REGenableMED

A Social Science Analysis of Regenerative Medicine

Regenerative medicine in the United Kingdom

Manufacturing

Policy Briefing October 2016

"How do you scale up? If it's autologous how are you going to manage a large number of parallel processes? If it's allogeneic how are you going to get the cell numbers that you need and actually culture them and keep them the same cell type if it's differentiation? - Industry expert.

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Overview

- Manufacturing represents a major challenge in regenerative medicine (RM), which spans scientific, engineering, regulatory and economic domains
- RM will require a range of novel or redistributed manufacturing 'micro-factory' systems
- Innovation is needed to develop cost-effective manufacturing platforms for producing large quantities of RM product
- The Cell and Gene Therapy Catapult's new manufacturing centre will provide sufficient GMP compliant capacity for phase 3 trial and commercial supply
- An ATMP Taskforce has been launched to identify ways in which manufacturing capability can be fostered in the UK
- EU guidelines for the GMP manufacturing of ATMPs have been greatly improved in response to public consultation. The new guidelines aim to account for the complexity of ATMPs while providing necessary flexibility
- Key priorities for policy are identified in the final section of this document

Background

REGenableMED (2014-2017) is an ESRC-funded social science project examining the ways in which institutions and agencies are interacting and 'readying' themselves for regenerative medicine (RM), focusing mainly on the UK. It identifies the various institutional, legal, social and political factors that enable and hinder the development of new RM/stem cell therapies. The aims of the project are:

1. To provide an overview of the current RM landscape in the UK, and also in the EU and US.
2. To explore how actors navigate logistical, legal, regulatory and reimbursement challenges.
3. To identify the challenges associated with the upscaling, and the implementation and dissemination of RM products in clinical settings.
4. To identify and explore the roles various stakeholders play in enabling the development and potential adoption of RM.
5. To identify common business models and their relationship to regulatory, social and political factors.
6. To predict how RM is likely to evolve, and provide recommendations aimed at supporting responsible research and innovation within RM

Manufacturing – Introduction

Regenerative medicine (RM) involves using cells, tissues, or genetic material to treat and manage disease. It represents a significant departure from conventional, drug or device based therapies, and it has been identified as having the potential to deliver major clinical and economic opportunities. In several countries including the UK, RM has been identified as an important element of their industrial strategy, and government-supported initiatives have been launched to facilitate the emergence of an RM industry.

A diverse range of RM products and procedures are currently under development, involving a range of tissue types, such as adult stem cells, human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs). Specifically, advanced developments include the T-Cell immunotherapies for cancers, gene therapies, the use of adult, bone-marrow derived mesenchymal stem cells (MSCs) for autoimmune conditions, chondrocyte implantation for cartilage repair, limbal stem cell transplantation for limbal stem cell deficiency, and hESC-derived retinal cells for the treatment of age-related macular degeneration (AMD). Some therapies entail using the patient's own cells or tissues (autologous), while others entail the use of material that has been expanded from an original donor (allogeneic).

The novelty of RM presents a range of innovation challenges, and there is some concern that the great promise of the field will fail to materialise. This Briefing reports on a major area of concern and activity that exemplifies the interconnected scientific, technical, regulatory and economic difficulties of the field: manufacturing.

The manufacturing challenge

The production of cell and gene-based therapies typically entails the isolation, modification and expansion of cell lines (and subsequent isolation of viral vectors in the case of gene therapies); processes underpinned by stringent quality control and assurance systems. The live, sensitive nature of the material means that this is a complex process, requiring new infrastructures and skills sets, and a new model of production that differs significantly from the 'Fordist' model of small molecule pharmaceutical production. First, tissues and cells are extremely responsive to surroundings: seemingly minor adjustments in their growing environment can drastically affect the safety and potency of the material. This places limits on how many cells can be grown within a single vessel. Second, the inherent variability within cell lines means that the 'chemicals' based concept of 100% 'product purity' and reproducibility may not be possible, or indeed desirable as different cells types interact and indeed may be needed for effective therapy. Additionally, for some projects there is uncertainty regarding which cell parameters are relevant to safety and potency and so need to be characterised when monitoring and adjusting production processes. Third, the 'shelf life' of this material is very limited, meaning that decentralised, distributed 'bed-side' closed system manufacturing models will be necessary, especially for autologous therapies. These raise complex issues for medical and hospital liability. Fourth, autologous therapies often require that the patient undergo preconditioning, meaning that the window of administration is narrow, leaving little scope for manufacturing delays or errors. Fifth, many of the currently available reagents and materials needed to carry-out such processes are high-cost and variable in quality. And additionally, current regulatory frameworks mean that the manufacturing of most RM products must take place within a clinical-grade Good Manufacturing Practice (GMP)-licensed facility. These are costly to maintain.

