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**TSB REGENERATIVE MEDICINE PROGRAMME:
VALUE SYSTEMS AND BUSINESS MODELS**

REALISE PROJECT

**METHODOLOGY FOR THE ANALYSIS OF LIFE SCIENCE INNOVATION
SYSTEMS (ALSIS) AND ITS APPLICATION TO THREE CASE STUDIES**

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Roslin Cells



KLCE Consulting



Contents

Executive Summary	4
1. Introduction	7
2. Interdisciplinary methodology for the analysis of life science innovation systems (ALSIS).....	7
Figure 1. Innogen Centre Research Programme	8
2.1 Business Models	9
Figure 2. Structure of the ALSIS Methodology.....	10
2.2 Value Chains	10
2.3 Value Systems	11
2.4 Scenario Analysis.....	11
3. Regenerative medicine therapies and their commercial potential.....	11
4. Application of the ALSIS methodology: data inputs and analytical approaches	15
4.1 Data Collection for Innogen research.....	15
4.2 Development of qualitative business models and value systems	15
4.3 Quantitative analysis and scenario development.....	16
5. Conclusions.....	17
5.1 General Conclusions	17
5.2 ALSIS Methodology	18
5.3 Insights from Case Studies	19
References.....	20
Annexes	23
Level 2 maps (Figures A1.1, A2.1 and A3.1)	23
Level 3 maps (Figures A2.2 and A3.2).....	23
Annex 1. Clinical Grade Pluripotent Stem Cells Case Study.	24
A1.1 Background.....	24
A1.2 Description and Analysis of the Value System Map	24
A1.2.1 Starting Material Procurement (dark blue boxes)	25
Figure A1.1 Level 2 Value System Map – Summary Model of Clinical Grade Pluripotent Stem Cell Lines (print on A3 paper for legibility)	26
A1.2.2 Product Development from the Starting Material within the Company (light blue boxes).....	27
A1.2.3 Markets and Commercial Outcomes (yellow boxes).....	28
A1.3 Scenario: Variation in Ability to Supply Clinical Grade Stem Cell Lines	29
A1.4 Conclusions	30
Annex 2. Bio-Artificial Liver Device Case Study.....	32
A2.1 Background.....	32
A2.2 Description and Analysis of the Value System Map	32
Figure A2.1 Level 2 Value System Map – Summary Model for BAL Device Development (print on A3 paper for legibility)	33
A2.2.1 Cell line procurement and differentiation	34
A2.2.2 Bioreactor and Cell Combinations	34
A2.2.3 Possible Partnership and Business Models.....	35
First Business Model – Path A	35
Second Business Model – Path B	36
Third Business Model – Path C.....	36

A2.3 Scenarios and Critical Points for the BAL Device Case Study: Impact of Manufacturing Decisions on Product Delivery	37
A2.3.1 Issues regarding the type and number of cells required for the BAL Device	37
Figure A2.2 – Level 3 Value System Map - Critical Points in the BAL Device Value System Model (print on A3 paper for legibility).....	38
A2.3.2 Cryogenic preservation and logistic issues.....	39
A2.4 Conclusions	40
Annex 3. Red Blood Cells Case Study.....	41
A3.1. Background.....	41
A3.2. Description and Analysis of the Level 2 Value System Map.....	42
A3.2.1 Cell line procurement and differentiation	42
Figure A3.1 Level 2 Value System Map – Summary Model of RBC Development (print on A3 paper for legibility)	43
A3.2.2 Manufacturing path	44
A3.2.3 Regulatory path (up to Phase 2 Clinical Trials).....	45
A3.2.4 Phase 3 trials and final product development.....	46
A3.3. Scenarios and Critical Points.....	47
A3.3.1 Step Change in Manufacturing Technology for Niche market	47
Figure A3.2 – Level 3 Value System Map - Critical Points in the Value System Model (print on A3 paper for legibility).....	48
A3.3.2 Impact of Regulatory Uncertainty or Changes During Development	50
A3.4. Conclusions	51

Executive Summary

The REALISE project, funded by the UK Technology Strategy Board, addressed the following questions as they apply to early stage regenerative medicine commercial developments in three case studies based on human embryonic stem cell developments: Pluripotent Stem Cells themselves, a Bio-artificial Liver (BAL) Device and Red Blood Cells (Annexes 1 – 3).

1. How far the opportunities to realise value for the UK regenerative medicine industry are enhanced or inhibited by factors outside the boundaries of individual businesses or specific value chains;
2. How value realisation can be critically affected by relationships with sources of finance;
3. Collaborations with universities, regionally, nationally and internationally;
4. Logistics, point of care and end user issues; and
5. Regulatory and fiscal frameworks.

We developed an interdisciplinary methodology that can be applied to the Analysis of Life Science Innovation Systems (ALSIS) in general and applied it to the three case studies as they evolved over the two year period of the project. The methodology provides an overarching framework that acts as a basis for interdisciplinary integration across academic disciplines, across business and stakeholder perspectives and across a wide range of areas of application, in interaction with regulatory, stakeholder and market influences. It links the business models that interact to form a value chain, embedded within a value system that brings in the wider systemic influences on business success. Scenario analysis is then used to assesses the future prospects for value creation for an RM therapy, taking account of the actors, roles and ambitions involved at different levels in the overall value system.

Conclusions about the case studies

In all three cases we could be considerably more optimistic about the possibility of achieving a viable business model at the end of the project than we had been at the beginning. However, although some problems had been resolved, others had emerged, e.g. the Brustle patent decision was causing participants in each case to reconsider their business models. At the beginning of the project, human embryonic stem cells (HESCs) had been the favoured starting material but by the end of the project all three companies were planning to switch to induced pluripotent stem cells.

Regulatory issues were a concern across all three case studies although in different ways. For the company developing clinical grade pluripotent stem cells, the main concern was about how regulatory decisions yet to be taken and uncertainties still to be resolved might affect the market for their stem cell lines, particularly those derived from HESCs. Those involved in the BAL device case study had taken an early decision to avoid if possible becoming involved in clinical trials and related concerns. However this decision was placing constraints on the kind of business model they were able to develop and they could see how the regulatory system might have an impact, positive or negative, on those with whom they might partner in future value chains. Participants developing RBCs were the most engaged of the three cases with the need to meet the requirements of regulatory systems and were confident about their ability to do so at least up to Stage 2 clinical trials.

General conclusions

In responding to the five questions posed by TSB at the beginning of this executive summary, we can come to the following general conclusions.

1. How far the opportunities to realise value for the UK regenerative medicine industry are enhanced or inhibited by factors outside the boundaries of individual businesses or specific value chains

This is precisely the question addressed by our value system level analysis. The most important factors for case study participants were:

- uncertainty about the nature of future regulatory and reimbursement systems;
- the nature of future markets and the extent to which competitors will have captured a key market by the time a RM therapy has passed through all its development stages;
- the future costs and availability of materials for cell manufacture and the impact on eventual costs of the therapy;
- new science and technology developments arising elsewhere, but required for successful product development (e.g. related to cryo-preservation of liver cells or to scale-up technologies for cell manufacture);
- changes in the IP/patent landscape, e.g. the Brustle patent decision had changed participants assessments of the value of HESCs, relative to iPSCs as a starting material for developing RM therapies.

2. How value realisation can be critically affected by relationships with sources of finance.

Our case studies were at an early stage of product development and not yet seeking commercial investment. However, concerns about future abilities to finance development did feature in their projected business plans, and it was already clear that the process of developing the value system maps was an aid to planning even for these long term considerations. Specifically, our value system maps, and their accompanying descriptions, highlight the critical points in which different types and levels of investment may be required.

3. Collaborations with universities, regionally, nationally and internationally.

Many of the participants in our case studies held university appointments and were in the process of commercialising their research or had future plans to do so. All had strong links with other universities regionally, nationally and internationally and were using these links to resolve some of the uncertainty surrounding development of their products.

4. Logistics, point of care and end user issues.

Logistical issues did not feature strongly in the current planning of our case studies but they were seen as major factors in projected business models. Planned approaches to marketing and the need to build international partnerships to deliver final products were heavily influenced by the expected short shelf life of some cellular products and the fragility of others. Inability so far to cryo-preserve liver cells was a major potential constraint on BAL device distribution and marketing.

5. Regulatory and fiscal frameworks.

For clinical grade pluripotent stem cells, most regulatory aspects of their value system environment had already been internalised and were part of standard operating procedures. Regulatory issues did loom large as future constraints relevant to the other two case studies. The BAL device was chosen as a product for development by the company partly because, being an extra-corporeal device it was assumed (perhaps incorrectly) to be subject to a lighter touch regulatory system. The factor of most immediate concern for the RBC case study was the question of testing the product on animals as a prerequisite for entering stage 1 clinical trials, as well as uncertainty about number of post marketing trials that may be required for alternative

blood markets. For both these case studies, regulatory uncertainty was seen as a much more important factor than the nature of the regulatory system as it evolves.

Conclusions about the methodology

For the companies involved it was clear that the process of using the methodology allowed them to visualise future business models in a helpful way, forming a basis that would enable easy adaptation to future changes in the business model or value system environment.

