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ARTICLE

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End-to-end continuous bioprocessing: Impact on facility design, cost of goods, and cost of development for monoclonal antibodies

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Abstract

This article presents a systematic approach to evaluate the business case for continuous processing that captures trade-offs between manufacturing and development costs for monoclonal antibodies (mAbs). A decisional tool was built that integrated cost of goods (COG) with the cost of development models and new equipment sizing equations tailored to batch, hybrid, and end-to-end continuous processes. The COG analysis predicted that single-use continuous facilities (sized using a dedicated downstream processing train per bioreactor) offer more significant commercial COG savings over stainless steel batch facilities at annual demands of 100–500 kg (~35%), compared to tonnage demands of 1–3 tons (~±10%) that required multiple parallel continuous trains. Single-use batch facilities were found to compete with continuous options on COG only at 100 kg/year. For the scenarios where batch and continuous facilities offered similar COG, the analysis identified the windows of operation required to reach different COG savings with thresholds for the perfusion rate, volumetric productivity, and media cost. When considering the project lifecycle cost, the analysis indicated that while end-to-end continuous facilities may struggle to compete on development costs, they become more cost-effective than stainless steel batch facilities when considering the total out-of-pocket cost across both drug development and commercial activities.

KEYWORDS

chemistry, manufacturing and controls, cost of development, cost of goods, end-to-end continuous processing, monoclonal antibody manufacture, process economics

Nomenclature: $C_{CMC\text{-}MFG}$, total cost of goods related to the CMC manufacturing activities to ensure a market success; $C_{CMC\text{-}PD}$, total cost of CMC process development activities to ensure a market success; $C_{CMC\text{-}Total}$, cost of CMC development and manufacturing activities to ensure a market success; $C_{COMM\text{-}MFG}$, total cost of goods over a 10 year commercial manufacturing period; $C_{Lifecycle}$, a project's lifecycle out-of-pocket cost to ensure a market success and supply the market for 10 years; CMC, chemistry, manufacturing and controls; COG, cost of goods; FTE, full-time equivalent; PPQ, process performance qualification; SS-Batch, a stainless steel batch facility; SU-Batch, a single-use batch facility; SU-EE, a single-use and end-to-end continuous facility; SU-Hybrid, a single-use and hybrid facility (with batch and continuous unit operations).

1 | INTRODUCTION

Continuous processing has been the subject of renewed interest in recent years as a contender to traditional batch processing in the biopharmaceutical industry for products such as monoclonal antibodies (mAbs). This can be attributed to the benefits of continuous manufacture that include higher productivities and equipment utilization rates compared to traditional batch processes, which can translate into reduced facility footprints, capital expenditure, and manufacturing costs as well as the ability to rely on single-use technologies (Farid et al., 2014; Konstantinov & Cooney, 2015; Pollock et al., 2017; Schofield, 2018; Walther et al., 2015). Furthermore, technology gaps are being overcome with new solutions that make it easier to envision configurations for end-to-end continuous bioprocesses. However, there is debate on whether the uptake of continuous processes will streamline process development and validation efforts during drug development or increase them (Croughan et al., 2015; Farid et al., 2014; Kaltenbrunner, 2018; Konstantinov & Cooney, 2015). Process development and clinical manufacturing have been estimated to contribute up to 17% of the total R&D cost, which translates into hundreds of millions of dollars per market success (Farid et al., 2020). Hence, it is important to be able to explore the balance between manufacturing cost savings and implications on the process development effort to achieve them when considering switching to new technology platforms. This article presents a decisional tool to evaluate the business case for end-to-end and hybrid single-use continuous bioprocessing that captures trade-offs between manufacturing and development costs applied to mAbs.

The sector is debating and evaluating differing degrees of adoption of continuous technologies. On the upstream processing (USP) front, this has been enabled by the introduction of external retention devices (such as alternating tangential flow or tangential flow filtration technologies) for perfusion culture that overcome the limitations of earlier technologies and allow higher cell culture productivities and smaller manufacturing trains compared to batch methods (Clincke et al., 2013; Lim et al., 2006; Pollock et al., 2013; Xu et al., 2017). On the downstream processing (DSP) front, continuous unit operations, specifically for bioprocesses, have been developed more recently. These include multicolumn chromatography, single-pass tangential flow filtration (SPTFF), and continuous virus inactivation (Casey et al., 2011; Gjoka et al., 2017; Jungbauer, 2013; Mahajan et al., 2012; Pagkaliwangan et al., 2019). With this toolbox of continuous unit operations, partially integrated continuous processes have been established to specifically improve DSP productivity and equipment utilization. These processes have commonly consisted of perfusion cell culture coupled with multicolumn capture chromatography or fed-batch cell culture with a continuous DSP train (Gjoka et al., 2017; Pollock et al., 2017; Warikoo et al., 2012; Xenopoulos, 2015). Advancements have been made towards more end-to-end continuous processes that have typically used perfusion cell culture, multicolumn capture and intermediate chromatography steps, and flow-through polishing (Godawat et al., 2015; Walther et al., 2015). Arnold et al. (2019) incorporated continuous viral inactivation (VI) and SPTFF operations to aid continuous flow within their fully integrated continuous process and minimize the size and number of surge tanks employed.

Due to the promising nature of continuous processing, many studies have specifically looked at the cost savings it offers. Often, the manufacturing-related costs of batch and continuous processes at commercial manufacturing scales have been compared. Such studies have shown that continuous facilities can typically result in a reduction in the commercial cost of goods (COG) between 10% and 30% (Arnold et al., 2019; Hummel et al., 2019; Pollock et al., 2013, 2017; Walther et al., 2015; Xu et al., 2017). Even greater cost reductions in capital investment estimates have been reported at between 40% and 50% (Pollock et al., 2013; Walther et al., 2015). This is largely attributable to a reduction in the size of manufacturing trains and the ability to implement single-use technologies at these smaller scales. Pollock et al. (2017) have also been able to demonstrate these savings in the COG within clinical manufacturing facilities. In addition to manufacturing costs, some studies have gone further to examine the cash flows and demonstrated increases in net present value (NPV) (Walther et al., 2015) and savings in net present cost (NPC) (Pollard et al., 2016) in the order of hundreds of millions of dollars.

As continuous processing is still in its infancy compared to traditional batch processing (which has experienced a great deal of evolution over the past few decades) within the biopharmaceutical sector, a larger development effort and cost could be required to establish a continuous process (Croughan et al., 2015; Farid et al., 2014; Kaltenbrunner, 2018). The potential cost savings in manufacturing costs that continuous facilities can provide are yet to be weighed up against the higher process development costs they may incur. Furthermore, the definition of end-to-end continuous processing is evolving as new technologies emerge and the design of such processes requires careful sizing considerations. This article presents a decisional tool comprising a COG model to estimate manufacturing costs and a cost of development model to estimate process development and clinical manufacturing costs for different technology platforms. The tool also incorporates a mass balance and sizing model that has been developed specifically for the inherent features of continuous processes. With these attributes, it made it possible to apply this integrated decisional tool to a set of case studies that address the following questions: Do end-to-end continuous facilities offer manufacturing cost savings over traditional stainless steel or single-use batch facilities? Does the degree of manufacturing cost savings vary depending on the scale, company scenario or the extent to which continuous manufacturing is adopted? What are the cost-critical parameters that should be optimized within a continuous facility to ensure target cost-saving thresholds are met? Are potential savings in manufacturing costs outweighed by the additional effort to develop and validate continuous processes? These are important points to consider so that the industry can make informed decisions on where to focus their efforts so that valuable and competitive continuous processes are established.

2 | MATERIALS AND METHODS

2.1 | Decisional tool description

An object-oriented decisional tool was developed that integrated an advanced COG model, underpinned by mass balancing, equipment sizing, and scheduling equations, with a cost of development model to capture the costs of chemistry, manufacturing, and controls (CMC) activities. The tool was built in Python linked to Microsoft Excel and operated through Jupyter Notebook. The tool structure with its key inputs, outputs, and calculations is shown in Figure 1. The tool's database and key process economics equations were adapted from previous UCL work (Farid et al., 2020; Pollock et al., 2013, 2017; Simaria et al., 2012). New features built into the tool included: (a) extending the repertoire of continuous technologies in the unit operation library and database from perfusion and multicolumn chromatography to include also continuous versions of VI, ultrafiltration, and diafiltration operations; (b) new design equations to capture end-to-end continuous dynamics; (c) updating the database of unit costs and default process parameters, and (d) correlations between batch and continuous CMC process development costs.

Table 1 shows the equations used to calculate the main costs examined in this article: the COG and the cost of CMC to ensure a market success ($C_{CMC\text{-}Total}$). The COG includes the direct (e.g., materials and labor) and indirect costs (e.g., facility-related overheads) incurred during manufacturing. The indirect costs are derived from the fixed capital investment (FCI), which is calculated using the Lang factor method (Lang, 1948). The Lang factors used for stainless steel and single-use facilities were calculated based on the methods described in Novais et al. (2001) and Pollock et al. (2013). $C_{CMC\text{-}Total}$ covers the portfolio costs related to the process development, validation, and manufacturing activities across the drug development cycle, from preclinical trials to the submission of a licence application for regulatory review (e.g., BLA or MAA), as defined by Farid et al. (2020). As a result, $C_{CMC\text{-}Total}$ includes the costs spent on failed drug candidates and the development activities performed at-risk.

2.2 | Facility designs modeled

This tool was used to compare the COG and $C_{CMC\text{-}Total}$ of four facility types: stainless steel batch (SS-Batch), single-use batch (SU-Batch), end-to-end continuous (SU-EE), and hybrid (SU-Hybrid). The SU-Batch process adopts single-use unit operations over the stainless steel versions used in SS-Batch wherever possible, such as single-use bioreactors, pre-packed chromatography columns, and hold bags. Figure 2 shows the flowsheets used and the scheduling of each unit operation for the facilities modeled in this study. A typical mAb flowsheet was used for the batch processes (Gronke & Gilbert, 2018; Kelley, 2009).

