Regenerative Medicine: Navigating the Uncertainties

VALUE Project Final Report

March 2012

VALUE is a two year project sponsored by the Technology Strategy Board and conducted by a consortium of businesses and organisations actively engaged in research, development, commercialisation, adoption and financing of regenerative medicines. The aims of the VALUE project are to clarify the uncertainties currently hindering successful delivery of these promising new therapies to patients and to provide tools, guidance and recommendations for policy change to support the emerging UK regenerative medicine industry.

Technology Strategy Board
Driving Innovation

Project No: 100809
TP No: BZ010B

Table of Contents

EXECUTIVE SUMMARY **3**

PROJECT LEAD: CATHY PRESCOTT – BIOLATRIS LTD 3

PROJECT OVERVIEW **7**

CONTACT DETAILS FOR VALUE CONSORTIUM PARTNERS **9**

WHO BENEFITS, WHO PAYS?: BARRIERS AND POTENTIAL SOLUTIONS FOR ACCESS TO CAPITAL BY THE REGENERATIVE MEDICINE INDUSTRY **10**

LEAD AUTHOR: CATHY PRESCOTT - BIOLATRIS LTD 10

BY WHAT ROUTES WILL REGENERATIVE MEDICINE PRODUCTS BE INTRODUCED INTO THE NHS? **19**

LEAD AUTHOR: MARG PARTON – NHS TECHNOLOGY ADOPTION CENTRE 19

IS THERE A RAPID BUT ROBUST WAY FOR THE INDEPENDENT HEALTHCARE SECTOR IN THE UK TO KNOW WHETHER IT IS APPROPRIATE TO FUND REGENERATIVE MEDICINES? **29**

LEAD AUTHOR: GIN WARREN, CO-AUTHOR: BRIAN MATTHEWS - BUPA 29

REGULATION: WHAT ARE THE REAL UNCERTAINTIES? **35**

LEAD AUTHOR: CHRISTOPHER BRAVERY 35

WHAT ARE THE MAJOR ISSUES FOR DEVELOPERS OF CELL-BASED THERAPIES WHEN CONDUCTING CLINICAL TRIALS IN MULTIPLE COUNTRIES IN ORDER TO ACHIEVE REGULATORY APPROVAL AND REIMBURSEMENT? **47**

LEAD AUTHOR: PATRICK GINTY – LOUGHBOROUGH UNIVERSITY 47

WHAT ARE THE ALTERNATIVE MANUFACTURING AND SUPPLY MODELS AVAILABLE TO RM COMPANIES AND HOW DO THE FINANCES STACK UP? **55**

CO-AUTHORS: MARK MCCALL AND DAVID WILLIAMS - LOUGHBOROUGH UNIVERSITY 55

HOW DO COMPANIES ASSESS THE EFFICIENCY AND COST EFFECTIVENESS OF THEIR SUPPLY CHAIN EARLY ENOUGH TO MAKE A BUSINESS IMPACT? **66**

LEAD AUTHOR: SIMON ELLISON - NHS BLOOD AND TRANSPLANT 66

Executive Summary

Project Lead: Cathy Prescott – Biolatris Ltd

Progress of the regenerative medicine industry is currently hindered by a series of uncertainties. The VALUE consortium is a microcosm of the sector and over the past two years has gained an in-depth understanding of, and developed solutions to, many of the market barriers.

The VALUE project has delivered a series of tools to enable developers, manufacturers and funders to understand regulatory requirements, supply chain logistics and reimbursement decision processes. In addition, the project has developed an innovative model to understand critical manufacturing costs and initiated the development of a new investment paradigm; it has also identified areas of public policy that require further debate.

This report highlights key issues and provides viable solutions and recommendations.

Regulatory Highlights

- The fundamental issue is not the regulatory process, but an uncertainty as to the data that are required to establish quality, safety and efficacy of a cell-based therapy.
- There are regulatory issues that impact commercialisation of cell-based therapies principally relating to marketing authorisation and manufacturing.
- Subtle differences exist between EU and US GMP requirements and particular attention should be paid to sterile processing, documentation and quality control requirements.

Value of Outcomes to Industry

- Increased awareness and understanding of the regulatory requirements for cell-based therapies. The outcomes have delivered a series of tools:
  - PAS83 – legislation and guidance for developers
  - PAS84 – glossary of terms
  - PAS94 – Characterisation of human cells for clinical applications
  - Navigation tools that aid the teaching and explanation of concepts and issues to the developers.

Example Benefits to VALUE Partner(s)

- CAB Ltd – In depth analysis of regulatory specifications (EU and US) resulting in enhanced consultancy services, business development and increased efficiency of delivery.
- Loughborough – enhanced understanding of EU and US GMP regulations.
- Cell Medica and Quy - clarification of regulatory challenges and options for resolution.
- Biolatris and CAB Ltd – development of an integrated training program for industry (in progress).
- Pfizer – analysis of cell banking models with CAB Ltd.

Key Recommendations

- Raise the regulatory readiness levels for UK industry by investment in regulatory science and training. This could be delivered by the CATAPULT centre and the support of the Research Councils.
- Increase UK industry understanding of the issues relating to manufacturing at scale.
- Developers are recommended to take note of the regulatory consultation processes and become actively involved.

Adoption/Reimbursement Highlights

- The current pathway for adoption of innovative and disruptive healthcare solutions into the NHS is clear, but poorly understood and utilised by both industry and the NHS. This has a significant impact on the uptake of cell-based therapies.
- Development and adoption into practice by Bupa of the clinical decision algorithm for regenerative medicines.
- The commissioning process in the UK is currently fragmented and therefore the adoption of regenerative medicines in the UK is disadvantaged relative to countries with a national reimbursement mechanism.
- Risk sharing models for reimbursement should facilitate adoption of regenerative medicines.
- Some regenerative medicines will be applied as beauty therapies or cosmetic procedures. Self-pay clients of these are potentially vulnerable and naive purchasers and therefore may need regulatory protection.

Value of Outcomes to Industry

- Bupa has developed and adopted a clinical decision process for regenerative medicines.
- Bupa algorithm is available for adoption by all medical insurers.
- Clarity for cell-based therapy developers on the evidence and information requirements of different decision makers within the NHS and independent sector.
- Preparation of a 'How to Why to Guide' for Cytovir CMV which has the potential to be used as a paradigm for cell therapies targeted at orphan and ultra orphan indications.

Example Benefits to VALUE Partner(s)

- Clarity of the clinical decision process for Bupa.
- TiGenix – enabled reimbursement decisions by Bupa and other private insurers for ChondroCelect® and recommendation to seek NICE approval.
- Cell Medica – feedback regarding private reimbursement status and commissioning of a new 'How to Why to Guide' for Cytovir-CMV.
- Biolatris – increased awareness and education of factors that influence the independent healthcare sector and access to key opinion leaders.
- Quy – increased awareness of requirements to meet reimbursement criteria.

Key recommendations

- Healthcare providers can make use of the Bupa algorithm.

- Developers should note the requirement for high quality clinical research output on safety, efficacy and long-term follow-up.
- Formation of a single national commissioning structure for regenerative medicine products and procedures.
- Instigation of an education programme for commissioners regarding the unique aspects of regenerative medicines.
- Development of innovative reimbursement models for regenerative medicines whose benefits accrue over the long-term.
- NICE must ensure a robust and clear range of evaluation options and routes for disruptive technologies as they emerge from the regulatory process. Suitable comparators and clear indication of the effectiveness of the pathways that become available will be key to the evaluation process.

Finance Highlights

- Access to adequate capital on a timely basis continues to be a significant barrier to the regenerative medicine industry.
- An understanding of the full value of regenerative medicines and how this is leveraged will be key to access new finance.
- A clinical dataset continues to be the key factor that determines company valuation pre product market launch.

Value of Outcomes to Industry

- Understanding and awareness of factors that influence the rate and extent of market penetration facilitates early product development and thereby diminishes the risk of market failure.
- Recognition of the potential value of regenerative medicines in a major industry sector.
- Potential to raise new finance based on an innovative investment and business model.
- Value system's unit of scale-cost model provides an understanding of the impact of any significant changes relating to development, duration and cost.

Example Benefits to VALUE Partner(s)

- Biolatris – access to new industry partners and their commitment to provide resource to quantify the potential impact of regenerative medicines. Biolatris will continue to work with the new stakeholders. The development of new tools to support and enhance business development and access to further funding support.
- Quy – business strategy support.
- Biolatris and CAB Ltd – development of an integrated training program for industry (in progress).
- Biolatris and Loughborough collaboration allowed the development of the VALUE "value systems model".

Key recommendations

- Public funding for regenerative medicine companies is crucial, requires an efficient and timely decision making process and long-term commitment

- The level of funding and associate terms should take into account the current lack of venture or corporate funding

Manufacturing and Supply Highlights

- Critical links have been identified that exist between manufacturing practice, business strategy, regulatory burden and clinical demand.
- The unit of scale of manufacture is critical and it dictates what economies of scale can be achieved for products.
- The supply chain/logistics comprise a significant cost within manufacturing that is often under-estimated and must be considered within early stage product development.

Value of Outcomes to Industry

- The delivery of a computational model that predicts the cost, associated-risks and bottlenecks inherent in the cell-based therapy development process. This facilitates decision making for developers.
- A tool/algorithm to clarify supply chain requirements for all types of cell therapies.
- NHSBT has been able to develop a CMO business strategy to optimally serve the national and international regenerative medicine industry.
- The UK Department of Health and BIS acknowledge NHSBT as pivotal to the delivery of governmental strategy.

Example Benefits to VALUE Partner(s)

- NHSBT – enhanced understanding of customer requirements enabling the development and adoption of new procedures and business strategy to deliver high quality services to the cell therapy industry. This has the potential to attract overseas customers and establish the UK as the major manufacturing centre in Europe.
- Loughborough – development of proven approaches to value systems modelling within a broad context. Enhanced understanding of the manufacturing and regulatory requirements for near patient processes, complementing the direction of work in the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine.
- Quy, TiGenix and Cell Medica – clarity and optimisation of the supply chain requirements for products in development.

Key recommendations

- At an early stage, developers should undertake a holistic approach to estimate the manufacturing and supply chain costs throughout the product development cycle.
- The use of a structured cost framework, analytical cost models and simulation models, such as those developed in VALUE, can provide the ability to predict cost of goods supplied (COGS) and development costs.
- Manufacturing strategies requiring multiple manufacturing sites increase regulatory complexity and validation costs; these can be managed by using contract manufacturing organisations to exploit economies of scope.
- Therapies seeking to exploit near patient/point of care processing with cell expansion require new science in order to influence regulation to enable economies of scale that will permit alternative clinically pulled business models.

Project Overview

Background

This report summarises the detailed findings from VALUE, a two year project sponsored by the Technology Strategy Board that was completed in March 2012. The project was conducted by a consortium of businesses and organisations actively engaged in research, development, commercialisation, adoption and financing of *regenerative medicines. The aims of the project were to clarify the uncertainties currently hindering successful delivery of these promising new therapies to patients and to provide tools and guidance to support the emerging UK regenerative medicine industry.

Approach

The project initially focused on four major areas of uncertainty (regulation, finance, reimbursement and manufacturing/supply) and these formed the basis of distinct work packages. Work in these areas was informed by the development of product specific case studies which provided real world insights and experiences to the development of work package outputs. The methods used included analysis of company specific and public domain data, interviews, information gathering at conferences and through literature searches and lively debate within the project. The areas of uncertainty have been crystallised into a series of key questions for reporting purposes (see below).

Key Questions Addressed by the VALUE Project

- **Who benefits, who pays?: Barriers and potential solutions for access to capital by the regenerative medicine industry** *Lead: Cathy Prescott Biolatris Ltd*
- **How are reimbursement decisions for regenerative medicines made in the independent sector?** *Lead: Gin Warren. Co-author: Brian Mathews – Bupa*
- **By what routes will regenerative medicine products be introduced into the NHS?** *Lead: Marg Parton NHS Technology Adoption Centre*
- **Regulation: What are the real uncertainties?** *Lead: Christopher Bravery Consulting on Advanced Biologicals Ltd.*
- **What are the major issues for developers of cell-based therapies when conducting clinical trials in multiple markets in order to achieve regulatory approval and reimbursement?** *Lead: Patrick Ginty Loughborough University*
- **What are the alternative manufacturing and supply models available to RM companies and how do the finances stack up?** *Lead: Mark McCall Loughborough University Co-authors: David Williams Loughborough University*
- **How do companies asses the efficiency and cost effectiveness of their supply chain early enough to make a business impact?**
  Simon Ellison NHS Blood and Transplant

In addition, a selection of product case studies is provided in the Appendix to this report as a further source of information to regenerative medicine stakeholders.

Four product categories were identified for case study development:

1) Non-medicines: Lead- Karen Hodgkin, Cell Medica Ltd

2) Autologous Products: Leads: James Blann, TiGenix and Paul Ripley, Quy Biosciences Ltd

3) Allogeneic Products: Lead Tim Allsopp, Neusentis (Pfizer)

4) Other Products: Lead Patrick Ginty, Loughborough University

Reporting of Project Outcomes

Specific outputs from the project include recommendations to policy makers and the regenerative medicine community, publications and new tools to support decision making, product development strategy, therapy awareness, business development and information sharing. This report provides a detailed summary of the work conducted by the VALUE consortium and the project outcomes some of which were shared at a public meeting on Friday February 24th, 2012. VALUE event 24FEB2012 Meeting materials

Dissemination of the project findings continues via national and international conference presentations and posters, peer reviewed publications, briefing sessions with key stakeholders and through the ongoing business interactions of the VALUE consortium partners.

Contact details for the authors are provided on the following pages for further information and debate on conclusions offered.

*Regenerative medicine is a broad term which encompasses not just cell-based therapies but also some recombinant proteins and possibly even small molecules. For the purposes of this report,' regenerative medicine' refers to cell-based therapies (also variously referred to in this report as cell-based medicinal products (CBMP), cell therapies, cellular therapeutics).

Contact details for VALUE Consortium Partners

VALUE Partner	Contact details	Organisation
Cathy Prescott Project Leader	cprescott@biolatris.com www.biolatris.com	Biolatris
Christopher Bravery	T: +44 (0)20 7159 0864 M: +44 (0)7773 427460 cbravery@advbiols.com www.advbiols.com	Consulting on Advanced Biologicals
Gin Warren	T: +44 (0)20 7656 2049 Virginia.Warren@bupa.com www.bupa.co.uk	Bupa
Brian Matthews	T: +44 (0)20 7656 2113 brian.matthews@bupa.com	
Margaret Parton	M: +44 (0)7748 115404 marg.parton@gmail.com www.ntac.nhs.uk	NHS Technology Adoption Centre
David Williams	T: +44 (0)1509 227668 D.J.Williams2@lboro.ac.uk www.lboro.ac.uk	Loughborough University
Patrick Ginty	T: +44 (0)1509 564890 P.J.GINTY@lboro.ac.uk	
Mark McCall	M: +44 (0)7814 338311 m.mccall@lboro.ac.uk	
Simon Ellison	T: +44 (0)1865 440012 M: +44 (0)7515 761089 Simon.Ellison@nhsbt.nhs.uk www.nhsbt.nhs.uk	NHS Blood and Transplant
Karen Hodgkin	T: + 44 (0)20 7554 4070 Karen.hodgkin@cellmedica.co.uk www.cellmedica.co.uk	Cell Medica
Tina Crombie		
Paul Ripley	T: +44 (0)1233 758410 paul@ripleyconsulting.co.uk	Quy Biosciences Ltd.
Jo Miller	www.vetcell.com	
James Blann	M: +44 (0)7788 745752 James.blann@Tigenix.com www.tigenix.com	TiGENIX Living Medicines
Tim Allsopp	T: +44 (0)1304 643483 M: +44 (0)7803 584066 www.pfizer.com	Neusentis Pfizer
Val Lucas Project Manager	val.lucas@gmail.com	Downbarton Consulting

Who benefits, who pays?: Barriers and potential solutions for access to capital by the regenerative medicine industry

Lead Author: Cathy Prescott - Biolatris Ltd

1. Background

A major challenge facing the regenerative medicine industry is the need to access adequate levels of funding in a timely fashion. However, access to capital is an increasing challenge as global biotech investment trends (1) have shown a steady decline over the past years reflecting the impact of the economic crisis (2), increased competition by other sectors such as the technology sector (3) that generate favourable returns over short-time scales (4), volatile IPO (Initial Public Offering) markets and increasing regulatory demands for clinical safety and efficacy.

The goal of this work was to identify the barriers and potential solutions for access to capital by the regenerative medicine industry by addressing the following:

1. Understand and compare the current biotechnology and regenerative medicine business models and strategies;

2. Understand the current biotechnology investment trends, models and drivers and how these impact investment in to the regenerative medicine sector;

3. Identify the benefits and challenges unique to regenerative medicines and align these with relevant stakeholders.

4. Define an alternative investment and business model.

2. Approach Used

A series of proprietary tools were developed during the course of this programme in order to support the deliverables.

1. A finance database of dilutive and non-dilutive sources of funding available to UK-based biotech companies. The database includes details of available funds according to their size, and where relevant, the diversification limit and investment mandate including stage (e.g. seed, early, expansion), geography (regional, national, international) and focus (e.g. biotechnology, medtech, diagnostics). The database includes an extensive collection of relevant reports and links to source materials that track biotech investment trends in the UK and US. Investment in to the UK-based regenerative medicine companies is also tracked according to the source (Figure 1).

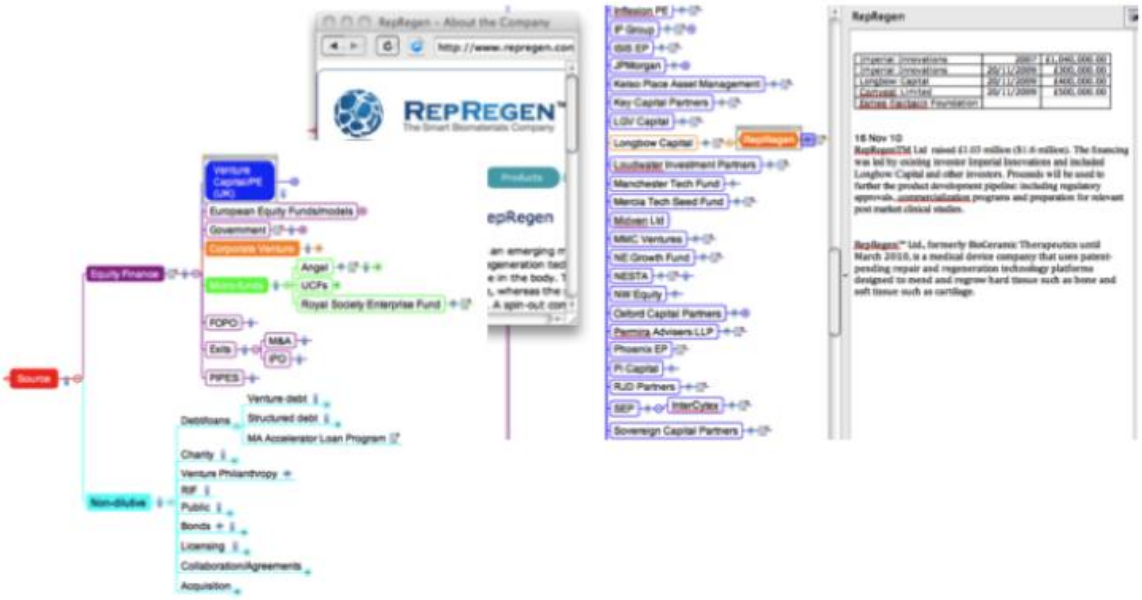


Figure 1: Extract from the finance database showing a portion of the venture capital/private equity funds and associated data linked to a regenerative medicine company (Repregen).

2. A database of contacts categorised according to key sectors (e.g. finance, industry, professional, public sector, charity and trade associations). Each sector is sub-categorised (e.g. finance includes investment banks, corporate funds, debt, angels, venture capitalists, public sector finance, not-for-profit and advisors) to facilitate rapid data retrieval.
3. A library of reference materials linked to stakeholders and value drivers identified though interviews with key opinion leaders and desk research (Figure 2).