From our point of view, as analysts, the project provided validation of the methodology. The early stage of development of the product in each case study meant that there was considerable uncertainty about many future aspects of the technology itself and of the business operating environment so the quantitative aspects of the application of the methodology have still to be tested fully. However, the strategic mapping approach used to categorise the value system in each case was very effective, enabling easy adaptation of strategies as new information became available and also constructive comparisons across case studies.

1. Introduction

The Technology Strategy Board (TSB) has identified research on value systems and business models as essential to developing a better understanding of where and how value can be created and captured in regenerative medicine (RM), seen as an example of high value manufacturing. The Advanced Institute for Manufacturing (AIM) report (2008) defines high value manufacturing as "...manufacturing firms that do not compete primarily on cost. Instead they deliver value for one or more of their stakeholder groups by contracting for capability, delivering product/service innovation, establishing process excellence, achieving high brand recognition and/or contributing to a sustainable society."

The most important foci identified by the TSB for RM therapy development were:

6. how far the opportunities to realise value for the UK regenerative medicine industry are enhanced or inhibited by factors outside the boundaries of individual businesses or specific value chains;
7. how value realisation can be critically affected by relationships with sources of finance;
8. collaborations with universities, regionally, nationally and internationally;
9. logistics, point of care and end user issues; and
10. regulatory and fiscal frameworks.

These questions were addressed by the REALISE project, led by the Scottish Stem Cell Network, the Innogen Centre's contribution (funded by the Economic and Social Research Council) being the development of a novel methodology for the analysis of life science innovation systems and its application to three case studies, based on human embryonic stem cell developments, where the shape and viability of future value systems is uncertain and therefore speculative: (1) Pluripotent Stem Cells, (2) a Bio-artificial Liver Device and (3) Red Blood Cells.

The methodology and its applications, along with the conclusions from the research, are described in Sections 2 – 5 of this report and the outcomes of the three case studies are described in detail in Annexes 1 - 3.

2. Interdisciplinary methodology for the analysis of life science innovation systems (ALSIS)

The Innogen Centre's research programme (Wield, 2008; Lyall *et al.*, 2011) (Figure 1) is based on the premise that, in the context of life science-related innovation, the main drivers of success or failure in innovative developments will arise from interactions between:

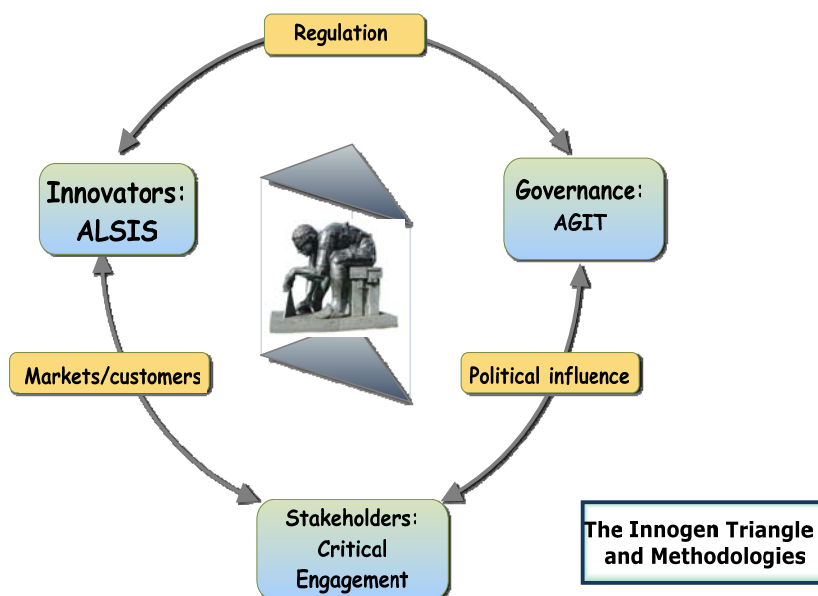
- innovators (scientists, technologists, industry);
- policy makers (including regulators and emerging new institutions and processes of governance); and
- public and stakeholder groups.

We have developed the ALSIS methodology based on our experience in pesticide development and GM crop production, biofuels, drug development, pharmacogenetics, synthetic biology, stratified medicine and translational medicine (Chataway *et al.*, 2006; Tait and Chataway, 2007; Tait, 2007; Tait *et al.*, 2008; Mitra *et al.*, 2011; Tait and Barker, 2011; Lowrie and Tait, 2011; Mitra and Tait, 2012). The methodology provides an overarching framework that acts as a basis for interdisciplinary integration across academic disciplines, across business and stakeholder perspectives and across a wide range of areas of application, in interaction with regulatory, stakeholder and market influences. For this project we

have applied the methodology to the early stages of development of regenerative medicine therapies.

The core of the methodology is a hierarchy of analyses from company or sector business models, through a group of businesses that interact to form a value chain, embedded within a value system that brings in the wider systemic influences on business success, for example regulation, finance and market related factors. Each level in this hierarchy involves additional sets of actors, roles and ambitions. To assess the future prospects for value creation for an RM therapy, e.g. through scenario analysis, it is essential to visualise the perspectives and interactions (enabling and constraining) that will determine the prospects for each business operating as part of a value chain within the overall value system to deliver value to patients and to the developers of the therapy (see Figure 2). The methodology uses quantitative and qualitative data related to analysis of business models, value chains and value systems, depending on the nature of the decision at a particular point and data availability.

Figure 1. Innogen Centre Research Programme



The management science literature often uses the terms ‘business model’, ‘value chain’ and ‘value system’ loosely and does not define them in a way that distinguishes them from one another (Kaplinsky and Morris, 2001). We have used the following definitions to set these terms within the hierarchy of activities that forms the basis of our methodology.

Business model

Business models are generic models, based on an in depth understanding of the business plans being developed by companies in a specific sub-sector with a common set of business goals and expected means to attain these goals, playing a common identifiable role within an overall value chain. They describe the processes by which value is created from a set of technological opportunities that is common to that sub-sector, i.e. they provide a rationale for how firms within the sub-sector create, capture and deliver value.

Value chain

The value chain describes the full range of activities required to bring a product from conception to end use and beyond, including design, production, marketing,

distribution and support to the final consumer. The value chain can be restricted to a single, probably large, firm or distributed across multiple firms, nationally, internationally or globally. Depending on the nature of the opportunity and the complexity of the route to exploiting it, the value chain will encompass a number of firms with different business models operating in sequence or in parallel.

Value system

The value system embeds one or more value chains in the wider economic, regulatory, societal and political contexts, incorporating external factors that will either enable or constrain the ability of the participants involved in the value chain to implement their individual business plans and to cooperate nationally and internationally to create and deliver value to stakeholders.

Scenario analysis

A common characteristic of life science innovation systems is that development of business plans and business models begins at very early stages of product development, typically up to technology readiness level 3 (broadly translatable as the 'proof of concept' stage)¹, when many products will be ten to fifteen years away from actual market launch. Scenario analysis is therefore a useful tool for planning at this stage of development. It is most likely to be based on qualitative data about future developments (Scenario 1, Figure 2) but in some cases there will be data that can be used to develop quantitative scenario models (Scenario 2, Figure 2).

As implied in the green arrows at the bottom of Figure 2, data for these analyses came from published and unpublished literature, workshops (some conducted specifically for this project and some more general) and interviews with scientists, regulators and company managers.

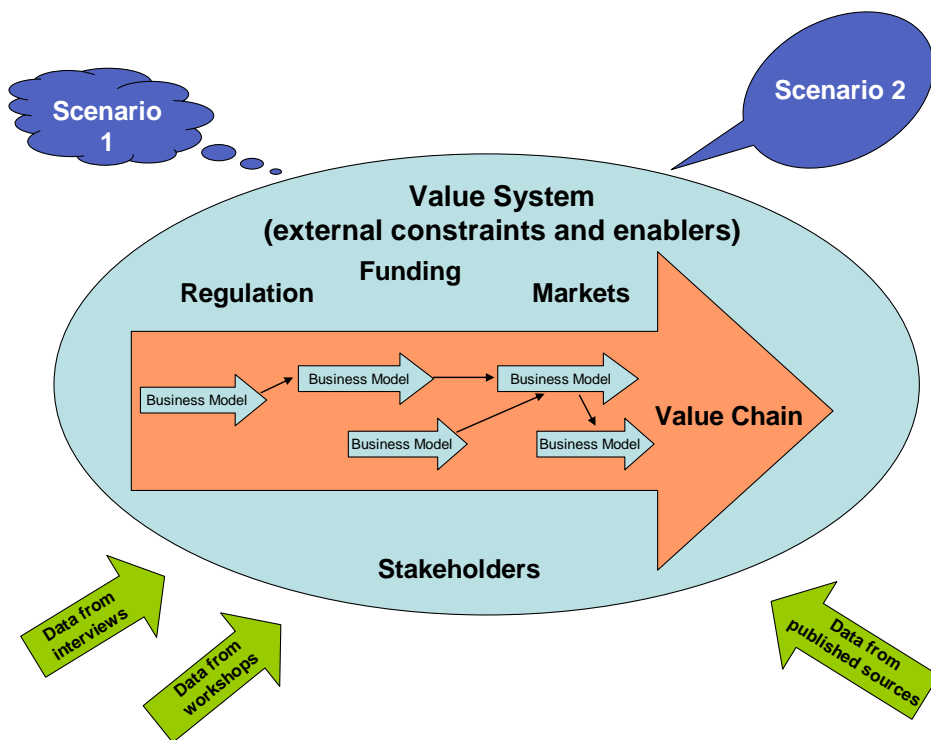
2.1 Business Models

Casadesus-Masanell & Ricart (2010) describe a business model as being tied to the strategy and tactics of a business; it is the logic of the firm, the way it operates and how it creates value for its stakeholders. A firm's business model determines the range of tactics available to it, and this plays a central role in determining how much value the firm will be able to create and capture.

