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Current Opinion in Chemical Engineering

Review

Towards a Net Zero, socially sustainable and eco-efficient biopharma industry: how far are we?

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Clinical advances in the space of next-generation vaccines and medicines, together with the advent of platform technologies, have revolutionised the modus operandi of the biopharmaceutical industry. The industry's core mission for uninterrupted delivery of high-quality, efficacious drugs is now further challenged by bold and necessary targets to operate sustainably. In this paper, we discuss how threefold sustainability that integrates economic, environmental, and social objectives can be achieved through a combination of technological advances, expert knowledge and transparent dialogue. We summarise recent advances in biomanufacturing in terms of novel technologies, intracellular and process-level analytics, and computational models before providing an outlook on how Industry 5.0 principles can be adopted and applied to advance industrial practice.

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Current Opinion in Chemical Engineering 2024, **44**:101027

This review comes from a themed issue on **Pharmaceutical Manufacturing**

Edited by **Kimberley B McAuley, Salvador García Muñoz** and **Jonathan McMullen**

For complete overview of the section, please refer to the article collection, "Digital Design of Pharmaceutical Manufacturing Processes desalination and Water Treatment"

Available online 17 May 2024

https://doi.org/10.1016/j.coche.2024.101027

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Introduction

Current status of biopharmaceutical manufacturing

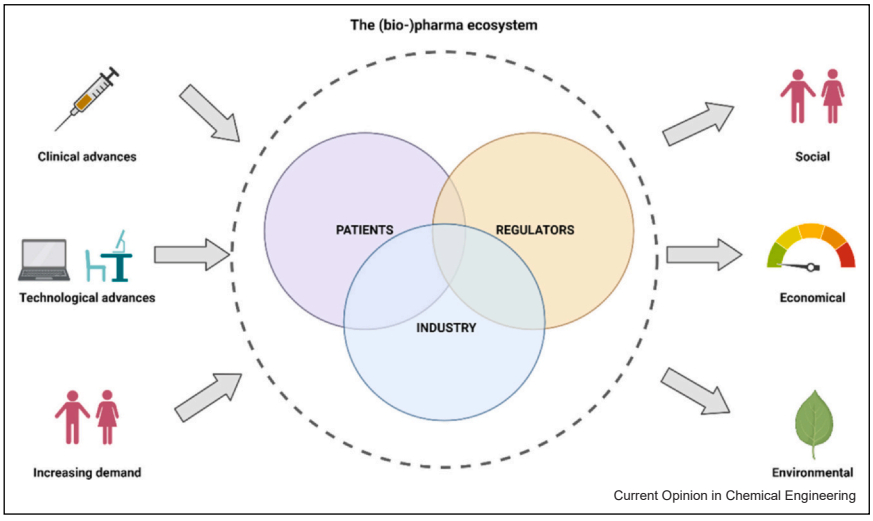
Biopharmaceuticals represent a rapidly growing part of the pharmaceutical industry thanks to their promising clinical outcomes and resulting commercial success. An example is monoclonal antibodies (mAbs), the market of which is forecasted to grow from $120 billion in 2018 to $300 billion in 2025 [1]. This is against a background of decline in the approval and launches of traditional modalities, from 65% in 2017 to 55% in 2022 [2]. As personalised medicine and treatments for previously incurable diseases are becoming increasingly possible [3], the (bio-)pharmaceutical development pipeline is changing.

The manufacture of biopharmaceuticals relies on the culture of living cells, which is the main step of the upstream process (USP). This is then followed by a series of separation steps focused on the purification of the final product (downstream process [DSP]). Technological advancements in the field of biomanufacturing offer a portfolio of solutions for the design and optimisation of processes. Those include, but are not limited to, single-use and/or stainless-steel equipment, fed-batch and/or continuous manufacturing, advanced analytics, as well as in-tandem digital solutions to assist bioprocess control. The choice and optimisation of the modus operandi have been traditionally led by product purity, functionality, process operability and yield considerations, without explicitly considering the environmental footprint. This could be partially attributed to the fact that the industry's positive impact on society has, so far, outweighed the environmental footprint of the sector. However, Net Zero initiatives are now at the heart of the broader Life Sciences sector, with concrete commitments in place by as early as 2030 [4–6]. It is, therefore, timelier than ever to address how sustainability can be integrated into bioprocess design and optimisation.