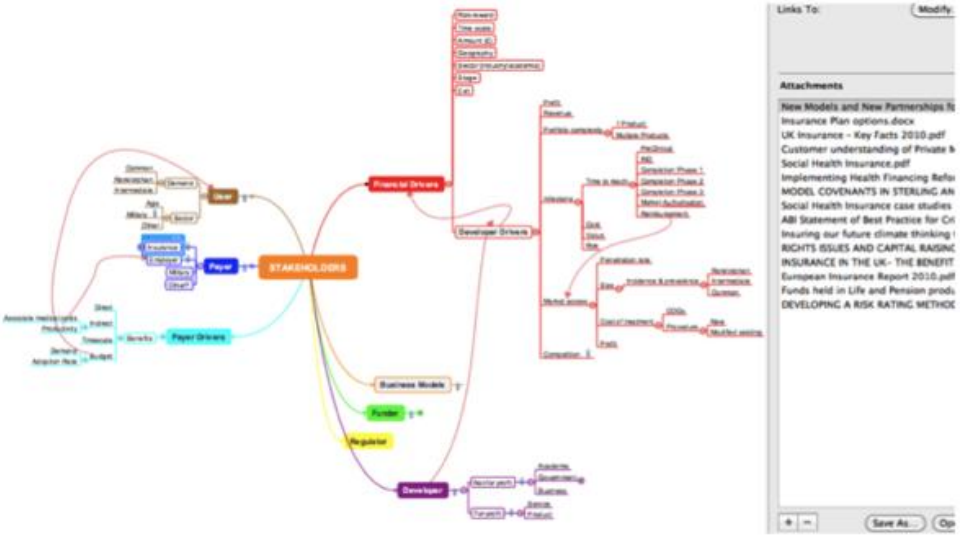


Figure 2: Extract from the stakeholders and value drivers map with an example of reports related to the insurance industry (top level).

3. Results/Conclusions

Barriers to raising finance by the regenerative medicine sector

- Investments include a degree of risk and therefore risk management is a key part of the decision-process. The route to market for traditional therapeutics ('soluble factors') is relatively well understood (5) and investors are able to make informed decisions regarding anticipated funding requirements, time and route to exit and risk management. For regenerative medicines many investors perceive the route to market to be poorly understood, the risks unknown and therefore present a challenge for risk management.

- Investors are becoming increasingly risk-adverse resulting in a skew towards companies with at least one product in clinical phase 2 or later (6). Consequently raising funds for many early-stage companies is an increasing challenge (the 'valley of death').

- BVCA data (7) show that in 2010 the UK biotechnology sector attracted just 1% of overall technology investment activity by BVCA members (relative to 5% in both 2009 and 2008). The number of biotechnology companies receiving investment increased in 2010, however the actual amount invested fell by 26% relative to 2009 and by 34% relative to 2008.

- According to the 3Q 2011 MoneyTree report, overall investments in the Life Sciences fell 18% in dollar terms and 21% in deals representing a decline to the second lowest quarterly deal volume since the first quarter of 2005.

- A trade-sale is the preferred exit for many biotech investors (6). To date the large pharmaceutical corporations have only engaged in a relatively limited way in the regenerative medicine sector (8,9,10) thereby diminishing the prospects of a trade sale. Furthermore, a lack of endorsement by a third party for the underlying technology may also have a negative impact on an IPO valuation. Accordingly the current venture capital model is at best, sub-optimal for investment in regenerative medicines.

- The pharma industry is reticent to engage in the regenerative medicine sector for one or more of the following reasons (10):
    - (i) the relative lack of clinical and safety data;
    - (ii) high manufacturing costs that challenge the success of gaining reimbursement and a viable profit margin;
    - (iii) the lack of familiarity with regard to the commissioning and adoption processes and,
    - (iv) the basis of a viable business model

- US-based companies are able to access significant levels of debt finance. The BVCA reported that approximately 67% of all US start-ups employ venture debt, equating to approximately $2-3bn per year for venture capital backed companies. Financial analysis of the debt/asset ratio for a series of US-based public regenerative medicine companies (Figure 3) (based on annual reports between 2006 and 2009) showed that debt finance is a key source if capital.

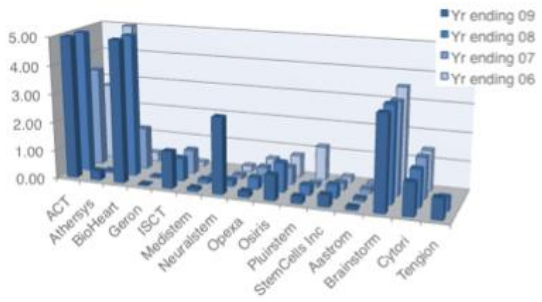


Figure 3: Historic trend data of debt/asset rations for US-based public companies focused on developing regenerative medicines.

- Access to debt finance by the European biotechnology sector has significantly declined in recent times (11). European biotechs secured the least number of overall loans due to the size of loan required (typically £5m) and the risks associated with any one fund being dominated by large loans: if the loan is written off this would result in a loss of both the upfront investment as well as the money that could have earned by recycling that investment into more companies from the fund. Cellerix SA (merged with TiGenix Feb 2011) did raise €10m in debt financing in 2008 (12).

- Characteristic of the biotech sector, regenerative medicine companies deploy a wide range of business models including:
    - (i) Early stage virtual business models contracting clinical research support from the academic or professional sectors;
    - (ii) Public-private partnership models including those with no basic research and funding dedicated to clinical development;
    - (iii) Mixed product and service business models, typically with multiple alliances and key pipeline agreements to source innovation.

- Some US investors are moving towards an asset-centric model to minimise investment risk and promote a trade sale exit (unencumbered by 'staff'). This model would not be suited to buyers seeking to gain access to the regenerative medicine sector through acquisition of expertise.

Benefits and challenges unique to regenerative medicines

- The spiralling cost of health care is a global economic challenge (Figure 4) (13). By 2020 US national health spending is expected to reach $4.6 trillion and comprise 19.8% of GDP (14). National healthcare expenditure in the UK is estimated to rise by 12% from £118bn in 2010 to £133bn by 2015 (15).

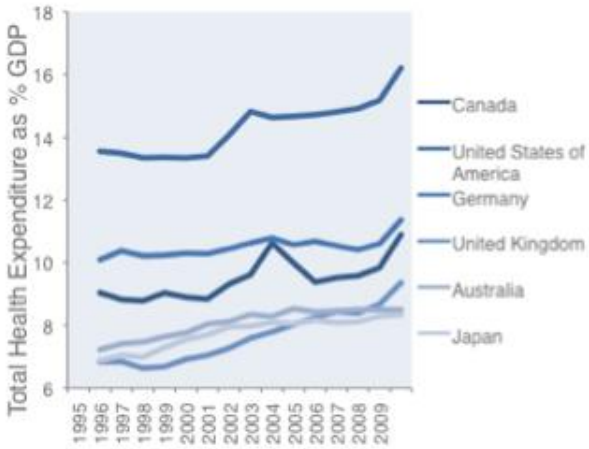


Figure 4: Total healthcare expenditure as a percentage of GDP for selected nations.

Increasing healthcare expenditure is due to one or more factors including:

- The increasing incidence and prevalence of chronic diseases (13). The number of people in England with chronic conditions is predicted to rise from 15.4 million in 2010 to 18 million by 2025 (16).

- Patients with multiple chronic conditions cost up to seven times as much as patients with only one chronic condition (17,18).

- Poor compliance by patients with long-term treatment regimes and the lack of adherence to requisite improvements in lifestyle.

- A shift in the number and relative size of the ageing population (19), which also account for approximately 75% of overall health expenditure (20).

- Increasing demand for and availability of high-tech and new medical innovation. Approximately half of the increase in medical cost increase is driven by new health care technology (21).

- Increasing R&D costs and declining success in bringing new drugs to market (22). Furthermore, only 2 of 10 marketed drugs are reported to have returned revenues that match or exceed R&D costs (23).

- Currently chronic conditions cannot be cured and so are controlled with the use of medication that enables patients to manage their disease over the long-term.

- Regenerative medicines have the potential to restore the function of a diseased or damaged tissue and thereby offer a cure for chronic diseases.

- Restoration of function is predicted to delay the timing of on-set of the co-morbidities – representing a potential cost-saving benefit (accrued over time).

- A viable business model depends on multiple factors, including the ability to manufacture products that are eligible for reimbursement; generate a profit-margin sufficient to recover R&D-costs (and for a profit-based business, exceed these cost), and the extent and rate of market penetration.

- For those cell-based products where high manufacturing-costs may pose a major challenge the Headroom Method (24) provides a means to estimate the maximum cost for a technology to be considered cost effective, which can be applied at the early stage of development. The maximum cost can be used as one of a series of assumptions to model the relationship between the extent of market penetration and profit margin (across a range of costs for the interventional procedure including manufacturing costs) required to underpin a viable business model.

- Market access governed by both social- (e.g. NHS, Medicare, Medicaid, Veterans Health Administration) and private (e.g. Bupa) healthcare providers may represent a challenge for regenerative medicines whose benefits accrue over extended periods of time. In the UK, long-term care of chronic diseases is managed within the NHS and not by private medical insurance. In principal the NHS has a lifetime perspective on the patient whereas private medical insurers (PMIs) have a short-term perspective with contracts renewed on an annual basis and individuals typically remaining with any one insurer for 3-5 years (slightly longer for group insurance).

- Regenerative medicines aim to restore function, and therefore have the potential to shift the paradigm for a chronic disease requiring long-term care to a one-off (or a limited number) interventional procedure which could in principle, meet the criteria for private healthcare.

- Although the NHS has a long-term perspective on a patient, budgets are managed on an annual basis. Therefore, if a treatment is relatively expensive and benefits (and risks) accrue over timescales that go beyond the budget cycle, then adoption may be compromised due to the pressure to allocate limited resources to maximally benefit the population. Whilst the budget may be less restricted within the private sector, if treatment costs reflect benefits that accrue over timescales beyond the length of the contract, then this maybe a disincentive to pay for treatment. Resolution of this challenge may be achieved by the introduction of creative reimbursement models such as ratcheted payments made over time.

- Allocation of limited resources may mean that the level of demand for an effective but relatively expensive treatment becomes an issue of ‘affordability’.

- Treatment for a rare or orphan disease is likely to have a minimal impact on a budget and the decision switches from a financial to political one: healthcare providers being careful to avoid negative publicity if a treatment is withheld. This is particularly true in the US where patient advocacy groups are powerful lobbyists.

- Treatment for prevalent disorders, and especially those chronic disorders which represent the leading causes of death and disability (25) (e.g. stroke, cardiovascular diseases, Chronic obstructive pulmonary disease, diabetes) means high demand for an expensive treatment would have a major economic impact and risks becoming a ‘budget buster’.

- Economic risk, as well as the risks linked to treatments that are not as effective in practice as the clinical efficacy data (the efficacy-effectiveness gap) (26) may be managed by the healthcare provider by limiting the use of a therapy to a subset of eligible patients and/or by seeking to off-set some of the burden of cost. The latter is achieved by either sharing some of the treatment costs with the developer or by not paying for non-responders. The National Institute for Health and Clinical Excellence (NICE) and NHS have already established a precedent of creative reimbursement for Lucentis, Velcade, Sutent and Revlimid, amongst others (27).

- The shift in liability to the developer has implications in terms of the cost and need to monitor patient compliance with the treatment regime. Poor-compliance maybe less of an issue for cell-based interventions administered in a clinical setting and over shorter periods of time.

- The primary economic burden of chronic disease is due to the loss of productivity rather than expenditure on healthcare (28). If regenerative medicines improve health, enabling a return to work and reduce the dependence on social care, then their cost-effectiveness could take into account cost savings and productivity benefits. However, generating the evidence based value proposition would pose a major challenge and significantly increase the cost and complexity of clinical trials.

- In the US, employer-sponsored insurance (ESI) is paid for by businesses on behalf of their employees as part of an employee benefit package. ESI plays a major role in financing US healthcare, representing over 60% of the non-elderly population and accounts for 90% of the private insurance market (29). Major employers determine the terms of their group insurance which, is typically retained for longer than individual insurance. Employers have a vested interest in worker productivity and therefore, be incentivised to include the use of regenerative medicines under the terms of the insurance policy. Similarly, the department of work and pensions should have a vested interest in any productivity-benefits arising from regenerative medicines.

An alternative investment and business model

Development of a new investment and business model has been dependent on gaining insight into:

- Supplier and demand priorities and why the current venture funding model is suboptimal;
- The potential benefits of regenerative medicines and how they could influence the value of existing products and services;
- The route to quantify the value proposition in order to determine whether the value is sufficient to incentivise a new/potential stakeholder to support the development and adoption of regenerative medicines;
- Options to leverage the value proposition.

This work has led to the identification of a potentially new stakeholder group who have undertaken an initial assessment of the proposal and subsequently agreed to work with Biolatris to quantify the value proposition and if successful (i.e. of sufficient value), explore

how the value could be leveraged. The work is commercially sensitive and therefore the outcome of this deliverable is not available at this time.

4. Recommendations

- Public funding for regenerative medicine companies is crucial and requires a long-term commitment. The level of funding and associate-terms should take in to account the current lack of venture or corporate funding.

- Regenerative medicines have the potential to 'cure' a chronic disease and delay the timing of on-set of co-morbidities (cost-saving benefit). Designing and implementing complex clinical trials over extended periods of time has significant cost and cash flow implications for the industry. Investment is therefore recommended to:
    - Identify and validate affordable predictive biomarkers and;
    - Develop a reference source of key value outcome measures for disease-related clinical care pathways.

- Benefits that accrue over time (beyond the fiscal cycle) or for which the cost and demand are anticipated to be high (the 'affordability issue'), may benefit from the development of innovative reimbursement models such as a staged payment scheme. Staged payment maybe either:
    - from the healthcare provider to the developer (relative to outcomes e.g. payment by results/cost savings) or
    - if staged payment is not a viable option for the developer (i.e. 'low profit margin'), then payments could be negotiated between a central account holder (Treasury?) and the healthcare provider.

- Regenerative medicines have the potential to shift the paradigm for a chronic disease requiring long-term care to a one-off (or a limited number) interventional procedure. If successful, the chronic disease market could be targeted by the PMI sector.

5. What are the benefits of these findings to the UK regenerative medicine industry?

- Increased awareness of the potential of regenerative medicines to impact a new stakeholder group.
- Preliminary assessment of the potential value of regenerative medicines on products and services. The assessment has led to the agreement to commit resources to work with Biolatris to quantify the value proposition.
- New model for investment and business that has the potential to address the current funding gap and drive the development of new products.
- Innovative reimbursement model may increase market penetration.

6. References

1 Yang, W. (2011) Biotech plummets in 3Q11. Nature Biotechnology 29, 962.

2 Ernst and Young: Beyond borders: global biotechnology report 2011.

3 JP Morgan Market Insight (2011): Why Invest in the Technology Sector?

4 FierceBiotech (April 2011). VCs: Chill sets in on biotech as social networking gets hot. http://www.fiercebiotech.com/story/vcs-chill-sets-biotech-social-networking-gets-hot/2011-04-05

5 FDA Review.org: The Drug Development and Approval Process http://www.fdareview.org/approval_process.shtml

6 HMB Pharma/Biotech M&A Report: 'Trade Sales of Pharma and Biotechnology Companies H1 2011'.

7 BVCA Private Equity and Venture Capital Report on Investment Activity 2010.

8

9 Prescott, CD (2010) Investing in Regenerative Medicine: What Drives the Investor? In The Delivery of Regenerative Medicines and Their Impact on Healthcare eds Prescott, CD and Polak, J. CRC Press ISBN 9781439836064.

10 McKernan, R., McNeish, J. and Smith, D. (2010) Pharma's Developing Interest in Stem Cells. Cell Stem Cell 6, 517-520.

11 BVCA Report (2010). The Rise of Venture Debt in Europe.

12 Cellerix Press Release (2008) Cellerix obtains a 10M€ debt facility with ETV. Capitalhttp://www.cellerix.com/content/view/full/280

13 World Health Organisation: Global Health Expenditure Database.

14 Centers for Medicare & Medicaid Services National Health Expenditure Projections 2010-2020.

15 UK Public Spending http://www.ukpublicspending.co.uk/index.php

16 Department of Health (2008): Raising the Profile of Long-Term Conditions Care.

17 The US Department of Health and Human Services Research in Action, Issue 19: The High Concentration of U.S. Health Care Expenditures.

18 Sultan, N. Payment-by-Outcome in Long-Term Condition Management. A report by 2020 Public Services Trust.

19 US Census Bureau: Projections of the Population by Selected Age Groups for the United States: 2010 to 2050

20 Centers for Medicare & Medicaid Services: Health Expenditures by Age (2004).

21 Swiss Re Centre for Global Dialog (2010) Risk Talk on Medical Innovation.

22 Citeline Intelligence Solutions (2011): Pharma R&D Annual Review 2011.

23 Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2011 (Washington, DC: PhRMA, April 2011).

24 McAteer HL, Lilford R (2009). Investing in Medical Technologies: the Headroom Method Brochure.

25 World Health Organisation The 10 leading causes of death by broad income group (2008) http://www.who.int/mediacentre/factsheets/fs310/en/index.html

26 Eicher, HG., Abadie, E., Breckenridge, A., Flamion, B., Gustafsson, LL., Lefkens, H, Rowland, M., Schneider, CK and Bloechl-Daum, B. (2011) Nature Reviews Drug Discovery 10, 495-506.

27 NICE Guidelines http://guidance.nice.org.uk/

28 DeVol, R. and Bedroussian, A. with Anita Charuworn, Anusuya Chatterjee, In Kyu Kim, Soojung Kim and Kevin Klowden (2007) An Unhealthy America: The Economic Burden of Chronic Disease.

29 The National Bureau of Economic Research: Employer-Sponsored Health Insurance and Health Reform.

By what routes will Regenerative medicine products be introduced into the NHS?

Lead Author: Marg Parton – NHS Technology Adoption Centre

1. Background

It is well documented that the UK NHS is a late and slow adopter of innovation both in terms of technologies and procedures. From the initial Wanless report in 2002, through to the latest Innovation Review commissioned by Sir David Nicholson and published in December 2011, numerous strategies have been devised to reduce the impact of this issue on patients and services but with little success.

In 2007, the NHS Technology Adoption Centre (NTAC) was established to look at this issue in more detail, develop a new understanding of the key barriers and develop a strategy for overcoming these barriers. NTAC selected twelve technologies which fitted the following criteria:

- Available to the NHS for one year or more
- Strong, independently reviewed evidence for improved patient outcomes or systems efficiencies.
- Adopted at less than 5% of expected levels.

These technologies were adopted by three to four Trusts in each case working with project support managers from NTAC. The adopting Trusts engaged to:

- Procure the technology
- Make any changes necessary to the patient pathway and internal structures necessary to enable the benefits of the technology to be drawn down for both patient and system.

Normally the NHS would have operated these as a series of pilots, where technology is given to the Trusts for a short 'trial' which did not involve making service line changes, but the strategy above enabled a much broader view of the issues around integration of the technology into 'standard of care' and the impact of commissioning and procurement.

The technologies were based in primary, secondary and tertiary care and the projects enabled the NHS to understand and overcome the main barriers to uptake in the system. A How To- Why To Guide was produced for each of the technologies to enable other Trusts to adopt the technology more quickly by following the routes identified in each study.

In 2009 NTAC was asked to join the VALUE Consortium and use its understanding of the NHS Innovation routes to:

- Review the current NHS adoption pathway for innovative and disruptive technology
- Understand how some of the case study products would currently fare in that mechanism
- Identify the key changes which would need to be considered if these products were to be adopted widely within the NHS.

The 'New NHS' – A Health warning!

In July 2010 the newly elected Coalition Government published a White Paper on the future of the NHS. *Equity and excellence: Liberating the NHS* proposing radical changes to the NHS infrastructure, funding, targets and management. This was put out for extended consultation and provoked wide ranging opposition from many both inside and outside the system.