Teece (2010) has proposed that good business model design is central to creating and building a sustainable competitive advantage. It involves determining: which market segments should be targeted; what benefits the product/service will deliver to the customer; which features/technologies will be embedded within it and how they can best be assembled and offered to the customer; how the revenue and cost structures of the business should be designed (and, if necessary, redesigned); and how value will be captured and competitive advantage sustained.

¹ The concept of 'technology readiness levels' (TRLs) has been developed by the US military establishment to facilitate decision making about the development of innovative defence technologies (http://en.wikipedia.org/wiki/Technology_readiness_level) and it has been adopted by the TSB as an aid to considering whether potential projects are sufficiently well developed to be funded by them. However, although the concept is occasionally referred to in articles about life science innovation, it gives insufficient attention to the long lead time and expensive regulatory process required for most life science innovations and requires further development before it becomes a useful aid to decision making in this area.

Figure 2. Structure of the ALSIS Methodology



For many RM therapies, there is no pre-defined business model or body of experience that can be analysed and adapted to give the firm a competitive advantage over other similar companies. The tactics and strategies being chosen today by firms attempting to develop RM therapies *will define* future business models rather than *being defined by* them, emphasising the importance of experimentation in business model creation and development in this area (McGrath, 2010). Such a state of flux, characterised by experimentation and failure, will subside only after a set of key decisions results in the emergence of a superior design (Tushman and Murmann, 1998). Such experimentation often involves levels of investment that are unlikely to realise a return, particularly given the lengthy translation process required for the development of RM therapies.

2.2 Value Chains

The term 'value chain' is used here to incorporate the interactions whereby networks of firms and organisations cooperate, often internationally, to create and deliver value to their stakeholders and this project has aimed to contribute to the development of prototype value chains for the delivery of innovative RM therapies.

In making the link from business models to value chains, tactical interactions occur when one firm's business model is linked to that of another firm, leading to consequences for both, so that the business model employed by a firm determines the tactics available to it to compete against, or to cooperate with, other firms in the marketplace (Casadesus-Masanell & Ricart, 2010).

The ideas contributing to the development of the value chain concept were developed for industry sectors with very different value propositions from those of life science based companies (Kaplinsky and Morris, 2001). However, there is a small but growing literature applying value chain analysis to pharmaceutical and biopharmaceutical product development (Cooke, 2005; Nature, 2002).

Several papers discuss the process of translating stem cell related innovation to RM therapies in terms that could contribute to a value chain analysis. For example, Mason and Manzotti (2009) have noted the disruptive challenges for companies attempting to develop RM therapies, requiring integration across pharma, biotechnology and engineering disciplines. They also note the need for novel discovery, development and manufacturing approaches along with a service infrastructure to support the deployment of a therapy in the market place, requiring the development of new business models and, by implication, value chains.

Also relevant to value chain development, Mason and Dunnill (2008) suggest that few stem cell therapeutic start-up companies will become major players if they lack collaboration with established companies, highlighting the important role likely to be played by pharmaceutical multinational companies (MNCs) or by other large companies operating in the health sector, for example developing devices and delivery systems. Small companies are likely to remain niche players, in the sense of contributing a narrowly specialised component to an overall value chain, rather than being in a position to expand their operations to become major players in their own right.

2.3 Value Systems

The ALSIS methodology makes a formal distinction between the value chain itself and the systemic environment, the value system in which it is embedded, that either enables or constrains the development of RM therapies (Tait, 2007). This value system environment includes regulatory, financial and market-related factors, and stakeholder influences. The value system concept thus distinguishes factors that are under the control of the firms involved in the value chain (related to the development of the various business models) and factors in the wider value system environment, over which firms can have little or no control.

In a similar manner, Casadesus-Masanell and Ricart (2010) conceive most business models as being located within the boundaries of a particular set of constraints. Over time, such constraints may change and favour an existing business model or threaten it in favour of a new business model. New business models and, by implication, value chains, are often able to emerge when a systemic constraint is lifted; likewise old models may lose their viability when a new systemic constraint emerges. The challenge is to identify the value to be derived from partners and collaborators, their knowledge, skills and competencies, to explore and produce radically innovative ideas within the value chain.

The ALSIS approach allows us to explore the impact of systemic environmental factors that are often manipulated by governments, at national and international levels, to enable more effective translation of basic knowledge to viable therapies.

2.4 Scenario Analysis

As in the case of research involving business modelling and value systems analysis, scenario analysis has been widely but uncritically adopted so that it can now cover a very wide range of methodological approaches to foresight and futures studies (Varum and Melo, 2010; Bradfield *et al.*, 2005). In this project we planned to use scenario analysis as developed by Van Der Heijden (1996), based on the original approach developed for Royal Dutch Shell, to test our preliminary conclusions about value system development in our three case studies. This approach is essentially qualitative in the first instance but allows for quantitative modelling at specific nodes in a value chain where appropriate data are available.

3. Regenerative medicine therapies and their commercial potential

Stem cell research is seen as being capable of revolutionising healthcare and improving human health. Cells corresponding to specific tissues (for example heart or

liver) differentiated from human embryonic stem cells (HES cells) or induced pluripotent stem cells (iPS cells) are already being used by many pharmaceutical companies for toxicology testing of new drugs, but regenerative medicine (RM) including cell and tissue replacement therapy is expected to deliver the ultimate promise of stem cell biology (McKernan *et al.*, 2010).

The potential economic impact of RM therapies has been estimated to be \$2 - 5 Billion, and the annual growth rate of the global stem cell component of this market has been forecast to be 29.2%, with sales of \$11 billion by 2020 (Regenerative Medicine: Industry Briefing, 2009). Savings in direct health care costs in the USA were projected to be \$250 billion per year arising from cures for chronic diseases such as late-stage Parkinson's disease, new cases of spinal cord injury, heart failure, stroke, and insulin-dependent diabetes (Mason & Dunnill, 2008). However, such projections at the early stages in development of innovative technologies often prove to be over-optimistic, or are focused on unsustainable eventual applications.

McKernan *et al.* (2010) have pointed to several factors that currently constrain engagement by pharmaceutical companies in this area: insufficient demonstration of efficacy; regulatory and safety concerns; a concern that RM therapies will not offer sufficient benefit over existing treatments; the complexity of product development; and lack of familiarity with appropriate business models for commercialising cell-based products. In addition, much of the scientific expertise needed for the development of RM therapies is found in specialised biotechnology companies (Webb, 2010) and early stage spin-out companies (Regenerative Medicine: Industry Briefing, 2009), requiring collaboration between companies and between industry and academia.

Two contrasting visions for the future thus form the back-drop to the development of RM therapies. On the one hand RM is seen as a sector that will be able to shift the boundaries of innovation and enable UK companies to prosper in a new global value system (Kemp, 2006; Lysaght *et al.*, 2008; Office for Life Sciences, 2009; Tralau-Stewart *et al.*, 2008; Medical Research Council (MRC), 2012). On the other hand there are predictions of difficulties and many failures in attempting to realise this potential value (Rowley and Martin, 2009). Both are likely to be true to some extent.

Supporting those who are sceptical about future revenues, Kemp (2006), in an assessment of RM business models, found that with early products, such as those for skin lesions, a turnover of US\$30 million was required to sustain research and development, but that more sophisticated RM products seeking high-return markets carry much higher costs and demand substantial investments in clinical trials. Likewise, Geron, having committed US\$100 million to acquire the data to file an Investigational New Drug application with the US Food and Drug Administration for its lead spinal injury product (Okarma, 2006), has now withdrawn entirely from the development of cell therapies, quoting regulatory costs and uncertainties required to take the product through to final approval as a therapy (Franz, 2012).

Such large expenditures are only likely where there is effective protection of intellectual property. However, McKernan *et al.* (2010) suggest that an allogeneic cell bank may be able to deliver therapeutic outcomes for a variety of conditions if the owner of the cell lines can control access to and commercialisation of the cell lines, irrespective of the patent position. This very important question of physical ownership of cell lines has been considered in the context of the UK Stem Cell Bank (Courtenay *et al.*, 2011). Unlike some other areas of life science innovation, exclusive physical possession of a cell line may be more important for the development of a viable value chain than intellectual property protection. However, retaining this exclusive physical possession may be difficult in the context of a complex value chain that involves multiple players, perhaps operating internationally.

Different types of value chain will be relevant for different RM end markets. Creating autologous therapies on a small population scale will be a different business from the traditional operating model of a pharmaceutical company (Smith, 2009). New firms face the challenge of how much should be customised and how much can be standardised (Mason and Hoare, 2006). Using allogeneic cells with a large potential downstream market is expected to be closer to a pharmaceutical model, involving a globally coordinated value chain and more intensive competition.