Towards threefold sustainability in biopharmaceuticals

Across the years, the (bio-)pharma industry has advanced its practices and tools to adapt to the Industrial Revolutions. This decade finds the industry at a pivotal point, concentrating efforts to develop and apply breakthrough medical and technological advances to respond to rising global demand. Industry 5.0 comes in addition to that, mandating a harmonious environment within which humans, machines, and technology work together seamlessly [7]. Such breakthrough changes are highly challenging, particularly for an industry that

Figure 1



The (bio-)pharma ecosystem. Created with BioRender.com.

operates within a tight, multistakeholder environment, within which patient, regulatory and industrial needs must be met (Figure 1).

Contributing directly to the UN Sustainable Development Goal (SDG) of Good Health and Well-Being (SDG 3), biopharma is now pressured to deliver high-quality products in sufficient volumes while actively contributing to reducing its environmental footprint (SDG 13) [8]. Currently, the climate footprint of the health care sector is 4.4% of global net emissions [9], at 260 million tCO_2 equivalent [10]. There is an intrinsic, relatively high use of material and energy for biopharmaceutical product production. For example, a typical mAb manufacturing process has a processes mass intensity (PMI) of 7700 kg/kg, with macromolecular medicines using 100 times more water than small molecule pharmaceuticals [11]. Adopting sustainable methods in the development and manufacture of current and future products can therefore have significant impact on net global emissions.

Delivering sustainability starts from identifying areas of technology and supply chain activities with the largest footprints on the environment as focal points for decision-making and innovation. In addition, process intensification and digitalisation can help achieve greater sustainability from lower costs and emissions per unit product. In this paper, we review current research to support sustainable decision-making for biopharmaceuticals and enablers for process intensification. First, we focus on environmental assessments of equipment technologies, which help identify pressure points in the sustainability of technology alternatives. Second, we discuss the opportunities for and challenges of intensification through continuous manufacturing and the role of digitalisation in this context. Finally, we discuss how overall sustainability can be achieved at a broader industrial and supply chain level.

Stainless-steel versus single-use equipment

Deployment of single-use technologies (SUT) has accelerated as manufacturers adopt SUT at commercial scale [12], driven by many advantages, including reduced risk of contamination, modularity of facilities and scale, and lower capital investments. With important implications in scale-up planning, SUT use assists manufacturers in adjusting production levels faster [13]. Studies demonstrate approximate capital and operating expenditure savings of up to 50% when shifting from stainless steel to SUT [14]. The plug-and-play modular design of SUT allows for production on demand, with quick changeover times between campaigns and products, making them ideal for multiproduct manufacturing. The removal of costly and time-consuming cleaning and steam in place (CIP/SIP) operations is another reason for adopting SUT [12,14,15]. A study reports that energy requirements for SUT-based facilities are reduced up to 23% and 6%, respectively, for Class D and Class U facilities [16]. Further research comparing the same process scale for mAbs production highlighted that the energy demand for the SUT process was > 38% lower than for stainless steel processes [17], which is expected to have a knock-on effect on energy costs.

However, concerns over environmental impact due to increased solid waste have emerged [18]. It is reported that approximately 770 kg of single-use equipment is used per 1.5 kg of mAb drug substance [19]. In this context, Life Cycle Analysis studies have argued that

SUT use in mAb manufacturing reduces environmental footprint in terms of climate change, human health, ecosystem quality, natural resources and freshwater withdrawal compared to stainless steel [20]. This was predominantly relating to the removed requirement for CIP/SIP, subsequently reducing use of energy-intensive water for injection (WFI) and resin utilisation. Specifically, the use of SUT equipment leads to reductions up to 75% and 95% for WFI and purified water compared with stainless steel facilities [16]. Additionally, SUT introduction in DSP removes the need for caustic chemicals for postprocessing treatment and sanitisation, which reduces the number of effluents in waste streams.