On 6 April 2011, the Government announced that it would take advantage of a natural break in the legislative timetable to "pause, listen and reflect" on modernisation plans and bring about improvements to the Health and Social Care Bill where necessary.

An eight-week NHS Listening Exercise was announced. The objective was not to repeat the formal public consultations which had already taken place, but to reflect on the areas which had prompted the most heated discussion and debate and bring forward improvements to the legislation where necessary. The four core themes of the NHS Listening Exercise were:

- Choice and competition
- Clinical advice and leadership
- Patient involvement and public accountability
- Education and training

The NHS Future Forum, chaired by Professor Steve Field immediate past Chairman of the Royal College of GPs, was established as an independent advisory panel to drive engagement around the listening exercise, listen to people's concerns, report back on these and offer advice to the Prime Minister, Deputy Prime Minister and the Secretary of State for Health on how the Government's modernisation plans for the NHS might be improved.

Following this exercise and some amendments to the White paper, the Health and Social Care Bill began its route through the parliamentary process creating further resistance in both Houses. There were strong indications early in 2012 that the Bill would not pass into law without radical amendments (on top of the three hundred and forty already in place).

The Health Social Care Bill is now passed through into Law as an Act of Parliament and many uncertainties as to the decision making process have been removed. All new structures are expected to be in place by March 2013. However, it will take some time for all the new commissioning bodies to come to grips with their new responsibilities and it is as yet unclear what tariff structures, both local and national, will be applied.

The Quality Agenda remains one of the key drivers within the new structure and this will provide a significant boost for new regenerative medicine products as they enter the market.

2. Approach used

Stages of Process

1. Review of current 'innovation pathway'
2. Use case study products to gain information on how they would have been managed through the pathway and into use within the NHS.
3. Identify key issues for regenerative medicine products in the current pathway
4. Review how potential changes by the Health and Social care Bill and the Chief Executives innovation Review: Innovation Health and Wealth might accelerate the uptake of Regenerative medicine products into the system.

The overall view of the structure of the pathway was gained from the initial work carried out by NHS Technology Adoption Centre in its initial work on the barriers to adoption and the engagement needed with the key players in the production of the 'How to Why To Guides' http://www.ntac.nhs.uk/HowToWhyToGuides/How-to-Why-to-Guides.aspx

The pathway is very clear but is poorly understood and utilised by both industry and the NHS System. The pathway is made up of:

- National Horizon Scanning Service.

  The National Horizon Scanning Centre is funded by the National Institute for Health Research and aims to provide key policy makers with advance notice of selected new and emerging health technologies that might require evaluation, consideration of clinical and cost impacts, or modification of clinical guidance up to 2-3 years prior to launch on the National Health Service (NHS) in England.

  The scope of the horizon scanning activity includes pharmaceuticals, medical devices and equipment, diagnostic tests and procedures, therapeutic interventions, rehabilitation and therapy, and public health activities. Although The Centre has been reviewing Regenerative medicine Technologies since 2008 they have since launched a work stream on Regenerative medicine in early 2010.

- NICE

  NHS Institute for Health and Clinical Excellence (NICE) is a special health authority of the English NHS but serves both English and Welsh NHS Initially established in 1999 to ensure access to effective and safe treatments which were cost effective.

  NICE publishes guidelines in three areas. The use of health technologies within the NHS (such as the use of new and existing medicines, treatments and procedures), clinical practice (guidance on the appropriate treatment and care of people with specific diseases and conditions) and guidance for public sector workers on Health promotion and ill-health avoidance. These appraisals are based primarily on evaluations of efficacy and cost-effectiveness in various circumstances.

  Since its inception it has increased the scope of its activity, creating NHS Evidence and NHS pathways as well as the new quality standards likely to be used if the Health and Social care Bill comes into the statutes book.

In 2007, as part of Lord Darzi's Next Stage Review of the NHS NICE was asked to create a new single evaluation pathway for Medical Devices and Diagnostics. This was in recognition of the difference between these technologies and pharmaceuticals and the much lower evidence base available for these technologies compared to Phase 2 and 3 trials normally available for new therapeutics.

The Medical Technology Evaluation Programme (MTEP) accepts nominations from manufacturers and can then select a number of options for appraisal:

- Interventional Procedures – considering the efficacy and safety of new procedures which are often utilising new technology.
- Health Technology Appraisal for devices that have a substantial evidence base. Considers efficacy and cost effectiveness. This looks at the cost consequence of the use of the new technology.
- NICE Diagnostics programme for use with both *in vivo* and *in vitro* devices
- Medical Technology Advisory Committee (MTAC) Review. Used for technologies with a lower evidence base.

Guidance is issued by MTAC and the process takes 48 weeks from initial submission.

- Commissioning Structures

Commissioners are the budget holders for the health economy and will commission services as local, regional or national level from a wide range of providers:

- Hospital Trusts
- Primary Care Groups
- Opticians
- Dentists
- Pharmacists

Primary Care Trusts: There are currently one hundred and twenty-five Primary Care Trusts and these have a sub regional base and commission healthcare provision from the range of providers above. The Commissioning is usually on a cost and transactions basis and will in most cases use the tariffs established by the Payment by Results team within Department of Health.

Specialist Commissioning Teams are regionally based and are responsible for commissioning specialist services. They carry responsibility for the more expensive procedures and also those that involve lower patient numbers. There will be a pricing structure set for these procedures but are often negotiated on a named patient basis at an increased tariff where appropriate.

Procedures involving low number of patients (orphan or ultra orphan when applied to Pharmaceuticals) are managed through a National Commissioning Group. About sixty highly specialised services are commissioned nationally by the National Specialised Commissioning Team.

The Advisory Group for National Specialised Services (AGNSS) is a committee that advises health Ministers on which services should be nationally commissioned and the centres that should provide them. Given the small number of patients or procedures involved and the

very high level of clinical expertise required to provide such treatments, most nationally commissioned services are provided in a very small number of centres, usually no more than three or four.

- Procurement Systems

There are a number of procurement structures within the NHS system, national regional and local. However, they are all bound by EU rules on procurement which indicates that the procurement of any item which will accrue a cost of more than £111,000 in any one year has to be subject to a tender process through the official journal if the European Union(OJEU).

- National- often high turnover consumables but increasingly looking at a much broader range of categories including high value capital equipment.
    - NHS Supply Chain
    - Buying Solutions
- Regional - Usually buying on behalf of a Consortium of Trusts
    - Shared Business Services
    - Procurement Hubs
- Local - Hospital Trusts do not need to use any of the above and many have their own procurement departments

The information was gained using both structured interviews and semi structured group discussions with the key players within each stage of the pathway.

Each of the steps in this pathway will need different data and information.

3. Results/Conclusions

Having identified the key players within the pathway along with their data and information requirements it was clear that the pathway would be suitable for a wide range of Regenerative medicine Technologies although issues were identified at each stage which could slow recognition of the likely benefits of the technology and create barriers to uptake.

NHSC

Its dedicated pathway is now recognising the emerging regenerative medicine technologies at an early stage and it has already detailed and is tracking them through the development pathway and into market. However as their remit is high impact technology those technologies for smaller indications are unlikely to be taken forward to policy makers.

NICE

NICE are already considering their response to regenerative medicine technologies. The initial thinking laid out in the discussions is that they would be initially directing the technologies through the Interventional Procedures Pathway in the first instance reviewing efficacy and safety. They have stressed that good follow up data will be a key requirement.

They would then consider a health technology appraisal (HTA) to examine cost effectiveness and cost consequences. This clearly raises an issue re time scales doubling the time for this stage of the process.

There is also issue on which comparator would be used in evaluating cost effectiveness. Their first efforts with Apligraf® failed to recognise the cost savings accrued from 'healing' a chronic wound quickly and effectively.

Currently uptake of NICE Guidance is not mandatory and overall uptake of all guidance currently stands at around 40%. It is likely that this will change if the recommendations of the Innovation Review are accepted. This lays down that if organisations chose NOT to apply NICE guidance they have to justify this and if they are unable to do so they will lose the Commissioning for Quality and Innovation (CQIN) payments which recognise innovation in the commissioning process.

Commissioning

It seems likely that most products will come under Specialist commissioning processes either nationally or regionally. There is some flexibility built into the pricing structure by way of 'Innovation payments' but, with current budget constraints, these are rarely being awarded currently and it is time consuming to negotiate these with each relevant commissioner.

If the NHS Commissioning Board comes into being, it is likely that all Specialist Commissioning will be their responsibility which should reduce the number of levels of engagement required. For very rare applications clinicians are seen to be the best judge of what technologies they will apply and the overall cost of the treatment will absorb any additional costs with a view that the impact of the technology will reduce costs elsewhere in the pathway.

Procurement

For the foreseeable future, and with most treatments being autologous, procurement responsibilities are most likely to reside with individual Hospital procurement departments. With so few treatments currently available the situation regarding tenders may not arise but when the patient and treatment numbers rise it is likely that most will go through a single provider tender.

Against this background NTAC assessed two very different technologies to see how they would currently be brought into using this pathway.

Table 1 ChondroCelect® from TiGenix Ltd

	Current NHS Strategy	**Changing Landscape**
Indication and Market size	Orthopaedics. Repair of the articular cartilage of the femoral condyle. Patient Prevalence =1100 per year.	Larger emphasis placed upon exercise meaning that we wear our joints out more prematurely. Want to stay active longer.
Product Characterisation Medicine/non medicine/Autologous/ Allogeneic	Autologous	Product pipeline based upon Stem Cell technology = move towards allogeneic.
Development Stage	Regulatory Approval gained. Now available on market in Europe. Being sold in NHS using pass through payments system. Have these been registered?	Post market authorisation clinical study underway.
<u>Adoption Filters</u>		
National Horizon Scanning Centre	Report Available	NHSC system is now changing and Regen Med will be a main strand. However NICE no longer using NHSC for Medtech area.
NICE	Could be submitted to NICE single evaluation pathway by TiGenix (manufacturer has to submit) Could then be routed to Interventional procedures or HTA. High level of RCT evidence might enable technology to gain an HTA approval.	NICE now pushing ahead to create 150 Quality standards. Need to know what Orthopaedic procedures are included. Built on current guidelines? Chance to influence standards development.
NHS Early Adopters, KOLs	Early Adopters already implementing procedure	UK Clinicians often resistant to KOLs from overseas.

Table 2 Cytovir CMV from Cell Medica Ltd

	Current NHS Strategy	**Changing Landscape**
Indication and Market size	Infusion of antigen-specific T cells from a healthy donor into an immunosuppressed patient following stem cell transplant, in order to reconstitute the patient's immunity to prevent or treat infection from the targeted virus. This individualised cellular therapy is referred to as Virus Specific Immune Reconstitution (VSIR) Orphan Indication	It is now expected that the NHS National Commissioning Board will hold overall responsibility for Specialist Commissioning
Product Characterisation Medicine/non medicine/Autologous/ Allogeneic	Allogeneic non-medicine	
Development Stage	Completing confirmatory trials to generate pharmacoeconomic data but also currently available to transplant centres because of its regulatory classification	
Adoption Filters		
National Horizon Scanning Centre	Has been picked up by the Horizon Scanning Centre but they have not produced a full outline due to its orphan status.	NICE is no longer using NHSC for Medtech area.
NICE	Again Orphan status would not normally attract NICE appraisal but could potentially be included in a Clinical Guideline on transplants	Under new emphasis on NICE approvals and Guidance would be useful to get treatment into a Clinical Guideline
Commissioning and Tariff Impact	Clinically led uptake. Clearly reduces the overall cost of managing patients who develop infections	Providing evidence on safety, efficacy and improved patient experience to NICE for inclusion in any appropriate clinical guideline will assist in a faster adoption curve if the Innovation Review recommendations are implemented.
NHS Early Adopters, Key Opinion Leaders (KOLs)	Clinicians already requesting early access to treatment	Potential to move from a treatment to a prophylactic substantially increasing market size. 500 to 1500 in UK

4. Recommendations

- TiGenix to submit ChondroCelect® for NICE approval.
- NICE to be asked to consider running Interventional Procedures and HTA processes in parallel to accelerate time to decision and uptake.
- Discussions between NICE and Industry as to suitable comparators for HTA. Cost consequence model critical to the process as use of technology significantly impacts the pathway.
- A single national commissioning structure for regenerative medicine products and procedures
- Education programme for Commissioners as to the unique aspects of this form of treatment.
- Prepare 'How to Why to Guide' for Cytovir CMV which has the potential to be used as a paradigm for cell therapies targeted at orphan and ultra orphan indications (in progress).

5. What are the benefits of these findings to the UK regenerative medicine industry?

- Identification of key decision makers within the pathway and the basis on which they make decisions.
- Clear route to market
- Opportunity for educating and influencing decision makers about this new technology.

6. References

Cooksey, D. A review of UK health research funding. December 2006. HM Treasury. Available from http://www.hm-treasury.gov.uk/d/pbr06_cooksey_final_report_636.pdf (accessed March 2012).

Greenhalgh T, Robert G, Bate P, Kyriakidou O, Macfarlane F, Peacock R. How to Spread Good Ideas. A systematic review of the literature on diffusion, dissemination and sustainability of innovations in health service delivery and organisation. Southampton: National Co-ordinating Centre for NHS Service Delivery and Organisation R & D; 2004. Available from: http://www.sdo.nihr.ac.uk/files/project/38-final-report.pdf (accessed March 2012).

David Nicholson. Implementing the Next Stage Review visions: the quality and productivity challenge http://www.dh.gov.uk/en/News/Recentstories/DH_101712 (accessed March 2012).

David Nicholson. Innovation, Health and wealth. December 2011 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131784.pdf

Wanless, D. Securing Good Health for the Whole Population: Final Report. February 2004, HM Treasury. Available from:

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4074426 (accessed March 2012).

High Quality Care for All NHS Next Stage Review Final Report
www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_085826.pdf (Accessed March 2012)

Kings Fund Review of Health and Social care Bill 2011
www.kingsfund.org.uk/current_projects/the_health_and_social_care_bill/nhs_reforms.html

NICE Single Evaluation Pathway
www.nice.org.uk/media/FCC/17/2009_068_-_Medical_Technologies_Programme_and_MTAC_APP.pdf (Accessed March 2012)

NICE 2009.
http://www.nice.org.uk/aboutnice/whatwedo/niceandthenhs/fasteraccesstomoderntreatment/faster_access_to_modern_treatment.jsp

Is there a rapid but robust way for the independent healthcare sector in the UK to know whether it is appropriate to fund regenerative medicines?

Lead Author: Gin Warren, Co-author: Brian Matthews - Bupa

1. Background

Regenerative medicines (RM), which can be thought of as those that cause organs or tissues to re-grow or support them while they do that, are a relatively novel mode of treatment. Organisations funding healthcare are used to evaluating the safety and efficacy, and indeed cost effectiveness, of interventional procedures and drugs and biologicals. This familiarity does not exist for cell-based therapies. Although Carticel® was approved by the FDA for use in the US as long ago as 1997, this has not produced a literature on methods for the health technology appraisal (HTA) of cell-based therapies. Searching Pub Med using the MeSH headings 'Technology assessments, biomedical' and 'Regenerative Medicine' only produces one article (1). ChondroCelect® was licensed as an Advanced Therapy Medicinal Product by the European Medicines Agency in 2009. It was the first; other products are in development. Healthcare organisations need a robust mechanism for deciding whether or not these products will be available to the populations for which they purchase care. The output of this Work Package starts to fill this methodological gap.

2. Approach Used

Bupa Health and Wellbeing UK (BHW) purchases hospital care for approaching three million people in the UK: Bupa has no shareholders and invests surpluses back into health and care. The Financial Services Ombudsman requires UK private medical insurance businesses to 'Treat Customers Fairly'. One aspect of achieving this is being able to evaluate new tests and treatments rapidly and so decide whether they should be funded or not when ill members enquire about them. For the clinical element of this, Bupa uses algorithms produced in-house which are populated using information which is quickly and easily available in the public domain. The sources of information used both to gather information on the new test or treatment and to understand its context (current best standard care) include: ClinicalTrials.gov, UKCRN portfolio, PubMed, British National Formulary, Oxford Handbook of the relevant speciality, Cancer Research UK website, NZ DermNet. The process, which relies on a focus on clinical outcomes relevant to patients using good literature searching and critical appraisal skills rather than detailed knowledge of the topic, is not only rapid (in hours or days, as expected by patients in this sector) but robust. The output of the 'interventional procedures' (IP) algorithm (fig 1) can be audited against the UK's National Institute for Health and Clinical Excellence (NICE) Interventional Procedures Guidance. Initial audit showed 90% agreement (2) and the December 2011 36 month cumulative figure was 91.1 %. The other algorithms are for use with medicines and tests; they structure thinking and are used in the same way as clinical guidelines viz they are not slavishly adhered to, but reasons for variance must be clear.

Figure 1: Interventional procedures (IP) algorithm

Health Technology Appraisal of Interventional Procedures

Box	Description	Outcome
A	Is the IP described for this indication in a standard text e.g. Oxford Textbook of Surgery, Oxford Textbook of Gynaecology or in an Oxford Handbook, or is a similar IP?	If Yes: Fund Routinely If No: Go to Box B
B	Does NICE IP straightforwardly say 'evidence on safety & efficacy adequate' for this indication?	If Yes: Go to Box C If No: Go to Box E
C	Are there major economic issues with this IP for this indication?	If Yes: Go to Box D If No: Fund Routinely
D	Are there contraindications to this member having the / a standard procedure for this indication?	If Yes: Fund as One-Off If No: Not Currently
E	Has NICE IP issued guidance on this IP for this indication?	If Yes: Go to Box F If No: Go to Box I
F	Is it safe?	If Yes: Go to Box G If No: Not Currently
G	Is there a relevant trial recruiting in the UK currently?	If Yes: Fund In Trial Only If No: Go to Box H
H	Is this procedure the member's only treatment option?	If Yes: Fund as One-Off If No: Not Currently
I	Is there a relevant trial recruiting in the UK currently?	If Yes: Fund In Trial Only* If No: Go to Box J
J	Are there results of relevant RCTs available in papers or peer reviewed journals?	If Yes: Go to Box K If No: Go to Box L
K	Do RCTs suggest that the procedure is safe and useful for the given indication?	If Yes: Fund Routinely* If No: Not Currently*
L	Are there positive (i.e. 'safe' and 'useful') register or big case series results in papers or peer reviewed journals?	If Yes: Fund as One-Off If No: Go to Box M
M	Is this procedure the member's only treatment option?	If Yes: Fund as One-Off* If No: Not Currently*

*Log with NICE IP if relevant to NHS.

The VALUE project has considered fourteen products (see Report Appendix for Case Study examples), some being developed and/or marketed by VALUE participants. Early in the project (2010), we explored whether it was possible to evaluate all these products using the interventional procedures (2) or medicines algorithms (3). A major problem was encountered with cell-based allograft products: the need for reassurance that cells had been ethically sourced. Discussions with the regulatory expert in the VALUE consortium showed that there was not a website, or a small number of websites, that specifically gives information on the sourcing of donor cells for allograft use and/or on Good Manufacturing Practice. Given the need for rapid health technology appraisal (HTA) in the independent sector, it was argued pragmatically that any product which had ever been subject to formal clinical research logged on ClinicalTrials.gov could reasonably be regarded as being ethically sourced and properly handled. This is because listing on the site implies Research Ethics Committee/ Institutional Review Board approval, (though the quality assurance on this for studies based outside the US is apparently questionable). A new cell-based therapies algorithm (Figure 2) was developed using the same 'application-of-evidence-based-medicine' principles as the established IP and medicines ones.