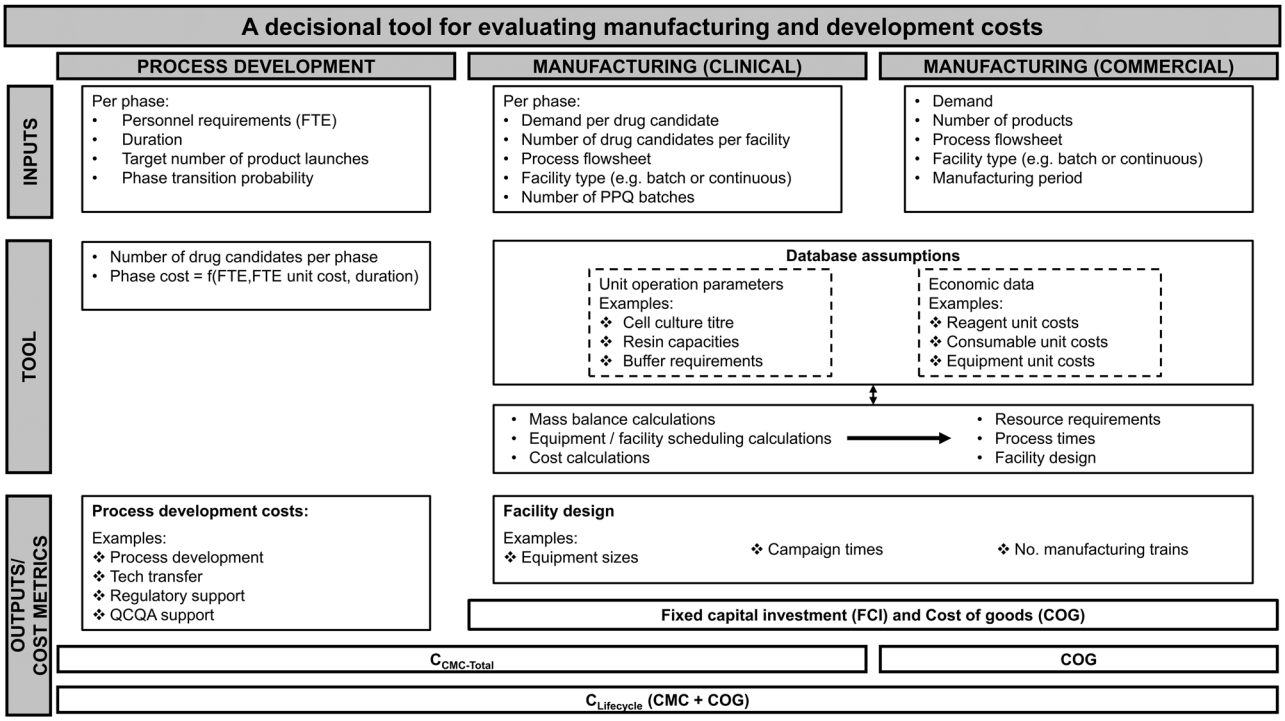


FIGURE 1 Structure of the decisional tool used in this study. The cost of CMC ($C_{CMC\text{-}Total}$) includes the costs related to the process development, validation, and manufacturing activities across the drug development cycle, from preclinical trials to the submission of a licence application for regulatory review. In this study, the COG associated with commercial manufacturing scenarios is usually calculated over a period of one year unless specified otherwise. CMC, chemistry, manufacturing and controls; COG, cost of goods

TABLE 1 Summary of the cost calculations used within the model

COG calculations		
Cost category		**Equation**
DIRECT/campaign	Reagents[a]	Units used per campaign × Unit cost
	Consumables	Units used per campaign[b] × Unit cost
	QC materials	QC batch release test cost × No. QC batches per campaign
	Operating labor	No. operators[c] × Wage × Campaign duration
	Supervisors	0.2 × Operating labor
	Quality control & quality assurance	1 × Operating labor
	General management	1 × Operating labor
INDIRECT/campaign	Maintenance	0.1 × FCI/No. campaigns per year
	Local taxes	0.02 × FCI/No. campaigns per year
	Insurance	0.01 × FCI/No. campaigns per year
	Depreciation	FCI/Depreciation period/No. campaigns per year
	General utilities[d]	Utility cost per unit area × Facility footprint/No. campaigns per year
COG/campaign		DIRECT + INDIRECT
COG/g		(COG/campaign)/Campaign demand
CMC cost calculations		
Cost category		**Equation**
$C_{CMC\text{-}PD}$[e]		$\sum_{i=1}^{n}$ [Process development cost per candidate at phase i × No. candidates at phase i]
$C_{CMC\text{-}MFG}$		$\sum_{i=1}^{n}$ [COG per candidate at phase i × No. candidates at phase i]
$C_{CMC\text{-}Total}$		$C_{CMC\text{-}PD} + C_{CMC\text{-}MFG}$

Note: For symbol definitions please refer to the nomenclature section.

[a]The term reagents is used as an umbrella term for process reagents (e.g., media and buffer) and direct utilities (e.g., WFI and steam used for CIP/SIP).

[b]For consumables the number of units used per campaign account for the reuse limit.

[c]This is a function of the number of operators scheduled to be working each day and their utilization on the manufacturing floor. For example, the operator utilization on the manufacturing floor is proportional to the number of reactors running in each facility to meet the target demands and the utilization will increase as more reactors and batches are required in each facility.

[d]The general utility cost per unit area is assumed to be \$525/m^2. This cost accounts for the utility charges (e.g., HVAC) to run a facility.

[e]This is the sum of the costs incurred across each phase of development from preclinical trials to the submission of a licence application for regulatory review to ensure a market success.

For SS-Batch or SU-Batch processes, each unit operation is carried out sequentially and sized using standard mass balancing equations that are based on the mass entering each unit operation per batch. The rationale behind the setup of the SU-EE facility was to convert the standard batch process into an end-to-end continuous process that enables the continuous flow of material from the production bioreactor to the final DSP unit operation. This was achieved through the use of unit operations that are specifically designed for continuous bioprocesses, such as perfusion cell culture, multicolumn chromatography, and SPTFF for concentration and diafiltration.

When simulating SU-EE, the outlet from perfusion cell culture is directly loaded onto the multicolumn capture system. The discrete elution pools generated by each capture column are then collected into a VI vessel. The continuous VI system uses two alternating vessels so that while one vessel collects chromatography eluates, the other carries out inactivation and feeds material onto the following unit operation. Next, the eluates from cation exchange chromatography are pooled into a collection vessel. When enough eluates have been pooled, this vessel is drained at a constant rate so that a process stream can be continuously fed through the remaining unit operations, which are inherently run in flow-through mode. Arnold et al. (2019) have already been able to demonstrate a fully integrated continuous process using most of these unit operations. Additionally, to avoid the need for large surge vessels and hold times between unit operations, the flow rate of the process stream between the outlet of one unit operation and the inlet of the next must be as

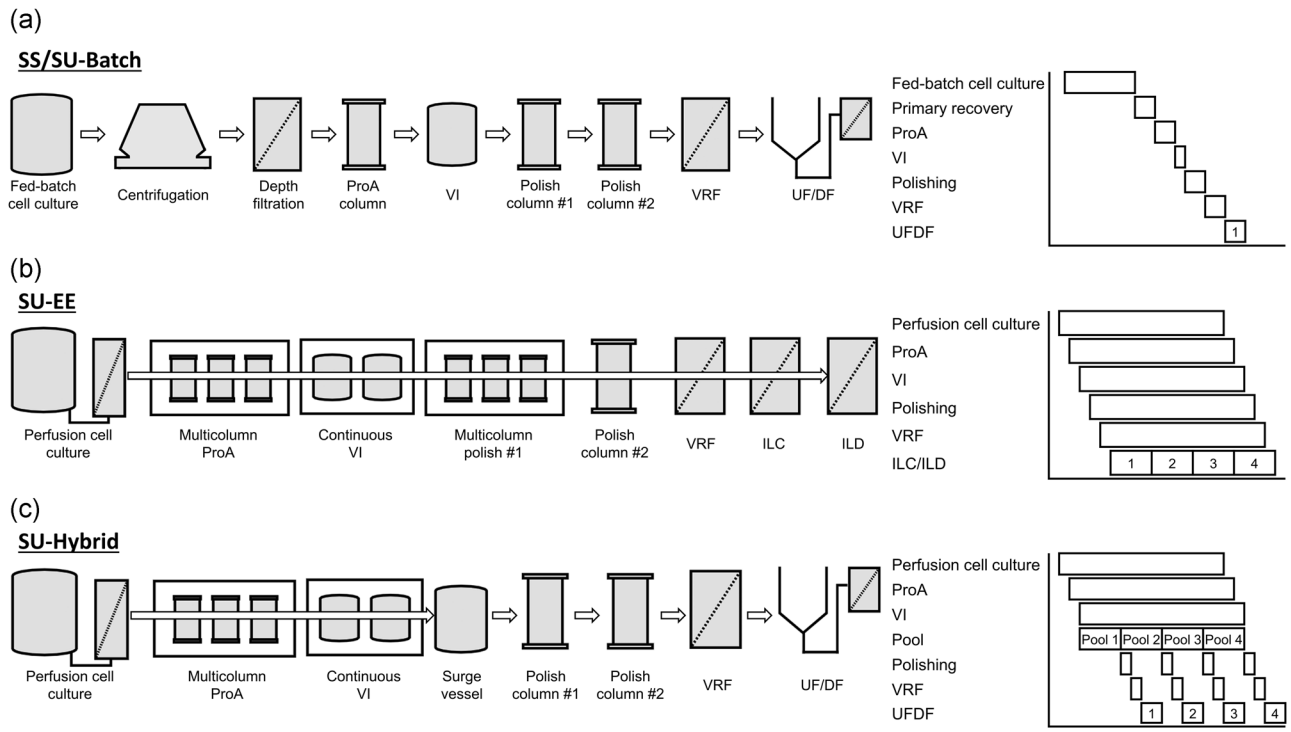


FIGURE 2 Flowsheets, process flows, and schedules for: (a) SS/SU-Batch, (b) SU-EE and (c) SU-Hybrid. The numbers on the final concentration and diafiltration steps represent the number of QC batches produced over time. When perfusion cell culture is used, QC batches and release tests occur in parallel with cell culture. ILC/ILD, inline concentration and inline diafiltration; Polishing, cation and anion exchange chromatography; Primary recovery, centrifugation followed by depth filtration; ProA, protein A chromatography; QC, quality control; SS-Batch, a stainless steel batch facility; SU-Batch, a single-use batch facility; SU-EE, asingle-use and end-to-end continuous facility; SU-Hybrid, a single-use and hybrid facility (with batch and continuous unit operations); UFDF, ultrafiltration/diafiltration; VI, low pH viral inactivation; VRF, virus retentive filtration

close as possible. Therefore, all unit operations running in continuous mode are sized based on the flow rate of the outlet of the previous unit operation. Table S1 in the Supporting Information Material shows the design equations used for this method.