Hinterhuber (2002) has commented on the need for 'value chain orchestration', whereby an internal analysis on costs and value added at each step is undertaken, as is proposed (where data are available) in the ALSIS methodology. In the case of RM this can provide a first view of the total value added and the effectiveness of internal operations, allowing conclusions to be drawn in comparison with other therapy pathways and with the activities of collaborators and competitors.

These influences on the progress of stem cell therapies are not independent. For example the cost and timescale involved in meeting regulatory requirements has been identified as an important factor contributing to the high cost of product development, the resulting difficulties in obtaining funding and the high price of the end product. The uncertainty that still surrounds each of these influences is compounded by the complexity of the interactions among them with the result that there are no established business models to guide companies considering investing in RM therapies, and the value chains that will need to be established to enable translation to viable therapies do not yet exist in most cases.

Given the early stage of development of the three case studies below, it is not unexpected that the nature of, and the commercial prospects for, the value chains in each case has been subject to potentially dramatic change over the 18 month period of this project and specific developments are discussed in the case study annex. However, in general it has become clearer that successful development of RM therapies will require the co-evolution of a range of supporting technologies, most of them also arising in research labs and/or small spin-out companies. These include new materials technology to develop scaffolds for large scale production and/or delivery of stem cells and the development of specialised devices for delivery of therapies to patients.

The three cases studied for this project were chosen to represent different types of application in the field of RM and hence the need to develop different types of business models and to cope with different systemic influences.

Clinical grade pluripotent stem cells (HESCs and iPS cells)

The value system within which pluripotent stem cells are being developed as a marketable product is relatively well specified compared to the other two case studies. Some of the regulatory uncertainties have been resolved but others remain problematic, and the cost of meeting regulatory requirements for the development of cells to clinical grade GMP standard is significant. The company has dealt with the complexities of altruistic donation of HESCs and is moving into development of iPS cells, seen as the most viable future route for the development of RM, given recent patent-related developments in the EU. The cells produced by this company are the starting material for the other two case studies.

Bio-artificial liver device (BAL)

The BAL device is extra-corporeal. The patients' blood will be separated from the hepatocytes within the device by a semi-permeable membrane that prevents any cell transfer to the patients. This could potentially reach clinical use more rapidly than other allogeneic stem cell based therapies. However the required marriage of cell biology with advanced materials science and

engineering to create a device that will incorporate living cells to provide a therapeutic treatment for patients is challenging and will only be delivered if all the components can be incorporated within a well functioning value chain (Mitra and Tait, 2012, in press). In addition, several practical considerations related to manufacture and robustness of the SC derived liver cells have yet to be resolved.

Red blood cells from HES cells.

Red blood cell production from HES cells offers the prospect of a major transformation in modern healthcare but to achieve this will require a significant investment in new technology and bioprocessing capacity, including a well structured commercialisation strategy to identify multiple stages for the investment process and to stratify the overall market to identify niche areas which are less sensitive to the cost of goods. This case highlights the challenges related to lowering the costs of production and the use of large scale bioprocessing technology to deliver a commercially viable product. It also illustrates some remaining challenges related to cell differentiation and regulatory processes.

All three case studies are at an early stage of technology readiness, up to TRL 3 or 4 and the companies and organisations involved are pioneers in both the scientific sense and the business sense. The following challenges for the companies were identified in this project:

- the companies are dealing with new scientific discoveries, and unexpected scientific developments can give advantage to competitors, resolve current blockages in development processes, open up or close down market opportunities;
- there are uncertainties around the nature of the eventual dominant technology (HES cells vs iPS cells; autologous vs allogeneic cells);
- there are uncertainties about feasible future production scales (large scale centralised production with attendant delivery challenges or small scale localised production with cost and market scale implications);
- the regulatory system is still evolving and is not well synchronised with the basic scientific discovery and innovation agendas;
- companies must learn to cope with a demanding regulatory system with no precedents to build on; and
- complexities are introduced by interactions among all these factors.

The ALSIS methodology thus brings together the following aspects of value system analysis for the development of RM therapies:

- Market identification and analysis
- Manufacturing processes and their scale and location
- Distribution processes for vulnerable living materials (Blackburn and Scudder, 2008)
- Partner selection and collaborative/networking approaches
- Intellectual property and access to cell lines
- Managing clinical trials and other regulatory approvals
- Controlling costs and identifying alternative sources of value

4. Application of the ALSIS methodology: data inputs and analytical approaches

As indicated in Figure 2, data relevant to application of the ALSIS methodology were derived from case studies, interviews, workshops, published data and 'grey' literature building on research methods ranging from basic scientific research to economics, policy analysis, survey data or focus group discussions. Our data collection built on two other components of the REALISE Project:

1. The Therapy Realisation and Pathway Tool (TRPT) developed by the Scottish Stem Cell Network;
2. A detailed product development and commercialisation plan for each case study², including quantitative data on the cost of individual aspects of product development.

4.1 Data Collection for Innogen research

Data for business model development and as a basis for value system analysis were collected from published sources and other reports, and meetings, workshops and interviews.

The following meetings were attended:

- Workshops related to development of the TRPT by SSCN, where Innogen staff contributed data and insights to the process, as well as learning more about RM innovation systems from other participants at these meetings;
- Meetings with Kevin Bruce and Aidan Courtenay (Roslin Cells) to ensure a good understanding of the data incorporated in the product development and commercialisation plans for each case that formed the starting point for our business models;
- Meetings with Ken Snowden (KLCE Consulting) to capture his expertise on companies working in this area and also regional innovation system incentives and constraints;
- Open meetings organised by SSCN and others, throughout the UK, that were relevant to RM therapy development and regulation.

We also organised a series of workshops specific to each case study (at least four half-day workshops for each case study) discussing development of their business models with key actors in each case study. Workshop discussions were tape recorded to enable us to capture the qualitative and quantitative information they contained for value system development and scenario analyses. We continued to collect data up to March 2012, to take account of emerging scientific understanding, regulatory changes and uncertainties, and changes in the background business environment for the technology.

4.2 Development of qualitative business models and value systems

It became clear as the REALISE project evolved that none of the case studies was likely to involve a 'value chain', as defined above.

- In the case of Clinical Grade Pluripotent Stem Cells, formal collaborations with other companies were not necessary to deliver the final pluripotent cell product (our end point for the business model), although collaborations were expected to emerge beyond that point.
- For the BAL device, where the company concerned was developing the cell-based component, it was clear that there would need to be involvement of at

² Developed by Kevin Bruce, Roslin Cells.

least one more company with a device-related business model. However, the company has not yet been identified and there is not a settled understanding of what that business model is likely to be.

- For the Red Blood Cells case, collaboration with other companies in a value chain will be required at later stages in project development but it is not yet clear which types of company will be involved and what their role will be.

Given the early and speculative stage of development of the business plans for each of our cases, we cannot claim to have modelled relevant value chains although our methodology is clearly capable of doing so. Although we focused on the business plans being developed for specific cases, the business models we developed for this project could be seen as generic and applicable to other similar business cases.

In the case of Clinical Grade Pluripotent Stem Cells, there was a well developed and functioning business model, but in the other two cases it was not clear what the most successful future business models would be when the products were in later stages of development. For these cases we developed increasingly refined models over the 24 months of the project, charting the companies' or researchers' expectations for future business models as the project evolved and as new scientific discoveries emerged to change expectations.

The software tool, Banxia Decision Explorer³, was used to develop strategic maps of the evolving business models in each case, and to explore the relationships between the business model and the value system in which it is embedded. It was notable that those involved in workshops and discussions to develop and refine these business models found the process a very useful adjunct to their own planning, rather than seeing it as a one-way process of giving their time to our research.

Three levels of value system maps were developed for these case studies (see Annexes 1 – 3).

- *Level 1 Value System Maps - full value system models.* The product development and commercialisation plan for each case study formed the basis for the first draft of the business model/value system map. The structure and content of these draft maps were then developed and clarified in subsequent interviews and discussions to develop the full value system models. These detailed and complex models included all the information about the case study and its development available to us at the time. They were used as a basis for discussion with interviewees and workshop attendees to check our understanding of the processes involved in the case study and they progressed through several rounds of revision and refinement during these discussions. These 'work-in-progress' models are not included in this report.
- *Level 2 Value System Maps - summary models.* The complex initial models were refined in discussion with case study participants to develop summary models that captured the key relevant information.
- *Level 3 Value System Maps - key decision nodes.* From the level 2 maps, for case studies 2 and 3, additional models were developed identifying key decision nodes for closer attention in scenario development.

4.3 Quantitative analysis and scenario development

As noted above, the value of the methodology in these case studies was in facilitating exploration of future business models and value systems, rather than in further developing existing models or value chains. The quantitative data available

³ <http://www.banxia.com/dexplore/how-to-make-cognitive-maps.html>

were limited and generally highly speculative and participants in the same case study with different areas of expertise sometimes had very different perceptions of the probabilities and consequences of outcomes at key decision points. The scenarios described here thus provide a useful basis for further qualitative and quantitative analysis as issues are clarified in this fast moving area.

Quantitative analysis focused on the key decision nodes identified in the third set of strategic maps and this formed the basis for very rudimentary scenario analyses to model potential responses to changes in the business model and its environment, to evaluate the impact on the development of future value chains, and to begin to develop criteria on which to base future financial judgements.

