(1) Title page

Full Title: Bioprocessing automation in cell therapy manufacturing: Outcomes of Special Interest Group Automation workshop

Running Title: Cell bioprocessing automation workshop outcomes

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(2) Abstract

Phacilitate held a Special Interest Group workshop event in Edinburgh, UK, in May 2017. The event brought together major 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 summarise 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 optimisation, quality assurance (QA)/ quality control (QC), batch failure control, adaptive manufacturing, and regulatory demands, but a lack of precedent and technical opportunity can complicate such efforts. Sparse standardisation across product characterisation, 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 optimisation. 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 as few hardware options exist

and novel solutions require case-by-case validation, but automation can present attractive regulatory incentives.

(3) Key words

Automation, bioprocessing, manufacturing, standards, strategy, supply chain.

(4) Abbreviations

CAR-T = Chimeric Antigen Receptor T-cells

CapEx = Capital expenditure

CBT = Cell based therapy

CMO = Contract manufacturing organisation

COGs = Cost of goods

CPP = Critical process parameters

CQAs = Critical quality attributes

FTE = Full time equivalent

IP = Intellectual property

PST = Patient specific therapy

OTS = Off the shelf

SIG = Special Interest Group

QA = Quality Assurance

QC = Quality Control

QMS = Quality management system

(5) Main body

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. 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 product's specific demands and the control of their respective manufacturing and supply chain. Bioprocess automation is expected to play a major role in achieving this. 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 workshop-style format. 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. 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 vs patient-specific treatment modalities.

Automation feasibility and associated cost-improvement analyses should be undertaken in parallel to 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 prioritise 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 (Figure 1) and it was clear that the optimal strategies is heavily case-dependent. Implementing end-to-end automation simultaneously, most often a bespoke system, may offer an 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 organisations (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 characterised 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.

	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

Figure 1: Major technical decision dynamics of bespoke vs off-the-shelf (OTS) automation.

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 once a process is validated it should remain fixed and does not require flexibility, while others felt that flexibility offered greater product development opportunities and that any extra cost incurred by enabling process modifications would be justified in the longer term. Flexibility at an early product development stage is critical whether automation is adopted through an OTS or bespoke model, as processes undergo constant improvement through tuning and adaption, and face the complexity of a developing regulatory environment.

It was agreed that although a major innovation gap currently exists in automated off-the-shelf hardware solutions, this is expected to change rapidly over the coming 5 years as novel manufacturing options for CBTs come onto the market. Solutions may be enabled by increasing elucidation of technical needs therapeutics developers have within their manufacturing process. A collaborative strategy to resolving manufacturability barriers was repeatedly highlighted as a major theme, confirming the need for industrial stakeholders to work together, sharing information, and distributing development risks

and costs to achieve both company-specific goals and serve the industry at large.

Defining manufacturing processes

Understanding the need to define manufacturing processes

A clear theme emerged that therapeutics developers often do not understand either the intrinsic biology or extrinsic mechanism of action of CBTs sufficiently to make the most of opportunities in bioprocessing automation, whether due to confidentiality limitations or inadequate product knowledge. There was agreement upon the consequential need to further understand and more closely define CBT products and their respective manufacturing processes. Characterisation assays are expensive and often time-consuming to undertake, but comprise the foundation of specification design, manufacturing control, and regulatory assessment. Moving away from the 'process is product' paradigm through advanced biological and technical understanding allows the exclusion of unnecessary or onerous assays, simplification of existing assays, and development of novel in-process tests. Bioprocess cost-efficiency improvements through automated CPP testing are only possible with a well-characterised product process.

Several leading CAR-T companies are integrating bespoke and proprietary bioprocesses with varying degrees of automation, either in-house or through CMOs. Automated bioprocessing facilities aim to reduce manufacturing times from around 14 days for first-generation products to 5 days for second generation, enabled by an increased understanding of the product and the effects of each bioprocessing step.

A major advantage in automating manufacture is de-risking comparability studies. There was a general expectation that installing identical, closed-process equipment across

manufacturing sites removed environmental factors such as human operation, increasing the repeatability and robustness of the manufacturing process.

Benefits of implementing CPPs

Increasing manufacturing control by integrating CPPs within and along the supply chain can enhance robustness, reliability, and consistency to offer value in three main areas (although it was agreed that these were a non-exhaustive 'top three'); quality assurance QA/QC, lowering cost of goods (COGs), and enabling support for adaptive manufacturing (Figure 2).

Firstly, while informative in their own right, the value of CPPs should be fully leveraged by exploring their inter-relationships and respective impacts on critical quality attributes (CQAs). Linking CPPs with CQAs may validate CPP use in QA and QC, reducing the need for end-stage batch-release QC testing through real-time release and 'predictive production'. QA/QC was identified as a major time and expense demand in most manufacturing processes, and its optimisation through reducing full time equivalents (FTEs) and mitigating QA/QC-related time constrains was seen as a major attraction. The insufficiency of manual solutions in releasing thousands of products annually was unilaterally agreed, positioning QA/QC central to the benefit of bioprocess automation.

