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Bioprocessing automation in cell therapy manufacturing: Outcomes of special interest group automation workshop

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Abstract

Phacilitate held a Special Interest Group workshop event in Edinburgh, UK, in May 2017. The event brought together leading stakeholders in the cell therapy bioprocessing field to identify present and future challenges and propose potential solutions to automation in cell therapy bioprocessing. Here, we review and summarize discussions from the event. Deep biological understanding of a product, its mechanism of action and indication pathogenesis underpin many factors relating to bioprocessing and automation. To fully exploit the opportunities of bioprocess automation, therapeutics developers must closely consider whether an automation strategy is applicable, how to design an 'automatable' bioprocess and how to implement process modifications with minimal disruption. Major decisions around bioprocess automation strategy should involve all relevant stakeholders; communication between technical and business strategy decision-makers is of particular importance. Developers should leverage automation to implement in-process testing, in turn applicable to process optimization, quality assurance (QA)/ quality control (QC), batch failure control, adaptive manufacturing and regulatory demands, but a lack of precedent and technical opportunities can complicate such efforts. Sparse standardization across product characterization, hardware components and software platforms is perceived to complicate efforts to implement automation. The use of advanced algorithmic approaches such as machine learning may have application to bioprocess and supply chain optimization. Automation can substantially de-risk the wider supply chain, including tracking and traceability, cryopreservation and thawing and logistics. The regulatory implications of automation are currently unclear because few hardware options exist and novel solutions require case-by-case validation, but automation can present attractive regulatory incentives.

Key Words: *automation, bioprocessing, manufacturing, standards, strategy, supply chain, cell therapy, gene therapy*

Introduction

The cell-based therapy (CBT) market is set to boom over the coming decade, and the industry must be able to sustain this growth by developing high-quality products and robust supply chains [1]. CBTs are highly complex products with extensive variability both across technology types and within a defined manufacturing process; bioprocessing needs must be catered for through a careful understanding of the product's specific demands and the control of their respective manufacturing and supply chain [2]. Bioprocess automation is expected to play a major role in achieving this [3]. Phacilitate held a Special Interest Group (SIG) for automation in CBT manufacturing in May 2017, uniting leading figures in the space to discuss issues around CBT bioprocess automation in a roundtable workshop-style format. Approximately 130 individuals participated in the event, primarily hailing from the US and UK. The vast majority of attendees were in senior-level industry positions; around eight research academics from British institutions were also present. Here we present the overarching themes from the event and discuss proposed solutions to the major challenges identified.

Preparing for automation

A pretext to discussions around CBT automation is the question of whether there is a valid business case to justify investing in and implementing automation.

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Manufacturing sufficiently high-volume batches, which represent many therapeutic doses, may be justifiably served through a manual or semi-automated process, and strategic decisions on what extent to automate a bioprocess must be made on a case-by-case basis. This paradigm is a clear example of the diversity of technology types and the disparity of their respective needs, particularly regarding allogeneic versus patient-specific treatment modalities.

Automation feasibility and associated cost-improvement analyses should be undertaken in parallel with other process development goals, validating the relevance and cost-utility of each process development step. It is pertinent to note that a change of raw material is considered a more extensive process modification than the use of the same material through a different or larger-scale operation; thus, selection at an early stage of low-cost, widely available, *xeno*-free growth media suitable for cost-effective, large-scale and/or automated manufacturing is considered to be good practice. Identifying high-risk bioprocessing steps through a simple risk analysis review can support strategic decision-making in identifying which unit operations to prioritize when implementing automation. Accurately triaging priorities will inevitably be influenced to some extent by hardware availability, and bespoke solutions may need to be developed in response. Hardware innovation gaps present particular challenges in implementing critical process parameter (CPP) controls.

A risk to implementing automation in a stepwise manner is the tendency to simply replace manual steps with robotic steps operating in a similar modality. This type of automation is generally suboptimal; best practice automation with the lowest operational costs is to implement manufacturing steps designed to be automated from the ground up. This highlights the need to plan a long-term process development strategy with automation as the end goal.

Identifying the decision-maker for capital expenditure and involving them in technical decisions and process development strategy planning was suggested to facilitate the implementation of automation and otherwise de-risk manufacturing development and design. Mismatch between technological process development needs and capital availability can cause conflict within a company and it is important to align strategic milestones across company areas to overcome this.

Implementing automation

There are two main approaches to implementing automation (Table I) and it was clear that the optimal strategy is heavily case-dependent. Implementing end-to-end automation simultaneously, most often a bespoke system, may offer optimally cost-efficient manufacturing processes, but this strategy requires major capital commitments (incurring associated risk) and relies upon comprehensive understanding of the product process for successful design, knowledge which is often inadequate. Manufacturing hardware is often inflexible, risking redundancy as technical innovations offer new opportunities. Many leading therapeutics manufacturers have commissioned bespoke automation solutions from large contract manufacturing organizations (CMOs), largely understood to be out of necessity rather than choice, although these systems have historically not been successful in producing cost-effective manufacturing systems. The alternative is step-wise, modular implementation, whereby individual unit operations are automated as the process is sufficiently characterized and/or relevant bioprocessing devices become available. This strategy offers a lower time-dependent capital risk profile, but may result in lower end-stage cost-efficiencies than that of a bespoke end-to-end automation strategy. There was no clear preference for one model over another owing to the disparate needs of CBT product processes, corporate strategies and design of supply chain infrastructure.

In either case it is clear that automation must be considered from an early stage of process development, and steps taken to prepare for its implementation. Discussion around the need for flexibility in automated systems was mixed; some felt that

Table I. Major technical decision dynamics of bespoke vs OTS automation.

	End-to-end automation	OTS unit function automation
Positives	Potential for lower operational costs and higher efficiency	More amenable to modification and lower-risk CapEx profile
Negatives	Higher upfront CapEx and less scope for modification	Limited by instrument availability and lacks support framework

OTS, off the shelf; CapEx, capital expenditure.