5. Conclusions

5.1 General Conclusions

The concerns of TSB in this funding call that were relevant to our analysis were related to the opportunities for the UK regenerative medicine industry and how value can be realised given the range of potential constraints and opportunities arising within and beyond the value chain. For the five key questions raised by TSB, we indicate below how our analysis has provided some answers.

All three case studies are operating at the earliest stages of development of RM value chains and, for the companies and research groups concerned, the business models we have developed are more like exercises in technology foresighting than descriptions of current reality. However, many of the uncertainties and knowledge gaps that existed at the beginning of this project have, over the two year period, been informed by significant new developments, and we have been able to reflect these developments in our evolving ALSIS models.

1. How far the opportunities to realise value for the UK regenerative medicine industry are enhanced or inhibited by factors outside the boundaries of individual businesses or specific value chains

This is precisely the question addressed by our value system level analysis. The factors beyond the boundaries of case study business models and hence outside the control of participants included:

- uncertainty about the nature of future regulatory and reimbursement systems;
- the nature of future markets and the extent to which competitors will have captured a key market by the time a RM therapy has passed through all its development stages;
- the future costs and availability of materials for cell manufacture and the impact on eventual costs of the therapy;
- new science and technology developments arising elsewhere (e.g. related to cryo-preservation of liver cells or to scale-up technologies for cell manufacture);
- changes in the IP/patent landscape, e.g. the Brustle patent decision had changed participants assessments of the value of HESCs, relative to iPSCs as a starting material for developing RM therapies.

2. How value realisation can be critically affected by relationships with sources of finance.

Our case studies were at an early stage of product development and not yet seeking commercial investment. However, concerns about future abilities to finance development did feature in their projected business plans, and it was already clear that the process of developing the value system maps was an aid to planning even for these long term considerations. Specifically, our value system maps, and their

accompanying descriptions, highlight the critical points in which different types and levels of investment may be required.

3. Collaborations with universities, regionally, nationally and internationally.

Many of the participants in our case studies held university appointments and were in the process of commercialising their research or had future plans to do so. All had strong links with other universities regionally, nationally and internationally and were using these links to resolve some of the uncertainty surrounding development of their products. For example in the BAL device case study (Annex 2) a link with a university in another region had opened up possibilities of using novel polymers as a basis for stem cell manufacture, enabling at least an order of magnitude increase in the level of scale-up.

4. Logistics, point of care and end user issues.

Logistical issues did not feature strongly in the current planning of our case studies but they were seen as major factors in projected business models. Planned approaches to marketing and the need to build international partnerships to deliver final products were heavily influenced by the expected short shelf life of some cellular products and the fragility of others. Inability so far to cryo-preserve liver cells was a major potential constraint on BAL device distribution and marketing.

5. Regulatory and fiscal frameworks.

For clinical grade pluripotent stem cells, most regulatory aspects of their value system environment had already been internalised and were part of standard operating procedures. Regulatory issues did loom large as future constraints relevant to the other two case studies. The BAL device was chosen as a product for development by the company partly because, being an extra-corporeal device it was assumed (perhaps incorrectly) to be subject to a lighter touch regulatory system. The factor of most immediate concern for the RBC case study was the question of testing the product on animals as a prerequisite for entering stage 1 clinical trials, as well as uncertainty about number of post marketing trials that may be required for alternative blood markets. For both these case studies, regulatory uncertainty was seen as a much more important factor than the nature of the regulatory system as it evolves.

5.2 ALSIS Methodology

This project has been the first major application of this version of the ALSIS methodology, although previous projects have applied some of the ideas incorporated in it. We believe that its use in this project has been an important step towards its validation and it has been or is being applied in other areas: the wheat value chain, stratified medicine and biofuels.

We had to make one important adaptation in that our three case studies could only be described as constructing future business models, given their early stage of development. Although partnerships with other companies to form value chains were talked about, none was sufficiently developed to form part of a formal value chain analysis.

Nevertheless it was clear that, for the case studies concerned, we had started an important process that was enabling them to visualise future business models in a helpful way and that formed a basis that would lead to easy adaptation as future changes in the business model or value system environment made a more sophisticated analysis possible. We would particularly like, in future, to be able to conduct economic analyses at key decision nodes in these models and for key external influences like regulation, logistics, markets and sources of finance. At this stage of development all these factors were too uncertain to form a useful basis for analysis

The ease with which the methodology allows future updating as a business plan develops relates to the fact that the value system maps form the starting point for analysis of our data. The maps are developed directly from tape recordings of meetings and workshops and the Banxia software allows easy and flexible updating. The written descriptions in the Annexes are provided as a way of helping to understand the content of the maps for those who were not involved in developing them. Adapting these written descriptions to take account of future developments would be a much more onerous task without the system maps to act as a framework.

The maps also provide for constructive comparison of the business models of different companies or sectors. Placing two or more summary maps on a table side by side allows the analyst or the company participants to draw insights that would not otherwise be obvious and can lead to development of new strategies and ideas, or to development of more effective partnerships within a value chain (e.g. Mitra and Tait, 2012).

5.3 Insights from Case Studies

Conclusions for each case study are given in Annexes 1 – 3.

One general point to emerge was the rate of change in science and technology relevant to the case studies. In all three cases it was possible to be considerably more optimistic about the possibility of eventually achieving a viable business model at the end of the project than it had been at the beginning. Advances in the ability to scale up manufacture of cells for RM therapies had been particularly dramatic, even if not yet to a sufficient scale to satisfy a market in any case.

However, although some problems had been resolved, others had emerged, e.g. the Brustle patent decision which was causing participants in each of the three cases to reconsider their business models. At the beginning of the project, HESCs had been the favoured starting material, but by the end of the project all three cases were planning to switch to iPSCs at some time in the future and were more confident that before that the remaining problems with these cells could be resolved in the relatively short term.

Regulatory issues were a concern for each of the case studies, although in different ways. In the context of clinical grade pluripotent stem cells, the main concern was about how regulatory decisions yet to be taken and uncertainties still to be resolved might affect the market for their stem cell lines, particularly those derived from HESCs. Those involved in the BAL device case study had taken an early decision to avoid if possible becoming involved in clinical trials and related concerns. However this decision was placing constraints on the kind of business model they were able to develop and they could see how the regulatory system might have an impact, positive or negative, on those with whom they might partner in future value chains. Participants developing RBCs were most engaged with the need to meet the requirements of regulatory systems and were confident about their ability to do so at least up to Stage 2 clinical trials.

In general the operating environment for companies and researchers who want to develop regenerative medicine therapies has improved considerably and there is renewed optimism in the sector, particularly given recent major funding initiatives from the TSB and the Research Councils.

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ANNEXES

The following three Annexes describe the case studies in detail. The cases are described in the text and these descriptions correspond to, and assist in understanding, the value system maps.

The maps were the primary product from our data collection. As noted above in Section 4, this mapping approach to data analysis enabled us to continue data collection with case study and REALISE project participants up to March 2012. This allowed us to refine and update the maps as our understanding of the cases evolved, and as scientific and technological developments changed the prospects for our business models. The maps reproduced here are simplified versions of these full maps.

The following are the main points to bear in mind when reading these maps:

- The maps consist of boxes containing 'concepts' (short statements, for example about components of a strategy, causes of a problem or means of improving a situation).
- Links (arrows or lines) describe relationships between concepts, forming a line of argument, a description of a problem or the components of a strategy. The links used in the following maps (A → B) indicate that concept A leads to, contributes to, or affects concept B

We have used the following colour coding for the concepts in these maps:

Level 2 maps (Figures A1.1, A2.1 and A3.1)

- Thick red arrows – define the business model, showing critical paths to markets
- Thin black arrows – causal or sequential influences on the business model.
- Light purple – science and technology related factors
- Dark purple – IP related factors
- Yellow – markets and commercial outcomes
- Green – regulatory issues
- Dark blue – starting material procurement
- Light blue – product development and manufacturing issues
- Brown – logistics related issues

Level 3 maps (Figures A2.2 and A3.2)

In addition to the above:

- Dark green boxes – important decision nodes in business models

These dark green boxes highlight decision nodes on the critical path of the business model that require significant step changes in knowledge, scientific or technological developments, or company capacity and that have the potential to make or break the product and/or the company.

ANNEX 1. CLINICAL GRADE PLURIPOTENT STEM CELLS CASE STUDY.

A1.1 Background

In this case study, the company's core expertise and business model has been built around the provision of clinical grade GMP Human Embryonic Stem Cells (HESCs) and their differentiated progeny for use in the development of new reagents, drugs and cellular therapies. The Company will develop strategic partnerships with academic, clinical and commercial partners, nationally and internationally, to ensure their cell line products are widely used. Commercial options being considered include: an initial exclusive or limited use arrangement for the right to evaluate a range of cell lines for efficacy with the user's specific protocols; and subsequent licensing arrangements for a cell line with a full history.

HESCs have a diverse range of commercial and non-commercial applications, for research, drug screening and toxicology, cell therapy, and as substrates for the manufacture of biological products. The larger commercial markets in cell therapy and biologicals' manufacture are longer term aspirations for this company, but there are several more immediate, although less lucrative, uses of these cell lines for research, for early therapeutic applications and for drug discovery/toxicology.