The SU-Hybrid facility aims to provide a manufacturing method that does not involve changing the entire traditional batch flowsheet. This process operates in the same way as SU-EE up to VI, that is, with perfusion culture, multicolumn capture chromatography, and continuous VI. After this point, material is pooled for a set duration, generating discrete pools. Each pool is then individually processed in a batch manner by the remaining polishing chromatography and filtration unit operations.

2.3 | Case study assumptions

2.3.1 | Commercial manufacturing

Table 2 shows some of the key assumptions made for each facility. A degree of automation was assumed within the continuous facilities (SU-EE and SU-Hybrid), so fewer operators were required per shift compared to the batch facility (Konstantinov & Cooney, 2015). However, when multiple perfusion bioreactors are required they must run in parallel, whereas the harvest of multiple fed-batch bioreactors can be staggered along the DSP train and processed sequentially. This is why a team of operators can handle more fed-batch bioreactors over perfusion bioreactors. When reviewing cell culture performance, fed-batch methods have previously given titers between 2 and 3 g/L, but 5 g/L is now becoming more common and there are reports stating even 10 g/L can be achieved (Kelley, 2007; Lindskog, 2018; Xu et al., 2017). Perfusion has the ability to offer higher cell densities and hence productivities that are greater than fed-batch by over sevenfold (Pollock et al., 2013; Walther et al., 2019). Therefore, a titer of 5 g/L for fed-batch cell culture and a volumetric productivity of 3 g/L/d for perfusion cell culture were used unless specified otherwise. Greater resin loading capacities were also assumed when using multicolumn chromatography due to the ability to increase the utilization of resin capacity when adopting this method (Jagschies, 2018; Pollock et al., 2013).

The definition of a batch is also very important for continuous processes. In this article, a "QC batch" is defined as the amount of

TABLE 2 Key assumptions used in the COG model

Key costs			
Cost parameter	**Value**		
Fed-batch media ($/L)	33[a]		
Perfusion media ($/L)	19[a]		
Buffer ($/L)	3		
WFI ($/L)	1.5		
Clean steam ($/1000 kg)	72		
QC batch release test cost ($/batch)	35,000		
Labor requirements			
Parameter	**Value**		
	Batch	**Continuous**	
USP operators per shift	6	3	
DSP operators per shift	6	3	
Number of shifts per day	3	3	
Number of bioreactors managed by one team	4	2	
Key unit operation assumptions			
Unit operation	**Parameter**	**Value**	
		Batch	**Continuous**
Fed-batch or perfusion cell culture	Collected titer (g/L)[b]	5	2
	Cell culture time (d)	14	28[c]
	Volumetric productivity (g/L/d)[d]	0.4	3
	Perfusion rate (vv/d)[e]	N/A	1.5
Protein A chromatography	Loading capacity (g/L_{resin})	40	65
	Bed height (cm)	20	10
	Resin reuse limit (cycles)	200	200
Cation exchange chromatography	Loading capacity (g/L_{resin})	60	100
	Bed height (cm)	20	20
	Resin reuse limit (cycles)	100	100
Ultrafiltration/Diafiltration	Membrane reuse limit	30	30
	Diafiltration cycles	7	13

Abbreviations: COG, cost of goods; DSP, downstream processing; QC, quality control; USP, upstream processing; WFI, water for injection.

[a]The media cost includes the cost of a base and feed media. For fed-batch and perfusion cell culture the proportion of feed media is 25% and 10%, respectively, of the total media consumed during cell culture.

[b]Collected titer is measured in grams of product per litre of harvested cell culture fluid.

[c]For perfusion cell culture it was assumed that product collection started after the initial growth and ramp-up phase (8 days).

[d]Volumetric productivity is measured in grams of product produced per litre of the bioreactor working volume per day.

[e]Perfusion rate is measured as the equivalent number of bioreactor vessel working volumes (vv) exchanged per day.

TABLE 3 Key assumptions used to calculate the total CMC cost to ensure a market success ($C_{CMC\text{-}Total}$)

Phase	Fed-batch cell culture manufacturing scenario per drug candidate			
	Titer (g/L)	#Batches	kg/batch	Bioreactor volume (L)
Preclinical	2.5	1	0.5	400
Phase I	2.5	1	2	2000
Phase II	2.5	1	2	2000
Phase III	5	4	10	4000
Reg. review[a]	5	3	10	4000
Commercial	5	20	10	4000
	Perfusion cell culture manufacturing scenario per drug candidate			
	Volumetric productivity (g/L/d)	#Batches	kg/batch	Bioreactor volume (L)
Preclinical	1.5	1	0.5	30
Phase I	1.5	1	2	100
Phase II	1.5	1	2	100
Phase III	3	2	20	500
Reg. review[a]	3	3	20	500
Commercial	3	10	20	500
	Number of drug candidates per phase			
	Large company	Small company		
Preclinical	12	6		
Phase I	9	4		
Phase II	5	2		
Phase III	2	1		
Reg. review	1	0.5[b]		
	Process development costs per drug candidate ($M)			
	SS-Batch/ SU-Batch	SU-EE	SU-Hybrid	
Preclinical	0.9	1.8	1.35	
Phase I	0.9	1.8	1.35	
Phase II	–	–	–	
Phase III	6	12	9	
Reg. review	7.2	14.4	10.8	

Note: The overall process yield for batch processes was 64%. The overall process yield for continuous processes (Hybrid and EE) was 68%.

[a]This is for the production of PPQ batches that feed into the licence application submission for regulatory review.

[b]It has been assumed that a small company launches one drug every 2 years.

material qualifying for a QC batch release test. For a continuous process, this is the amount of material produced every four days, which is equivalent to the period of time that occurs before switching out the final filter in the manufacturing train. When referring to a "batch" this includes the amount of material produced over the duration of one cell culture run, regardless of the facility type used. A "QC batch" and a "batch" for SS/SU-Batch are synonymous.

2.3.2 | CMC activities during drug development

Table 3 highlights the assumptions used to estimate $C_{CMC\text{-}Total}$, which is a sum of the total cost of CMC process development ($C_{CMC\text{-}PD}$) and the total COG related to the manufacture of material for (pre-) clinical trials as well as PPQ batches ($C_{CMC\text{-}MFG}$) per market success. $C_{CMC\text{-}PD}$ was taken to include all bulk process and formulation development as well as analytical effort for process characterization and validation studies and the technology transfer activities (Farid et al., 2020). Process development was assumed to be carried out each time there is a change in scale and facility used to supply material for clinical trials, for example, from preclinical to Phase I and from Phase I to Phase III. The development activities for regulatory review accounted for the major process characterization and validation studies typically carried out in parallel with Phase III trials in preparation for the licence applications (e.g., BLA or MAA). The cost of process development at each stage was based on a breakdown of the personnel required to carry out these activities on a full-time equivalent (FTE) basis and the time they spend on development. The cost per FTE was assumed to be $150,000, which includes overheads as well as a salary. The personnel requirements for process development, as well as the size and number of batches required to supply clinical material (shown in Table 3), were drawn from recent benchmark values published by Farid et al. (2020). As the manufacturing process is typically locked at Phase III, the size of the manufacturing facility here is based on the optimal size to meet a target market demand of 200 kg/year. The number of drug candidates modeled in this study and shown in Table 3 was calculated based on the target number of market successes for each company and the attrition rates at each phase provided by Paul et al. (2010).

As mentioned in the introduction, the cost to develop a continuous process can be higher than a standard batch process. With the additional level of parameters that need close monitoring and complex unit operations, more experimental data may be required for process characterization to demonstrate process robustness and product quality from a company adopting continuous processing for the first time. In addition, those working in regulatory support may need to be more diligent to ensure the process is compliant with guidelines from regulatory bodies.

At each phase of process development, scale-up and/or optimization occurs, which means many of the challenges noted above will be experienced up to the regulatory review stage. To prevent the extra process development activities associated with a continuous process falling on the critical path and causing delays to clinical trials, additional personnel may be necessary. As there has not been a suggestion of the actual process development costs for continuous processes, the costs used in this study have been calculated based on

the increase in time and additional personnel that may be needed to develop a continuous process. It was estimated that development costs are two times greater for the SU-EE process compared to the batch processes modeled in this study (SS-Batch and SU-Batch). When developing the SU-Hybrid process the increase in process development costs may only be 1.5 times greater than SS/SU-Batch, as more than half of the DSP unit operations are carried out in a standard batch mode.

