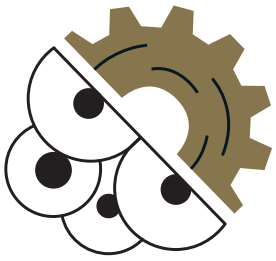


Phacilitate

Special Interest Group

AUTOMATION

The ROI of automation in cell-based therapy bioprocessing and supply chains

REPORT: EXECUTIVE SUMMARY

EXECUTIVE SUMMARY

Cell-based therapies (CBTs) are an innovative, cutting-edge field of medicine, and show immense potential to treat a range of serious and chronic diseases. Advances in basic cell biology and cancer immunology have synergised with genetic engineering and cell culture advances to produce a generation of new therapies. A range of cell types are being exploited, from embryonic stem cells (ESCs) to induced pluripotent stem cells (iPSCS) to adult stem cells (ASCs) and mature somatic cells. Chimeric antigen receptor T-cells (CAR-Ts) are the most commercially developed technology type; the extraordinary clinical results seen have attracted substantial investment, and two products are expected to reach the market this year. However, CBTs are intrinsically highly complex, often poorly understood, and can be prohibitively expensive to manufacture. Optimising the bioprocess solutions involved in CBT manufacture is therefore critical to commercial success, and automation is likely to play a substantial role in this.

Here we undertake an analysis of current bioprocess solutions for cell-based therapies, including extracellular vesicles, and investigate both their utility and amenability to automation. We investigate different models for implementing automation, the benefits of bespoke vs off-the-shelf bioprocessing, and decision making around integrated vs outsourced manufacturing. We carried out quantitative research on KOL attitudes towards various aspects of bioprocess automation, and conducted interviews with a number of industry leaders, generating insight into the current state of automation, and illuminating some of the challenges and opportunities within the field.

INTRODUCTION TO CELL BIOPROCESSING

CBT bioprocessing aims to establish reproducible and robust manufacturing and supply chain solutions. Producing CBTs for proof-of-concept research or clinical trials is usually achieved through small-scale, labour-intensive, and nominally defined bioprocesses. Translating this into a commercial-scale process capable of meeting regulatory requirements necessitates a better defined and scalable process, likely requiring substantial automation.

CBT therapies can be either autologous, whereby a patient's own cells are processed into a therapy which is then re-administered, or allogeneic, where donor cells are processed in large batches for the treatment of multiple patients. These two models hold vastly differing supply chain issues; while allogeneic therapies can generally achieve economy of scale through the use of larger bioreactors and higher volume throughput, autologous therapies must instead be scaled out through multiple parallel bioprocesses. Coping with the demands of each supply chain model on the commercial scale also depends on the cell type and thus specific bioprocess requirements, but in both cases, early consideration and planning around scalability is crucial, as is a robust quality by design approach and amenability to automation.

CELL TYPES IN CBTS

Two major treatment modalities exist in the CBT space; regenerative approaches using stem cell-based products aiming to repair and restore damaged tissues, and interventional approaches mainly in oncology which aim to intercept or prevent a disease pathology.

STEM CELLS AND REGENERATIVE MEDICINE

Embryonic stem cells (ESCs) can differentiate into any human adult cell type and have high potential for therapeutic application; however, their use is subject to ethical and technical complications, and few advanced therapies are ESC-derived. The inception of iPSC technology in 2006 allowed terminally differentiated somatic cells to be reprogrammed to a stem-like state. Despite a short history of technical safety concerns, iPSC-derived cells are now starting to enter the clinic. Adult stem cells (ASCs) are multipotent stem cells which give rise to a set of downstream cell types to replenish tissue-specific cell populations and are widely used either directly, or to derive cell types of therapeutic interest.

IMMUNE-ONCOLOGY AND IMMUNOTHERAPIES

Immunology and particularly immune-oncology are currently major focuses of CBTs. Dendritic cell vaccines were one of the first commercial oncology CBT products, with chimeric antigen receptor (CAR) T-cells and increasingly CAR natural killer (NK) cells now major areas of industry focus. Investment in CAR-T technologies currently dominate the CBT industry and at least two market approvals (from Novartis and Kite Pharma) are expected this year. Beyond oncology, CBTs are aiming to target autoimmune diseases and other pathogenic immunological over-activations. Further, T-regulatory cells and mesenchymal stem cells (MSCs) are in trials for autoimmune disorders and graft vs host disease (GvHD).