The primary product in this case study will be a cryo-preserved undifferentiated pluripotent stem cell line, currently derived from HESCs. These cell lines, produced in vials, will be used to develop a Master Cell Bank. The business model assumes that a cell line would be purchased by a customer who would then maintain their own master and working cell banks for their specific product manufacture.

The profile of the Company's cell lines is as follows:

1. **Quality:** the GMP lines meet the highest standards with regard to quality of manufacturing and the appropriateness of the starting material, data traceability and quality control data. Quality can also be guaranteed for features such as stability/shelf life, practical storage conditions, packaging, instructions and ease of use.
2. **Safety:** Release criteria will highlight the quality of the product, including its safety data to demonstrate the product is free from adventitious agents, genetically stable, free from animal components and immunocompatible.
3. **Characterisation:** the cell lines will be fully characterised in terms of identity, morphology, stem cell markers and immunocompatibility.
4. **Utility/Potency:** the usefulness and flexibility of the potency of each cell line will be exemplified by data from Quality Control testing. It will be important to demonstrate that a line has the propensity to differentiate into either single or all lineages.

The following section provides a full description of the value system for this case study; including the opportunities and challenges for product development and identification of the key value points. We then explore the scenario relating to variation in the ability to supply clinical grade stem cell lines at a reasonable profit. The Company has built its reputation so far on the development of HESC lines, but for the reasons outlined below is now considering other SC sources, particularly iPSCs so that its business can best be described as designed to deliver clinical grade pluripotent stem cells (CGPSCs) from a variety of sources.

A1.2 Description and Analysis of the Value System Map

The Level 2 value system map (Figure A1.1) (see Main Report Section 4.2) illustrates the critical path (the red arrows), showing the steps, options and decision points along the business model from acquiring the starting material for a HESC line (blue

boxes on the left side of the map) to a number of product development and commercialisation options (yellow boxes on the right side of the map).

The business model for HESC production has three stages, beginning with starting material procurement, involving sourcing and initial inspection of embryos. Sourcing requires developing good relationships with clinics, developing and defining consent processes, obtaining consent; and obtaining tissue for transportation to the Company's GMP facilities. Early inspection involves the initiation of cell production process with quality assessment and instigation of the GMP process. The second stage involves product development through quality control, processing, archiving and validation of the cell line, which is where most of the regulatory requirements must be met. The final stage is distribution of the cell line, which requires expansion/scale up and deal-making in order to extract commercial value. We will explore each of these stages in the context of the value system map.

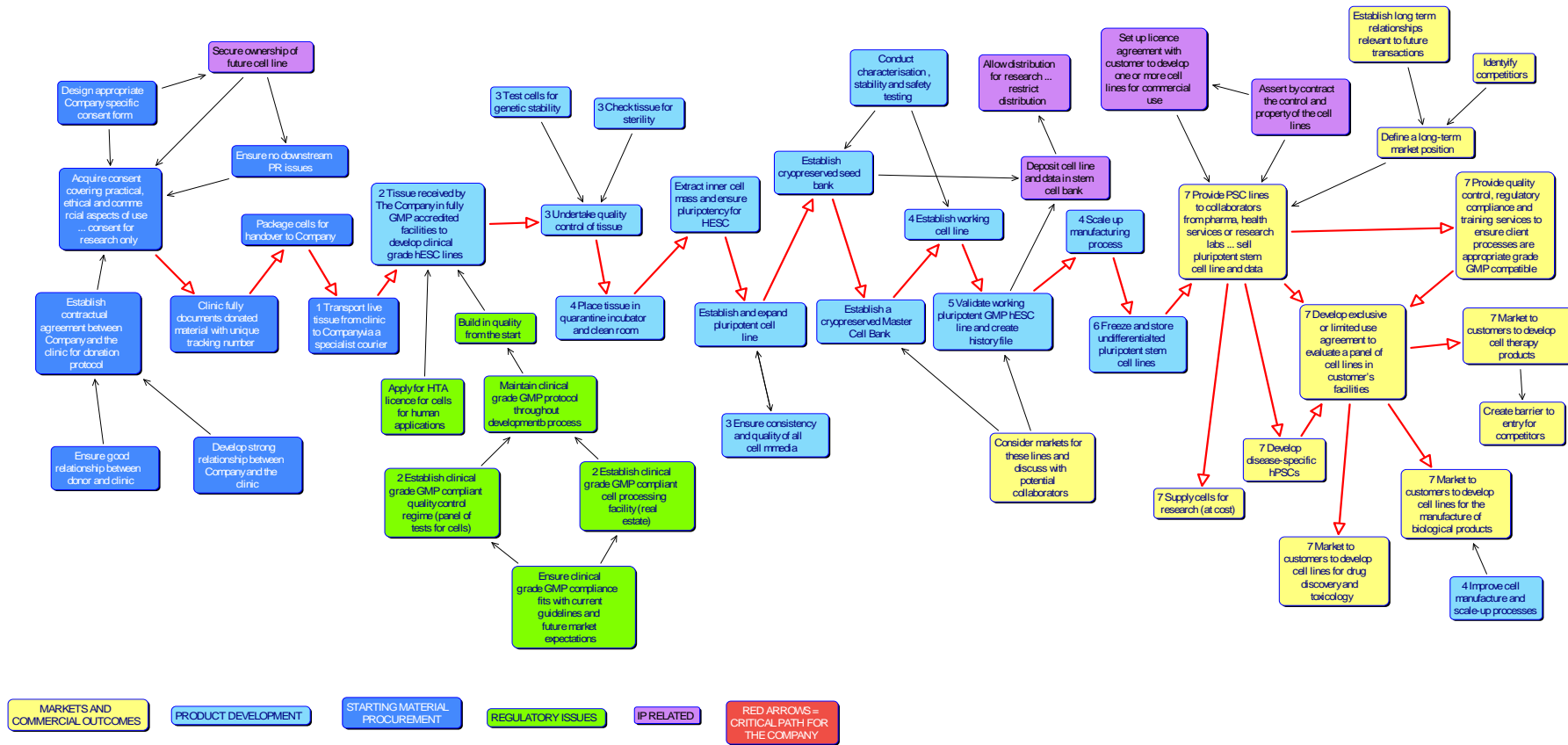
A1.2.1 Starting Material Procurement (dark blue boxes)

A number of activities must be undertaken in order to acquire the starting material ethically. For HESCs, the first stage of the process is to acquire donor consent for the derivation of stem cells from embryos, requiring an HFEA license. For this company's purposes, this consent should enable potential commercial use, in addition to the basic ethical approval for research and non-commercial purposes. The stem cell lines produced by this company are expected to be used for both clinical and non-clinical purposes, and either case could involve commercial transactions. This consent procedure is therefore more complex than that for research or other types of tissue donation, since the intended use of the cells is in 'one-to-many' rather than 'one-to-one' donations. This type of consent can be seen as providing the company with freedom to operate in future.

Robust consent procedures and subsequent good tissue management practice are important for all types of stem cell lines, not just HESCs. First, a legally watertight company specific consent form is needed, covering all potential uses of the resultant cell line and securing proprietary rights over any commercial stem cell line product. Due diligence with regard to donor consent will also ensure that there are no negative downstream PR issues or a situation where future commercial opportunities cannot be exploited due to issues with the original consent form. Second, it is important to establish contractual agreements between the company and the clinic for donation protocols. Developing and maintaining strong relationships with donor clinics and (for HESCs) embryologists is a key part of this business plan. It provides a potential barrier to entry for competitors in the development of pluripotent cell lines who may not have well-established relationships with clinics. Having cultivated these relationships over many years, the Company has an advantage that it is important to sustain and that forms a major part of the 'value-added' to the Company.

Once consent has been acquired, the clinic must fully document the donated material with a unique tracking number and package the cells for handover to the Company. Transport will require use of a specialist courier so the tissue received by the Company can enter clinical grade GMP facilities for development into a pluripotent stem cell line, currently from HESCs but in future also including iPSCs and this requires logistical and distribution channels to be established and maintained.

Figure A1.1 Level 2 Value System Map – Summary Model of Clinical Grade Pluripotent Stem Cell Lines (print on A3 paper for legibility)



A1.2.2 Product Development from the Starting Material within the Company (light blue boxes)

Once the stem cell sample, from whatever source, has been received by the Company, a number of regulatory processes (green boxes) must be satisfied to progress the starting material. The first requirement is to ensure that an HTA licence to develop cells for human applications is acquired. Quality needs to be built into the process from the start and clinical grade GMP maintained throughout the development process (although research grade facilities may be used for non-clinical applications). This includes both a GMP compliant quality control regime (the panel of tests for the cells) and GMP compliant cell processing facilities (real estate). The cost of setting up a GMP facility for a number of clinical grade cell lines will be in the region of £10-12 M. In establishing GMP compliance, the Company should seek to ensure this fits with current guidelines and requirements as well as future market expectations.

Once the tissue has been received by the company and subjected to standard quality control tests such as pathogen screening, further quality control of the tissue will include testing the cells for genetic stability and sterility. Only approximately 40% of the tissue received by the Company will be of sufficient quality to take forward from this point.