Figure 2: Cell-based therapies algorithm

Health Technology Appraisal of Cell-based Therapies

Box	Description	Outcome
A	Licence for given indication (stage and 1st or 2nd line treatment, as well as pathology)?	If Yes: Fund Routinely If No: Go to Box B
B	Convention that the treatment is used for given indication although licensed for something else, or compelling phase III trial result in a peer reviewed journal paper?	If Yes: Fund Routinely If No: Go to Box C
C	Formal UK trial (any phase) investigating use in given indication and currently recruiting?	If Yes: In trial only If No: Go to Box D
D	Has the product ever been subject to formal clinical research as shown by listing on e.g. Clinicaltrials.gov?	If Yes: Go to Box E If No: Not Currently
E	Is it patient's only treatment option?	If Yes: Go to Box F If No: Not Currently
F	Is it a common disease (e.g. OA / ordinary breast ca / prostate ca) ?	If Yes: Go to Box O If No: Go to Box G
G	Is it a very rare disease?	If Yes: Go to Box H If No: Go to Box K
H	Is it biologically plausible that the treatment might work?	If Yes: Go to Box I If No: Not currently
I	Is there any evidence that it is efficacious?	If Yes: Go to Box J If No: Not Currently
J	Is it safe, in the context of the severity of the disease?	If Yes: Yes as a one-off If No: Not currently
K	Is there a phase II trial recruiting or in follow-up abroad?	If Yes: Yes as a one-off If No: Go to Box L
L	Is it biologically plausible that the treatment might work?	If Yes: Go to Box M If No: Not currently
M	Is there any evidence that it is efficacious?	If Yes: Go to Box N If No: Not currently
N	Is it safe, in the context of the severity of the disease?	If Yes: Yes as one off If No: Not currently
O	Is there a phase III trial recruiting / in follow-up abroad?	If Yes: Yes as one off If No: Go to Box P
P	Is it biologically plausible that the treatment might work?	If Yes: Go to Box Q If No: Not currently
Q	Is it likely to be efficacious? (e.g. ASCO abstract / paper reporting phase II trial) ?	If Yes: Go to Box R If No: Not currently
R	Is it safe, in the context of the severity of the disease?	If Yes: Yes as one off If No: Not currently

Two of the fourteen VALUE case study products were sufficiently far through development for the cell-based therapies algorithm to categorise them as appropriate for funding in the context of formal research (Cytovir CMV), or as clinically ready to be funded routinely (ChondroCelect®). These were presented to commercial colleagues at the May 2011 session of the BHW Policy Panel. It was agreed that members would receive discretionary funding to participate in the relevant research on Cytovir CMV (NCT 01077908, NCT01220895). Beyond that, it was not anticipated that there would be any issues with funding becoming

routine should these randomised controlled trials report positively, given the context of the cost and side effect profile of the current best standard care that use of the cells would replace. ChondroCelect® raised questions of cost effectiveness which relate both to its price and to its efficacy relative to current best standard care. This links to 'Treating Members Fairly' and the parallel issue of expensive oncology drugs which extend life, but only by weeks not months.

The suite of algorithms were then tested for fitness-for-purpose in the context of the clinical evaluation of the RM funding queries received by Group Medical from other Bupa teams (predominantly BHW, some from overseas, one from a hospital) by the Group Medical Team during 2011. Between them, the algorithms were able to cope with all twenty queries. The eight clinically evaluated using the cell-based therapies algorithm were (algorithm output in brackets):

Ceramic implant and autologous cells for non-union of femur (Not currently)

Dendritic cell vaccine and hyperthermia for metastatic breast cancer (Not currently)

Autologous peripheral blood progenitor cells and hyaluronic acid for knee cartilage lesions (NCT01076673 only)

Cytokine induced killer cells - dendritic cells for recurrent ovarian cancer (Not currently)

Autohemotherapy for colon cancer (Not currently)

Autologous mesenchymal stem cells for brachial plexus injury (Not currently)

Autologous adipose-derived stem and regenerative cells for breast reconstruction after lumpectomy for breast cancer (Not currently)

Allograft chondrocytes for lesion (?osteoarthritis) at ankle (Not currently)

Of the twenty (remainder evaluated using either the IP or the medicines algorithm), two were categorised as ready for routine funding, two for funding only in clinical research, one was recommended for funding as a one off because of the member's clinical circumstances and fifteen were categorised by the algorithms as inappropriate to fund currently.

3. Results/Conclusions

- The algorithms usefully facilitated the rapid clinical evaluation of all the 'real life' regenerative medicine funding and provision queries.
- Regenerative medicines are not special from the point of view of organisations purchasing healthcare on behalf of populations of patients - they are just another mode of care, like surgery, drugs or radiotherapy.
- There are regenerative medicines being rigorously developed which do address pathologies with high burdens of disease (when that is taken to equate to severity, rather than high incidence or prevalence) which look as if they will be cost effective e.g. Cytovir CMV.

4. Recommendations

- Organisations purchasing and providing healthcare should consider using the algorithms to structure their thinking (assuming they have staff with suitable background knowledge and skills e.g. people on the GMCs Specialist Register for Public Health, or General Practice Register. Specialist knowledge of a specific hospital speciality is arguably a hindrance in health technology appraisal, which in this context goes across many hospital specialities).

- The interventional procedures (IP) algorithm is appropriate for use for cell-free regenerative medicines which need to be surgically sited. The medicines algorithm is appropriate for cell-free regenerative medicines which do not need to be surgically sited.

- Developers of regenerative medicines should note the necessity for high quality clinical research output on safety and efficacy.

- Developers of regenerative medicines should note the necessity for a long-term follow-up (in the context of the natural history of the disease and of the remaining life expectancy of characteristic patients) for their research, especially if the regenerative medicine is expensive or claims to be curative.

- Developers of regenerative medicines should seek to price their products proportionately to the relative efficacy of their product compared with the price and efficacy of current best standard care.

The "real life" experience suggests that:

- National and international licensing bodies should ensure that the indication specified for a regenerative medicine is sufficiently detailed to facilitate the provision of the regenerative medicine to patients with high capacity to benefit from it, and only to such people.

- Public education is needed on regenerative medicine and its potential to improve health, because regenerative medicines may be over-hyped, especially to vulnerable patients. (*A request was received for treatment with mesenchymal stem cells for brachial plexus injury, to be delivered via lumbar puncture. The German team offering this treatment in Egypt were asked to confirm Bupa's impression that they were not conducting formal medical research to evaluate this regenerative medicine and that there were no relevant peer reviewed clinical papers in the literature. Their reply did not address these issues).*

- Government and consumer organisations should note that some regenerative medicine products will be offered to self pay customers as beauty treatment or cosmetic surgery. These people are likely to be naive purchasers of regenerative medicine and so potentially need the protection of regulation.

- Those responsible for clinical governance at clinics offering cosmetic surgery should make sure that potential clients (they are not patients) have a clear understanding of what change/improvement can be expected from the regenerative medicine and how long any effect will last before they commit themselves to having the treatment and paying for it.

5. What are the benefits of these findings to the UK regenerative medicine industry?

- Clear understanding of the information expectations (in terms of output of rigorous clinical research) of potential funders of care using their product. Ethical providers of care will have similar expectations.

6. References

1 Mason C Regenerative medicine: revolution in the making. Med Device Technol 2005;16:22

2 Warren V. Health technology appraisal of interventional procedures: comparison of rapid and slow methods. Health Serv Res Policy 2007;12:142-6

3 Warren VJ Paying for expensive medicines. Oncologists and top ups. BMJ 2009:338:b2530

Regulation: What are the real uncertainties?

Lead Author: Christopher Bravery

1. Introduction to the Regulatory Uncertainties

The overall aims of this work package (WP1) were to identify and understand the available regulatory routes for marketing authorisation in the EU and the US for selected cellular therapeutics. The products were selected within the consortium to be representative of the range different cellular therapeutics under development, these selected products being the 'case studies' used across the work packages. Regenerative medicine is a broad term which encompasses not just cellular therapeutics but also some recombinant proteins and possibly even small molecules, but since the regulatory pathway for such molecules is well established they were excluded from this analysis. However, the case studies were deliberately chosen to include cell transplantation products, cell-based medicinal products (CBMP) and products regulated as medical devices by the US FDA.

Throughout the project data were collected relating to the regulatory landscape for advanced therapy medicinal products (ATMP's) in the EU, however these were not the main focus of the project so have as yet not been completely digested. A snap shot of these data are provided in Section 2.1.

Analysis of the two regulatory frameworks included a gap analysis of the differences to identify if and where significant differences exist that might impact development of cellular therapeutics in a global market. The results of this analysis are discussed in Section 2.2.

The second more ambitious objective was to use the case studies as a basis to map out the regulatory route to marketing approval (hence excluding reimbursement considerations for simplicity) to understand how this might be different for different product types, with a view to creating generic regulatory pathways for defined product categories. This is discussed in Section 2.3.

The final major objective was to identify where the regulatory framework might be ineffective or inappropriate in order to identify possible areas for improvement. In particular this objective intended to try and address the strong views of some stakeholders that the application of a regulatory framework originally devised for small molecules was not appropriate for CBMP. This work is presented and discussed in Section 2.4.

Inevitably a number of issues came out of the gap analysis and three of these were selected for further consideration and are discussed in Section 2.5.

2. Results

2.1 EU Regenerative Medicine Industry: A Regulatory Perspective

While the core analysis includes both the EU and US regulatory frameworks, much of the analysis of the industry was focussed on the UK's position within the EU and whether both the UK and wider EU regulators are adequately and appropriately supporting the evolving RM Industry.

Regulation 1394/2007 [1], the so-called ATMP regulation, made it mandatory for all ATMP's to use the centralised procedure (CP) for marketing authorisation and consequently removed the possibility for national marketing authorisations. Member states still retain responsibility for

authorisation of clinical trials occurring within their borders, and have the option to exempt certain products used on a non-routine basis for unmet clinical need (in particular the 'Hospital Exemption'). The main reason for this change was to allow European member states to pool regulatory expertise at European Medicines Agency (EMA) level, including the formation of a new Committee for Advanced Therapies (CAT). Since the end of December 2009 the CAT is now responsible for classification of ATMP's and scientific evaluation of ATMP marketing authorisations. Shortly after its formation the CAT also took over two existing working parties, the cell-based products working party (CPWP) and the gene therapy working party (GTWP), and formed the EMA/CAT and Medical Devices Notified Body (EMA/CAT-NB) Collaboration Group to allow exchange and dialogue with notified bodies for combination ATMP's and possibly for issues related to complex delivery devices.

The following sections will summarise some of the work of the CAT and EMA to support ATMP developers. Although CAB Ltd accumulated considerable data during the VALUE project, much of this remains to be analysed and compared to other sources. Since other aspects of the work have been disseminated in publications, a snapshot of these data are provided in the following sections, although no firm conclusions have yet been drawn, some preliminary conclusions will be made where appropriate.

ATMP Classifications

The CAT classification procedure is not mandatory and consequently not all developers may feel they need to request one, or may request a classification from their national competent authority (NCA). Understanding how the EMA are applying the rules is important, particularly for borderline products, yet the summaries provided on the EMA website do not provide much insight. The EMA attempted to address this during 2011 by increasing the detail in the published summaries, but the additional detail does not provide any real additional insight. Consequently the conclusion of WP1 is that the EMA need to be more transparent about their reasoning, since many stakeholders still struggle to accept many classifications, especially those that border cell transplantation and CBMP.

Early Agency Interactions

The EMA has an innovation task force (ITF), deliberately set up to provide a multidisciplinary first point of contact for developers wishing to initiate discussions, primarily on new technologies.

Of the seventy-two ITF briefing meetings held during 2005 to 2009, 69.4% were for ATMP's, of which 66% were for CBMP, the remaining for gene therapy products [2], a more detailed breakdown is provided in Figure 2. What is interesting is that in the two years prior to the publication of regulation 1394/2007 there were several ITF meetings for CBMP, suggesting at least some developers realised these might be considered medicinal products.

Orphan designations

The orphan drug register was downloaded from the EMA website and analysed line by line to identify CBMP. Of the six hundred and forty-three products on the register (as of 2010), twenty-seven (4%) were identified as CBMP. Of those products requesting agency advice (see p39) around 40-50% are for orphan indications.

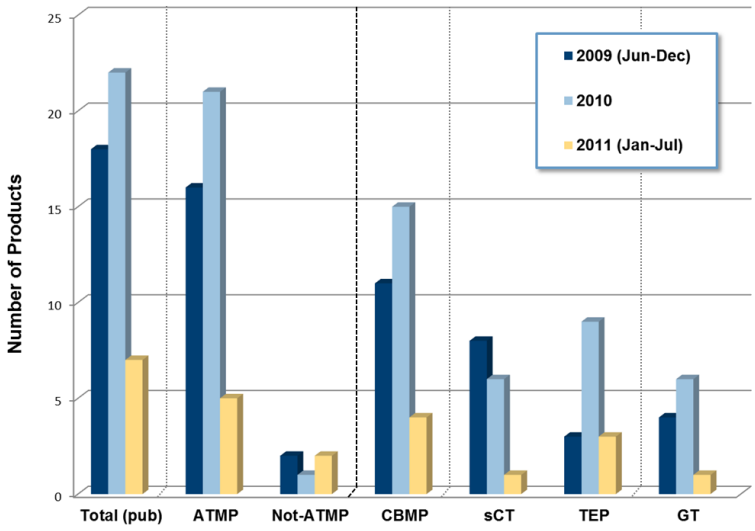


Figure 1: Classifications undertaken by the EMA/CAT between June 2009 and July 2011

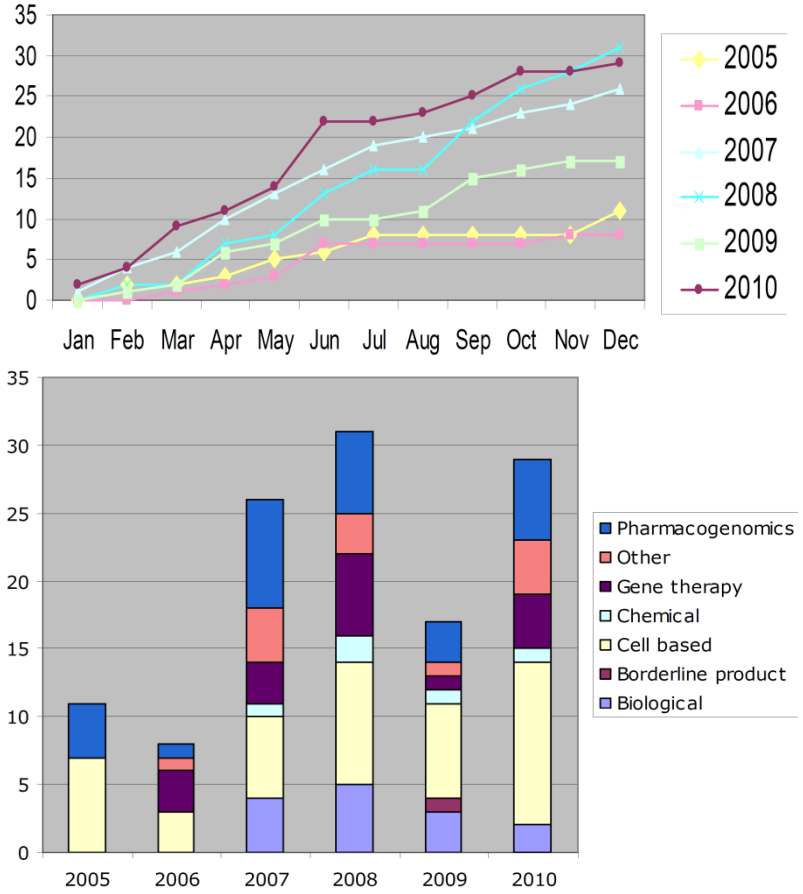


Figure 2: EMA Innovation Task Force (ITF) Meetings, 2005-2010 [3].

Top: Cumulative meetings by year

Bottom: Areas discussed at ITF meetings by year.

Clinical Trials in the EU

Most of the published data on trends in clinical trials for CBMP focuses on data available from clinicaltrials.gov, and so may not give a clear impression of clinical trials outside of the US. The EU has a centralised clinical trials database called EurdraCT, however these data are not available to the public. A recent initiative has attempted to open limited data from this system to the public, but so far has rather limited information.

However, EU NCA's and the EMA have from time to time provided some insights into these data, some of these data were captured during this work. Figure 3 is a slide presented in June 2011, although these data raise more questions than they answer, there is a clear increase in clinical trials over time.

Cell-based MPs EudraCT Clinical trial applications (3Q 2005 – 4Q 2009)

	3Q / 2005	3Q / 2006	3Q / 2007	3Q / 2008	4Q / 2009
Cancer immunotherapy	3	23	45	70	103
Cardio-vascular therapies	4	17	31	44	49
Skin/liver/eye/diabetes/intestine/bone TE	5	12	28	48	74
Neurological	1	4	5	6	7
Lymphohistiocystosis (HLH)	-	1	1	1	1
AIDS	-	1	1	1	1
Infertility	-	1	1	1	1
Products (trials)	**13 (25)**	**59 (73)**	**112 (132)**	**171 (213)**	**236 (329)**

Data from Dr. E.Flory/Eudra CT **246 (2010)**

Figure 3: EU clinical trials with CBMP by year [4].

Note: Data from 2003-2008 are for the first 3 quarters of the year only. No information was included on the stage of the clinical trial or whether they were commercial or non-commercial.

There are numerous publications, both formal and blogs, which attempt to identify the number of products currently under development. Since most of these use sources such as clinicaltrials.gov which tend to be US-focussed it is interesting to see how these compared to the EU agency data in Figure 3.

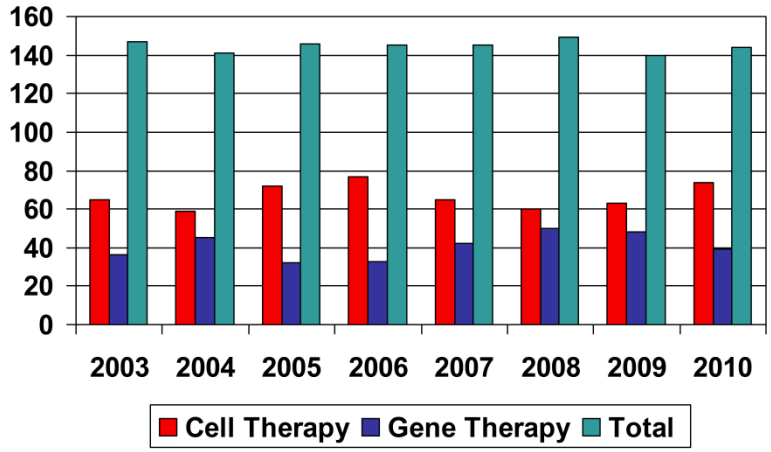


Figure 4: New Submissions to FDA: Investigational CT & GT Products [5].

Note: Data from 2003-2008 are for the first 3 quarters of the year only. No information was included on the stage of the clinical trial or whether they were commercial or non-commercial.

It can be concluded that across the EU there are around two hundred to two hundred and fifty products in clinical trials, and something like three hundred to three hundred and fifty separate clinical trials applications per year (figure for 2010 not known). By contrast, in 2010 there were between seventy and eighty new INDs submitted for CBMP to the FDA [5]. Considering the EU population is approximately five hundred million and the USA approximately three hundred and fifty million, this suggests more clinical trials are on-going in the EU. However, the EUDRACT database covers thirty member states and a clinical trial must be submitted in each country for each trial; whereas in the US an IND is submitted for the whole US for a clinical phase. So it is very difficult to make a useful comparison. This work was not pursued further for these reasons.
Any attempt to connect up these various data sets is unlikely to yield a reliable answer, so the data collected from the EMA website and agency presentations is being collated by CAB Ltd with a view to publication; however, this was not a primary focus for VALUE.

Agency Advice

The monthly figures for scientific advice and protocol assistance (scientific advice for orphan products) were analysed from 2009 to October 2011. Some doubts exist as to the accuracy of figures in the early part of 2009 since it is not entirely clear when the EMA started to group ATMP's separately to other biological products. The numbers suggest that around 5% of all advice procedures during this time were for ATMP's, 36% for other biological medicinal products and 60% for chemical entities; the short-fall being defined as 'other innovative'.

The main observation from this analysis, since the extent of the data was limited, is that ATMP developers are much more likely to ask quality (CMC) questions, see Figure 5.

Similar figures for nonclinical and clinical advice requests show little difference between different therapeutic entities. This observation is not unsurprising, manufacturing quality for biological products poses significant challenges over chemical entities, and the additional complexity of living cells inevitably brings uncertainties as to what will be expected.