These challenges become most apparent as developers attempt to scale-up or scale out production. Pre-clinical studies and early, phase 1 & 2 trials require a small amount of RM product. Currently, such quantities are typically produced in labour-intensive, 'open systems' within small academic or hospital GMP-licensed manufacturing facilities. Phase 3 trials and commercial supply will likely require a much greater level of production and automation to drive down the cost of goods. If new systems are developed to produce the required quantity, it is necessary to carefully ensure that the final product is equivalent to the product trailed in the earlier stages. The development of such systems thus necessitates the establishment of suitable standards for assessing quality, potency and safety. However there are difficulties being experienced in adapting the chosen chemicals-based regulatory system to biological products and in developing standards and guidelines for cell manufacturing. Manufacturing challenges thus span scientific, engineering (including equipment design and fabrication), regulatory and economic domains of expertise, and interdisciplinary collaborations are necessary to develop cost-effective, large-scale manufacturing processes.

A government-supported ATMP taskforce has been launched to identify ways of fostering cell and gene therapy manufacturing in the UK. It is co-chaired by Ian Cubbin of GlaxoSmithKline, and it includes representatives from Pfizer, AstraZeneca, InnovateUK, ReNeuron, the ABPI and others. Three specific themes are being explored: technology and manufacturing; people, skills and training; and international competitiveness.

The UK context

Currently in the UK there are approximately 50 clinical trials underway of RM products or procedures. These are at phases 1 and 2, and thus involve a relatively small quantity of product, typically produced in labour intensive, open systems. There are 22 GMP facilities in the UK with the capability to manufacture cell and gene-based products.[i] These are operated by academic institutions, hospitals, and the NHS Blood and Transplant (NHSBT) service, and a small number by commercial institutions such as Oxford Biomedica and Cobra Biologics. These often operate as contract manufacturing organisations for other SMEs, and the financial viability of these facilities derives from their ability to be flexibly utilised for a variety of research and production applications. However if UK organizations use, for example, US contract manufacturers or those with geographically distributed manufacturing sites, this raises the

issue of EMA and FDA regulatory comparability and authorisation.

In many respects the UK has been well placed for the development of, and manufacturing of, cell and gene-based therapies at this earlier state in the developmental pipeline (phase 1 and 2 trials). It has considerable expertise in cell-biology, high-end manufacturing and electronics, and it has an improving culture of interdisciplinary collaboration, actively encouraged by funding bodies. Regenerative medicine has government support, and it is broadly supported by medical charities and industry associations. The presence of world-renowned, research intensive hospitals and the existence of the well-coordinated NHSBT provide an important platform for regenerative medicine. The latter in particular has considerable expertise in the handling of blood, tissues and cells, and negotiating relevant regulatory provisions, though primarily related to early phase trials. Proximity to continental Europe and excellent transport links mean that the UK is an attractive potential European hub for manufacturing, and the internationally well-respected regulatory climate of the UK can instill a sense of confidence in UK-based manufactured products.

However, there are specific concerns about the UK's manufacturing capability. There remain concerns about a lack of suitably-trained graduates to tackle manufacturing challenges,[ii] and current manufacturing capacity is inadequate: researchers have had to obtain material from EU and US centres. More significantly, the UK lacks manufacturing capacity required to produce the quantity of product that would be needed for phase 3 and commercial supply. This may discourage investment in RM in the UK, and it is unlikely that, at least initially, a commercially-operated facility of this size would be financially viable. Additionally, Brexit has created an additional sense of uncertainty that may discourage investment.