The tissue will then be placed in a quarantine incubator and clean room. For HESC lines, the inner cell mass will be extracted and pluripotency ensured. Approximately 50% of the material that has reached this point will develop into blastocysts – so from the starting material received by the Company, attrition is very high. A further 40% of this material is likely to be lost later in the process so that approximately 10-12% of embryos that enter the process will be successfully developed into viable stem cell lines.

The situation for IPS cells would be very different. While the success rate for reprogramming any single cell would be much lower (1% at best), the fact that there is an abundant supply of starting material would make it a more viable value proposition as IPS cells would be much cheaper. The approximate cost of developing a single HESC line is in the range of £100 - 200K, whilst that for a single IPSC line it is approximately £10 K, higher for a clinical grade line. These figures explain the Company's preference for working with IPS cells if the current technical problems with their safety and scalability can be resolved.

The next step in the business model is to establish and expand the pluripotent cell line, ensuring consistency and quality of all cell media, before establishing a cryo-preserved seed bank. Characterisation, stability and safety testing of this seed bank is then performed, including genetic stability and sterility testing. By this point in the process one can be fairly certain of having a viable cell line product.

From here, a Master Cell Bank is developed and future working cell lines will be drawn from this. At this point it is appropriate to consider what will be done commercially with the cells (the degree and form of expansion will depend on whether the market is pharmaceutical toxicity testing or one of a number of potential therapeutic markets). The size of the master and working cell banks will also depend on what function they will later serve and the manufacturing process required for final use. For example, one might have a relatively small master cell bank if the line will only be used for research purposes. If the final product is to be a cultured red blood cell product, an extremely large master cell bank would be required. In developing cells for toxicity testing in drug discovery, the final product will be the differentiated progeny of HES or IPS cell lines (e.g. hepatocytes or cardiomyocytes). So at this

point the Company needs to decide whether a cell line will be best taken down a clinical grade therapeutic route, or alternatively it will best serve a research pathway. Discussions and collaborations with potential partners interested in using a cell line should be initiated at this point.

Decisions must also be made about whether the cell line will be held exclusively or will be distributed. For example, for HESCs, once the cell line has been validated and a historic record created, a sample must be deposited in the UK Stem Cell Bank (UKSCB) and the cell line must be made available to other researchers for non-commercial and non-clinical use. In this case there is no right for the developer to retain exclusive use of the cell line – this is another of the attractions of using IPS cells. These UKSCB requirements are a key point of tension between competition and collaboration strategies and a translational challenge for developers of stem cell therapies (Courtney *et al.*, 2011). One consequence of this policy is that those who deposit or subsequently develop a stem cell line are unable to prevent release of samples from their cell line to third party researchers, other than for a limited period and in a limited area of research. Such use by a third party could threaten the reputation of a cell line that may be destined for commercial therapeutic development.

The final steps in these product development processes include scaling up manufacture of the cell lines (if the Company is to be involved in the development of larger markets than supplying cell banks) and cryo-preserving and storing the undifferentiated stem cell lines.

A1.2.3 Markets and Commercial Outcomes (yellow boxes)

The Company's preferred commercial option is to provide pluripotent stem cell lines to collaborators in the pharmaceutical industry, health services or research labs, and to work with them to develop products, rather than simply selling the lines and associated data. This is seen as more commercially lucrative, given that the Company will be selling the cells along with its expertise and support. For this model, license agreements will be required with the customer to develop one or more cell lines for commercial use, and the control and ownership of the cell line should be asserted in contract. These are important IP considerations that will affect commercial viability of therapy development and also the continued viability of the Company. Nevertheless, cells should also continue to be provided for research (at cost) to ensure all potential revenue streams are exploited.

From here, the Company could collaborate in developing well characterised disease specific GLP grade cells as the platform for future development of CGPSCs. An exclusive or limited use agreement might be negotiated with the customer to evaluate a panel of cell lines in the partners' own facilities (essentially trialling a range of cell lines to meet the specific needs of the customer). A number of markets could emerge from this:

1. Market to customers to develop cell lines for drug discovery and toxicology
2. Market to customers to develop cell lines for the manufacture of biological products. The Company could help improve cell manufacture and scale-up processes.
3. Market to customers to develop cell therapy products and, in so doing, create a barrier to entry for new competitors.
4. Provide quality control, regulatory compliance and training services to ensure client processes are appropriate grade GMP compatible.

For all these markets, it is important to define a long-term market position and ensure that all potential opportunities are exploited. This will require identifying competitors,

establishing long-term relationships relevant to future transactions and regularly evaluating the IP landscape.

The business model for this product is relatively robust as markets already exist and the technology is well established. It is clear from the map that there is a number of potentially viable markets and options for product development (including switching to IPS technology). However, much of the long-term value of the business model resides in: the craft knowledge around processes for developing CGPSCs; the expertise in, and facilities for clinical grade GMP manufacture and scale-up; and, crucially for HESCs, the relationships with the clinics that provide the source material. The proprietary consent forms and procedures also add value. There are therefore many commercial opportunities for long-term and sustainable value-creation and most of the uncertainty resides in the demand side for specific types of cell lines and applications (that are highly susceptible to rapid change in the value system environment, particularly regulation), as discussed in the following scenario.

A1.3 Scenario: Variation in Ability to Supply Clinical Grade Stem Cell Lines

For this case study we consider one important scenario that encompasses a number of important demand and supply issues with the potential to impact significantly on the business model. The scenario can be summarised as the need to cope with variation in the company's ability to supply clinical grade stem cell lines at a reasonable profit and thereby sustain the overall business model. For HESCs this could result from changes in the technology landscape, from IP issues that could affect the commercial viability of embryonic stem cell technologies and products emerging from HESC lines, and from changes in demand for particular types of cell lines.

Given the Company's reliance on craft knowledge and informal relationships with upstream collaborators, along with its inability to capture intellectual property from products and processes related to HESC development, it is vulnerable to competition from other companies with a larger funding base who could overtake its capacity to generate viable stem cell lines. This would be particularly problematic if there was a sudden increase in demand for stem cell lines that the Company's could not satisfy quickly and at the right price. This scenario is a test of whether the business model can deal adequately with these scalability and supply issues.

Variation in demand for CGPSCs could be caused by:

1. Changes in technology so that, for example, IPS cells can successfully compete with HES cells, leading to a lower demand for HESC lines. The question is whether the Company has the capability to switch technology if this change arises.
2. The combination of the Brustle Patent decision coupled to the UK SCB open source requirements could lead to firms losing control of their business model, although it would not necessarily lose all value. These regulatory impacts could greatly reduce the demand for HESCs and therefore commercial business models based on this technology.
3. Efficacy data from clinical trials might affect demand for cell lines and/or manufacturing requirements for SC lines. If some cell lines are particularly efficacious, there may be a sudden increase in demand for such lines, which would then need to be manufactured quickly. This might also affect the price of the cell lines, particularly if more cells are required to meet efficacy requirements. Alternatively, clinical trials may show that particular cell lines perform poorly, or have safety issues, which will then lead to reputational damage to those specific cell lines.

A number of potential scenarios could provide solutions to the problem of unexpectedly high demand for HESC lines, including increasing the number of clinics supplying primary tissue and improving the clinics' processing standards to improve the quality of the embryos they provide. As was mentioned earlier, the attrition rate for HESCs from securing of the primary tissue to creating a viable seed bank is less than 10%, so there is scope for creating more efficient processes. The Company's close relationships with the clinics supplying the material gives it an advantage in this market and it has the capability to improve the derivation processes, so this scenario is unlikely to pose a major threat to the business model.

In such a case, the Company could also establish collaborations and alliances with major downstream players that wish to differentiate cells for therapy, and so take a more active role in monitoring/predicting changes in downstream demand so that it is able to respond quickly. Another option would be to develop new manufacturing and scale up processes or build into the business model the capability rapidly to switch technology if the market so demands.

The problem of a sudden increase in demand for HESC lines is one that the business model, as it is currently structured, should be able to deal with. However, the regulatory and market challenges from the broader value system environment that could lead to lower demand for HESC lines and potential loss of control over certain parts of the business model is more significant. The Brustle patent decision is not on its own seen as a major threat to the commercial viability of HESC lines, provided the Company can retain sole ownership of a cell line. However, when coupled with the requirements to deposit all HESC lines in the UKSCB, the Brustle patent decision is likely to lead to a reduced demand for HESC lines in future, with developers choosing to switch to more lucrative and less problematic iPSC lines.

The key issue for this case study is that the potential to lose control of the commercial value of the HESC lines through these regulatory requirements undermines the long term viability of a business model built solely around HESCs in the UK and potentially throughout Europe. To create value around the supply of stem cells developers will need to have the capability to switch between different types of stem cell sources. The Company in this case study has sufficient complementary knowledge, skills and expertise that are directly applicable to the development of iPSCs. The business model and the overall value system for this case study is therefore robust enough to deal with this scenario of rapid change in the demand for HESCs (both increasing and declining).

In summary, much of the craft/tacit knowledge that the Company has, and the expertise in GMP cell production it has built over many years, would be applicable to a variety of different sources for cultivating stem cells and can continually be improved. The product development phase of the value system map is sufficiently flexible and transferable to allow for parallel or replacement processes for different cell types and options for manufacturing to different scales. The market and commercial options at the end of the system map are also sufficiently diverse to capture new and emerging sources of value and respond to rapid changes in the value system (including regulatory and market factors) that may close certain commercialisation options but also bring new opportunities.