3 | RESULTS AND DISCUSSION

The integrated drug development (CMC) and manufacturing (COG) economics tool was used to determine the rankings of batch, hybrid and end-to-end continuous facilities initially from a commercial COG perspective and then from a total project lifecycle out-of-pocket cost perspective that weighed up COG against CMC costs. Scenarios using different starting assumptions are presented to highlight how this impacts the rankings of the facilities in terms of COG, CMC, and total lifecycle out-of-pocket cost.

3.1 | COG at commercial scales

3.1.1 | Base case analysis across demands of 100–3000 kg/year

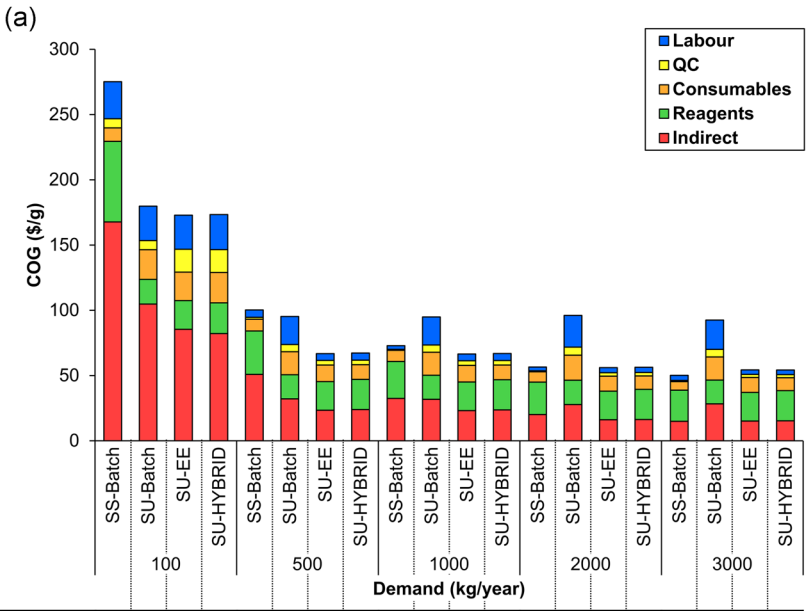
Figure 3 shows the COG/g modeled across a range of commercial scales of production, from 100 to 3000 kg/year, as well as the key features of each facility type using the base case assumptions highlighted in Table 2. This figure demonstrates that single-use facilities (continuous or batch) are able to offer a COG advantage of ~35% over SS-Batch at the smallest scale of 100 kg/year. Beyond 500 kg/year, SU-Batch starts to become less favorable and from 1000 kg/year the continuous facilities start to offer COG values similar to or greater than SS-Batch (±9%).

The COG breakdowns and facility features highlighted in Figure 3 demonstrate how changes in the importance of each cost category and the attributes of the manufacturing trains can influence the cost rankings relative to SS-Batch. For example, at smaller scales of production, investment-driven indirect costs dominate the total COG. As SU-Batch is able to reduce the fixed capital investment by shifting some of the equipment costs to consumable-related costs, notable savings in the indirect costs and the total COG are achieved. This COG saving is also driven by a reduction in the reagent costs by 70% as the requirement of clean-in-place (CIP) and sterilization-in-place (SIP) is eliminated when using single-use technologies. Figure 4a shows that CIP and SIP contribute to the majority of the total reagent costs for SS-Batch at 100 kg/year. As the scale increases, SU-Batch loses its COG advantage over SS-Batch due to the requirement for multiple bioreactors given the 2000 L size limitation typically assumed for single-use bioreactors (see embedded table in Figure 3a). At the ton scales, the need for parallel production lines (each with multiple staggered bioreactors sharing a DSP train) increases the indirect, labor and quality control (QC) costs incurred, and makes SU-Batch the least favorable facility type in terms of COG/g.

In contrast to SU-Batch, the single-use continuous facilities are able to offer COG reductions up to 2000 kg/year and only require multiple bioreactors at the tonnage demands modeled. This is driven largely by the reductions in indirect costs. Figure 3a demonstrates that the total bioreactor volume is smaller when using continuous facilities over batch facilities by sixfold to sevenfold, due to the higher productivities reached when using perfusion cell culture. Additionally, the generation of small harvested culture volumes from perfusion also permits the use of a smaller DSP train. Altogether, the reduction in size of the whole manufacturing train and implementation of single-use technologies means that continuous facilities, particularly at the smaller scales, are able to offer lower indirect costs than SS-Batch and SU-Batch. At 100 kg/year, SU-EE and SU-Hybrid both offer a reduction in indirect costs of ~50% compared to SS-Batch, which is greater than the ~40% reduction when using SU-Batch. However, unlike the batch facilities, when an additional bioreactor is required within a continuous facility, it was assumed that this would be supported by an additional dedicated DSP train working in parallel with the perfusion bioreactor. When two or three continuous parallel trains are required at the one to two ton demands, the model predicted that continuous facilities can still offer indirect cost savings (20%–30%) and hence capital investment savings. However, once four or more parallel trains are required (three ton demand), there are no longer savings in indirect costs for SU-EE or SU-Hybrid relative to SS-Batch.

Switching to both single-use and continuous processes results in multiple competing impacts on the material costs. Compared to SS-Batch, the overall reagent cost per gram is lower or similar despite the 1.6-fold higher media cost per gram (18 $/g) with perfusion culture; this can be attributed to the removal of CIP/SIP with single-use technology and the reduction in buffer costs (by 25%–40%) with smaller continuous DSP processes. Compared to SU-Batch, the reagent cost per gram for the SU-EE and SU-Hybrid options is ~20% higher as the higher media costs outweigh the decreases in buffer costs with a smaller DSP. As the scale increases, the media and DSP buffer costs per gram remain constant as expected (18–19$/g SU-Batch; 22–23$/g continuous). However, the total reagent cost per gram is not constant for SS-Batch as the CIP reagents for vessels were calculated as a function of a vessel's diameter (American Society of Mechanical Engineers, 2016), resulting in lower CIP quantities per unit vessel volume as scale increased. Hence the removal of CIP/SIP has a much greater impact on the reagent cost at 100 kg/year (−65%) than at 3000 kg/year when it becomes similar to SS-Batch. At the tonnage scale, media becomes the largest contributor to the total reagent costs for all facility types (see Figure 4c,d). This is also reflected in Figure 3b, which shows the increasing contribution of USP to the total COG value.

The consumable cost per gram for the single-use continuous options (10–13$/g for ≥ 500 kg/year) is over 30% higher than the SS-Batch option, in contrast to the SU-Batch option that is at least double the SS-Batch. The higher consumable costs can be attributed to the single-use nature of the processes with the impact being less for the continuous options due to the greater



% difference in COG between each SU facility and SS-Batch	-	-35%	-37%	-37%	-	-5%	-33%	-33%	-	+30%	-9%	-8%	-	+70%	-1%	0%	-	+85%	+8%	+8%
Reactor size (kL)	2	2	0.3	0.3	10	2	1.5	1.5	19.5	2	1.5	1.5	19.5	2	2	2	15	2	2	2
ProA diameter (cm)	45	45	13	13	100	45	25	25	140	45	25	25	140	45	30	30	120	45	30	30
Total Batches/campaign	20	20	10	10	20	80	10	10	20	160	20	20	40	357	30	30	79	500	40	40
USP reactors : DSP train	1	1	1	1	1	4	1	1	1	4	1	1	2	6	1	1	4	5	1	1
Parallel trains	1	1	1	1	1	1	1	1	1	2	2	2	1	3	3	3	1	5	4	4
QC batches/campaign	20	20	50	50	20	80	50	50	20	160	100	100	40	357	150	150	79	500	200	200
FCI ($M)	58	36	29	28	89	56	40	41	114	111	80	82	141	196	113	114	158	301	160	162

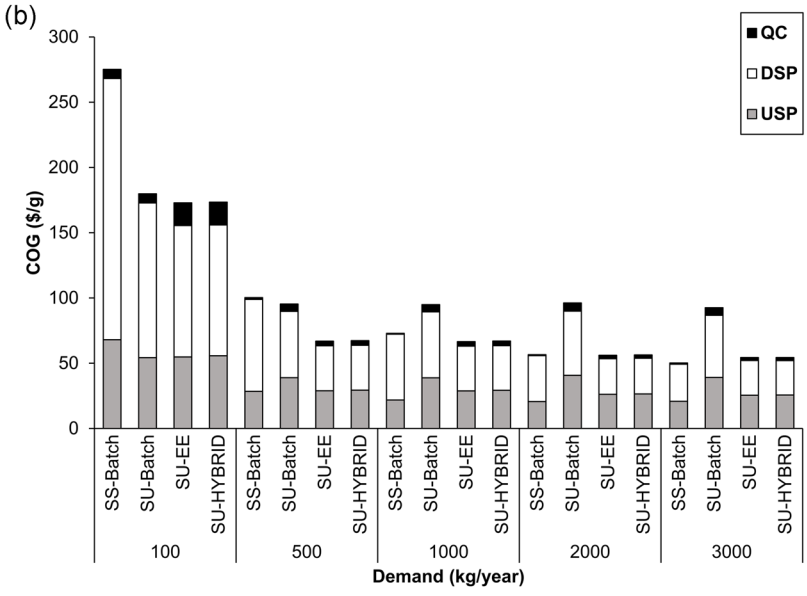


FIGURE 3 (See caption on next page)

process intensification. At the smaller scales, these increases in consumable costs with the single-use continuous options do not impact the rankings due to the dominance of the indirect costs. At 3000 kg/year, there are no longer any significant savings in indirect and reagent costs to outweigh the higher consumable and QC costs associated with SU-EE and SU-Hybrid and their COG values become 8% higher than SS-Batch.

Even if the constraint of single reactor trains was lifted and the same level of indirect cost savings of ~50% could potentially be achieved at all scales of production, a decline in the total COG savings that continuous facilities provide will still be seen at the ton scales due to the reduction in the importance of indirect costs at the ton scales of production. The ability to see savings in the COG by pooling multiple bioreactors should also be weighed up against the need for larger DSP trains and the higher risk of discarding more material if the harvest from one of the pooled reactors fails to meet quality criteria.