In another study, the global warming potential of the SUT facility was found to be up to 30% lower compared with the stainless-steel facility due to a reduction in electricity usage which offset the impact of plastics use [17]. On this point, a similar study [19] focusing on SUT facilities highlighted that most of the emissions resulted from the use phase of the process (22.7 tonnes of CO_2 per kg drug substance), with the procurement of SUT technologies resulting in only 1% higher emissions compared with stainless steel installations. The actual disposal of the plastics via incineration or recycling only contributed to 3% of impact across all categories. Instead, electricity to power the infrastructure was determined as a dominating factor out of the impact categories assessed, with contributions of 58–90%.

Batch versus continuous manufacturing

Opportunities of continuous manufacturing for sustainability

Continuous manufacturing demonstrates a paradigm shift for the biopharmaceutical sector as it can enable intensification and flexibility. The industry is currently largely based on batch or fed-batch manufacturing, which involves discrete unit processes requiring off-line quality testing, storage between process steps and may require shipping of intermediates between facilities. Continuous manufacturing allows end-to-end flow of products on a single uninterrupted production line [21]. This enables the establishment of platforms located in a single facility, with increased productivity and efficiency [11]. Continuous manufacturing is further promising reductions in cost, environmental footprint and increased flexibility of plant operations that enables rapid scale-up. This is expected to improve supply chain resilience to disruptions, derisk product availability and reduce shortage risks [22]. Substantial progress in recent years has been supported by several international research initiatives, including the Novartis-MIT Center for Continuous Manufacturing [23]. Nevertheless, there remain some technical and regulatory challenges, which currently hinder broad adoption.

The key economic benefits of continuous manufacturing platforms stem from lower production costs and high-volume production in smaller equipment. Research shows this would offset initial setup costs and capital investment and can achieve overall cost reductions of up to 60% per gram of product compared with batch manufacturing [24–27]. Additionally, continuous USP requires fewer production trains [22]. In DSP, the lower dilution requirements reduce buffer usage and investment in equipment for concentration and waste management [22]. Water is considered the greatest contributor to environmental impact of batch manufacturing. Water usage in biologics is > 100-fold higher than that in small molecule manufacturing and contributes to > 90% of batch manufacturing PMI [28]. For a USP operating in perfusion, higher volumes of growth medium are employed; however, studies suggest that this is offset by increased productivity of the process, which results in 23% lower PMI compared with batch or fed-batch counterparts [28]. In DSP, high and low pH buffer consumption can be reduced up to 44% through multicolumn continuous chromatography steps, which achieve higher loading capacity and shorter residence times and reduce buffer requirements [29]. This would result in less waste for post-treatment processing and buffer neutralisation. Adopting flow-through and membrane chromatography has been reported to result in buffer consumption reductions of up to 90% and > 50-fold increase in volumetric productivity [30].

Continuous manufacturing is closely tied with the use of SUT, including prepacked, disposable chromatography columns, cell bags, filters, and connectors [12]. It is expected that the argued substantial reductions in water consumption would offset SUT drawbacks, such as increased plastic waste. Additionally, energy usage in continuous technologies has been reported to achieve reductions up to 16.7% compared with batch manufacturing [31].

Challenges of continuous manufacturing

Technical challenges that slow down the uptake of end-to-end continuous processes start from the mismatch between USP perfusion rates and DSP purification rates [32]. Hybrid processes integrating batch and continuous steps are therefore feasible short-term alternatives [21]. Continuous USP systems are widely studied and have reached the required scale of production through perfusion and chemostat reactors, with focus on cell banking, inoculum expansion, cell retention and separation devices and process analytics technologies (PAT) tools to assure high cell culture density and viability [33–36]. In DSP, ongoing efforts are focusing on increasing equipment capacity to manage increased USP titre levels, from viral inactivation to scalable continuous chromatography steps [37–41].