AUTOMATION IN BIOPROCESSING

Automation is a broadly defined concept and has complex implications. The underlying theme of automation in CBT bioprocessing is to substitute manual, labour-intensive steps with robotic or otherwise automated functions to lower operational costs, decrease the chance of batch failure, increase robustness, and improve product consistency. Automation is highly amenable to closed process manufacturing, process optimisation, and future scalability. Automated in-process testing allows up and downstream feedback and detailed end-to-end batch monitoring, identifying suboptimal process parameters for batch rejection or compensatory process modification. The complex and inherently variable nature of CBTs suggests that advanced levels of automation are paramount to optimally and consistently producing a well-defined product.

In this report, we highlight the need for deep product characterisation, process design, scalability, and thus automation from an early development stage. Process modifications such as implementing automation following late-stage clinical trials may require expensive and time consuming bridging studies, if not repetition of one or more clinical trials. Historical examples such as Provenge and ChrondroCelect, where market-authorised products have been commercially unsustainable due to labour-intensive and inefficient manufacturing, validate this rationale.

AUTOMATION IN TRACK AND TRACE

Tracking and traceability are vital elements of a high quality CBT supply chain, and strict regulations exist around tracing medicinal product batches. This can be particularly demanding in autologous supply chains, where a tissue sample must be traced vein-to-vein, from its original donor through the entire supply chain and back to the same patient. A quality system must be in place to minimise the risk of mismatching patients with their products, a potentially life-threatening failure. Supply chain automation in combination with barcode or RFID batch tracking, in combination with supply chain management tools such as TrakCel, offers an optimal solution.

The Drug Supply Chain Security Act (DSCSA) is gradually coming into force in the US, and requires end-to-end traceability on all medicinal products, requiring detailed tracking of each batch within the supply chain. The EU equivalent (Directive 2011/62/EC) legislated as the Falsified Medicines Act in the United Kingdom comes into force in 2018. Although cell-based advanced therapy medicinal products (ATMPs) are legally exempt, many CBT manufacturers may intend to voluntarily follow the directive.

AUTOMATION IN PROCESS OPTIMISATION

Foundational to the design of any good bioprocess is a comprehensive understanding of the cell product. A deep and comprehensive understanding of the cell biology behind a product and its mechanism of action is crucial to accurately identifying and testing key quality attributes (CQAs), and therefore designing critical process parameters (CPPs). CQAs are the core, defining characteristics of the cellular product deemed crucial to the intended function of the cell. CPPs are the testing procedures that must be undertaken throughout the bioprocess to ensure the CQAs are met by the finished product. Designing and implementing a valid and useful set of CQAs and CPPs does not require automation; indeed, these should be specified from the earliest stages, and should be constantly developed and refined throughout the research and development process. However, the implementation of automation offers a great opportunity for comprehensive and informative in-line CPP process tests, generating a valuable body of data that can be leveraged for process optimisation.

AUTOMATION IN BIOPROCESSING SURVEY

We undertook a survey of key opinion leader attitudes towards automation in CBT bioprocessing, developing a rich set of quantitative data on a range of issues. A series of interviews with key opinion leaders was undertaken, illuminating the state and extent of current CBT bioprocess automation. The relationship between investor-centric decision making and the need to consider early investment in bioprocess automation was analysed, and the utility of bioprocess automation across cell types was explored, stratified by major cell type or by cell adherence needs, plus extracellular vesicle bioprocessing.
A high-level analysis of the most important bioprocessing steps to automate was generated (Figure 1), showing substantial variation between bioprocessing needs across technology type. Final release testing, and process and media development, are major automation priorities for adherent cell types such as mesenchymal stem cells. The main expansion stage was identified as by far the most significant automation priority need for non-adherent cell types, followed by seed train expansion and volume reduction and washing.

Additional areas of investigation include:

- Stage of development to invest in automation for optimal return on investment, stratified by cell type
- Most important aspects of bioprocessing to automate both generally and for the optimal reduction in COGs
- Optimal bioreactor volume at which to implement automation, for both autologous and allogeneic therapies
- Analysis of modular bioprocess solutions versus bespoke