3.1.2 | COG sensitivity analysis

The base case demonstrates that the continuous facilities modeled do not offer the best manufacturing costs at every scale of production when compared to batch facilities. At 100 kg/year there is only a 4% reduction in COG between the continuous facilities and SU-Batch. At 3000 kg/year, the COG values of SU-EE and SU-Hybrid are higher than SS-Batch by 8%. As continuous manufacturing has not experienced the same level of development as batch, this can be expected. A sensitivity analysis was carried out to determine which parameters have a significant impact on the COG value for each facility type at the different scales modeled. These parameters are shown in Figure 5. From this figure it can also be seen under what conditions it is best to implement batch or continuous facilities. This was made possible by simulating scenarios which use parameter values that are either better or worse than the base case. It can then be determined what process improvements could be made within a continuous facility to make it more economically competitive with a batch facility, or under what conditions batch processing is still the most cost-effective option.

In this section, only SU-EE is compared to the batch facilities. SU-EE and SU-Hybrid give a similar COG breakdown at every scale modeled and their key cost drivers are relatively similar. This is because the majority of the COG (~70%) are associated with the unit operations before the polishing steps. In addition to this, SU-Hybrid is still able to provide a smaller DSP train from the polishing steps onwards, compared to the batch facility, due to the smaller scale of the continuous unit operations.

Figure 5a demonstrates that the ability to reduce the number of QC tests or the number of operators for SU-EE can improve the percent difference in COG between SU-EE and SU-Batch at 100 kg/year. However, the impact of these parameters is not as significant when looking at the percent difference in COG between SU-EE and SS-Batch at 3000 kg/year (Figure 5b). Figure 4 highlights that fixed costs (e.g., QC and labor) do not contribute as much to the total COG values at larger scales of production as the scale-dependent costs do (e.g., reagents).

Improving parameters that impact the total cost of media per campaign for perfusion cell culture can make SU-EE more cost-effective at any scale. In the base case, the consumption and cost of media per campaign for perfusion is ~2.8- and 1.6-fold greater, respectively, than fed-batch at all scales. When the best media unit cost is used for SU-EE, the total cost of media per campaign is only 1.2-fold greater for fed-batch cell culture. As the total cost of media contributes more to the total COG at 3000 kg/year, for all facility types, its impact on the percent difference in COG between SU-EE and the batch facilities is greater than at 100 kg/year. For these reasons, improving any parameter that impacts the total cost of media for perfusion (such as perfusion rate or volumetric productivity) can make SU-EE more cost-effective than SS-Batch at 3000 kg/year by ~10%–15%. Alternatively, when the worst values of these parameters are used, SU-EE can give significantly higher COG values compared to the batch facilities. As seen in Figure 5a,b, when the perfusion media cost is similar to the fed-batch media cost, the COG value for SU-EE becomes the same as SU-Batch at 100 kg/year or significantly worse than SS-Batch at 3000 kg/year by ~25%. At both scales, this higher unit cost of perfusion media increases the media cost per campaign (~2.4-fold), but the impact of this is greater at 3000 kg/year given that material costs dominate the COG/g.

FIGURE 3 COG breakdown on (a) a category basis and (b) a process stage basis for the base cases of the four batch and continuous facility types across commercial scales of 100–3000 kg/year. Here, maximum facility utilization was assumed so each fed-batch and perfusion reactor employed produces ~20 and 10 batches per year, respectively. The embedded table in (a) indicates the key facility features for each batch and continuous facility and can be applied to (b) as well. In (a) the category breakdown covers labor, QC, consumables, reagents and indirect costs. In (b) the process stage breakdown covers the total USP, DSP, and QC costs. One "parallel train" is classified as a group of USP reactors supported by one DSP train. For the continuous facilities, it was assumed that each perfusion bioreactor requires a dedicated DSP train and that parallel trains are installed when the maximum single-use bioreactor size available is exceeded. In this figure: fed-batch cell culture titer = 5 g/L and perfusion volumetric productivity = 3 g/L/d. The term reagents is used as an umbrella term for process reagents (e.g., media and buffer) and direct utilities (e.g. WFI and steam used for CIP/SIP). CIP, clean-in-place; DSP, downstream processing; QC, quality control; SIP, sterilization-in-place; SS-Batch, a stainless steel batch facility; SU-Batch, a single-use batch facility; SU-EE, a single-use and end-to-end continuous facility; SU-Hybrid, a single-use and hybrid facility (with batch and continuous unit operations); USP, upstream processing; WFI, water for injection

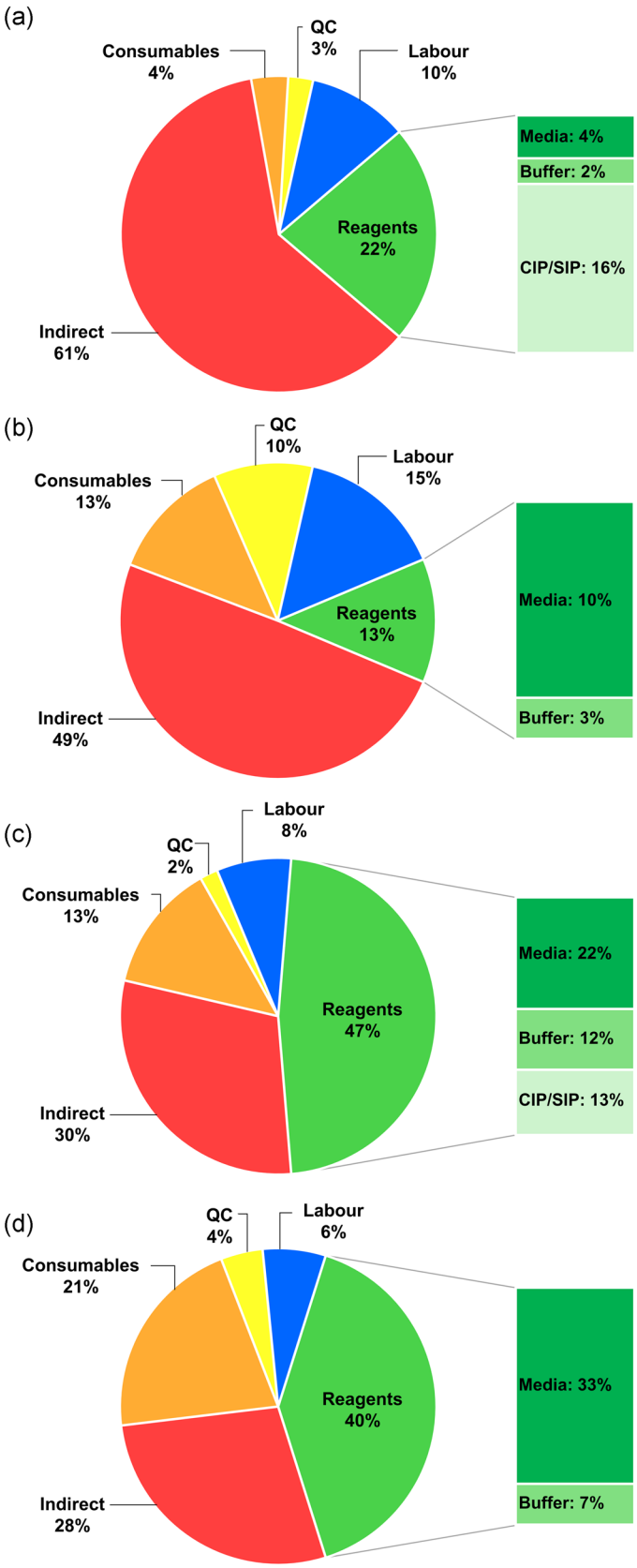
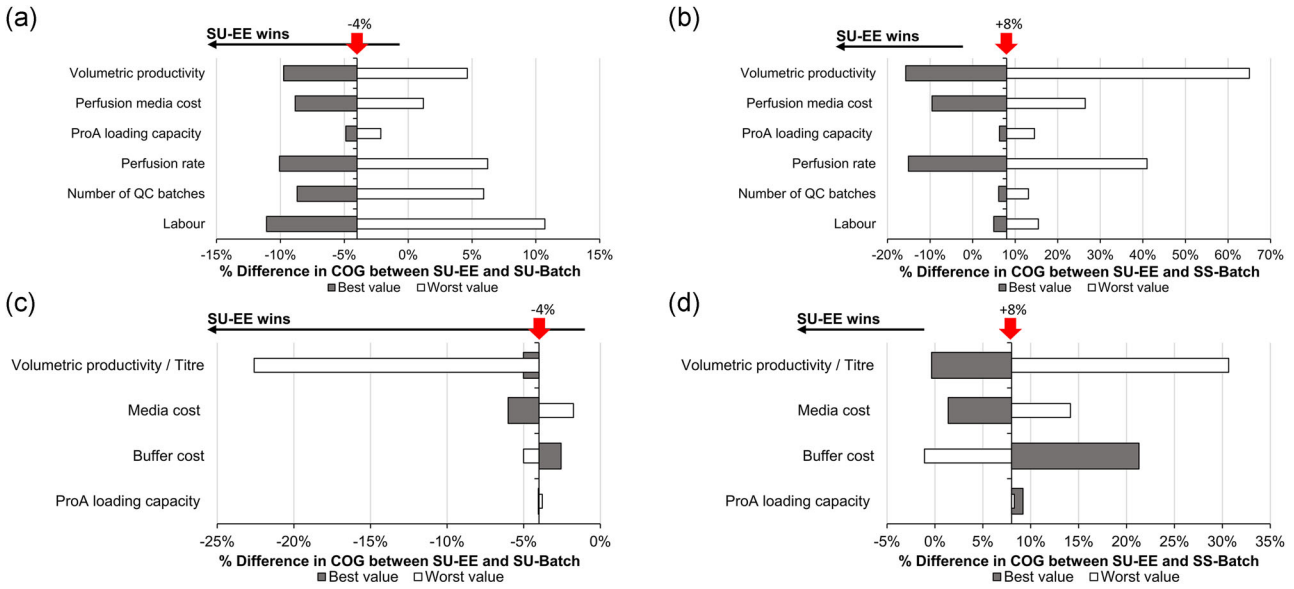