Further challenges to the adoption of continuous technologies are tied to a resistance of switching current functional batch processes and the administrative burden for obtaining regulatory approval to justify the change [32]. This stems from concerns regarding full-plant shutdowns in case of unit downtime, material losses during start-up and shutdown, additional capital investments, high cost of PAT and automation software. Recent regulatory guidance [42,43] provides the basis for the development of advanced control strategies incorporating Quality by Design (QbD) principles and risk management protocols.

Process automation

Robust process performance can increase process efficiency and support manufacturers in meeting quality, economic and environmental objectives. In this space, automated bioprocessing provides numerous advantages, including improved process control, enhanced product quality, reduced variability, increased efficiency and cost savings. To this end, computational tools play a key role. Currently, model-based control solutions are available for a variety of fed-batch bioprocesses; however, these are highly process specific, and the market currently lacks universal and easy-to-use model-predictive control (MPC) options for advanced bioprocess control.

Process models of cell metabolism [44], cell culture operation [45] and chromatographic purification [46] have been employed for flexibility analysis [47–50], process optimisation [51] and control [52]. In particular, the identification of a design space allows quantification of process flexibility and robustness to disturbances. This can address unit integration challenges in continuous manufacturing, through the design of flexible DSP units that better handle USP disturbances. Table 1 summarises recent contributions in the space of computer-aided biopharmaceutical process design and operation.

At an operational level, process modelling can underpin advanced PAT integration, which has been widely employed in other industries to aid process monitoring and estimate product profiles [64]. Table 2 provides a summary of key recent PAT developments and their application in biopharma. An ongoing and common challenge is that of infrequent and/or unavailable measurements. To this end, soft sensors can use a sensor signal for a measurable physical quantity and a mathematical model to estimate the value of a different, unmeasurable state of interest [65]. Current efforts are focusing on developing PAT for critical process parameters and deconvoluting complex signals so that they can be used to infer unmeasurable parameters [66–69]. Issues that may hinder wider adoption of soft sensors can stem from challenges in model validation, often related to nonlinear system profiles or sensor faults [65,70].

The development of process-wide control strategies will ultimately enable automated end-to-end continuous processing [63,80]. The possibility to coordinate different units in real time, manage process interruptions, enable adjustments to target performance and assist start-up and shutdown will further help minimise material losses, ensure process robustness, as well as cost- and resource-effectiveness.

Outlook

The biopharmaceutical industry is at the forefront of the development of medicines, improving patient lives. A primary goal is to ensure patient accessibility to life-saving drugs, with ongoing efforts focusing on intensifying current bioprocesses to increase resource efficiency and minimise drug shortages related to manufacturing failures. This is highly challenging and involves the optimisation of complex systems, the dynamics and connections of which are not always fully understood. In addition, the biopharmaceutical industry is governed by strict regulations and is required to meet the objectives and needs of multiple stakeholders, with

Table 1

Summary of recent contributions in computer-aided approaches to design, optimisation and control of biopharmaceutical processes.

Application	Process section	Contribution	Ref.
Modelling and optimisation	USP	Optimisation of product yield and enhanced understanding of process dynamics	[51,53,54,55]
		Development of data-driven methods for product profile prediction via multivariate data analysis	[56,57]
		Development of hybrid models for prediction of product profile dynamics	[58]
	DSP	High-fidelity modelling and validation of chromatographic operation	[59]
Design space identification	USP	Variance-based methods for bioreactor design space identification	[48,60]
	DSP	Surrogate-based and sampling-based methods for robustness flexibility analysis	[49,50,61]
Process automation and control	USP	Model-predictive control approaches based on kinetic, hybrid and multiparametric modelling	[52]
	DSP	Model-predictive control approaches based on multiparametric modelling	[59,62]
	End-to-end process	Integration of control for manufacturing units	[63]

Table 2

Examples of recent PAT for microbial and mammalian cell cultures.