In response to the lack of manufacturing capacity, the CGTC is building a large GMP manufacturing centre at a cost of £55 million. It will be located in Stevenage which, due to its proximity to well-connected international airports, will enable suitably quick transportation of RM products throughout Europe. The facility will contain 12 operationally-segregated, flexible modules with 100m^2 of clean room space that can be rented by other organisations. The first six modules should be available for hire in 2017. The facility is expected to act as an important demonstrator for the "qualification of small-scale, automated facilities for GMP-compliant" manufacture of cell-based products.[iii]

Found among most if not all of the written submissions to the latest House of Commons Inquiry into RM is the call for not only a national strategy for RM, but also the establishing of accredited centres to deliver RM therapies. How these would align with a distributed manufacturing model is yet to be determined.

Regulation and manufacturing

The development and manufacturing of RM products is governed by several regulatory frameworks.

Within the EU, regenerative medicine products that entail the transfer and expression of genes, or the use of cells that have been substantially manipulated or which are used in a 'non-homologous fashion', and that are industrially manufactured in order to be placed on the EU market will fall-under the jurisdiction of the medicinal products regulatory framework (Directive 2001/83/EC), and more specifically the Advanced Therapy Medicinal Products (ATMP) regulatory framework. The framework stipulates that ATMPs must be approved at the European Level by the European Medicines Agency, including the Committee for Advanced Therapies (based on evidence of quality, safety and efficacy) before they can be placed on the market, and that all ATMPs must be manufactured in a GMP licensed facility. It is the responsibility of the Member State's national regulatory body – the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK - to ensure that facilities are licensed appropriately (Directive 2003/94/EC). Indeed, a manufacturing authorisation is required both for medicinal products (article 40, Directive 2001/83/EC) and investigational medicinal products (article 13, Directive 2001/20/EC). In that context, the European Commission is preparing guidelines on GMP specific to ATMPs. After a first public consultation in November 2015 that gave rise to 48 contributions, the guidelines have been deeply improved and opened to a new public consultation that ended

in September 2016. It aims to capture the complexity and risks associated with ATMPs manufacturing while recognising some flexibility necessary to the specific characteristics of their manufacturing. Products that are not classed as ATMPs, but which entail the use of human tissues and cells, will be governed by the Tissue and Cells Directives (2004/23/EC, 2006/17/EC and 2006/86/EC) which outline mandatory standards for sourcing materials. All facilities in which activities of testing, processing, preservation, storage or distribution of human tissues and cells intended for human applications are undertaken have to be accredited, designated, authorised or licensed by the national competent authorities (Article 6, Directive 2004/23/EC). In the UK, the Human Tissues Authority (HTA) and the Human Fertilisation and Embryology Authority (HFEA) are responsible for implementing these standards and for granting the tissues and cells establishments' licenses.

Regulatory provisions do permit the use of unlicensed ATMPs outside of clinical trials. The Hospital Exemptions provision enables non-routine use of custom-made ATMPs within a hospital, prescribed by a medical practitioner for an individual patient. The way in which this provision is actually applied by Member States has differed, and the MHRA has taken a cautious, conservative stance. In the UK there is also a 'Specials' scheme which permits clinicians to prescribe unlicensed products (which can extend to ATMPs) to meet the special (clinical) needs of individual patients. The MHRA is responsible for granting 'specials' and 'hospital exemption' licenses to manufacturing facilities, and in both provisions, the products must be produced under GMP conditions. The 'specials' scheme, unlike the hospital exemption one, permits products to be imported or exported.

Navigating the regulatory systems can be complicated, and the ATMP framework is generally seen as a regulatory hurdle for manufacturers and clinicians. Considerable costs are involved in adhering to the framework, potentially placing academic institutions and SMEs at disadvantage. Some special provisions have been established at EMA for SMEs (certification procedure, fees reductions, SME Office) but are not available to academic centres (this exclusion has been a point of contention). These considerations are probably one reason why currently many products under development seek 'orphan' status, which reduces the regulation fees required, and provides other regulatory incentives (protocol assistance, 10 years of market exclusivity). Although targeting only small numbers of patients with 'rare diseases', the particular and often unmet medical needs of those patients may also increase the willingness of commissioners to reimburse providers.

Given the high degree of technical uncertainty in the field, regulators encourage that manufacturers engage with them earlier in the development process. This is particularly true both at the European level at EMA, and in the UK where Innovation, Regenerative Medicine and/or SMEs Offices have been established.