The second core area of CPP advantage was in lowering COGs. Measuring the precise in-process and outputting parameters of every manufacturing step generates a wealth of data highly valuable in process optimisation. Leveraging this data could allow the exclusion of unnecessary steps, minimising the use of culture media and other raw

materials/consumables. An ability to link CPPs with CQAs could enable the system to identify batch failures at an earlier stage, rejecting failed batches earlier in the manufacturing process and thus saving time and media usage or allowing for relevant process adaptation to correct suboptimal batch characteristics.

Well-defined CPPs enable the possibility of adaptive or flexible manufacturing. Although lacking precedent, a relevant regulatory basis, or even a clear need, the capability to modify the precise bioprocessing steps on a batch-by-batch basis, accounting for inherent donor variability or process deviations, may present an opportunity to further de-risk the supply chain and manufacture higher quality products. This would require the extensive use of validated CPPs to justify, control and validate process manipulation.

Benefits	Barriers
• Augmented manufacturing controls and more granular specification • Enhanced robustness, reliability, consistency • Application to QA/QC may expedite batch-release and lower costs • Increased in-process data allow better process optimization • Can lead to reduction in COGs • Lower operational costs- earlier batch failure identification • Possibility of adaptive or flexible manufacturing to account for variability in patient-specific starting material • Support comparability studies	• Requires deep understanding of product and process • Risk of extraneous process development • Must identify those parameters critical to predicting manufacturing outputs • Bioprocessing equipment may not support in-process testing • Process must remain closed, limiting opportunity for testing • Sample collection can reduce batch volume • No regulatory precedence for CPPs contributing to QA/QC/batch release • CPP implementation requires extensive testing and validation

Figure 2: Benefits and barriers to implementing CPPs within the manufacturing process.

Barriers to implementing CPPs

The main barrier to implementing CPPs is a lack of technical knowledge regarding precisely which CPPs are relevant and useful to access. In tandem with this (both a cause and effect) is a lack of closed-process hardware solutions offering CPP testing for commercial scale CBT bioprocessing. To overcome this, technology providers should engage and work closely with solutions providers to design and develop relevant bioprocessing hardware.

Regulatory bodies have needed to rapidly respond to technical innovation for years, and the usage of CPPs in QA/QC is no different. There is currently no regulatory precedent for real-time release in CBTs and each strategy would need case-by-case approval by the relevant regulatory authorities. The lack of industry standards for both CPPs and CQAs across all CBT types complicates this effort further.

Developing standards

There was agreement that a lack of standardisation is consistently frustrating the industry's efforts to advance bioprocessing techniques across three main areas; cell characterisation and functionality assays, hardware components, and software platforms.

There is poor consensus on which parameters of cell functionality are necessary to measure for many cell types, and therapeutics developers are having to design their own functionality profiles which may or may not share common parameters. This is a result of both poor product characterisation and the confidential nature of more advanced platforms. Hardware solutions such as tubing and connectors suffer from poor cross-compatibility and are faced with a significant innovation gap. Bespoke customisation is

available to some degree but this is expensive and limited in scope; devices offering unit-operation functions must be able to directly communicate and interact with upstream and downstream equipment to offer end-to-end automation. Software is perhaps one of the most important aspects to standardise. Equipment providers currently offer bespoke software for their respective platforms, and cross-compatibility is poor. Implementing cost-effective large-scale automation demands a single software platform with multiple drivers capable of interacting with and controlling all devices across the manufacturing process/ supply chain. There was consensus that such a system might best be open-source, allowing individual manufacturing solution providers to access the program and ensure full compatibility. Similar solutions currently exist in related applications, for example in scheduling and automating hospital-based blood testing.

Leveraging bioprocess data

The implementation of automated in-process testing can generate high volumes of data, particularly in patient-specific therapies (PSTs), that can be leveraged both to de-risk the supply chain and for product development opportunities. Developing an understanding of the relationships between CPPs and their bearing on CQAs could be achieved through advanced algorithmic approaches, and the use of artificial intelligence/ machine learning was proposed. Deeper process understanding could quantify the relative value of CPPs, identifying those most critical against those less necessary to control, as well as assigning a measure of risk to each, opening new opportunities in managing the manufacturing chain. Through a world model that allows the system to understand the implications of its actionable decisions, such solutions could be combined with ‘reasoned’ algorithms to actuate modifications or adaptations within the manufacturing process. The platform

should be capable of identifying and announcing pre-specified errors when necessary, the resolution of which can be incorporated systematically and even across manufacturing sites through operator interaction. Large-scale software platforms may be more applicable to facility or even supply chain-level implementation rather than process-level, which may require more specific software applications. The inclusion of raw materials, starting materials, and disposables providers within automated, computer-controlled supply chains would increase robustness and de-risk the delivery of high-value therapies by reducing the number of manual steps, FTE needs, and container-exchange points. PST supply chains may be particularly amenable to optimisation through such means.