FIGURE 4 Contribution of each cost category to the total COG value modeled in the base case for: (a) SS-Batch at 100 kg/year, (b) SU-EE at 100 kg/year, (c) SS-Batch at 3000 kg/year, and (d) SU-EE at 3000 kg/year. CIP/SIP refers to acid, caustic, WFI and steam that are required during the cleaning cycles of unit operations and hold vessels within the process. The cost of CIP/SIP is less than 1% for SU-EE so is not visible. The term reagents is used as an umbrella term for process reagents (e.g., media and buffer) and direct utilities (e.g. WFI and steam used for CIP/SIP). CIP, clean-in-place; SIP, sterilization-in-place; WFI, water for injection



(e)

	Best value	Base value	Worst value
Perfusion volumetric productivity (g/L/d)	4.9	3	1.8
Fed-batch titre (g/L)	8	5	3
Perfusion media cost ($/L)	10	19	29
Fed-batch media cost ($/L)	16	33	49
Buffer cost ($/L)	5	3	1
Continuous ProA loading capacity (g/L_{resin})	80	65	40
Batch ProA loading capacity (g/L_{resin})	50	40	30
Perfusion rate (vv/d)	0.5	1.5	3
QC batches	Every 8 days	Every 4 days	Every 2 days
Labour (% change from base case)	-50	0	+100

FIGURE 5 Sensitivity analysis on the percentage difference in COG between the SU-EE and batch facilities. (a) The percentage difference in COG between SU-EE and SU-Batch at 100 kg/year when the process parameters are changed for SU-EE only. (b) The percentage difference in COG between SU-EE and SS-Batch at 3000 kg/year when the process parameters are changed for SU-EE only. (c) The percentage difference in COG between SU-EE and SU-Batch at 100 kg/year when the process parameters are changed for both SU-EE and SU-Batch. (d) The percentage difference in COG between SU-EE and SS-Batch at 3000 kg/year when the process parameters are changed for both SU-EE and SS-Batch. (e) The values of the parameters used in the best and worst case scenarios modeled in (a)–(d), alongside the values originally used in the base case modeled in Figure 3. The red arrows in (a)–(d) show the base case percentage difference in COG between the SU-EE and batch facility at the corresponding production scale. COG, cost of goods; SS-Batch, a stainless steel batch facility; SU-Batch, a single-use batch facility; SU-EE, asingle-use and end-to-end continuous facility; SU-Hybrid, a single-use and hybrid facility (with batch and continuous unit operations)

The ability to improve certain parameters for continuous processes may also mean similar improvements can be achieved within batch facilities. For instance, the unit cost of a buffer can be the same regardless of the facility type modeled. Figure 5c,d show the impact when the most sensitive parameters are changed for both SU-EE and batch facilities. At 100 kg/year the impact that these parameters have on the percent difference in the COG between SU-EE and SU-Batch is minimal. The only parameter that causes a significant change at 100 kg/year is the worst fed-batch titer (of 3 g/L). A lower titer for fed-batch means more bioreactors are required to meet the target demand, which results in an increase in costs that make up a fairly large proportion of the COG at smaller scales such as QC and labor.

At 3000 kg/year, reagent costs (particularly media and buffers) are a significant proportion of the total COG, so have the ability to have a greater influence on the percent difference in the COG between SU-EE and SS-Batch. Figure 4 shows that media alone is 22% and 33% of the total COG for SS-Batch and SU-EE, respectively. Therefore, reductions in the total media cost through better unit prices, titers, and volumetric productivities for both facility types can narrow the difference in the COG between SU-EE and SS-Batch. When a smaller unit cost of media is used for both facilities, the total cost of media per campaign for perfusion is still higher than fed-batch by ~1.6-fold, but the proportion of the COG attributed to media is now 13% and 20% for SS-Batch and SU-EE, respectively. For this reason, even if the media cost and consumption is improved for both SS-Batch and SU-EE, the COG of SU-EE becomes more comparable with SS-Batch.

For companies that wish to make the switch from batch to continuous processing, a COG saving greater than a certain threshold such as 20% may need to be achieved to justify such a change. Even when the best values of the parameters shown in Figure 5 are used, this threshold is not reached at the scales presented. To reach a target COG reduction of 20% or above, multiple parameters need to be improved in parallel. Figure 5 shows that the volumetric productivity, perfusion rate and media cost have a large impact on the difference in the COG between the

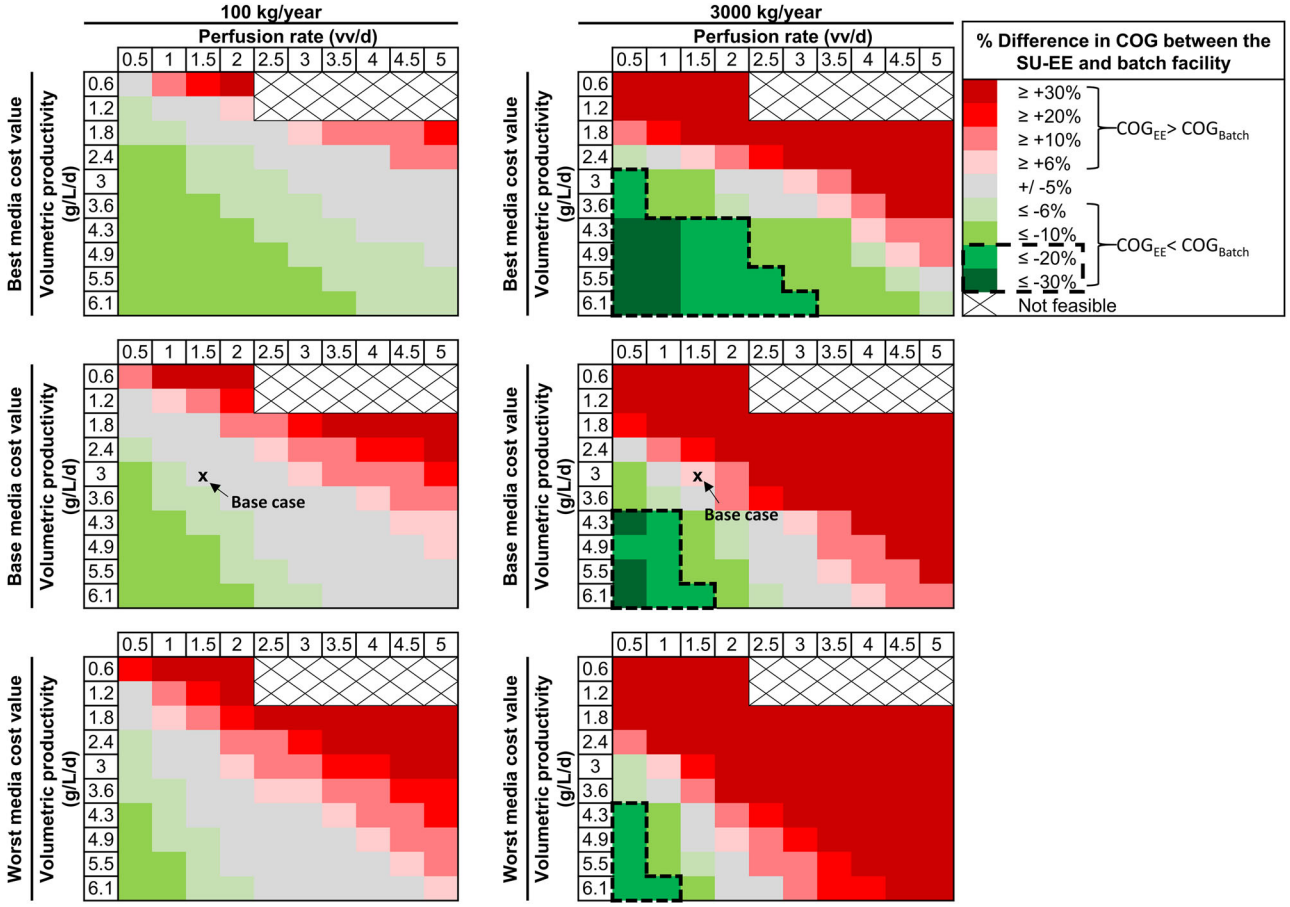
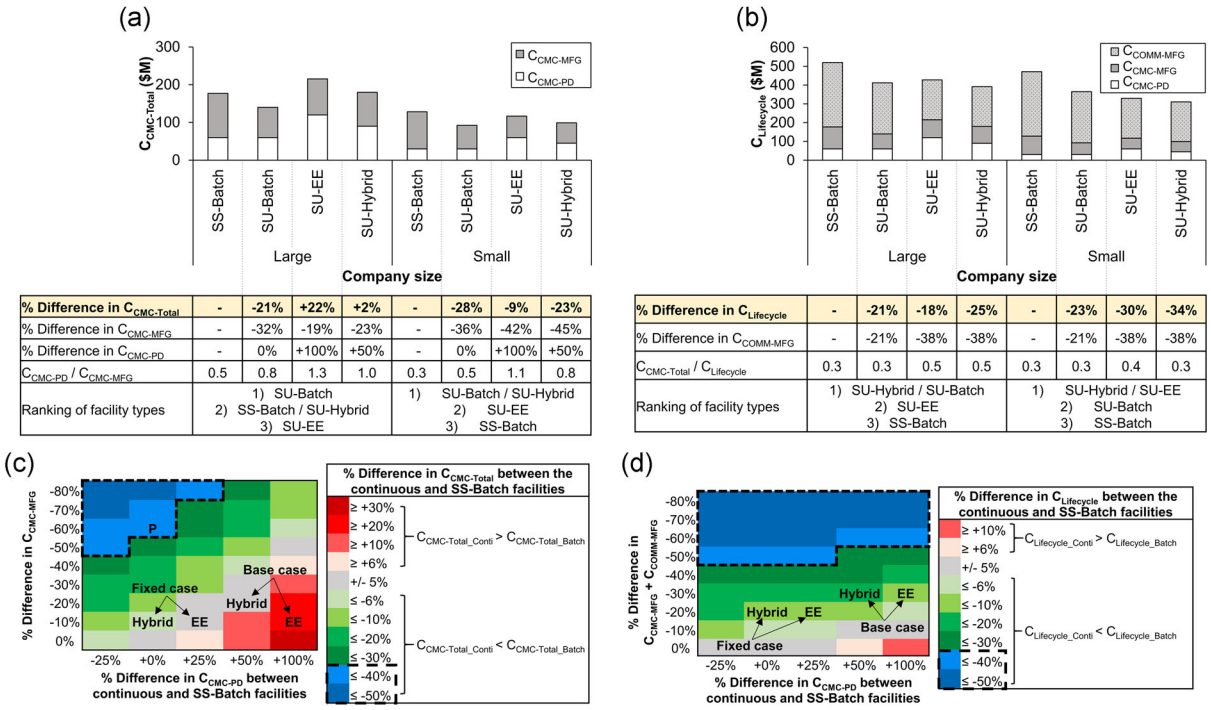