Developments in bioprocessing

Ultimately the cost-effective, large-scale production of RM products will depend upon the development of automated, modular, closed-system manufacturing platforms. For many therapies, it is likely that such platforms will need to be redistributed and in some cases 'at the bedside' rather than centralised, so that material can be quickly transferred to and from the patient.

There are some automated closed-system technologies available on the market, some of which aim to approximate a 'GMP or clean room in-a-box' system. These include Miltenyi Biotec's 'CliniMACS Prodigy System', for example, which can be used for cell cultivation, separation and expansion in the production of T-Cell therapies. As of June 2016 there were 16 such systems being used in the UK. Similarly, the Terumo BCT Quantum system for cultivating adherent cells (e.g. MSCs), T Cells as well as viral vector production can be used to replace labour intensive flask-based systems, and they demonstrated cost savings of 40% when they scaled out from a 1 to 10 system process relative to manual manufacturing processes. Such systems, however, can have a high-upfront cost which can discourage their adoption during the early stages of product development, especially for SME which desire to reduce their cash-burn rates, and if such systems are adopted at a later stage, considerable validation work is required to ensure the product is comparable. 3D bio-printing – the development of which is

supported by the EPSRC – may open up new innovation avenues in bioprocessing.

Some UK-based research is being undertaken to explore manufacturing models and improve bioprocessing systems, with key centres of research being the University of Sheffield Advanced Manufacturing Research Centre, the Bioprocessing Research Centre at UCL, and the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine which includes the Universities of Loughborough, Keele and Nottingham. Recent studies of note include an EPSRC-funded feasibility study led by academics at Loughborough, which examined alternative manufacturing models in regenerative medicine.[iv] It noted that the benefits of centralised manufacturing are off-set by the high cost of logistics, while the benefits of decentralised manufacturing are off-set by costs of assuring quality control between sites. Further proposed research will seek to resolve this tension with the goal of identifying the economic 'sweet-spots' between the two. Loughborough academics have also been involved in developing a method for cost-modelling bioprocessing systems which can be used to inform the design of more cost-effective methods.[v] The method was also used to explore scale-up costs, noting that these are prohibitively high for many SMEs due to the marked increase in necessary validation costs.

Conclusion: priorities for policy

- It is necessary to anticipate how redistributed models of manufacturing might align with the consolidation of existing centres or proposals for newly accredited cell therapy clinical centres of excellence. Such systems will also raise complex liability issues for hospitals.
- Whether the model for such centres is similar to that found in fields such as IVF and transplantation needs to be determined.
- How such centres meet the needs of scale-up, automation and delivery will be key
- How existing/new GMP-licensed centres might link to the NHSE's Specialised Commissioning process needs to be explored especially since commissioning itself is to be more formally rationalised across NHSE and the UK more widely.
- Where centres are established, these will need to be close to universities that can provide training in both manufacture and related skills sets.
- Work needs to be supported related to the socio-technical and organisational structures that might be developed to reduce manufacturing costs while maintaining quality and safety.
- Scenarios for the likely size and profiles of clinical populations treatable through different manufacturing modalities and scales should be developed to support national planning.
- Development of product, process and manufacturing standards and guidelines needs to be encouraged.
- There is an ongoing need to adapt existing regulatory systems to the emerging needs of RM as more knowledge is generated.

REGenableMED Advisory Group:
Jacqueline Barry, Cell and Gene Therapy Catapult
Carol Bewick, Fight For Sight
Angela Blake, Pfizer
Edmund Jessop, NHS England
Panos Kefalas, Cell and Gene Therapy Catapult
Fiona Marley, NHS England
Kath Mackay, Innovate UK
Robert McNabb, Cardiff University
Tony Pagliuca, KCL, Clinical Lead for RM NHSE
Magda Papadaki, ABPI
Bernie Stocks, NHS England
Mike Sullivan, Innovate UK
Ahmed Syed, NHS England

Further Information on the REGenableMED project:
www.york.ac.uk/satsu/regenablemed/
email/correspondence:
andrew.webster@york.ac.uk

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[ii] See ABPI submission to the HoC Regen Med inquiry.
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