Managing the sensitive and valuable data generated through digital supply chain tracking or automation instigates substantial demands. Any patient-specific health data must be treated with absolute confidentiality, and data access by supply chain partners should be carefully designed. Companies must assume responsibility for managing this data according to all relevant privacy protection laws and in accordance with patient wishes. Data backup systems require validation and testing, either on numerous geographically separated hard drives, cloud-based services, or a combination of both.

Decision-making and business strategy in automation

Adopting automation requires high level of capital and requires substantial input from business strategy decision-makers and investors as well as technical staff. This applies to not just automation but the model by which manufacturing infrastructure is accessed. The decision between virtual or integrated models can depend considerably on business strategy factors such as intellectual property (IP) needs, and the relative benefit of or need for additional IP around manufacturing solutions (Figure 3). Other factors contributing to

this decision include candidate pipeline maturity, capital availability, market size, trade secret presence, CMO availability, and market trends. It was suggested that no existing evidence supports the fundamental importance of IP to the commercial success of a CBT.

The innovation gap in CBT manufacturing hardware is a major defining factor when considering automation strategy. Therapeutics developers have previously tended to resolve this issue through commissioning bespoke solutions for their products from major manufacturing service providers. Such agreements must understand the need to share risk between the parties involved, with the manufacturing organisation taking on the cost risk of developing new devices (where necessary), and the therapeutics developer shouldering the risk of successfully leveraging the device for product success. Often there will be a limited period of exclusivity associated with use of the device (several years) before the device manufacturer can make the product publicly available. As is characteristic of the industry, collaboration is key to success in this regard.

<table>
<tr><th></th><th colspan="2">In-house</th><th>Outsourced</th></tr>
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Figure 3: Positives and negatives of in-house (modular and end-to-end) automation vs outsourced model manufacturing.

Supply chain concerns in cell-based therapy automation

SIG delegates concurred that PST supply chains were particularly high-risk owing to the potentially fatal consequences of the PST failing to complete its circular supply chain. Supply chain complexity was agreed to present high levels of risk across all cell types, and the need for simplification was thus agreed to be central to risk management. The two largest supply chain risk factors were batch mismanagement and manufacturing failure. Successful supply chain management requires robust and validated supply chain management software and hardware tools extending to a defined level of granularity. Low-level shipping studies should be undertaken at early clinical stage, with full and complete shipping studies by phase II or III, to ensure post-shipment products meet the specified criteria. Labelling is a crucial component in matching patients with their respective batch, allows individual batches and their constituent components to be traced from vein to vein. This level of control is a valuable capability when undertaking late-stage clinical studies, de-risking worst-case-scenarios and enabling contingency frameworks in the case of unexpected clinical complications.

Two technical opportunities were raised through which supply chains could be accelerated or de-risked, and the relative benefit of each varies across specific cases. Firstly, it was suggested that ‘smart packaging’ incorporating an electronic lock could secure an individual batch throughout shipping until QA/QC release were verified within the manufacturing facility, whereupon the batch could be remotely released. The strategy may be unnecessary in many cases but could offer valuable extensions to shelf life, or where QA/QC involves unusually high time constrains. Delegates foresaw a situation where fill and finish, shipping, and on-site release were automated across a single

platform.

The use of Bluetooth, WiFi, or RFID tags (in decreasing order of utility) were agreed as advantageous over a simple barcode when balancing ease of use against ability to communicate shipping conditions and the relative value of such control measures. Bluetooth controllers for individual shipping containers are cost-effective, disposable, and enable automated data transfer. It was agreed that always-on or highly granular shipping environment data reports are generally unnecessary, and that reporting the total parameter range at delivery is most often sufficient. Any data gaps while moving product between controlled environments were identified as a risk, particularly for cryopreserved products, and steps should be taken to control the environment throughout container transfer.

The level of supply chain management required by these strategies mandates a comprehensive, broad-reaching and validated quality management system (QMS). Some platforms offer solutions in this direction but none currently encompass the level of control required to implement the solutions proposed here.

Regulation

Automated manufacturing can facilitate ease of regulatory compliance and reduced FTE needs during regulator checks. Closed and automated processes, supported by in-process testing, are simpler and cheaper to validate and require fewer manual operators. However, the current innovation gap presents barriers. Specific areas of regulatory uncertainty were in chain of custody management (although not specific to automation), software validation, point-of-care manufacture, and the accepted methods and validation

of CPPs for QA/QC purposes. The use of CPPs in CBT manufacturing currently has no regulatory precedent and this must be managed to implement optimised automation.