FIGURE 6 Matrix of contour plots showing the sensitivity of the percentage difference in COG between the SU-EE and batch facilities to different combinations of volumetric productivity versus perfusion rate across different media cost and annual demand scenarios. The dashed line shows the regions where SU-EE offers a target COG saving greater than 20%. At 100 kg/year SU-EE is compared to SU-Batch and at 3000 kg/year SU-EE is compared to SS-Batch. The values of the best, base and worst perfusion media costs are \$10/L, \$19/L, and \$29/L, respectively. In all cases fed-batch cell culture titer = 5 g/L and fed-batch media cost = \$33/L. COG, cost of goods; SU-EE, asingle-use and end-to-end continuous facility

SU-EE and batch facilities at 100 and 3000 kg/year. These parameters can also be interdependent. For example, it has been found that media with expensive feed additions or higher perfusion rates can improve the volumetric productivity of perfusion cell culture (Clincke et al., 2013; Xu et al., 2017).

Figure 6 summarizes a two-way sensitivity analysis that was carried out to determine if parallel improvements in the perfusion media cost, volumetric productivity and perfusion rate within the SU-EE facility can result in a 20% target COG saving threshold over the optimal batch facility (SS-Batch or SU-Batch) at 100 and 3000 kg/year. The dashed box and shades of dark green highlight the combination of parameters where this is possible. At 3000 kg/year, the target COG saving can be reached even if an expensive perfusion media, of \$29/L, is used to achieve high volumetric productivities (greater than 3.6 g/L/d), as long as the perfusion rate is minimized to 0.5 or 1 vv/d. If a cheaper perfusion media is used, of \$10/L, a COG advantage of at least 20% can be seen across a wider range of perfusion rates up to 2–3 vv/d, as long as the volumetric productivity is greater than 3.6 g/L/d. However, the target COG saving of 20% cannot be achieved at the 100 kg/year scale in any scenario presented in Figure 6. This is due to the smaller influence that the total media cost has on the total COG value at this scale. At this scale, improvements in fixed costs such as QC or labor could also be considered to help achieve greater COG savings.

This sensitivity analysis demonstrates how the changes in the importance of certain cost categories at different scales of manufacture might change the focus of development for continuous facilities or even the motivation to choose continuous processing over batch. At smaller scales of production, the level of savings seen when adopting continuous facilities can be attributed to the level of automation within the process so the labor requirement can be reduced, or the amount of material that qualifies for a QC batch release test. At the larger scales of production, these fixed costs may be irrelevant and the decision to choose continuous over batch processing can potentially be solely based on the ability of perfusion cell culture to minimize the consumption and cost of media. At scales between 100 and 3000 kg/year, both scale dependent and



% Difference in $C_{CMC-Total}$	-	-21%	+22%	+2%	-	-28%	-9%	-23%
% Difference in $C_{CMC-MFG}$	-	-32%	-19%	-23%	-	-36%	-42%	-45%
% Difference in C_{CMC-PD}	-	0%	+100%	+50%	-	0%	+100%	+50%
C_{CMC-PD} / $C_{CMC-MFG}$	0.5	0.8	1.3	1.0	0.3	0.5	1.1	0.8
Ranking of facility types	1) SU-Batch 2) SS-Batch / SU-Hybrid 3) SU-EE				1) SU-Batch / SU-Hybrid 2) SU-EE 3) SS-Batch			

% Difference in $C_{Lifecycle}$	-	-21%	-18%	-25%	-	-23%	-30%	-34%
% Difference in $C_{COMM-MFG}$	-	-21%	-38%	-38%	-	-21%	-38%	-38%
$C_{CMC-Total}$ / $C_{Lifecycle}$	0.3	0.3	0.5	0.5	0.3	0.3	0.4	0.3
Ranking of facility types	1) SU-Hybrid / SU-Batch 2) SU-EE 3) SS-Batch				1) SU-Hybrid / SU-EE 2) SU-Batch 3) SS-Batch			

FIGURE 7 Comparison of the process development and manufacturing costs across all company sizes and facility types modeled in this study. (a) Cost of CMC development and manufacturing activities to ensure a market success ($C_{CMC-Total}$). (b) Project lifecycle out-of-pocket cost to ensure a market success and supply the market for 10 years ($C_{Lifecycle}$). (c) Sensitivity analysis, for the large company, to demonstrate how various levels of $C_{CMC-MFG}$ savings or changes in C_{CMC-PD} for the continuous facilities can impact the percentage difference in $C_{CMC-Total}$ between SU-EE/SU-Hybrid and SS-Batch. (d) Sensitivity analysis, for the large company, to demonstrate how various levels of the total COG savings ($C_{CMC-MFG} + C_{COMM-MFG}$) or changes in C_{CMC-PD} for the continuous facilities can impact the percentage difference in $C_{Lifecycle}$ between SU-EE/SU-Hybrid and SS-Batch. The dashed line in (c) and (d) show the regions where a target cost saving greater than 40% compared to the SS-Batch facility is achieved. All percentage differences shown in this figure are relative to SS-Batch. $C_{CMC-MFG}$, the total cost of goods related to the CMC activities, to manufacture material for (pre-) clinical trials and PPQ batches; C_{CMC-PD}, the total cost of CMC process development from preclinical trials to the submission of a licence application for regulatory review; $C_{CMC-Total}$, the costs related to the process development, validation and manufacturing activities across the drug development cycle, from preclinical trials to the submission of a licence application for regulatory review;$C_{COMM-MFG}$, the total cost of goods over a 10 year commercial manufacturing period, when producing 200 kg/year; $C_{Lifecycle}$, a project's total out-of-pocket cost to ensure a successfully launched product and supply the market for 10 years; CMC, chemistry, manufacturing and controls;COG, cost of goods; PPQ, process performance qualification

independent parameters may be important. For example, at 1000 kg/year, the ability to improve perfusion's volumetric productivity from 3 to 4.9 g/L/d can lead to a ~40% reduction in COG between SU-EE and SU-Batch. This is a large difference from the 9% saving SU-EE offers in the base case. Improving the volumetric productivity here not only reduces the media cost, which is 27% of the total COG, but also reduces the indirect cost as the number of parallel trains halves to one. Overall, the COG savings seen when adopting continuous manufacturing will be largely dependent on the company scenario.

3.2 | Cost of process development versus COG

The previous sections have highlighted that continuous facilities can offer competitive COG values at commercial demands between 100 and 500 kg/year when single manufacturing trains are required. To make a broader assessment of continuous processing, the potential increase in process development and validation costs need to be weighed up against any savings seen in the COG when manufacturing material for (pre-) clinical trials, PPQ batches and the market. For this reason, the following section provides a breakdown of the total out-of-pocket cost experienced across a project's lifecycle, spanning drug development activities, and commercial manufacturing, when implementing batch or continuous processing.

3.2.1 | CMC cost

Initially, the impact on the CMC cost ($C_{CMC-Total}$) was considered. This refers to the total cost of process development (including process characterization/validation) and manufacturing activities (for trials and PPQ batches) across the drug development cycle to ensure a market success. When assessing the costs related to drug development activities, such as the CMC cost, it is important to consider a company's portfolio size. As Table 1 highlights, the number of drug

candidates entering each phase of drug development will determine the total process development and manufacturing costs and as a result, their weight on the total CMC cost value. In this study, $C_{CMC\text{-}Total}$ was calculated for each facility type (SS-Batch, SU-Batch, SU-EE, and SU-Hybrid) and two company sizes, a large and small company. A larger company is assumed to have more drug candidates in the pipeline, which can lead to higher CMC costs, compared to a smaller company as they may have more frequent product launches. Table 3 shows the number of drug candidates entering each phase of development for these company sizes.

Figure 7a shows $C_{CMC\text{-}Total}$ for each facility type and company size. From the perspective of the large company, SU-EE is not able to compete with the batch facilities. The twofold higher total cost of CMC process development ($C_{CMC\text{-}PD}$) for SU-EE outweighs the ~20% saving in the total COG related to the CMC manufacturing activities ($C_{CMC\text{-}MFG}$). This leads to an overall 22% increase in $C_{CMC\text{-}Total}$ for SU-EE compared to the traditional SS-Batch facility, which translates into an additional expenditure of ~$40 M. Even though SU-Hybrid gives a 50% increase $C_{CMC\text{-}PD}$ compared to SS-Batch, the saving it provides in $C_{CMC\text{-}MFG}$ is just about enough to outweigh this and make it competitive with SS-Batch. Overall, SU-Batch provides the lowest $C_{CMC\text{-}Total}$ for the large company and results in a saving of ~$40 M compared to SS-Batch, as it is able to provide a reduction in $C_{CMC\text{-}MFG}$ without affecting $C_{CMC\text{-}PD}$.