Technology (*position*)	Measures	Benefits	Ref.
Free-floating, wireless biosensor (*in-line*)	Dissolved oxygen tension	❖ Faster response times and lower energy consumption than in-line optical sensors ❖ Free-floating system can be paired with a variety of electrochemical sensors ❖ Modular means of monitoring cell culture parameters	[71]
Screen-printed, multi-analyte biosensor (*in-line*)	L-lactate, D-lactate, formate and ethanol	❖ Current research focuses on creating *in situ* sensors for a single analyte ❖ Technology able to measure four analytes simultaneously without sensor crosstalk	[72]
Raman spectroscopy (*in-line or online*)	Product concentration, aggregation, glycosylation, membrane fouling, metabolite concentrations	❖ Nondestructive technique with no sample removal ❖ Compatible with aqueous media ❖ 25+ variants of Raman spectroscopy applications	[73] [74] [75]
Genetically coded biosensor for responsive feeding (*in-line*)	Ammonia	❖ Real-time monitoring of the nutritional state of *Escherichia coli* at a single-cell level ❖ Fluorescence triggered by detected nitrogen depletion activates NH_4Cl feeding ❖ Can extend methodology to different kinds of nutrients needed for cell growth	[76]
Mid-infrared spectroscopy using U-bent fibre-optic sensors (*in-line*)	Glucose and other analytes	❖ Can differentiate between different analytes ❖ A single spectrometer can couple with numerous fibre-optic sensors to allow analysis of multiple unit operations simultaneously	[77]
Optogenetics for cell monitoring (*online*)	Various	❖ Automation and control of cellular responses using light-sensitive proteins for monitoring various cellular functions. ❖ In one application, controlled the unfolded protein response to get a 60% higher production of the secreted protein of interest	Reviewed in [78]; UPR [79]

the most critical being those of patients. The tremendous positive impact of the industry on human health has been, so far, outweighing other performance indicators, such as its environmental footprint. The latter is now taking a central role in industrial modus operandi, with global manufacturers committing to ambitious Net Zero targets by 2030 [81,82].

To achieve the promised sustainability targets, while ensuring drug availability and quality, the biopharmaceutical industry has to make a step change across its functions, from process development to manufacturing optimisation and product distribution (Figure 2). Within manufacturing, continuous operation has been reported to improve process performance by reducing the environmental footprint while ensuring reproducible product quality. Continuous systems are usually smaller in size, achieving the same or higher productivity compared with larger facilities operated in (fed-)batch. Achieving end-to-end continuous bioprocesses could therefore lead to decentralised manufacturing networks to improve accessibility of medicines to patients globally, potentially reducing emissions from transportation and storage. Decentralised systems are attractive for high-value, low-volume medicines, often encountered in targeted and personalised health care [83]. Manufacturing in smaller facilities closer to patient treatment centres can also reduce response times and logistical burden. In this setting, flexible modular SUT-based manufacturing [15] may be more suitable in terms of modularity and upfront investment. The cumulative impact of the process on the environment and the overall economics would nonetheless need to be quantified and assessed. The distribution of biologics and advanced therapeutics may require (ultra) low temperatures (cold chain) that has a significant impact on carbon emissions, which could be mitigated by switching to greener fuels and more sustainable packaging options [84]. When designing the global supply chain network, one should consider such aspects in the decision-making process. For example, a key aspect that can be re-evaluated is the current practice of offshoring commercial manufacturing and resulting emissions. Regional differences exist across the globe in power grid's carbon intensities, with the Asia–Pacific region tending to be higher [10], so changing manufacturing geographies is environmentally significant as 53% of the health care sector's footprint stems from energy consumption [9].