Existing technologies offer some level of automation with varying degrees of flexibility and in-process testing opportunities. Any effort to leverage CPPs in defining a product or for QA/QC through existing systems must be validated with the relevant regulatory authorities on a case-by-case basis. It was agreed that sterility is the most demanding QC parameter, particularly considering the disparity in needs between the EU and US, and the duration of conventionally approved tests. Approval of rapid testing methods such as qPCR and similar methods may be necessitated for 'live' products relegated to critically sick patient populations. Delegates agreed that automation and CPP use may contribute to potential solutions through in-process sterility control, screening of raw and starting materials, and real-time release.

Conclusion

Automation in cell therapy manufacturing presents substantial opportunities to overcome many of the barriers to commercial success observed both historically and presently. Automation can de-risk many aspects of commercial success, including reduced operational costs (in particular by reducing the number of required FTEs), facilitate regulatory compliance, and improve process consistency. However, major technical and business strategy barriers exist to creating a scalable and automated manufacturing solutions (Figure 4). The level of CapEx required to design and fully implement automated bioprocesses may be unjustifiable at early stages of product development, but processes must be locked down before phase III trials. Therapeutics developers must be cognisant to avoid constricting their product to a small-scale manufacturing process, and

should ideally design automated systems from the earliest stage of development. Business strategy, investor, and technical staff should liaise closely around the adoption and implementation of automation into existing processes. Manufacturers are currently limited by the availability of technical solutions, and a major innovation gap exists around automated and scalable manufacturing. A lack of standardisation across software, hardware and specification design complicates automation efforts. To overcome these barriers, therapeutics developers must develop a deep understanding of their product's basic biology, mechanism of action, and CQAs, and leverage this understanding to develop a streamlined and efficient manufacturing process featuring validated in-process testing and controls. Process development and bioprocess automation should be undertaken following phase II trials at the latest, while many therapeutics developers aim to automate from preclinical process design stage. Implementing automation to existing product processes through a modular, unit function approach de-risks process development and its associated CapEx needs. Manufacturers should fully validate and justify the technical rationale behind in-process control parameters, and develop methods for their automation. Finally, investors and technical solutions providers should look to the innovation gap in cell therapy manufacturing as a commercial opportunity, and liaise closely with therapeutics manufacturers to design and develop appropriate automated solutions.

	Motivations	Barriers	Solutions
Technical	Consistency, reliability, traceability, predictive manufacturing	Biological understanding, equipment availability	Enhanced technical understanding, technical innovation
Strategic	Greater sales opportunities and competitiveness	CapEx justification in early companies, technical expertise	Outsourced manufacturing, technical innovation
Financial	Potentially lower manufacturing costs, including fewer FTEs	Higher upfront costs, more consumables	2nd generation automation, technical innovation
Regulatory	Faster/cheaper QA/QC & comparability, lower contamination risk	Poor precedent, little validation or standardisation	Communication with regulators, developing standards

Figure 4: Decision dynamics matrix for investing in cell therapy manufacturing automation. The exact strategy for automating any manufacturing solution is the product of scientific and technical, business strategy, capital and financial, and regulatory concerns.

(6) Acknowledgements

This publication is officially endorsed by: Achilles Therapeutics, Biolacuna, Cell and Gene Therapy Catapult, CellGenix, Celyad, Dark Horse Consulting Inc., ERA Consulting, Fraunhofer IPT, GE Healthcare, Kiadis Pharma, Lonza, MaSTherCell, MedCision, Medigene AG, MilliporeSigma, Miltenyi Biotec, PCT, Scottish National Blood Transfusion Service, Technische Universität München, Thermo Fisher Scientific. The authors would like to thank Phacilitate for organising the SIG Automation event, and in enabling and supporting discussions. The authors would also like to thank all those who attended the event and contributed to the conversation. This work was supported by Phacilitate.

(7) Disclosure of interest

Oliver Ball and Sarah Robinson are employees of Biolacuna Ltd, a company that

provides consulting services to life sciences companies. David McCall is an employee of Phacilitate, an events management company operating in the cell and gene therapy space. David Brindley is a Director of Biolacuna Ltd. Dr Brindley is a stockholder in Translation Ventures Ltd (Charlbury, Oxfordshire, UK) and IP Asset Ventures Ltd (Oxford, Oxfordshire, UK), companies that provide cell therapy biomanufacturing, regulatory, and financial advice to pharmaceutical clients (among other services). He is subject to the CFA Institute's codes, standards, and guidelines; this paper is provided for academic interest only and must not be construed in any way as an investment recommendation.

(8) References

None.

(9) Legends of Figures and Tables

(10) Tables and/or Figures

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