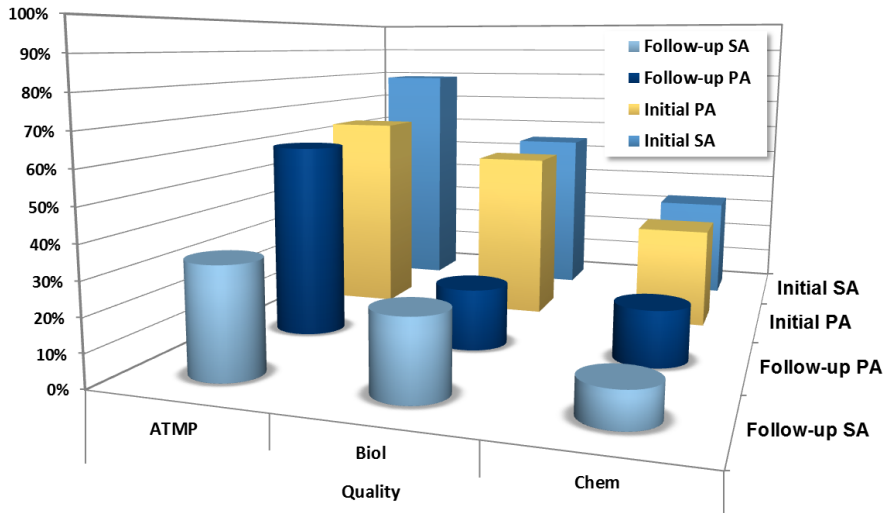


Figure 5: EMA Scientific Advice and Protocol Assistance requests 2009-Oct 2011: Quality Questions [6].

Figure showing the proportion of procedures requesting quality (CMC) advice grouped by nature of active substance; chemical, biological (excluding ATMP) or ATMP. Which sub-category of ATMP is not provided, although the limited text available suggests the greater majority are cell-based, whether or not they are also gene therapies. This figure shows that ATMP developers are much more likely to ask questions on quality than other biologics developers, which in turn are more likely to ask questions on quality than developers of chemical entities. Similar analysis of nonclinical and clinical requests suggests these are more comparable across active substances (data not shown).
SA, scientific advice; PA, protocol assistance (SA for orphan products).
Note: Initial advice means the first request for advice on that product; follow-up advice where questions have been asked previously, although not necessarily within the period reported.

Marketing Authorisation Experience

The EMA and the centralised procedure were introduced in the mid-1990's to provide a route to obtain a single MA for the whole EU/EEA. From the start biotech products based on recombinant DNA technology were mandated to use this procedure for much the same reasons it is mandated for ATMP's today, to pool expertise across the EU. The list of products mandated to use the centralised procedure has increased over subsequent years, but even where a particular product is not mandated to use the CP, it has always been possible to request a centralised MA based on technological novelty. It was for this reason that an MAA for Apligraf® was accepted by the EMA in 2001, even though it was 3 years before ATMP's were defined in the EU medicines framework (through Directive 2003/63/EC [7]). Aside from the gene therapy products identified in Table 1, only one other CBMP has been submitted for MAA prior to 2011. During 2011 and the beginning of 2012, three further ATMP's have been submitted [8], all of which are thought to be CBMP [9].

Behind this analysis we need to look at what the situation was at the national level prior to Regulation 1394/2007 coming into effect. It was estimated by the EMA, based on NCA feedback, that thirty to forty ATMP's [10] were legally available on national markets; and consequently to remain on the market after the end of 2012 these are required to be re-authorised by the EMA. Of the three MAA's submitted since 2011, only one is thought (unconfirmed) to be a nationally authorised product, meaning the remainder will presumably leave the market, or apply for national exemption (e.g. hospital exemption).

Table 1: List of ATMP's that have submitted a marketing Authorisation to the EMA

Product	INN	Company	Submission Date	Opinion	Finalisation Date
Apligraf	*None assigned*	*Novartis*	*Apr 2001*	*Unknown*	*Withdrawn 2002*
Cerepro	*adenovirus-mediated Herpes Simplex Virus-thymidine kinase gene*	*Ark Therapeutics*	*Oct 2005*	*Negative*	*Withdrawn Jul 2007*
ChondroCelect	None assigned	Tigenix	Jun 2007	**Positive**	**Jun 2009**
Advexin	*contusugene ladenovec*	*Gendux Molecular Limited*	*Sep 2007*	*Negative*	*Withdrawn Dec 2008*
Contusugene Ladenovec Gendux	*contusugene ladenovec*	*Gendux Molecular Limited*	*Jul 2008*	*Negative*	*Withdrawn Jun 2009*
Cerepro	*adenovirus-mediated Herpes Simplex Virus-thymidine kinase gene*	*Ark Therapeutics*	*Jan 2009*	*Negative*	*Dec 2009*
Glybera	alipogene tiparvovec	AMT B.V.	2009	*Negative*	Jun 2011

In contrast, at first glance it can seem that more products have been approved in the US, however, prior to 2010 only one of these was regulated as a CBMP (Biologic in the US, requiring a BLA), most have been approved as medical devices (PMA or HDE routes). So when we take into consideration products that were nationally authorised in the EU, it could be argued that a greater variety of products were available in the EU.

Table 2: List of FDA authorised Cell-based Products

Product	Type	Company	Type	Year
Carticel	Chondrocyte	Genzyme	BLA	1997
TransCyte	Engineered Skin	ATS/S&N (now Advanced Biohealing)	PMA	1997
Apligraf	Engineered Skin	Organogenesis	PMA	1998
Dermagraft	Engineered Skin	ATS/S&N (now Advanced Biohealing)	PMA	2001
Orcel	Engineered Skin	Ortec Internation (now Forticell)	PMA	2001
Epicel	Engineered Skin	BioSurface Technology (now Genzyme)	HDE	2007
Provenge	Immunotherapy	Dendreon Corporation	BLA	2010
LaViv	Skin rejuvanation	Fibrocell Technologies, Inc.	BLA	2011
Umbilical Cord Blood		New York Blood Center	BLA	2011
Apligraf Oral	Dental	Organogenesis	BLA	Pending

The conclusion of WP1 is that both regions have approved CBMP, although unlike other medicinal products an approval in one region has not to date been a predictor that the same product will be approved in the other region. However, and based on the core business of CAB Ltd it seems likely this will change as the industry matures since most commercial developers are clearly trying to develop products for both markets.

Conclusions

No firm conclusions have yet been reached from this work, however it can be concluded that ATMP's represent around 5% of the work of the EMA based on agency advice procedures and the proportion of the orphan drug registry. The introduction of a new committee and associated working parties is therefore evidence the role of CBMP is taken seriously by EU regulators. Furthermore, a series of specific guidelines have now been written with more to come, together with a series of stakeholder meetings, taken together are evidence this sector is taken seriously.

2.2 Gap Analysis of EU and US Regulatory Frameworks

The first objective of WP1 was to understand the regulatory expectations in both the EU and US, and more importantly to identify any differences in the two systems that would impact the development of CBMP for a global market.

PAS 83: Developing human cells for clinical applications

The primary output from the analysis of EU and US regulation is a publicly available specification (PAS 83) which will be published in May 2012 by the BSi. PAS 83 provides a high level overview of the legislation and guidance's available to developers, and broadly outlines the general approach to developing a CBMP.

Other publications

WP1 has also contributed significantly to PAS 84 (glossary of terms) and PAS 93 (characterisation of human cells for clinical applications) and all three are available as free downloads on the BSi website.

The work also allowed CAB Ltd to take the lead with a US consultant to write a white paper on potency for the ISCT Process and Product Development (PPD) sub-committee of the Commercialisation Committee. This paper will be completed by the middle of 2012 and published shortly afterwards (probably in Cytotherapy).

Web-tools

While collating the documents for PAS 83 and figuring out how to present the data in a useful way, it became apparent that the data could be used to produce a series of web-tools. In total fifteen web-tools have been developed and published for free on CAB Ltd's website [11]. A further more complex web-tool to aid ATMP classification is also under development.

Proprietary database

The detailed analysis behind these documents is being utilised by CAB Ltd to support our clients.

2.3 Roadmaps

When setting out to develop a CBMP it is essential to understand the development path in order to predict costs, timelines and data requirements; however CBMP vary significantly in their composition and nature and many other factors influence the development path including the indication, the source of cells and so on. The second main objective of WP1 was to attempt to map out the regulatory path for the case studies (deliberately chosen to cover major types of product) in the hope that generic roadmaps might be prepared as a guide to developers and identify a business model for the product. While it was useful to map out individual case studies in this way, it quickly became apparent that there are too many variables to allow predictive roadmaps to be designed. Consequently the main conclusion for this objective is that it is necessary to plan out each product case-by-case because there are too many overlapping variables to allow a generic plan. As a result the objective of this part of the project became to identify which variables might have a significant impact on the value-chain and focus on understanding what their impact might be. Three major issues impacting the commercialisation of CBMP became apparent, two of which are interrelated; these are discussed further in section 2.5.

2.4 Options to Improve the Regulatory Environment

The first issue of EU disharmony was published in a paper [12] that explained the flexibility of the current system in the EU as well as dispelling some of the myths around regulation. The process of preparing this publication identified more clearly that the fundamental issue is not the regulatory process, but the uncertainty as to the data that is required to establish quality, safety and efficacy of a CBMP.

2.5 Regulatory Issues Identified for Further Work

Multiple manufacturing sites and point-of-care manufacturing

For many CBMP, especially autologous products and those delivered fresh to the patient, time is critical since neither the donor material nor the product have a very long shelf-life unless frozen. The logistics of such products can be complex (cf. Provenge) and may necessitate several manufacturing sites even within one jurisdiction to ensure the donor material and the product can be transported in time. However, under a single market authorisation, multiple manufacturing sites can bring significant challenges. While replicating and qualifying the facility to GMP standards is fairly straightforward, establishing and maintaining comparability between sites is likely to become impossibly burdensome beyond two or three sites. This analysis will be published when complete.

Closely related to this is the clear advantage, again primarily for autologous products, of manufacturing the product in-theatre, at the bed-side or within the hospital using a closed automated system. Examples of this are already in use, for example CliniMACs (Miltenyi) and Celution (Cytori), but so far these have primarily been used for cell therapy products that are not regulated as medicines. However, these developers and others are already moving the technology forward, but the regulatory frameworks of the EU and US did not envisage this and consequently they do not currently fit the framework. Regulators both sides of the Atlantic are concerned, but so far do not appear to be considering how the framework might be changed to enable these approaches. The final analysis and conclusion from this work will be published when complete and will hopefully provide some suggestions as to how to enable this approach.

Cell banking strategy

It is assumed by many that the business model for allogeneic products will be similar to other biotech products since these are off-the-shelf products that can be made in large batches. However, unlike biotech products the cell banks in many cases will not supply enough cellular starting material to supply the product for the entire life-cycle and additional banks will need to be introduced from time to time. This brings a significant regulatory burden beyond that of a biotech product in that it can take at least 6 months and easily cost in excess of $0.5M to qualify a new cell bank. This necessitates careful consideration of the cell banking strategy and its possible impact on-market to ensure the product can be commercially viable. A manuscript is in preparation for this work.

Are biosimilar CBMP possible?

When considering protection of intellectual property in this area it is common to hear references to data protection periods as a form of protection. Data protection periods refer to the possibility for other developers to cross-reference non-clinical and clinical data from a marketed product rather than undertake the work themselves. This mechanism is designed to allow generic or biosimilar products a short-cut to market once the innovator has had a chance to recoup their costs such that generic competition will keep drug prices down. While a generic small molecule only requires analytical data to establish comparability to an existing small molecule, biological products require considerably more work, including some clinical data. For a number of complex reasons that are difficult to summarise in a few words, the biosimilar paradigm in the EU would not work for CBMP and consequently data protection periods are irrelevant and will remain so for the foreseeable future. A manuscript is in preparation on this topic.

3. Conclusions

The first conclusion from this work package is that regulation is not the uncertainty, it is basic research, and if the uncertainty is to be reduced we need to invest in basic research to enable better decision making during product development [12]. Analysis of the regulatory frameworks of both regions therefore also concludes they are fit for purpose. The main remaining issue is the conflict between the needs and wants of stakeholders and what regulators can realistically do to support them. With a legal regulatory framework that is flexible, the detail of what is expected needs to be conveyed through guidelines, and guidelines cannot easily be written without a deep understanding of the science surrounding a therapeutic approach, which can only come from the experienced gained in developing them. Consequently regulators can necessarily only offer limited advice on the development of CBMP at this time, even with licensed products available, the sheer diversity of CBMP means many issues will not yet have come to light. On the other side, some stakeholders feel the regulators should be able to provide solid clear guidance now, yet even if this were possible it would likely stifle further innovation since developers would be reluctant to ignore available guidance. Thus an overly proscriptive regulatory environment is not what is needed and developers need to understand there are no hard rules and that they need to apply scientific principles and knowledge to the development of their own product and determine the data requirements themselves. This concept of case-by-case is well established for the development of medicinal products, especially those of biological origin, but is perhaps not well understood within the relatively new sector of regenerative medicine.

This conclusion also covers the original intent to provide generic roadmaps for different product types. There are so many variables that influence the regulatory data requirements for CBMP that considerable detail on many hundreds of products (preferably late stage) would be required to find any clear commonalities between them. Consequently what the industry really needs is a better understanding of the principles of regulation. At a recent UK ATMP event a light-hearted poll was

taken as to how many thought they had read the available guidelines, and in essence few had read any at all, partly because they were unaware of their existence. A concept not discussed in this report was identified by this work, that of regulatory readiness levels (RRL); the UK should be looking to increase the general RRL of the sector here in the UK.

The deeper analysis of the regulatory frameworks did identify some issues where additional work and possibly minor changes in the law could help enable the industry. Three of these are discussed briefly in this report, with publications in preparation. In particular there are constraints imposed by the current regulatory structure to the approach to manufacturing infrastructure; the expectation is for one or two manufacturing sites with highly customised facilities. However, for many CBMP, in particular autologous products, there is a need to scale-out many manufacturing units either within the same facility or spread across many sites. In some cases a point-of-care manufacturing unit would make good commercial sense, but this in particular is simply not envisaged by the current framework. It was not possible to complete this last piece of work so a final conclusion is not yet available, but hopefully this work can be continued.

4. Recommendations

- The UK government should invest in regulatory science and training, a good vehicle for this would be the new cell therapy catapult centre.
    - The UK government should invest in providing regulatory training for UK companies, and providing regulatory advice to early stage companies with a view to raising the regulatory readiness levels of UK industry.
    - There should be investment in regulatory science as a separate discipline.

- Further work is needed to fully understand the issues around scale-out manufacturing approaches and how to enable these, especially point-of-care manufacturing.

5. What are the benefits of these findings to the UK regenerative medicine industry?

- Entry level: PAS 83 and companion documents PAS 84 and PAS 93 provide entry level information for those new to the development of cell-based medicinal products.

- Intermediate level: The web-tools will help developers identify key guidelines and understand regulatory principles during development.

- Expert level: In-depth publications on potency, biosimilar cell therapy products, cell banking strategy and point-of-care manufacturing provide a deep insight into those issues to help developers make more informed decisions.

- CAB Ltd: The experience of looking at regulation within the VALUE consortium has given CAB Ltd a deeper understanding of the value-chain and commercial landscape which should allow us to serve the needs of our clients better.

6. References

1 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Communities, L 324, 121-137

2 Lucia D'Apote, "Regulatory Roadmap for Stem Cell Therapies: A Regulatory Agency Perspective", presentation at UKNSCN conference, July 2010.

3 Lucia D'Apote, "Role of European and National Regulatory Authorities: Who advises on what?" CAT-ESGCT Workshop, Oct 2011. http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/02/WC500122176.pdf

4 Data from EudraCT database prepared by Egbert Flory (PEI, Germany) as presented by Paula Slamikangas (Fimea, Finland) at the PDA/Fimea workshop on ATMP's, Helsinki, Finland, June 2011.

5 Steven S. Oh, FDA; "Cell-Based Medicinal Products for Global Market: FDA Perspectives", CAT-SGCT Workshop, ESGCT Annual Meeting, Brighton, UK, October 27, 2011.

6 Data from CHMP monthly reports; www.ema.europa.eu

7 Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Text with EEA relevance). Official Journal of the European Communities, L 159, 46-94

8 CAT monthly reports; http://www.ema.europa.eu

9 CAB Ltd regulatory intelligence.

10 The exact number and details of ATMP's with national approval prior to December 2009 have not been made publicly available, but a number of agency speakers have eluded to the number of products being in the range 30-40.

11 www.advbiols.com/resources

12 Regulating interface science healthcare products: myths and uncertainties; J. R. Soc. Interface 7,7 (2010). Free content.

What are the major issues for developers of cell-based therapies when conducting clinical trials in multiple countries in order to achieve regulatory approval and reimbursement?

Lead Author: Patrick Ginty – Loughborough University

1. Background

As with any medicinal product, understanding the clinical trials process for cell-based therapeutics is critical to both the successful navigation of the regulatory pathways and manufacturing / supplying a product that is safe, efficacious and effective in a given market. However, the clinical development of cell-based therapies is especially challenging given the financial restrictions that many of the companies operating in this space are working under. Two key factors were identified that could potentially reduce the burden upon small businesses and start-ups in particular.

1. Developing an understanding of regulatory / payer requirements in multiple markets is key and is becoming highly desirable in order to maximise the commercial potential of a new product.
2. Increased interaction with all stakeholders, particularly regulatory agencies and healthcare providers, can inform the decision making process and reduce cost and risk during clinical development.

Based on the two key factors above, the goals of this piece of work were to (a) enhance the understanding of regulatory / payer requirements for cell-based products in the EU / US and (b) to facilitate the best use of resources by small businesses and start ups through raising awareness of differences and changes in the regulatory / payer landscape.

Breakdown of Deliverables

1. To provide a gap analysis for the regulatory requirements for cellular products in the EU and the US during clinical trials, in order to highlight major differences between them. This will be aimed at the level of clinical trial applications and good manufacturing practice (GMP) requirements only.

2. An investigation into the potential impact of the proposed changes to the clinical trials directive on manufacturers / developers and the proposed move to a permanent mutual recognition procedure for clinical trial authorisation (CTA) applications in the EU.

3. An investigation into the key requirements of payers and regulators during the clinical development of cell-based therapeutics using TiGenix (ChondroCelect®, EU) and Organogenesis (Apligraf®, US) as case studies.

2. Approach used

Deliverable 1

- The analysis was carried out for products that are classified as either; cell-based advanced therapy medicinal products (ATMPs) in the EU or, human cells, tissues and cell and tissue-

based products (HCT/Ps) that are regulated under section 351 of the public health service act in the US. The analysis was carried on EU and US regulatory documents related to clinical trial approvals and clinical manufacture (see Further information below) but not good clinical practice requirements as they are largely covered by a harmonised *international conference on harmonisation* (ICH) guideline (ICH E6). The analysis also did not include submissions for market approval / authorisation or post-market requirements.

- As the source material completely consists of current EU and FDA guidance / legislation, it did not need to be validated. The approach taken during the analysis of these documents is similar to that applied to products that are undergoing or, have already undergone clinical manufacture. Further validation of the analysis has come via assessment and guidance from Alison Wilson of CellData Services.

Deliverable 2

- The perceived weaknesses of the current European clinical trials directive for the implementation of multi-national trials were examined using the concept paper recently published by the EC, which describes potential changes to the procedural aspects of the applications process.
- Potential solutions to making the CTA application process more efficient and cost effective for multi-national trials were taken from the concept paper and conclusions drawn. Given the requirement for stakeholder responses in order to develop the new clinical trials directive in a democratic fashion, the deliverable is self-validating.

Deliverable 3

- Case examples were used to show the data requirements for regulatory bodies and healthcare providers / payers (US and EU) in order to achieve market approval and payment for cell-based therapeutics. The case examples were TiGenix's ChondroCelect® product and Organogenesis' Apligraf® product. Case data from the two studies in question was analysed and conclusions regarding best practices drawn. Validation of the successful approach taken by two companies in question as a model for others to follow is provided by virtue of their relative success in gaining both approval and reimbursement for their respective products.