It is evident that transitioning to innovative manufacturing setups and supply chain networks that can meet threefold sustainability is a challenging task that involves conflicting objectives. For this, practices relying

Figure 2

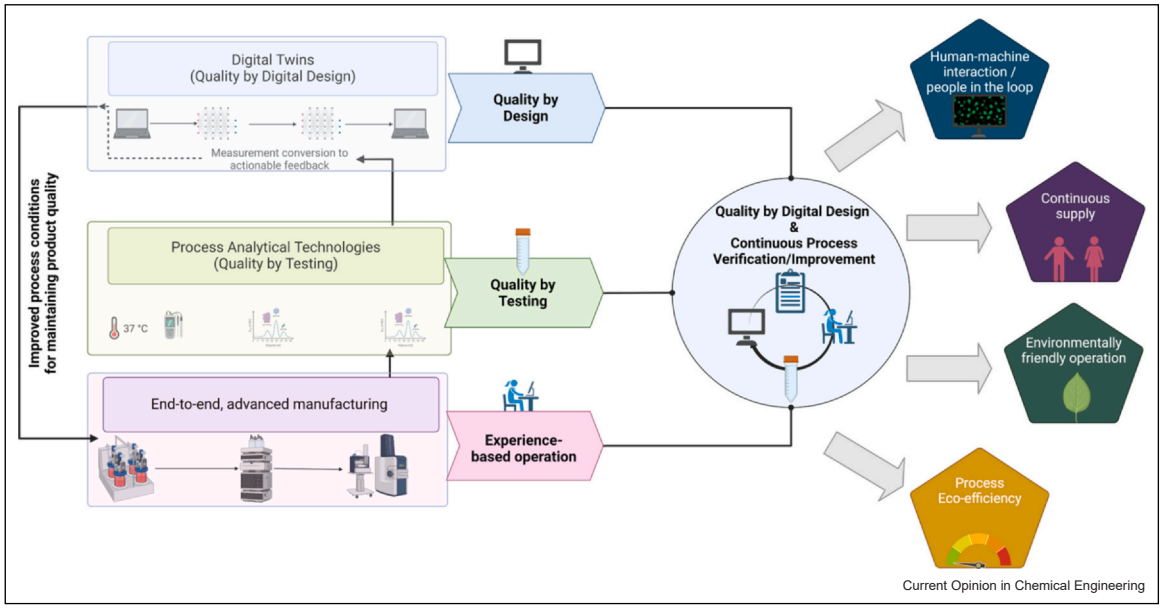


Illustration of the integration of QbD principles, technical innovation, and experts (Industry 5.0) towards the achievement of threefold sustainability in (bio-)pharma. Created with BioRender.com.

solely on know-how transfer and rule of thumb approaches are no longer sufficient. Therefore, a unique opportunity emerges for model-based planning tools to become an integral part when quantifying end-to-end sustainability of alternative network structures and manufacturing setups, proposing mitigation strategies [85,86]. Developing and employing such tools early on will allow the industry to expedite the decision-making while making their decisions robust to uncertainties related to manufacturing efficiency, raw material availability and distribution network failures.

The technological advances discussed in this paper are necessary but not enough to enable the transition to a Net Zero, socially sustainable and eco-efficient biopharma. People and mindset remain at the core of this breakthrough advancement (SDG 17). Industry, regulators, research, and academic institutions collectively should establish transparent routes for a continuous dialogue. This will accelerate the adoption of novel technologies and tools and help identify the skillset of the people necessary to enable and support the transition to Biopharma 5.0.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors have no competing interest to declare.

Acknowledgements

Funding from the UK Engineering & Physical Sciences Research Council (EPSRC) for the i-PREDICT: Integrated adaPtive pRocEss DesIgn and ConTrol (Grant reference: EP/W035006/1) and the digitalisation and automation of high-value biomanufacturing (EP/X024156/1) projects is gratefully acknowledged.

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