When considering $C_{CMC\text{-}Total}$ for the small company, SU-Hybrid becomes competitive with SU-Batch for the best facility. This is largely attributed to the reduction in the ratio of $C_{CMC\text{-}PD}$ to $C_{CMC\text{-}MFG}$. Unlike $C_{CMC\text{-}MFG}$, $C_{CMC\text{-}PD}$ is directly proportional to a company's portfolio size so the total value reduces by around half for the small company compared to the large company. A similar level of reduction in $C_{CMC\text{-}MFG}$ is not seen. Although the small company produces fewer batches at each phase of development, indirect or facility related costs still need to be paid, even if the facility is not fully utilized. Therefore clinical manufacturing costs are a larger proportion of $C_{CMC\text{-}Total}$ for the small company compared to the large company (see Figure 7a). For this reason, the 50% increase in $C_{CMC\text{-}PD}$ for SU-Hybrid can be compensated by the 45% reduction in $C_{CMC\text{-}MFG}$ and a $C_{CMC\text{-}Total}$ saving of 23% (equivalent to ~$30 M) is seen compared to SS-Batch. On the other hand, the saving in $C_{CMC\text{-}MFG}$ that SU-EE provides is just about enough to outweigh its doubling in $C_{CMC\text{-}PD}$ so that it can provide a $C_{CMC\text{-}Total}$ reduction by 9% compared to SS-Batch, but is still not enough to allow SU-EE to compete with SU-Batch or SU-Hybrid.

It can also be seen from the embedded table in Figure 7a that the reduction in $C_{CMC\text{-}MFG}$ seen by the continuous facilities can be lower for large companies compared to the small ones. This is mainly due to perfusion's extended cell culture time and the need for additional trains within continuous facilities when there are a large number of batches to be produced at each phase of development for large portfolios. As seen in the previous section, this can have an impact on the COG savings that continuous facilities provide. Consequently, SU-Batch offers better $C_{CMC\text{-}MFG}$ values compared to the continuous facilities for the large company. Further reasoning and a breakdown of the $C_{CMC\text{-}MFG}$ for each facility type at the drug development phases can be found in the Supporting Information Material.

3.2.2 | Project lifecycle cost

The ranking of the facility options can change as the out-of-pocket costs considered extend from the CMC costs (at the drug development stage) to the project lifecycle cost across the drug development and commercial timelines. In this article, the project lifecycle cost ($C_{Lifecycle}$) is considered to be the total out-of-pocket cost to ensure a successfully launched product and supply the market; this is a sum of the $C_{CMC\text{-}Total}$ and commercial manufacturing costs over 10 years ($C_{COMM\text{-}MFG}$). The commercial manufacturing scale modeled here is 200 kg/year, as the previous sections have shown that continuous facilities currently offer the most competitive and favorable COG values at demands between 100 and 500 kg/year, so are more likely to be implemented at commercial scales between these values. Figure 7b shows $C_{Lifecycle}$ for each facility and company size.

As highlighted in the previous section, from the CMC cost perspective, SU-EE was found to be similar or more costly compared to SS-Batch for small and large companies respectively. However, when considering $C_{Lifecycle}$, SU-EE and SU-Hybrid become competitive with SU-Batch and significantly better than SS-Batch (by −18% to −34%). This can be attributed to the fact that $C_{CMC\text{-}Total}$ is relatively small compared to $C_{COMM\text{-}MFG}$ and the continuous facilities are able to provide better $C_{COMM\text{-}MFG}$ values compared to the batch facilities (for the reasons detailed in Section 3.1.1), as shown in Figure 7b. Hence, the savings provided by SU-EE and SU-Hybrid in the COG at the commercial scale of production outweigh their increases in the total CMC process development costs ($C_{CMC\text{-}PD}$) in the long term. However, the CMC costs are a greater proportion of $C_{Lifecycle}$ for the large company compared to the small company, due to its bigger portfolio. For the large company, this is why the reduction in $C_{COMM\text{-}MFG}$ given by the continuous facilities is still not enough for them to outcompete SU-Batch by a substantial amount.

Different scenarios with alternative starting assumptions to the base case were explored to determine if the continuous facilities can currently offer better CMC and project lifecycle costs compared to the batch facilities for the large company. For example, this involved re-evaluating these costs for the continuous facilities when their manufacturing trains are locked at Phase I and scaled out to meet the larger material demands at the later phases (Farid et al., 2014; Konstantinov & Cooney, 2015). This could potentially reduce the development activities required at the later phases and bring down $C_{CMC\text{-}PD}$ and $C_{CMC\text{-}Total}$. However, it was found that the trends originally seen in the CMC and project lifecycle costs in Figure 7a,b do not change significantly. Even though development activities and costs for the continuous facilities are reduced from Phase III onwards, the COG savings are also reduced as the process optimization activities that would usually occur at Phase III do not

happen as the process cannot be changed after Phase I. As shown in Section 3.1.2, the COG savings achieved with continuous manufacturing are largely dependent on the development and optimization of certain process parameters, especially titers or volumetric productivities. The model inputs and results of this study are shown in the Supporting Information Material (Table S2 and Figure S2).

Considering the above, companies with larger portfolios may be more inclined to adopt single-use batch facilities over continuous facilities. For large companies that wish to adopt continuous processing, Figure 7c,d explore how better CMC and project lifecycle cost savings can be achieved over the batch methods. The dashed box and shades of blue in this figure highlight the target COG savings and $C_{CMC\text{-}PD}$ values that continuous facilities need to meet so that the large company can achieve $C_{CMC\text{-}Total}$ or $C_{Lifecycle}$ savings that are 40% greater than SS-Batch. This threshold was chosen as it also translates into a 20% reduction when comparing these costs for the continuous facilities to SU-Batch, the optimal batch facility in this case. The current positions of the continuous facilities are also highlighted within this heat map to demonstrate the jumps that need to be made to reach these cost saving targets.

From a CMC cost perspective (Figure 7c), to reach the target saving in $C_{CMC\text{-}Total}$, both $C_{CMC\text{-}PD}$ and $C_{CMC\text{-}MFG}$ are important and need to be reduced from the current values modeled in the base case. Within the highlighted threshold in Figure 7c, point "P" could be the most attainable if a platform continuous process is developed. In this case, companies should work towards establishing a continuous process that can be routinely optimized and scaled along the drug development pathway, so that the amount and cost of the CMC development activities ($C_{CMC\text{-}PD}$) become similar to what is required for a batch process. This reduction in $C_{CMC\text{-}PD}$ will need to be met with a reduction in $C_{CMC\text{-}MFG}$ from SS-Batch by at least 60%, which is significantly greater than the current $C_{CMC\text{-}MFG}$ saving of ~20%. If the $C_{CMC\text{-}PD}$ can become less than SS-Batch by 25%, this can reduce the target $C_{CMC\text{-}MFG}$ saving to 50%; such a scenario could correspond to having an optimized platform continuous process that is locked at Phase I and hence reduces the late phase process development costs.

From the project lifecycle cost perspective (Figure 7d), a 40% saving in $C_{Lifecycle}$ could be met more easily as this cost is relatively insensitive to $C_{CMC\text{-}PD}$, as $C_{COMM\text{-}MFG}$ dominates the total lifecycle cost. For example, the target $C_{Lifecycle}$ saving threshold can be met even at the current cost of process development ($C_{CMC\text{-}PD}$) for the continuous facilities (×1.5–2-fold), as long as a 60% saving in the total COG across development and commercial manufacture can be achieved. Currently, the total COG saving is ~30% for both SU-EE and SU-Hybrid, so work needs to be carried out to reduce the COG of continuous manufacturing further. If $C_{CMC\text{-}PD}$ for continuous is +25% or below compared to the cost for SS-Batch, the target total COG saving can be lowered to 50%, which could potentially be achieved with some of the improvements suggested in Section 3.1.

Overall, the analysis has presented an array of scenarios that can be mapped onto different company scenarios to help prioritize development efforts with continuous manufacture.

4 | CONCLUSION

This article demonstrated the development of an integrated drug development (CMC) and manufacturing (COG) economics tool to support a systematic analysis of the business case for the implementation of continuous processing for the production of mAbs. The tool incorporated new design equations that were specifically developed to aid comparison of the COG between single-use continuous processes (hybrid and end-to-end) and batch processes (stainless steel and single-use) across a wide range of company scenarios. Additionally, correlations to compare the cost of CMC development and manufacturing activities between continuous and batch processes were generated. This made it possible to determine if any savings seen in the COG at commercial and clinical scales would be outweighed by the large process development costs that continuous processes may incur. The analysis highlighted that continuous facilities offer COG savings when at smaller commercial demands where single USP and DSP trains are required. At larger scales, when parallel continuous trains are implemented and the cost of media dominates the COG, the cost effectiveness of continuous manufacture is reduced. The business case for continuous processing will depend on whether only a CMC perspective is considered or the total project lifecycle out-of-pocket cost across drug development and commercial activities. The tool predicted that although CMC costs with continuous processes are likely to be higher than batch processes when considered as a new technology, it is possible for continuous processes to be as or more competitive than the best batch process when the total lifecycle out-of-pocket costs are considered. Once future platform continuous processes are established that simplify process development, scaling, and optimization, it was predicted that this would make continuous facilities more attractive than batch processes in scenarios where they currently cannot compete in terms of cost.

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AUTHOR CONTRIBUTIONS

Hanna Mahal: Conceptualization, data curation, formal analysis, investigation, methodology, software, visualization, writing – original draft preparation, writing—review and editing. **Harvey Branton**: Resources, supervision, and validation. **Suzanne S. Farid**:

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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