3. Results/Conclusions

Deliverable 1

When the content requirements for a CTA application (1, 2) in the EU were compared with the US equivalent (an investigational new drug application (IND)) (3), the following key differences were found.

- A clinical trials database number (Eudra-CT) is required in the EU application but there is no US equivalent.
- The quality section of the IMP dossier (EU) should take the format of European Medicines Agency (EMA guideline) CHMP/QWP/185401/2004, where as the IND should use module 3 of the CTD as a guideline for quality / CMC and has additional requirements for environmental analysis (4).

- The EU requires the manufacturer to have a manufacturing license from the NCA before commencing a clinical trial, but there is no such requirement in the US.

		In operation (EU)	Dynamic (US)	At rest (EU)	Static (US)
EU Grade	**US Class**	**Max number of particles greater than or equal to 0.5 mm / m3**			
A	100	3,520	3,520	3,520	Not defined
No equivalent	1,000	None	35,200		Not defined
B	10,000	352,000	352,000	3,520	Not defined
C	100,000	3,520,000	3,520,000	352,000	Not defined
D	No equivalent	Not defined	None	3,520,000	No equivalent

Figure 1 Key differences in the maximum allowable particulate specifications for different processing areas used for the manufacture of sterile drug products in the EU and the US. This table combines information that would otherwise only be found in separate guidance documents.

The major EU / US differences in the clinical GMP requirements are summarised as follows:

- The most significant differences are found when comparing the sterile processing, documentation and quality control requirements. There are numerous differences between the sterile processing requirements in particular, such as disparities in the terminology used and specifications for allowable levels of particulates (Fig 1) and the measurement of microbial contamination.
- The approach taken to GMP compliance by the US and EU regulators is different. For example, in Europe, annex 13 provides specific requirements for investigational medicinal products but there are no specific *regulations* for the manufacture of *investigational* products in the US. However, in the US, products manufactured for Phase 1 trials are not subject to the GMP requirements in 21 CFT Part 211, where as there is no such "phase-specific" division of the requirements in the EU.
- The following key differences are taken from an EU perspective but they are not specific to cell-based products: (a) the necessity for a qualified person to certify and release the investigational product, (b) the requirement for 100% sampling of starting / packaging materials and (c) the need to carry out self-inspection.

Deliverable 2

- The perceived weaknesses of the European clinical trials directive (1) were summarised in the concept paper as the following: (a) Largely identical information has to be sent to several different Member States leading to unnecessary admin costs, (b) the requirements in the directive are applied differently by the different national competent authorities (NCAs) often

leading to conflicting points of view over data requirements and (c) the potential for a 30 - 180 day review window, thus potentially creating difficulty in trial coordination (Fig 2).

- Changes to the directive to improve these issues were circulated to stakeholders between Feb 2009 and May 2010 (5). A second concept paper was published based on these findings (Feb 2011) with a significant procedural change to the submissions process suggested (6). The suggested change was as follows; "cooperation in assessing and following up applications for clinical trials to reduce admin costs and harmonise timelines in different EU member states".

Options:

- Single submission with a separate assessment
- Single submission with subsequent central assessment by EU-wide committee
- Single submission with a subsequent coordinated assessment procedure (CAP)

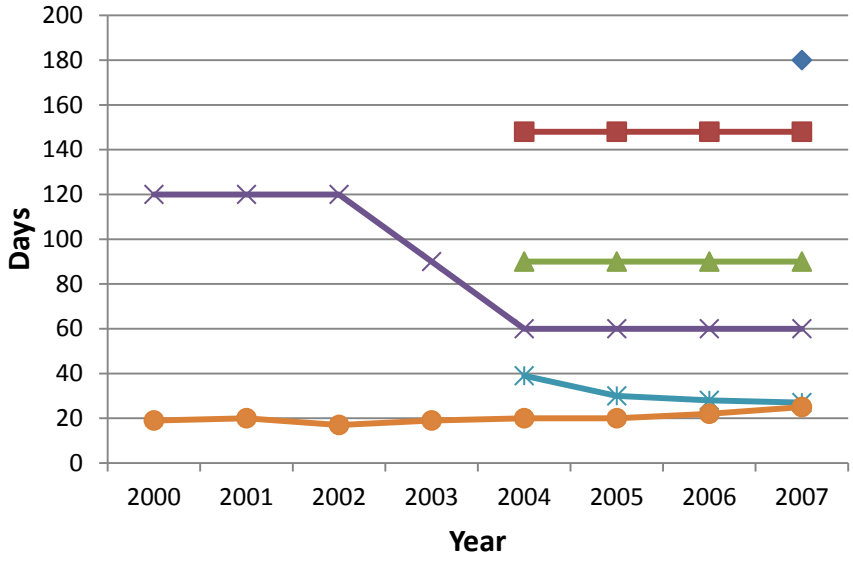


Figure 2 Average time to issue approval letter for trials with advanced therapies (7). These data are taken from the six different NCAs (anonymised) that approved clinical trials between 2000 and 2007.

The following conclusions were drawn from the public comment period:

- The vast majority favour a CAP procedure over a single assessment portal or an EU-led committee decision with a mandatory procedure in place for multi-national trials. This was partly due to some positive experiences with the trial of this procedure (the voluntary harmonisation procedure) whereby 26 applications were submitted in the first year of the trial and of those, an average approval time of 51 days was achieved.
- However, of the 143 companies that submitted comments, only one was associated with the development of cellular products. This indicates that those within the industry need to become more involved with comment periods for important pieces of legislation as they could help to shape the legislation into a form that meets the needs of the industry

Deliverable 3

Case Study 1 Key Facts – Apligraf® (Organogenesis (OI))

- Apligraf® is an allogeneic cellular product comprising a collagen sheet, a layer of expanded human dermal fibroblasts and a layer of expanded human keratinocytes. Apligraf® was approved as a Class III medical device by the FDA for the treatment of diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) (8,9,10).
- Despite gaining regulatory approval for Apligraf® from the FDA, the product did not succeed commercially at first, which was largely due to insufficient reimbursement from payers coupled with the high cost of development. The inability to gain sufficient reimbursement was put down to limited coverage and lack of suitable coding, the result of OIs limited knowledge of the reimbursement landscape at the time. However, the innovative nature of the product and its regulatory designation as a medical device (despite better fitting the description of a drug) were mitigating factors as this meant that both the company and the payers were treading new ground (10).
- A lack of interaction with the payers may also have hampered OIs reimbursement strategy, although this would not have been helped by the fact that the FDA and the major government healthcare provider (the centres for Medicare / Medicaid services (CMS)) were not able to share data – something that has since been addressed by the publication of a memorandum of understanding between the two government agencies (11).
- Several years after filing for Chapter 11, the company returned with a new reimbursement strategy whereby local coverage determinations were sought on a region-by-region basis. At this point, the company had the wealth of clinical data that had been collected since the product had been given market approval many years before. As part of this strategy, clinical cases studies were used to successfully demonstrate the effectiveness of Apligraf® to both public (e.g. CMS) and a number of private payers (12).
- In 2010, Apligraf® gained two new procedural codes from CMS that provide a better fit to the original FDA labelling. These codes prevent any unfair comparisons with lower priced treatments and so clinical benefit now has the greater emphasis (13).

Case Study 2 Key Facts – ChondroCelect® (TiGenix (TGX))

- ChondroCelect® (CC) is a cell therapy product comprising expanded autologous human chondrocytes derived from a biopsy of articular cartilage. The product was given approval as an ATMP in the EU in 2009 after receiving a positive opinion from the committee for advanced therapies for the treatment of repair of single symptomatic cartilaginous defects of the femoral condyle of the knee (ICRS grade III or IV) in adults. This was based upon CC having met the primary clinical endpoint of enhanced efficacy when compared to the current standard of care (microfracture) (14).
- Unlike the case of Apligraf® where much of the reimbursement strategy was devised post-approval, the payers were taken into consideration during the design of the pivotal trial as the secondary endpoint of the study was long-term durability of the joint after surgery. Despite being largely irrelevant with regard to regulatory approval, this data provided key cost-effectiveness evidence to payers (15).
- TiGenix have now gained national reimbursement for CC in Belgium as a result of the powerful clinical evidence that they provided to the payers and a novel strategy for a

managed entry scheme (*confidential*). However, the recently published hospital exemption clause to the ATMP regulation remains a threat to the commercialisation of cellular products if it is not implemented as intended, across Europe.

4. Recommendations

1. The EU / US GMP requirements are not always interchangeable. Many of the differences are subtle and particular attention should be paid to the differences in sterile processing, documentation and quality control requirements.
2. Work with the regulators / policy makers throughout clinical development. This can take the more conventional form of meetings with regulatory agencies or, by commenting on changes to important pieces of legislation that can affect your business.
3. Gaining a product code that provides a "best fit" to its labelling may facilitate reimbursement and end user acceptance.
4. Consider both national and European law when choosing your market. Several EU countries have national laws that may reduce your market by allowing products without an ATMP licence to be marketed legally.
5. Risk-sharing can facilitate payment as the majority of the financial risk is placed on manufacturer in the short term. However, confidence in the quality of the clinical data is paramount as early failure of an intervention / product will place the burden of cost on the developer.
6. In the short-term, European countries with national reimbursement (e.g. Belgium) are advantageous when compared to the fragmented region-by-region approach that must be taken in others such as the UK. However, in order for any product to reach the requisite numbers of patients, it may be necessary to apply several different strategies to cope with the different reimbursement landscapes in Europe.

5. What are the benefits of these findings to the UK regenerative medicine industry?

Deliverable 1

- This deliverable provided a publically disseminated gap analysis document, containing both the clinical trials submissions process and the clinical manufacturing requirements for cellular therapies in the EU and US. Therefore, developers will have a resource that allows them to understand the differences between the EU / US regulatory requirements and where they are specific to cellular / biological products.
- The output of deliverable 1 will is of particular benefit to early stage SMEs and any other institution / organisation looking to manufacture cellular products for clinical trials in both the EU and the US.

Deliverable 2

- This deliverable highlighted the procedural difficulties and protracted review times that developers of ATMPs face when submitting CTAs to multiple NCAs in Europe and how stakeholder contributions to the forthcoming revision of the European clinical trials directive will help to provide solutions to these issues.

- Many stakeholders may not have been aware of these developments and by emphasising the potential benefits of changes to the directive, it will act to raise awareness and encourage those that have not taken part this time to remain vigilant and become involved with any future developments, from which they may benefit.

Deliverable 3

- The final part of this deliverable provided two cases studies focussing on two companies (OI and TGX) that had received regulatory approval and reimbursement for cell-based products in the US (OI) and Europe (TGX). By understanding how the two companies approached the need to meet the requirements of both the regulator and the payer (and were then successful), a partial blueprint for success has been created, albeit using two very specific examples.
- The derivation and application of these two approaches, particular those taken with the healthcare providers / payers, should provide some understanding of how small companies can reach the market and gain reimbursement for their products.

6. References

1 EC Directive 2001/20/EC (Clinical Trials)

2 Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use (CT-1) 2010/C 82/01

3 21 CFR Part 312 (Investigational New Drug Applications)

4 Clinical Trial Application Form. Eudralex Volume 10 Annex 1

5 Revision of the Clinical Trials Directive 2001/20/EC. Concept Paper Submitted for Public Consultation. SANCO/C/8/PB/SF D(2011) 143488

6 Revision of the Clinical Trials Directive 2001/20/EC. Summary of the Replies to the Consultation on the Concept 'Paper'. SANCO/D/3/PB/SF/ddg1.d.3(2011)816084

7 Scherrer, B. ICREL Statistical Report: Impact of the Clinical Trial Directive on Competent Authorities (2007)

8 Falanga V., et al. Rapid realing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. *Arch. Dermatol.* **134**: 293-300, 1998

9 Veves A., et al. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care* **24**(2):290-295, 2001

10 Faria, K. Organogenesis Inc. Personal Communication (2011)

11 Memorandum of understanding between United States FDA and Centers for Medicare and Medicare Services. MOU 225-10-0010 (2010)

12 Montecalvo, A. Organogenesis Inc. Personal Communication (2011)

13 Apligraf reimbursement to benefit from new CMS codes. Organogenesis press release (November 2010). http://www.organogenesis.com/news/press_releases/press_release_new_cms_codes-11112010.html

14 Assessment report for ChondroCelect. Procedure No. EMEA/H/C/000878. EMEA/724428/2009

15 Blann, J. TiGenix. Personal Communication (2012)

Further information

1. EU and US GMP legislation and guidance used in the analysis for deliverable 1

Legislation and Guidance	
EU	**US**
1394/2007 (Advance Therapy Medicinal Products Regulation)* 2003/94 (GMP for Investigational Medicinal Products and Medicinal Products) EudraLex Volume 4 Part One - Annex 1 (Manufacture of Sterile Medicinal Products) - Annex 2 (Manufacture of Biological Medicinal Products for Human Use) - Annex 8 (Sampling of Starting and Packaging Materials) - Annex 13 (GMP for Investigational Medicinal Products) - Annex 15 (Validation) - Annex 16 (Certification by a Qualified Person and Batch Release)	21 CFR Part 211 (CGMP for Finished Pharmaceuticals) 21 CFR Part 600 (Biologics General) 21 CFR Part 1271 (Human Cells, Tissues and Cell and Tissue-Based Products HCT/Ps) -Product Recalls, Including Removals and Corrections (draft guidance) -Aseptic Processing of Sterile Drug Products (final rule) -Guidance for Human Somatic Cell Therapy and Gene Therapy (draft guidance) -CGMP for Phase I Investigational Products (final rule) -CGMP for Investigational New Drugs (draft guidance) -Points to Consider in the Characterization of Cells used to Produce Biologicals (draft guidance)

* EC Regulation 1394/2007 (Advance Therapy Medicinal Products)

What are the alternative manufacturing and supply models available to RM companies and how do the finances stack up?

Co-Authors: Mark McCall and David Williams - Loughborough University

1. Background

Manufacturing and supply of cell therapies remains complex due to high cost of goods, the cost of capital and the challenges of validation. This makes the early choice of the correct strategy important. This is difficult when information is limited early in cell therapy product development.

The aim of this work package was to understand the critical linkages between manufacturing practise, business strategy, regulatory burden and clinical demand. Key aspects of this work involved examining cost of goods supplied (COGS) for cell therapies, cost commitment and cost of cell therapy development. Early results formed the underlying structure of a computational model, which can be used to predict the cost of development for cell therapies and examine the risk and pinch points inherent in the new product development process.

This model is being used to clarify the impact of business, regulatory, manufacturing and supply models on cost of development and cost of goods (COGS). This information is useful in examining potentials for economies of scope and scale – informing the 'make or buy' decision for therapy developers.

This work package examined the available options, including the location of manufacturing relative to the patient and logistical implications. Techniques to assist developers in decision making and to understand the impact of decisions on the value system have been developed.

2. Approach used

The high level of complexity inherent in the development and manufacture of cell therapies resulted in the need to adopt multiple methods of analysis that allowed the work package to use both qualitative and quantitative data. Value project partner case studies were used to inform a framework for handling the factors that contribute to COGS.

This high level framework has four levels:

- Value system
- Supply chain
- Unit of scale
- Process economics

The four level approaches allowed VALUE to manage the information necessary in estimation of COGS. These four levels are represented in a cost framework called the Cell Therapy Cost Chain (CTCC) developed within VALUE.

Early COGS work highlighted that an industry knowledge gap existed in understanding the relative impacts of in market manufacturing and delivery costs and development costs. Exploratory case studies, undertaken in conjunction with WP4 (Finance and Business Models) gathered additional information regarding the interdependence and iterations present in new product development,

together with cash burn and duration of development activities. Financial data were collected for four companies developing cell therapies by analysis of publically available quarterly financial reports and compared with developmental milestones as highlighted by company press releases and publications.

This data allowed a simulation model to be built using the information-based approach of Eppinger's Design Structure Matrix (DSM) coupled with discrete event simulation and Monte Carlo methods to evaluate the distribution of risk, cost and value within the interdependent development activities undertaken in bringing a cell therapy to market.

The model provides a tool to assist informed discussion and projection of development task cost and duration including concurrency, iteration and rework, and can take account of learning. Results of the use of the simulation program can be used to compare the relative merits of alternative product, development and manufacturing strategies and the associated impacts on time to market, cash burn and return on investment.

3. Results/Conclusions

3.1 Manufacturing value and cost

Manufacturing as a tool for adding value to cell therapies

Manufacturing creates value and incurs cost. Evaluating the value of cell therapy innovations in their early stages of development offers several benefits but also holds significant methodological challenges. The creation of value, containment of cost and management of financial risk are critical proficiencies of companies developing cell therapies and are intrinsically linked to the correct choice of manufacturing strategy.

Cost of Goods for cell therapies

To develop an understanding of the costs and resources required to take a product to market as well as a firm predication of market price we must take into account the requirements of developers, investors and payers throughout the product development process along with the impact of operating a highly regulated industry. This research will need to examine the holistic system.

Cell Therapies also present unique challenges for development into products.

- Expansion of cells in culture is *extremely* time consuming
- All aspects of cell production must take place within a highly regulated and defined environment – GMP, GDP, GCP
- Manufacturing sites can be centralised or distributed but must produce identical products to those approved during development.
- Post production cell cultures must be maintained in highly defined environments
- All input materials must meet strict regulatory requirements
- Process consistency and yield is poorly understood and varies widely over the range of potential manufacturing systems.

A framework that describes the costs associated with developing, manufacturing and developing cell therapies has been built. The framework's structure helps manage the complexity of information

needed to understand COGS and how COGS is 'committed' into a therapy as it is developed. This framework is broken down into four levels.

Value system (Blue level)

Influences when COGS are committed into a system and relates COGS to business strategy and capital investment. This level has been examined by specific case study work (in conjunction with WP4) and a resulting computational model of the value system.

Supply chain (Green Level)

Correct structuring and integration of supply chain elements impact how COGS is distributed between point of manufacture and delivery. It also impacts the regulatory cost burden placed on a therapy. This work has been examined in detail by VALUE WP3 partner NHSBT (See NHSBT report p66).

Unit of scale (Yellow Level)

This describes the relationship of location, manufacturing strategy and scale to cost commitment (as capacity is built) and COGS as it dictates what economies of scale can be achieved, see Figure 1. This work was examined by analytical cost models and will be subject to addition work by VALUE partners upon project completion.

Units of Scale
Factory
Line
Processing Machine
Unit Process
Hub and Spoke
Enabled Clinic
Near Patient
GMP
Medical Device
Intra-operative

Figure 1 – Potential units of scale

Process economics (Orange Level)

Process economics of the central manufacturing process describes the costs incurred in physically creating the product value. This work is being undertaken by TSB Value systems project – REALISE. Work on this area has been limited to simple activity based costing practise but this area must be included in any comprehensive cost framework.

Figure 2 shows the components of the framework and the detail of build-up of costs at each level.

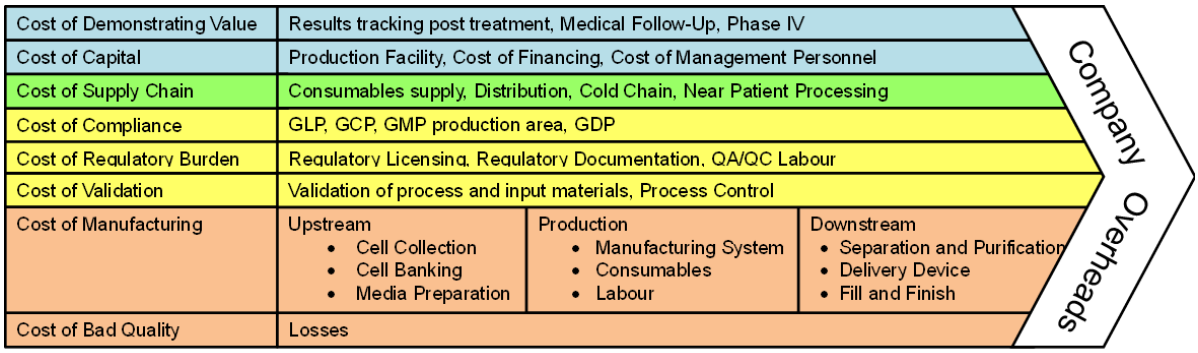


Figure 2– Cost Framework for Cell Therapies

Cost Commitment

For cellular therapies, like all medicinal products, the path to a marketed product involves a long and exhaustive journey through basic research, discovery of a therapeutically effective cell type, preclinical development tests, process development, increasingly complicated clinical trials and regulatory approval. Several years and significant financial investment is needed to undertake this process. Because of its complexity and the lack of maturity of the industry, a major risk in cell therapy development and commercialisation is the lack of information that can inform process development and investment decisions.

