Flexible integration

Flexible integration approaches based on automation expertise and bioprocess knowledge accomplish GMP control for continuous and connection biomanufacturing (Fig 7 and Table 2).

Table 2. Levels of automation integration

Unit level

Islands of automation for single unit operations

- Real-time monitoring, tracking, and optimization
- Reduced variability
- GMP documentation

Process level

Integration at process level for central control

- Manufacturing consistency
- Turn data insights into outcomes

Plant level

Distributed control system (DCS) for facility wide control

- Site data management
- Process, utilities, and HVAC

Fig 7. Visual examples of integration levels.

Reduced CAPEX

Reduced CAPEX is a culmination of modernization, intensification, and industrialization efforts, and is enabled by continuous and connected biomanufacturing (Fig 8).

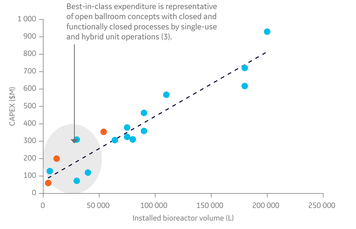

Fig 8. CAPEX as published by biopharma companies and CMOs (blue), recently constructed/announced single-use or hybrid facilities (orange). 15 plus years of facility construction history, corrected for inflation, typically showing greenfield construction

Summary

Benefits with start-to-finish continuous biomanufacturing when done right

Indirect financial benefits:

- Revenue and pipeline growth due to flexibility of scale and product mix
- Commercial scale for manufacturing drives the clinical scale
- Reduction of analytical complexity and cost
- Reduction of labor cost

Direct financial benefits:

- Smaller and less complex equipment
- Increased facility productivity
- Lower direct cost for supplied materials and consumables
- Lower cost of use for supplied equipment, consumables, and materials

Implementing start-to-finish processes requires a balanced approach

Table 3. Pros and cons for start-to-finish processing

Pros	Cons
Right size scale and CAPEX reduction	OPEX minimally lowered
Production scale drives PD scale	SU downstream adds risk with minimal improvement to ROI
Necessitates better operating space definition	Cell culture media cost requires management
Enables varied product mix	Overall risk is increased
Reduction of non-value added activities	Resource shift for development, tech transfer, and validation

Biomanufacturing of the future

Adoption of connected and continuous processing has been slow as basic changes in manufacturing paradigms take several years, in part due to inherent industry conservatism and the high regulation of the industry. The top concerns include contamination risk, process control challenge, and operational complexity. Continuous and connected processing is viewed as complex and susceptible to problems. These perceptions are not in line with the advances in the industry.

Both FDA and EMA have indicated openness due to the view of better process control, product quality, and easier application of PAT. Upcoming start to finish processes can understanding the challenges, as well as benefits, and balancing decisions to ensure successful results.

References

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3. With permission: Jagschies, G. *et al., Biopharmaceutical Processing: Development, Design, and Implementation of Manufacturing Processes*, Elsevier (2018) (graph updated)

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