Cell micro-factories: Feasibility of a redistributed manufacturing model for cell based therapeutics

Background and Objectives

Cell- and tissue-based therapeutics (CATBTs) generate commercial interest due to their capacity to restore function and to resolve disease. Scientific attention concentrates mainly on the invention step and the results of early clinical trials. In order to maximise patient access and benefit it is important to provide economical processes that can be managed at a scale that is commercially meaningful. Investors now favour 'capital-efficient' proposals that do not place large amounts of money at risk by purchasing expensive bespoke apparatus.

CATBTs are sensitive to conditions of manufacture, storage and transport. They are complex products and a satisfactory analysis to specification is a necessary but insufficient condition for the assurance of quality and safety. Assurance of quality depends on conservation of the important properties, or 'Critical Quality Attributes' (CQAs), by careful control of the manufacturing process and supply chain. The supply chain can be expensive and time-sensitive; responsive manufacture that is coordinated with clinical use is preferred, especially if cryopreservation for transit can be avoided. This may make CATBTs good candidates for redistributed manufacturing (RDM). The study brought together experts from industry, clinical practice, academia and regulatory affairs. The study examined a range of alternative business and manufacturing models for RDM and identified features that will improve the probability of success. It also identified topics that warrant focused research. 'Cell Microfactories' took as its case study the manufacture of a simple injectable therapy comprising mesenchymal stem cells (MSCs) for cartilage repair.

Method

Three techniques were applied in the study. A semi-structured interview technique was used to examine the principles, practitioner needs and strengths and weaknesses of the current arrangements. Operational models were constructed using Structured analysis and Design Technique. Cost analyses were performed using Activity-Based Cost Analyses and Flowsheeting.

The examples used in the interviews comprised: a) large factory ('scale up') i.e. single owner, single Manufacturing Authorisation and Marketing Authorisation; b) Multiple, smaller factories ('scale out') i.e. single owner, multiple Manufacturing Authorisations, single Marketing Authorisation; c) 'local hubs' i.e. single or multiple owners, multiple Manufacturing Authorisations, single or multiple Marketing Authorisations (depending on whether or not the hubs are owned by the company that owns the product (the 'innovating company'); d) 'in-hospital', in which the microfactory may be either sold as a device to aid in practice of medicine or may operate as a licensable facility to make goods that are licensed as DPs; e) 'franchise' i.e. multiple owners, multiple Manufacturing Authorisations, single or multiple Marketing Authorisations depending on the degree of control by the innovating company. The questions were aimed at eliciting insights from the perspective of the interviewee. A carefully chosen panel of sixteen subject experts, covering regulatory affairs, clinical practice, bioprocess manufacturing research, regenerative medicine manufacturing industry and consultancy in healthcare operations were questioned in order to establish current perception of RDM for the sector.

Results (main topics for further research)

Quality control and timing of release of goods
In order to make maximal use of fresh preservation (i.e. to ship at ambient temperature or 37°C) it is necessary to make a decision on release of goods for use very quickly. In redistributed manufacture the batches are small and there may not be enough material to provide a suitable retained sample. Sterility tests take up to two weeks to perform whereas product release may be needed in a few hours. Currently there is a large reliance on visual inspection and automated, rapid detection systems would be much preferred, especially if they can be incorporated in the closed production vessel. This is the objective of moving to real-time release technology which is recognised as desirable by the regulators but is challenging to achieve and requires extensive data mining to provide compelling calibration data sets.

Compliance at the redistributed operation
Several interviewees referred to a common problem observed when sending out product to multiple sites. There can be poor operator compliance; users tend to use inappropriate discretion in their practice and deviate from the instructions. This introduces a business risk: with no retained sample and a sepsis incident as a result of poor administration of product to a patient the innovating company needs a method to protect itself from unjustified litigation by the user. A solution already in use is to provide a kit to collect the wash from the cells on administration. This is returned for sterility testing.

Process control and adaptive licensing
The other QC technology gap for redistribution is the difficulty in defining a robust relationship between CQAs and measurands selected for the potency assays that are needed for release of goods. In order for tests to be carried out quickly and economically the industry would prefer surrogates for potency based on robust data mining.

Training and accountability
The locus of accountability in the chain of custody is very important in order to retain the confidence of the regulator in ownership of responsibility at each step of the value chain. Strict demarcation of responsibility is therefore an essential feature. Under the Good Manufacturing Practice ('GMP') guidance training must be conducted at the outset and refreshed at regular intervals.

Authority for release of goods
Release of goods must be authorised by a senior quality professional; in the EU by a 'Qualified Person' or QP. In redistributed manufacturing this will be difficult to manage because the presence of a QP at every site would be prohibitively expensive. This raises the question of whether it would ever be possible to create an autonomous manufacturing machine with an automated system for analysis and release that was of sufficient reliability and reproducibility to satisfy the regulators. Currently regulatory authority in the EU grants a Manufacturing Authorisation to one legal entity at a time, typically the centralised company. Incremental addition of sites requires a challenging workload in terms of repeated validation. The alternative would be to regard a system delivering fully automated 'GMP-in-a-box' at a remote site as being an extension of the innovating organisation. Satisfactory credentials for justifying this arrangement are a valuable topic for future engineering and metrology research.

Economics of automated platforms
The acquisition of an autonomous technology platform will be expensive. Externalising the skills required for manufacture of a CATBT in a redistributed manufacturing operation will require closed microfactories of great sophistication. In order for such a machine to operate economically there must be satisfactory value release over the microfactory lifetime to justify the acquisition and maintenance costs. One way of ensuring that this occurs would be to create a flexible microfactory, capable of operating as a manufacturing technology platform for more than one innovating company. This raises the further challenge of whether it is possible to justify licensing a machine to make multiple products with related processing needs.

The Team

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