During the development process critical decisions are often made with imperfect information. This can result in the need to redevelop or 'rework' parts of the development process. An example of this would be the need to redo some non-clinical and clinical testing following a change in manufacturing system, process or inputs. Early VALUE work highlighted how information improves over the process development and improvement process; instances of information required are shown in Figure 3.

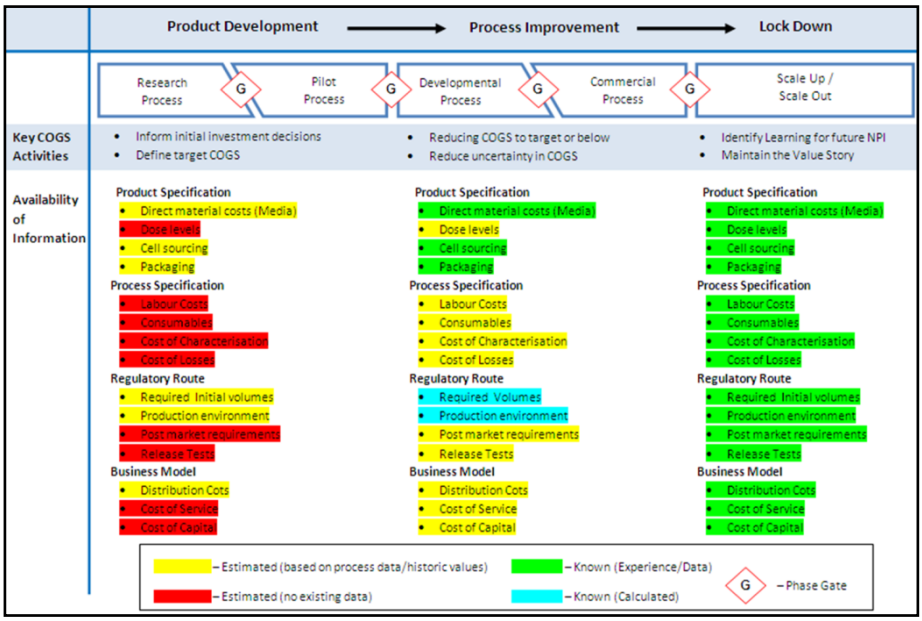


Figure 3 –Information Availability during Cell Therapy New Product Development

A method has been presented for scoping the gross commercial opportunity (or "headroom") by establishing a simple price ceiling available to a manufacturer based on an estimate of clinical effectiveness within a cost–utility model (1). The aim of this work was to provide a quick method for rapid decision-making that would support, for instance, the selection of promising concepts from a larger pool of options. However, the drawbacks to the 'headroom' method are that it is only applicable to healthcare systems where cost effectiveness is measured using the QALY (Quality-Adjusted Life Year) and it only provides information surrounding the possible market price of a cell therapy (or any clinical treatment).

The availability of the headroom method and problems associated with early stage decision uncertainty led to VALUE developing a modelling tool (the 'Value Systems Model' outlined below) that could illustrate how different development decisions would impact cost and time to market for cell therapies. This increases the value of early stage cell therapies by reducing risk to investors and allows for more accurate predictions of cost in market, leading to calculation of potential times and levels of return on investment.

Case Studies of Cell Therapy Company Development

Creation of the value systems model required additional information describing development costs and timeframes that could not be extracted from initial VALUE case studies. Additional case studies outside the VALUE defined case studies were therefore undertaken to capture the key value steps of a developing regenerative medicine company, their business context and their position in the new product development process in sufficient detail to understand development interdependencies, costs and timeframes. This also allowed for the study of value is created and distributed by the developing company to the surrounding value system of investors, regulators and healthcare providers.

Case studies of four regenerative medicine companies were compiled by recording their historic stock values and outstanding share levels. Aastrom Biosciences, Athersys Ltd, Cytori Therapeutics and Pluristem Therapeutics were chosen as they represent companies developing autologous and allogeneic products. Company value was measured using the market capitalisation of each organisation. Market capitalisation (market cap) is defined as equal to the share price times the number of shares outstanding of a publicly traded company. Newsflow was plotted alongside historic market capitalisation to determine if public dissemination of company information had influence on the publically perceived value of each company. Instances of financing by licensing agreements, stock offerings and private investment were recorded and examined to determine the strategies adopted by regenerative medicine companies in financing development and value creation.

3.2 Value Systems Model for Cell Therapy

A proven means to address and reduce problem complexity is through modelling. A model is a representation of reality that is built, analysed, and manipulated to increase understanding of that reality. A good model is helpful for testing hypotheses about the effects of certain actions in the real world, where such actions would be too disruptive or costly to try in the real situation. Here, we are interested in models that will help us represent, understand, manage, and improve the new product development process for cell therapies and its associated impact on cost and time.

Value systems modelling

To address such issues, a matrix-based tool called the Design Structure Matrix (DSM) has evolved. This method differs from traditional decision support techniques because it focuses on representing information flows rather than work flows. The DSM method is an information exchange model that allows the representation of complex task relationships in order to determine a sensible sequence for the tasks being modelled. While new to translational medicine, DSM models have a proven track record of use in other regulated and high value manufacturing industries such as aerospace and nuclear energy.

Adding quantitative information (cash burn and duration) to the DSM and the integration of Monte Carlo event simulation was used quantify the impacts of process interdependence changes on cost and time risk. The resultant models can be used in predicting and studying; i) the optimum order for process development tasks and ii) probability of moving from pre-clinical development to end of phase III studies within time and cost restraints. Organisations can use this method to model development scenarios before embarking on expensive development programs and help secure funding by better communicating and managing risk. Example outputs from this model – examining cost and duration for development of an orphan indication and non-orphan indication are included at the end of this report as Section 9, significantly this model allows rate of recruitment to clinical

trials to be taken into account. Modelling also demonstrated the importance of good early process design, importantly this has an large effect on last stage development costs. The model and results of exercising the model are described in full in McCall et al 2012 2.

3.3 Unit of Scale – Analytical cost models

Within VALUE we have studied different approaches that we currently foresee for validation of cell therapy manufacturing. The purpose of this work was to investigate potential manufacturing approaches that reduced – to a manageable level – the regulatory cost burden associated with cell therapy in particular the costs of the demonstration of *comparability* across multiple sites or units of production. This must be understood in order to both manage the complexities of the supply chain for living products and to generate scalable manufacturing solutions that allow recovery of economies of scale and progressively manage cost of capital.

Measured manufacturing cost approach implications

Current manufacturing approaches rely primarily on cross validation and comparison of products if manufactured at multiple sites – possibly requiring, as the worst case, for manipulated cells repeat of clinical trials to demonstrate mutual comparability of sites. We term this approach "measured manufacturing" as it primarily measures/characterises the outputs of a system as a means of risk reduction. For a measured manufacturing approach, the need to measure and compare the outputs of each unit of production against each other unit necessities a high cost of validation of the entire multi-unit system. Where;

n = number of units of manufacture

C = cost of validation of the first unit of manufacture

Cn = cost of validating each subsequent unit of production and measuring output against each other unit of production.

If each site needs to be compared against each other site then. It can been shown that

$$\text{Cost (Measured)} = \text{C} + \text{Cn}\frac{(\text{n}-1)}{2}$$

However this assumption assumes no learning or economies of scale from site to site. Future development work will be undertaken to establish what a reasonable level of C will be. As a consequence of the detail of the regulatory approach for cell therapies, C could be relatively low for manufacturing symptoms with limited manipulation (or no manipulation) of cells.

Controlled manufacturing cost implication

However at large value of n – for example an autologous near patient expansion system, one of the current most significant opportunities to deliver the benefits of cell therapies – the cost of managing regulatory burden under the above approach becomes overwhelming. We have examined a second approach to managing this burden. A controlled manufacturing approach validates multiple sites by developing a standardised process with well defined outputs that each subsequent site is validated against. For a controlled manufacturing approach, the need to measure and compare the outputs of each unit of production against a single standard process results in a different approach to estimating the validation cost of the systems.

Where:

n = number of units of manufacture
C = cost of validation of the first unit of manufacture
S = Additional cost of developing a controlled and standardised manufacturing process able to reap both economies of scope and scale by being comparable across a number of manufacturing sites
K = Cost of demonstrating the equivalence of each subsequent unit of manufacture to the standard process.

This gives

$$\text{Cost (Controlled)} = C + S + k\,(n-1)$$

3.4 Comparison

Figure 4 shows a comparison of the cost of the two approaches for some representative values of the variables indicating that the costs cross over and that there is a driver for controlled manufacturing – in for example multiple enabled clinics or via more widely applicable processing system platforms as it allows therapeutic *availability* at a lower cost burden. This reduction in burden will contribute to the financial headroom for the therapeutic incentivising developers and ultimately reduce system cost to the health economy.

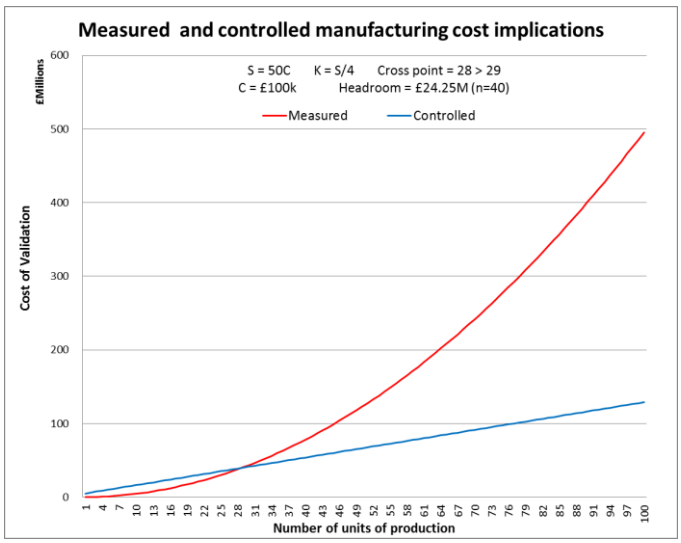


Figure 4 –Comparison of validation costs

We recognise that C, S and k require advances in manufacturing and regulatory science including capable measurement (process measurement and characterisation) systems and communication with the regulator as to appropriate and acceptable levels of validation and control. It is anticipated that approaches will be process (and indication) specific.

4. Conclusions

Cost frameworks

- To develop a comprehensive understanding of the factors that impact cost of goods supplied (COGS) for cell therapies a developer must understand how cost is influenced by the entire value system surrounding a cell therapy. Use of the developed framework can guide this process.
- Iterations and interdependencies within the value system have a high impact on cost and time needed for new product development for cell therapies.
- The unit of scale of manufacture is critical in relating location, manufacturing strategy and scale to cost commitment as capacity is built and COGS as it dictates what economies of scale can be achieved. Scale up needs automation and cost effective capable process development, design and validation to enable economies of scope and scale to be realised.
- Supply chain characteristics influence how COGS is distributed between point of manufacture and delivery. It also impacts the regulatory cost burden placed on a therapy. A supply chain algorithm developed by NHSBT (VALUE partner) interprets supply chain requirements to predict supply costs for cell therapies. More information on supply chain requirements is included in the following report by NHSBT.

Case Studies of Cell Therapy Company Development

- All the companies studied are based on a single product technology platform. This has benefits in generating value for the company as the platform can be leverage to target multiple indications, opening up more market opportunity for a comparatively low development cost. A single technology or process base has advantages in terms of regulatory burden. A single platform removes the need to repeat pre-clinical process development and transfer to GMP when diversifying
- In addition to standardised platforms, all the companies use at some point in the process partner companies in co-development. This has key benefits in terms of financing, but also in terms of investor's perception of value. If the company does not have the resources to develop all the potential markets of their technology they can licence the technology to another member of the value system. This generates cash flow which improves value. Partnering with a large pharmaceutical organisation as Pfizer-Athersys can cause a dramatic increase in share price. Partners may also provide access to short term loan financing during the periods between clinical milestones where investment is hard to get.
- Clinical data is the gold standard value creation mechanism. The successful filing of IND etc. is frequently enough to generate some interest and share price increase. However for long lasting value creation clinical data is needed. Investors are far more likely to invest once any form of statistically significant data is published.

Value Systems Model

- The newly developed model can be used to understand the impact of any significant changes relating to development duration and cost. As shown in the example at the end Section 9, the impact of a relatively small change can identify large savings in cost or time to

market. This will be expanded with further scenario analysis to assess changes in a variety of key areas to identify critical risks and decision points within the development pathway.

Unit of Scale – Cost Models

- The newly developed model can be used to understand the impact of any significant changes relating to development duration and cost. As shown on p65, the impact of a relatively small change can identify large savings in cost or time to market. This will be expanded with further scenario analysis to assess changes in a variety of areas to identify critical risks and decision points within the development pathway.

5. Recommendations

- Companies engaged in the development of regenerative medicine and cell therapy products need to understand the cost of delivering their product or service early in the development cycle. Early estimation of cost of goods supplied (COGS) and cost of development can provide information that aids development decision making. Investors in regenerative medicine companies can use this information to inform estimations of return on investment in conjunction with pre-established methods for prediction of the reimbursement price.
- The use of a structured cost framework, analytical cost models and simulations models can provide the ability to predict COGS and Cost of development. While models developed within VALUE have been built specifically using case studies of cell therapy development, this approach is applicable to any medicinal technology involving complex development processes.
- Unit of scale analysis has identified that important therapeutic approaches requiring manufacturing at a number of sites are particularly problematic. Allowing this option for therapeutics that require more than minimal manipulation requires new process and indication specific advances in manufacturing and regulatory science. Continued investments by the UK government in translational science should help overcome these issues and aid development of the regenerative medicine industry.

6. What are the benefits of these findings to the UK regenerative medicine industry?

Cost Framework

- This deliverable provided a structured framework that allows them to understand the impacts of different variables on cost of goods supplied (COGS) and how they should be accounted for. It will form the first part of a publication (mid-late 2012) in a commercially focused industry journal, allowing developers and other members of the UK regenerative medicine industry access to it.
- The dissemination of the cost framework work will is of particular benefit to early stage SMEs and any other institution / organisation looking to manufacture cellular products that has little experience of estimating and managing COGS.

Case Studies of Cell Therapy Company Development

- This deliverable highlighted the value transitions that must be accomplished by developers in bringing a new cell therapy to market. Many stakeholders may not be aware of the impact clinical and process development milestones have on securing investment. When published this work will act to raise awareness of how enterprise value is built (and retained) during company development.

Value Systems and Cost Modelling

- These models provide tools to assist informed discussion and projection of development task cost and duration. Results of the use of the simulation program can compare the relative merits of alternative development and manufacturing strategies open to developers which are informed by the analytical cost models.
- Models provides a tool for the reduction of risk and uncertainty for investors in regenerative medicine by informing estimations of return on investment in conjunction with pre-established methods for prediction of the reimbursement price of medical treatments. While built specifically using case studies of cell therapy development, the model structure and foundations are applicable to any medicinal technology involving complex development processes.
- Unit of scale analysis has indentified that important therapeutic approaches requiring manufacturing at a number of sites are particularly problematic and that allowing this option for therapeutics that require more than minimal manipulation requires new process and indication specific advances in manufacturing and regulatory science.

7. References

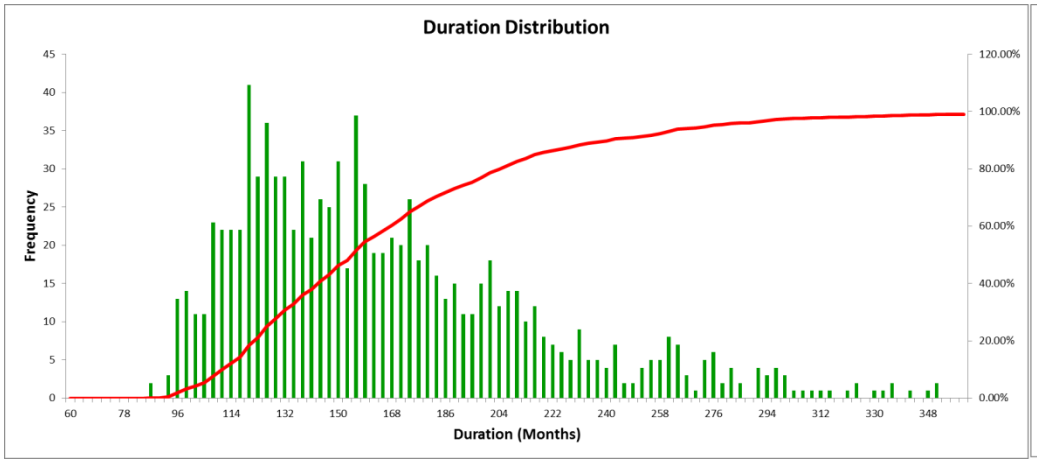
1 McAteer, Cosh et al. 2007

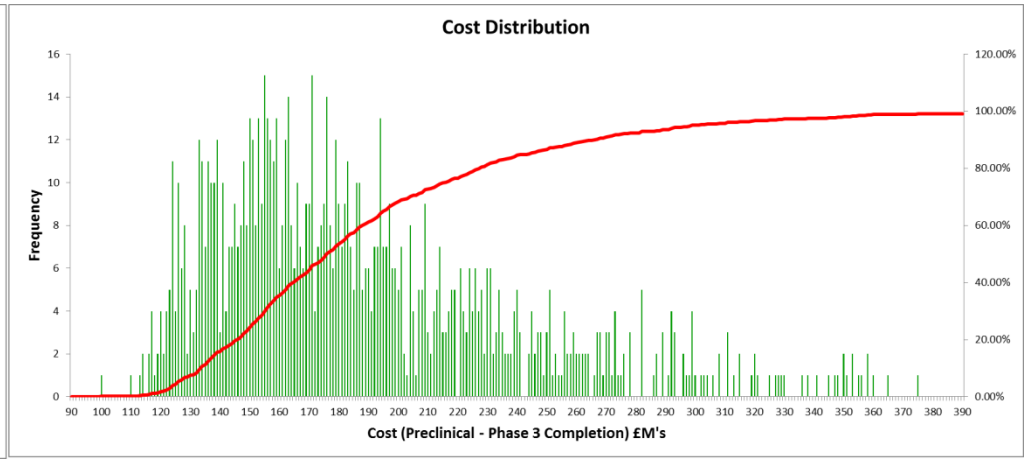
2 McCall et al. 2012

Loughborough University Working Paper HEG/104.0/11 - *Value Milestones of Regenerative Medicine Companies* M. McCall et al.
Loughborough University Working Paper HEG/105.0/11 - *Cell Therapies Value systems model.* M. McCall et al.
Loughborough University Working Paper HEG/106.0/12 - *Unit of scale for cell therapy – cost implications*. M. McCall et al

Further information: Value Systems Development Cost Model Example

These results illustrate the estimated time and cost of developing a cell therapy from pre-clinical development to end of phase III clinical trials. The cost and duration has been calculated for critical limb ischemia.





