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Centralised versus decentralised manufacturing and the delivery of healthcare products: A United Kingdom exemplar

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Abstract

Background. The cell and gene therapy (CGT) field is at a critical juncture. Clinical successes have underpinned the requirement for developing manufacturing capacity suited to patient-specific therapies that can satisfy the eventual demand post-launch. Decentralised or 'redistributed' manufacturing divides manufacturing capacity across geographic regions, promising local, responsive manufacturing, customised to the end user, and is an attractive solution to overcome challenges facing the CGT manufacturing chain. *Methods.* A study was undertaken building on previous, so far unpublished, semi-structured interviews with key opinion leaders in advanced therapy research, manufacturing and clinical practice. The qualitative findings were applied to construct a cost of goods model that permitted the cost impact of regional siting to be combined with variable and fixed costs of manufacture of a mesenchymal stromal cell product. *Results.* Using the United Kingdom as an exemplar, cost disparities between regions were examined. Per patient dose costs of ~£1,800 per 75,000,000 cells were observed. Financial savings from situating the facility outside of London allow 25–41 additional staff or 24–35 extra manufacturing vessels to be employed. Decentralised quality control to mitigate site-to-site variation was examined. Partial decentralisation of quality control was observed to be financially possible and an attractive option for facilitating release 'at risk'. *Discussion.* There are important challenges that obstruct the easy adoption of decentralised manufacturing that have the potential to undermine the market success of otherwise promising products. By using the United Kingdom as an exemplar, the modelled data provide a framework to inform similar regional policy considerations across other global territories.

Key Words: *advanced manufacturing technology, cell and gene therapy, cost of goods, decentralised manufacturing, organisational change, quality control*

Introduction

Disruptive changes in advanced therapy manufacturing

Centralised manufacturing has been the dominant model for large-scale production of goods since the Industrial Revolution [1]. Centralising workers and materials to benefit from economies of scale was pioneered by the early 'Fordist' factories and allowed costs to be contained [2]. Increasing attention is now being paid to the potential for a network of decentralised production facilities to provide cell and gene therapy (CGT) manufacturing capacity [3]. In common with other regions of the developed world, the United Kingdom is under pressure to increase the efficiency of manufacturing, to create valuable professional-level jobs across all regions [4] and to reduce carbon footprint associated with the shipping of thermally controlled goods over long distances [5].

Decentralised manufacturing (DCM) divides manufacturing capacity across geographic regions and thus represents a radical departure for most existing healthcare supply systems. To achieve this, significant changes must be made to the traditional flow of materials and information and the aggregation of manufacturing processes [2]. Both centralised and DCM paradigms can be conceptualised as 'process

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modules' and the options for each can then be examined separately (Figure 1).

Despite the challenges in terms of batch reproducibility that decentralisation of manufacturing facilities may introduce [1], it remains an attractive choice in principle for manufacturing certain CGTs. This is primarily due to the perishability of these products and the limited options for storage and shipping making long-distance transit undesirable [6]. Additionally, products that require a late-stage customisation or 'mass customisation', such as a bio-printed three-dimensional (3D) scaffold, are particularly suited to being manufactured close to a clinical setting [7].

A decentralised network allows manufacturing to be located proximal to treatment centres and this dictates to some degree the geographical location. The social function of the DCM suite and associated treatment centres demands that they should be situated in the heart of the society that they serve. Similarly, accessibility is paramount and the centres must be within reach of their users. Using an out-of-town brownfield site or suburban estate, it may be cheaper to establish a traditional manufacturing centre, but these do not necessarily suit delivery of products to users. Defining the catchment areas for treatment is a first step in deciding the location [8], however, there are a multitude of other regional pressures and business operational concerns that affect the implementation of a successful DCM network.

The decentralised manufacturing 'Smart Factory'

Production of CGTs has different requirements from pharmaceuticals or biologics. Attempts to use existing manufacturing strategies have yielded poor outcomes [9,10]. With the rapid advancements in the technical capability for CGT manufacturing systems, the promise of large-scale, small-footprint manufacturing is becoming a reality through, for example, autonomous biological factories. The purpose of such a factory is to operate to a pre-defined set of process instructions via installed firmware programs to reduce operator discretion. It is this reduction of operator discretion that would reduce variability across a DCM network and is thus a critical requirement for success. The interconnection of industrial environments has been an area of intense systems engineering research. The exact terminology varies between stakeholders and includes "Smart Factories" (IBM), "Industrial Internet" (GE), "The Factory of the Future" (Airbus) and "Industrie 4.0" (Germany) [11,12]. The key themes include next-generation manufacturing, use of big data, automation, logistics and supply chain management, smart networks and communication. Together these describe an interconnected manufacturing value chain with equipment configurations able to respond autonomously to demands and pressures with minimal operator interaction.

Although there are promising candidate 'smart factory' solutions both commercially available and under development [13], there is currently no truly autonomous solution able to claim successes in all of these defining areas of a 'smart factory'. Of the commercially available systems [13], two platforms are available that, with further modification, could begin to fulfil the requirements or an autonomous 'smart micro-factory' suitable for DCM. These two exemplar platforms are described in Figure 2. Both provide semi-autonomous culture of cell products, but differ in their approach with one using existing culture technology (flasks) and mimicking human processes while the modular stirred tank reactor scales the process up to facilitate greater culture potential in a smaller footprint. This scale-up approach is undoubtedly more cost effective [14] and has the additional benefit of being simpler than flask-based approaches to enhance when developments in sensory and manipulation technology justify retrofitting such technology.

A UK case study of progress toward DCM

With an active and capable manufacturing workforce, an actively engaged single-payer healthcare sector and a strong commitment from central government to place advanced therapy manufacturing at the forefront of investment policy, the United Kingdom remains an attractive choice for a hypothetical DCM environment. The recent vote to leave the European Union has generated intense dialogue around the topic of the relationship between the United Kingdom and its markets overseas and how the United Kingdom may capitalise on arising opportunities. This has taken place mainly between government and other stakeholders and provides useful perspectives on how investment, manufacturing, technologies and healthcare pathways can be deployed to encourage the commercial translation of CGTs. This provides a valuable context for examining hypothetical DCM scenarios.

A number of key points recommended in the recent Advanced Therapies Manufacturing Action Plan from the UK Medicines Manufacturing Industry Partnership [15] resonate strongly with DCM. Key recommendations from the report include a comprehensive strategy to secure inward investment, generation and retention of both manufacturing capability and a talented workforce within the United Kingdom and finally using novel social and regulatory approaches to help grow businesses within the United Kingdom.

With the addition of the Cell and Gene Therapy Catapult Manufacturing Facility to the UK infrastructure and the assignment of funding to three new Advanced Therapy Treatment Centres (see below), the