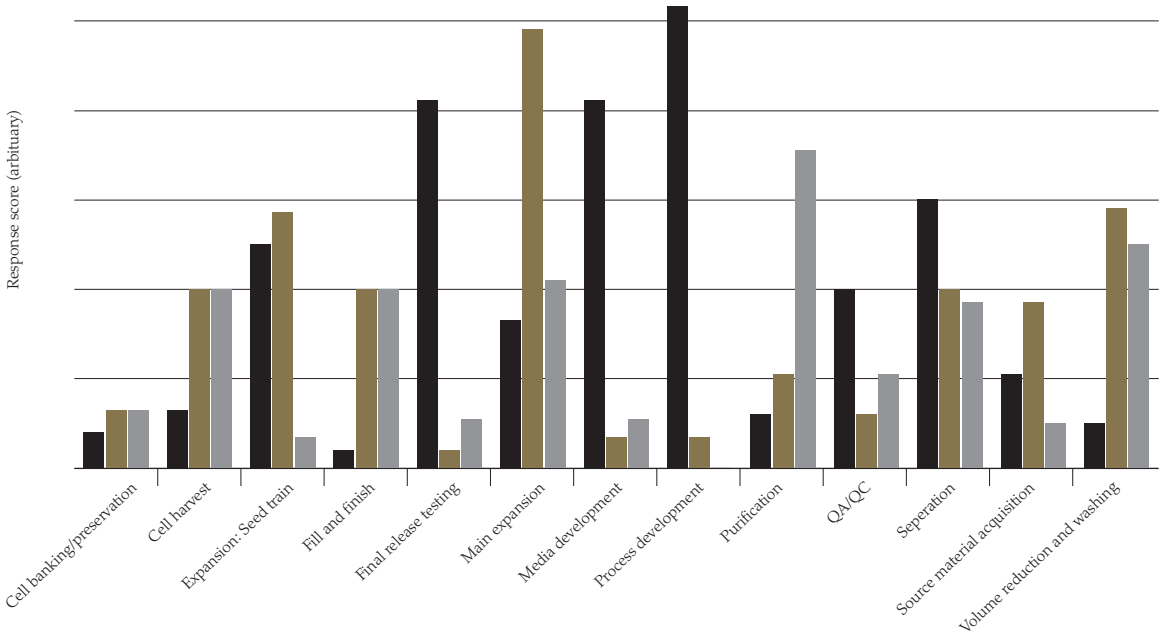
Through further questionnaire research and KOL interviews, we generated quantitative and informative data, exploring the implications and impact of automation on the following aspects of bioprocessing:

- Upstream and downstream supply chain issues
- Regulatory compliance
- Personnel change
- Manufacturing time per batch, stratified by major cell type
- Quality control and quality assurance
- Product quality, consistency, and purity
- Running costs and COGs

We assessed both the merit and drawbacks of either integrated manufacturing or outsourced, assessing the challenges and opportunities of each. No clear consensus can be demonstrably true in all cases; the decision must be made on a case-by-case basis depending on strategic intent and capital resource availability, and the report explores the major dynamics within this decision-making process.

FIGURE 1

WHICH BIOPROCESS ELEMENTS ARE THE MOST IMPORTANT TO AUTOMATE?



FUTURE OF CBT BIOPROCESSING

Our data highlight the importance of considering the amenability of an early-stage product process to scalability and automation from its conception. A quality by design, bottom-up and modular approach implementing automation where possible and allowing for later automation where not, provides a robust and futureproof design. A lack of available equipment for bioprocessing certain cell types, in combination with the rapid pace of innovation within the cell bioprocessing industry, mean that today's cell manufacturing solutions are likely to be outdated within 5-10 years- but manufacturers must also be able to meet clinical development and market manufacturing demands in the shorter term, while preparing for up-scaling. The report also investigates the potential for alternative supply chains such as bedside manufacturing, particularly in autologous therapies, how this might offer a step change improvement to many aspects of CBT commercialisation, and what the regulatory implications might be. Through leveraging KOL insights, we discuss the complex challenges facing CBT manufacturing and wider supply chain issues, and understand how automation may be deployed for their management. Several manufacturing centres are currently under construction and we assess the utility of their use for semi-virtual business models.

We describe the current state of automation within the CBT industry, explore the multi-stakeholder justifications behind these decisions, and speculate as to how these might change over the coming months and years.

CONCLUSION

This report offers deep insight to the varied and complex issues around bioprocess manufacturing and automation. Building context through an introduction to CBTs, the report discusses current and future CBTs, the cell types behind them, and their different bioprocessing needs. We find that current bioprocess solutions are generally insufficient for large-scale automated manufacturing, although the extent of this does depend on cell type and required level of manipulation. We identify cell selection as one of the most difficult steps to automate, and discuss the feasibility of automating other bioprocess steps.

Our survey gives quantitative data on a range of issues around CBT bioprocess automation, including the best time to invest for optimal ROI, the most important steps to automate, and how to reduce COGs most effectively. We find that off-the-shelf bioprocess solutions have major advantages including lower setup costs, amenability to process modification, and resilience to obsolescence, while bespoke solutions can have lower running costs and better technical support. KOL interviews identify the resistance of leading CBT companies to process automation and the reasons behind this, going on to discuss potential strategies for meeting market demand. The report offers valuable insight to any stakeholder looking to manufacture CBTs at scale and demonstrates how investing in automation at the right time can enhance ROI.