Probability of Success	20%	50%	80%	99%
Duration	122 months (~10yrs)	155 months (~13yrs)	204 months (17yrs)	351 months (~29yrs)
Cumulative Cost	$146.4M	$176.6M	$227.5M	$365M

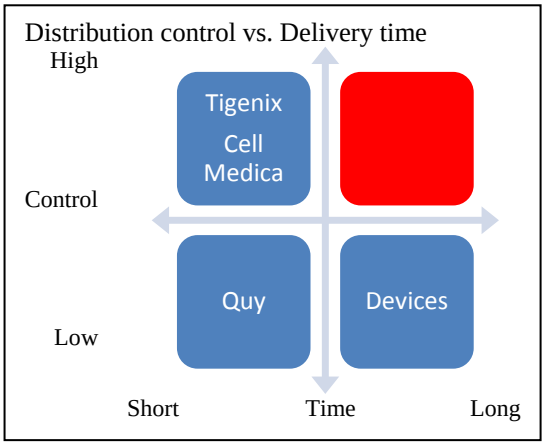
How do companies assess the efficiency and cost effectiveness of their supply chain early enough to make a business impact?

Lead Author: Simon Ellison - NHS Blood and Transplant

Summary

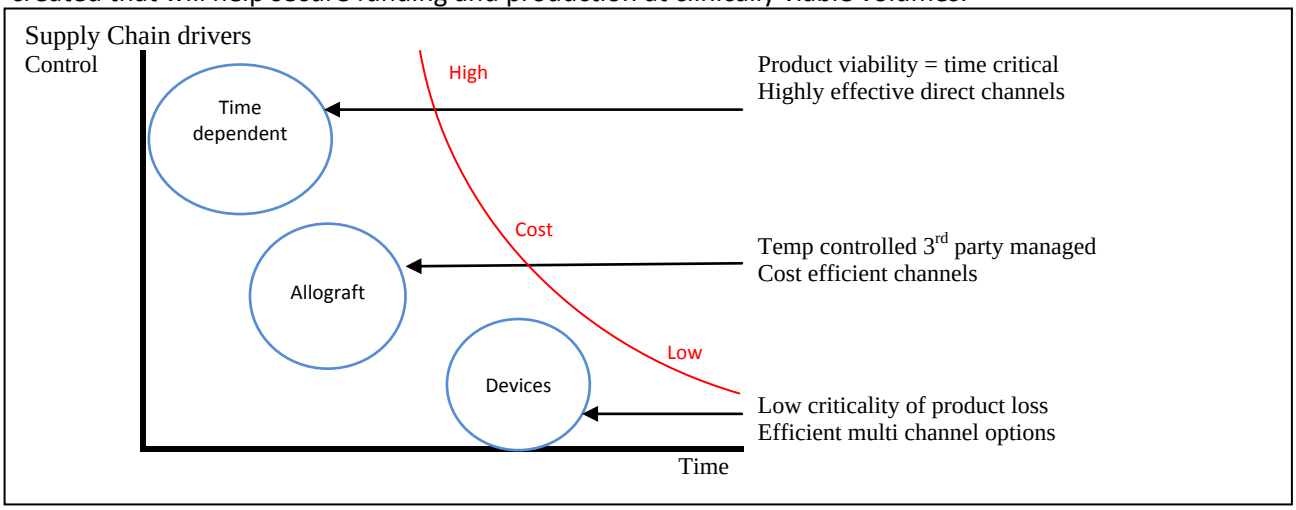
The aim of this work package was to understand the critical issues within cellular therapies relating to its cold supply chain, apply these learnings within current NHSBT operations, and look to understand how current supply chain can be used to deliver future needs. The learnings were then used to create a tool, which can be used by organisations to predict the most viable supply chain models and manufacturing strategies.

The data, produced through analysis of questionnaires compiled during case study interviews, led to conclusions that the critical objectives within distribution channel design are maintenance of product 'viability' through time, temperature constraints and/or the criticality of product delivery. All of the items in the case studies, bar those akin to medical devices, require that the critical item (inbound cell or outbound therapy) is not compromised from time and temperature considerations. That is to say that there is a requirement for the selling organisation to maintain control over the product in the pipeline to ensure both the product security in terms of guaranteed delivery and in maintenance of a viable product. The level of control required is the key driver of cost.



Therefore, the design of the distribution channel must deliver those objectives within the cost parameters. These are driven by the complexity of the product and the resultant supply chain, the level of competition, the volume of the market and the level of margin that the product and market will entertain.

The results and analysis led to the creation of an algorithm predicting; i) the best supply chain delivery systems, for both inbound cells and outbound therapies; and ii) the most likely manufacturing strategy (own assets vs. contract, etc). Companies can use this to model therapeutic delivery models before embarking on expensive R&D and to enable robust business models to be created that will help secure funding and production at clinically viable volumes.

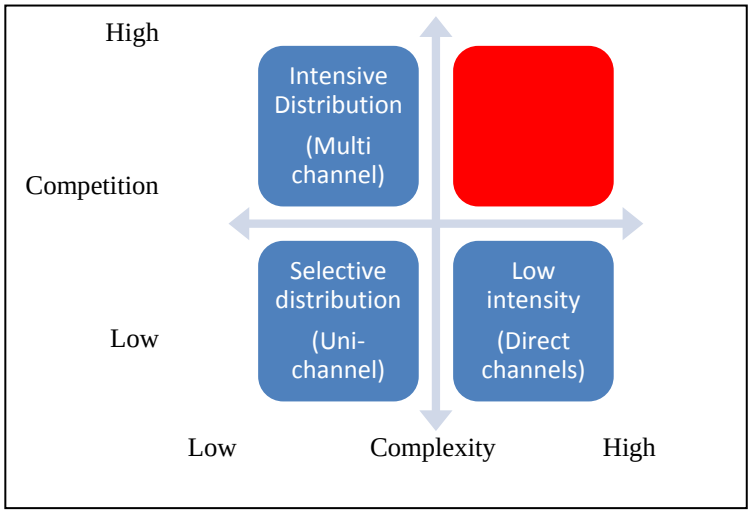


Key Drivers

Product complexity

The distribution channel has to ensure that 'explanation' of the product (how to use, training, etc) is properly achieved in the channel – the more complex the product, the more explanation required and the greater the need for the parent company itself to be active in the channel. This is more important the greater the degree of competition in the market as the need for competitive advantage comes into plan.

Figure 2 – Competition in the market vs. Complexity of the product offering



All the possible channels must conform to proper regulations for the types of product handled and these steps within the channel 'validated' to meet those regulatory requirements.

Thus the channel design for each product needs to manage the time and environment restraints and allow for explanation of the product effectively to its customers, in relation to the perceived 'value' of the product - in terms of competitive procedures and products, price/benefit of the product, all within the cost parameters determined by the margins achievable for the product. This is best show by TiGenix who have amassed clinical information to convince surgeons of the advantages and efficacy offered by ChondroCelect, and created a user guide to help overcome reimbursement hurdles by giving guidance and information to applicants.

Costs

In considering channel design the overall supply chain costs must be given full consideration. Generally, for cell therapies product manufacturing costs per unit are very high in relation to the potential distribution cost. The general cost of ownership of assets is also high. As a result, the total number of sites involved in the production of cells or is likely to be low and the need to maximise return on those assets becomes a very important factor. Potentially, sharing of those assets – contract manufacturing and leasing of space and equipment – will become a distinct consideration in the supply chain design, and/or maximising variable versus fixed costs – a 'plug and play' approach for collaborative supply chains that are designed to minimise investment and maximise return on IP.

Figure 3 –Allowable time to delivery vs. Market Volume

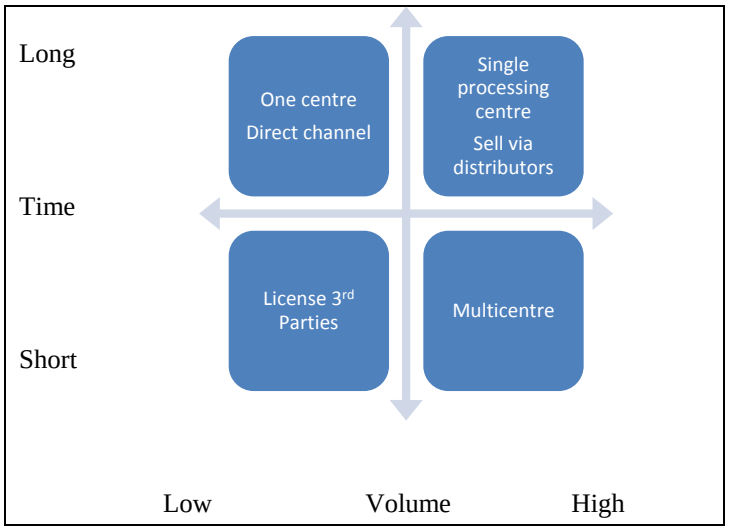
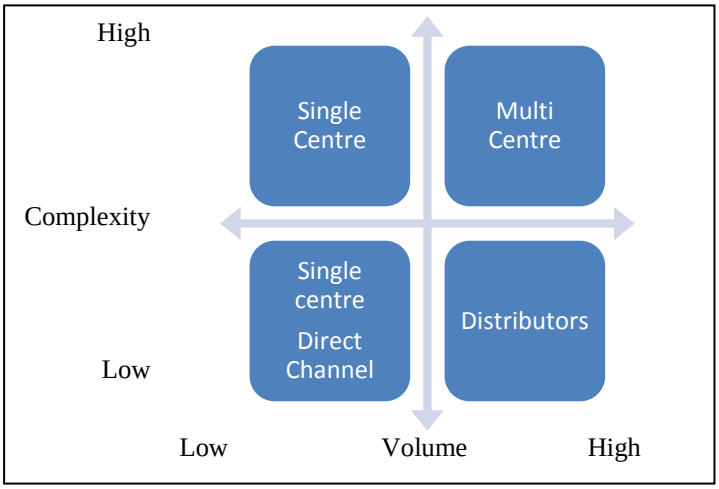


Figure 4 –Complexity of product offering vs Market volume



If patients are able to travel to specialist treatment centres, most often at a distance from the processing facility, but where there is considerable competition in the market and the volume in the market is relatively high or the product life-span is extremely short or badly affected by travel, there may be a requirement for dispersed facilities closer to the end-users.

Low cost treatments are the ones most likely to have the highest volumes in the markets with correspondingly higher number of treatment centres. This is problematic where low cost of treatment is accompanied by relatively low margins in the product whilst at the same time; the nature of the products requires a fairly rapid transit through the channel. To remain feasible these treatments are the most likely candidates for contract or licensing agreements.

Figure 5a – Effect of Gross Margin vs. Market Volume

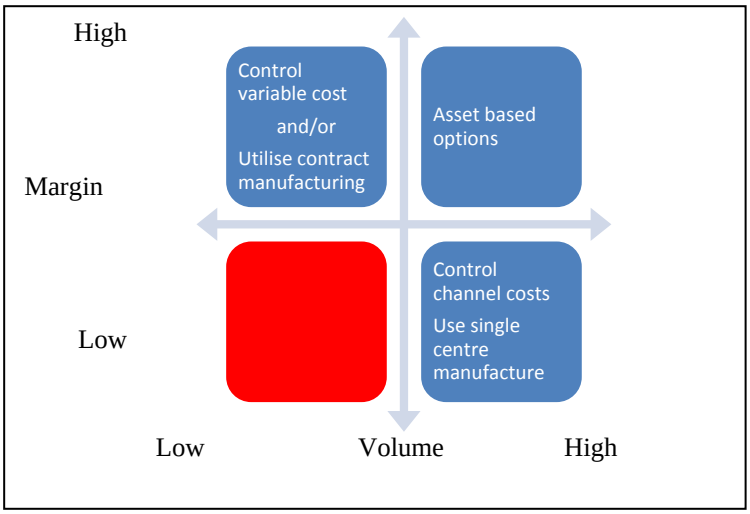
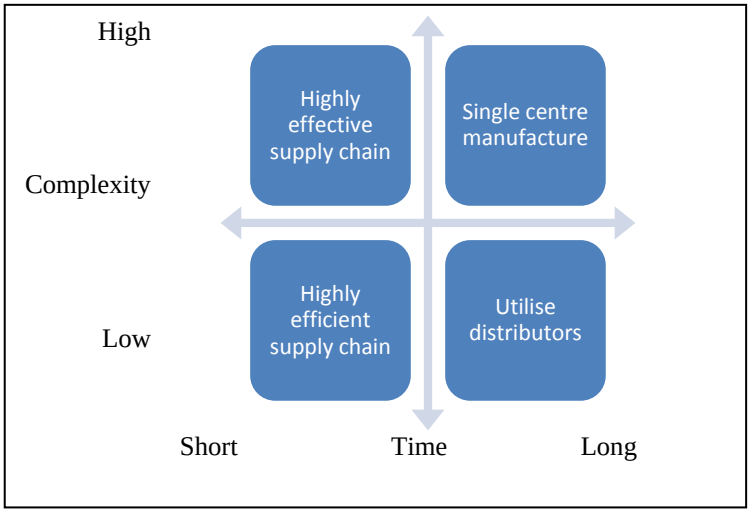


Figure 5b – Product complexity vs. Allowable time to delivery



In summary:

1. Where margins are high but volumes are low, a single processing unit at a distance from the end-market is likely to deliver the margin required to offset the higher distribution costs.
2. Lower margin, high volume products require routine, cost-efficient channels that maximise the contribution available.
3. Low volume products require effective, more agile channels that can meet variable needs.
4. High volume products require intensive distribution channels whilst low volumes require more selective channels to the market.

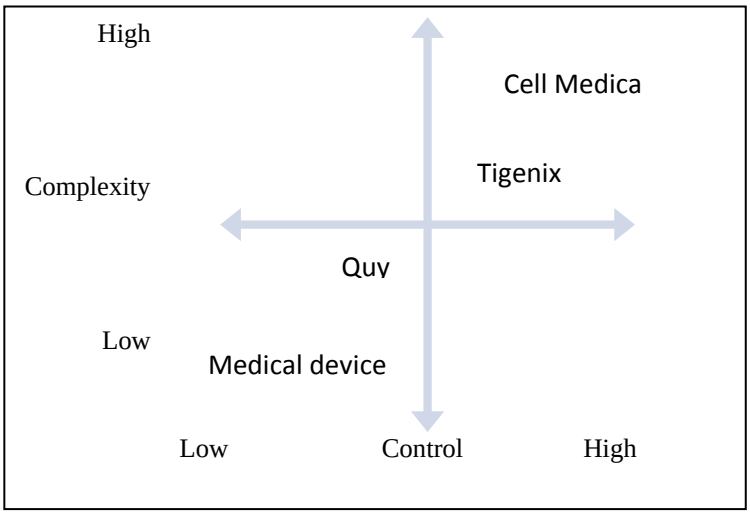
Risk

There is differentiation in the market between products that have uni-directional distribution requirements (i.e. Allogeneic models where few deliveries are required to create a master cell bank)

and those that have multi-directional channels (i.e. Autologous where every inbound shipment of cells is matched by an outbound therapy).

The degree of 'control' required in the uni-directional channel is much lower than that required in the multi-channels. To maintain control at acceptable costs these complex multi-directional channels also require being highly efficient and well practised. In these channels the physical loss or degradation of material in the channel at any point may well be more 'catastrophic' than in the uni-directional channels, again leading to a need for a higher degree of control (e.g. Cell Medica).

Figure 6 –Complexity of product offering vs. Control required within the distribution channel



Multi-directional channels have multiple and complex time management requirements (sample kits, biopsies, manipulated product etc) potentially multiple regulatory bodies to satisfy and possibly multi-step processing. Criticality for the products at any stage to reach the destination in time and environmentally intact is high. These channels therefore require a high degree of control by the selling company.

IPR

Affecting channel choice also will be the location of IP in the supply chain. Protection of the IP and its exploitation are key constraints in the marketing of these products. If IP is held in the processing of products then it is likely that ownership of processing facilities will be undertaken, even if this is contrary to channel indications. IP in the manipulation however allows broader choice in supply chain design – contracting of third party facilities and personnel or leasing of facilities becomes an option if the IP can be protected in these circumstances. IP in the membranes utilised in combination products may point to an opportunity to maximise utilisation – using owned facilities to manufacture the membranes then contract manufacture to expand cells and combine into a completed therapy.

Algorithm

Case study interviews and questionnaire responses enabled the creation and relative weighting of key drivers. These were built into an electronic algorithm balancing answers to 41 questions to deliver recommendations on the most viable supply chain and manufacturing solutions. To ensure

accurate results the algorithm was applied to current cell therapy organisations, producing recommendations analogous to the actual business models being delivered.

The challenge for many organisations, especially those emerging from clinical/academic backgrounds, is to understand what research concepts and business models are going to produce therapies at clinically viable volumes.

The algorithm can be used to understand the impact of any changes within the critical parameters of a therapy. As shown below, assessing the impact of a relatively small change can identify critical issues. This could be expanded within scenario analysis to asses' changes in a variety of areas to identifying targets and milestones within the development pathway.

Example

- Planned Outcome
  - Pre-clinical studies indicate that the cells/therapy is viable 24hrs after production
- Actual Outcome
  - Therapy is not efficacious post 12 hours
- Business Impact
  - Therapy cannot be delivered globally from a single manufacturing site, resulting in: -
    - Reduced market potential
    - Increased costs due to: -
      - Higher control required over supply chain to ensure delivery on time
      - Multiple manufacturing sites required to deliver to multiple markets

Conclusions

Overarching

For any therapy, regardless of position within its development cycle, distribution channel decisions can be made, by understanding the key areas discussed above and answering questions around:

- Degree of Control
- Market Size
- Competitive position
- Product Complexity
- Gross Margins
- Effect of cell/therapy loss in transport
- Temperature
- IP
- Time

These considerations lead to a determination of the channel requirements, built around parameters of:

- Efficiency vs. Effectiveness
- Direct or Indirect (From producer to end-user)
- Central or Dispersed distribution points
- Short or Long channels
- Fast or Normal delivery speeds

From these parameters it is possible to describe the method of delivery based on typical channels available:

- Over-night parcel deliveries (hub & spoke),
- Non-Dedicated but Accompanied ('milk-round' style delivery runs)
- Dedicated, Accompanied courier (point-to-point)

Current Supply Chains

"*Regenerative Medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function*"1. Cell Therapies are a sub section of this, requiring transport within complex regulated systems that control critical factors such as time and temperature. If viewed through a supply chain lens they can be seen as similar to the transport of blood, bone marrow, solid organs or clinical allograft.

The NHS, and other health providers throughout the world, currently receives significant volumes of these products. A future could therefore be foreseen where the supply chain for cell therapies is absorbed into current delivery models and delivered by the NHS, in the UK.

Algorithm

The algorithm has been built based on the conclusions above and validated with currently operational cell therapy businesses. Producing results based on relative weighting between each key consideration. Therefore although the algorithm is generic and cannot give all the answers, it does provide a key insight into the optimum delivery channels and is based on information available to early stage researchers. It can therefore be used at an early stage to fast fail therapies or optimise planned development pathways.

---

1 Mason C. and Dunnill P. A brief definition of regenerative medicine. Regenerative Medicine 3(1), 1-5, 2008

Further information: Algorithm Results

	Market and Product Characteristics							Supply Chain Characteristics						
	Effect of loss of inbound sample/biopsy	Effect of loss of outbound product	Market Volume	Product Gross Margin	Product Complexity	Degree of Competition	Degree of Control	Efficient vs. Effective	Direct/ Indirect	Central/ Dispersed	Short/Long	Fast/ Normal	Inbound	Outbound
Cell Medica	Problematic	Catastrophic	Speciality	High	Complex	Low	High	Effective	Direct	Central	Short	Fast	Courier	Accompanied
TiGenix	Problematic	Catastrophic	Limited	High	Highly Complex	Medium	High	Efficient	Direct	Central	Short	Normal	Courier	Accompanied
Quy	Problematic	Problematic	Limited	Medium	Highly Complex	Low	High	Efficient	Direct	Central	Short	Fast	Courier	Courier
Pluristem	Inconvenient	Problematic	Mass	Low	Complex	Medium	High	Efficient	Direct	Central	Short	Fast	N/A	Courier
Tengion	Problematic	Catastrophic	Speciality	High	Highly Complex	Low	High	Effective	Direct	Central	Short	Fast	Courier	Accompanied
Altrika	Problematic	Problematic	Limited	Low	Highly Complex	Medium	High	Efficient	Direct	Central	Short	Fast	Courier	Courier