A1.4 Conclusions

This case study describes a relatively well specified business model compared to many others in the regenerative medicine field. The technology for developing stem cell lines is well advanced and the Company has a range of potential products that can be commercialised. Furthermore, because the end point of the business model is the supply of stem cell lines, rather than the marketing of a specific stem cell therapy, there are few areas of major uncertainty along this particular business model. The

route to market is well established, although changes in the regulatory environment and changes in product development processes for therapies that may use these stem cell lines, have the potential to affect a number of value points along the HESC business model. In this context, because of uncertainties regarding the commercial opportunities for stem cell therapies in the clinic, it is not yet clear how much overall value can be created from these cell lines.

The business model seems viable for a not-for-profit company that can market its core competencies and expertise in sourcing starting material and derivation of pluripotent stem cells, distribute cell lines for commercial and non-commercial purposes, and build new capabilities and capacities for the creation of new types of cell lines. However, it may prove difficult for a commercial company to sustain a business model based on HESCs with an adequate revenue stream. Likewise, alternative technologies such as iPSCs also have issues in terms of safety, scale up and IP (the Sendai virus patent will add to the cost of development for commercial iPSC lines).

Nevertheless, the tacit and craft knowledge that has been built up around the derivation of HESCs in this case study gives the Company a unique selling point in the stem cell line market, as well as a scaleable and sustainable business model in the short to medium term.

ANNEX 2. BIO-ARTIFICIAL LIVER DEVICE CASE STUDY

A2.1 Background

The development of a BioArtificial Liver (BAL) device could represent a major opportunity for stem cell therapy. Liver disease is an important health problem that is comparatively poorly treated, and liver failure is a life threatening condition with transplant (if available) often the only cure. An effective BAL device will offer a chance for liver function to be sustained or improved, and in some cases to allow time for the liver to self-repair, avoiding the need for transplant. However, the device is conceived as being used in its early development phase in cases of acute terminal liver failure to sustain the patient's life while awaiting transplant.

The BAL device described here differs from previous attempts to deal with such problems because of its access to human hepatocytes derived from HESCs. This approach to the therapeutic use of stem cells is one where the cells are not introduced into the body and this will hopefully reduce the safety concerns about the therapy and ease the route to the market.

The BAL device business plan discussed here involves a complex device, the performance of which will be a function of both the cells and the bioreactor/device in which they are contained. Newco plans to focus its efforts on commercialising its core assets – the cells that form the basis of the functionality of the BAL device, requiring development and manufacture of the cells together with their incorporation into a suitable bioreactor cassette that will allow their optimal performance. Development of the entire BAL device (the cells incorporated in a bioreactor cassette that is then inserted in a larger device to enable extra-corporeal circulation and cleansing of the patient's blood) will require future collaboration with partners who have expertise in all these areas.

A2.2 Description and Analysis of the Value System Map

The BAL device Level 2 value system maps (Figure A2.1) (see Main Report Section 4.2) illustrates the steps, options and decision points along the critical path in the business model (red arrows) from the starting stem cell line to delivery of a therapy to patients, in the context of the value system-related factors that influence the Newco business model positively or negatively. This business model focuses almost entirely on development of the cellular component of the device. Developing a viable product will require collaboration of at least two additional companies with complementary competencies in a value chain that combines development of the bioreactor and of the device itself alongside development of the cells. However the choice of technology, and hence the partners, for this collaboration has not yet been made.

Reading Figure A2.1 from left to right, the main critical path branches into three potential developmental paths along the critical path of the business model: (i) based on large scale manufacture and distribution of the BAL device; (ii) based on the establishment of licensed, quality-controlled laboratories in different locations globally; and (iii) based on a local hospital centre of excellence.

A2.2.1 Cell line procurement and differentiation

The first step after obtaining a starting embryonic stem cell line is to create a master cell bank for Newco use, establishing a sufficient number of cells to perform the activities of hepatocyte differentiation and/or cell distribution without negatively affecting its initial stock of stem cells. Newco has still to determine what technology it will use to create this increased number of stem cells to establish the master cell bank and maintain the qualities of the original stem cells.

The next step will be to differentiate the cells into functioning hepatocytes for use in the bioreactor component of the BAL device. The differentiation of cells to hepatocytes under strict quality conditions is seen as one of the main contributions to the value that will be held by Newco. Hepatocyte production must balance function, cost and stability, including exposure of the cells to a range of different media in sequential stages of their manufacture through to their use in the bioreactor. The quality control system for Newco will be based on clinical grade GMP protocols developed by the company producing the starting stem cell line (Annex 1 Case Study) in three phases: the source materials; manufacturing process; and product testing. Quality control will also involve a full characterization of cells, cell products and other materials to document purity and potency.

Decisions about hepatocyte development will depend on the patient or client segment chosen which will determine the scale of cell production needed per treatment. Several different types of hepatocyte are involved in a functioning liver and all will need to be included in an effective BAL device. Over the past two years, Newco has greatly improved its ability to develop the full range of cells required and has also significantly improved the scale of production that can be achieved. These factors will play a role in the selection of a targets for BAL device development.

The selection of multi-factor cell combinations is an important feature of the BAL business plan. Decisions on how to combine different elements to provide a particular feature of the BAL device arise at different points along the business model.

A2.2.2 Bioreactor and Cell Combinations

The next step is to test the various combinations of bioreactor design with hepatocyte mix, as different bioreactor structures and media used may impact the therapeutic efficacy of different cell types. Amongst the bioreactor designs discussed so far (developed by other groups) are a '3D' model and a hollow-fibre cylinder model. Factors involved in selection of design combinations include varying performance regarding cell life span, toxic resistance and therapeutic quality. Newco will select the best combination of these factors to determine the bioreactor design. Partnering with other research groups or companies working on bioreactor design will probably be necessary. Alternatively, Newco could attempt to develop the bioreactor itself.

The bioreactor cassette containing the liver cells will be inserted into the larger BAL device unit (described as a small-refrigerator sized apparatus), for which Newco would partner with firms currently involved in producing and distributing kidney dialysis or similar machines due to potential synergies and common distribution channels. The production of cells, production of the bioreactor, and logistic considerations to deliver cells and the bioreactor to complete the larger BAL device are the only factors that directly concern Newco, from which point the firm responsible for the whole BAL unit would take over distribution.

Considering the different combinations of cells and bioreactor design and their relative benefits, the final bioreactor design will be selected. Following that the

appropriate scale-up technology for cell production can be confirmed. The scaled up production and manufacture of hepatocyte cells will have to deliver a minimum number of cells per device, based on meeting the performance of an estimated 20% of an endogenous liver (normally 1.5 kg – or 6×10^{10} cells); and estimates of total production based on a projection of 2500 to 5000 potential patients suitable for treatment by the BAL in the US/Europe. Because of the high culture concentration requirements, current suspension culture methods of production require tens of thousands of litres of culture per year, and the Newco business plan cites the need to move beyond this manufacturing technology to new high density suspension cell cultures, which will form part of the company's development path.

As it stands therefore, the two main sources of value added for Newco would be the differentiation of the cells and the high density production of cells. However, the feasibility of both these procedures is still not established and represents a critical juncture in the BAL device business model. It is also important to note that the medium for creating and storing the cells, as well as the medium in which they are placed for the bioreactor will likely change. The possibility of having to deal with different potential suppliers may affect the cost structure and potentially complicate supply lines.

Beyond this stage in the business plan, partnership arrangements can be confirmed – with partners selected for bioreactor production as well as BAL device unit production and, if necessary, large scale cell manufacturing. Confirming partners, however, should not be seen as an easy step. To begin with, Newco wishes to avoid, if possible, the regulatory burden associated with delivering the BAL device to patients, thereby placing this burden on potential partners who would deliver the complete BAL device. The willingness of partners to take on this burden, and in general to pursue the business opportunity offered by the BAL device, will depend on the cost versus return they can obtain and this will vary depending on which of the three business model paths outlined below is pursued.

According to the business plan figures regarding market opportunity, estimating a potential 50,000 target patient population in the US/Europe per annum, with 5-10% market penetration for the BAL and an initial estimated price for the BAL unit at \$50,000 USD, revenues for the overall operation would be between \$125M to \$250M. From this, Newco would hope to obtain 50% of the share of this revenue, although this may be over-optimistic if other companies are able to compete in the delivery of the cells themselves, seen by Newco as the current basis of its competitive advantage. Partnering agreements will form an important part of the business challenge.

A2.2.3 Possible Partnership and Business Models

Three possible partnership and business models were discussed with Newco.

First Business Model – Path A

The first model, branching off to the left hand side of the critical path, would involve large-scale manufacturing of hepatocytes and insertion into bioreactor cassettes from Newco's facilities. These bioreactors would then be shipped to clients (e.g. hospitals or clinics) who would have purchased or acquired a number of the BAL device units. The bioreactor cassette would then be inserted into the BAL device as needed. This type of arrangement would require the establishment of a commercial scale master stem cell bank for cell redistribution. Such a model would also require partners able to provide the logistics of cryogenic storage of a large quantity of cells at Newco's facilities as bioreactors are manufactured and stocked, and long-distance distribution of the bioreactors to client facilities. However, this model faces the challenge that it is not yet possible to cryo-preserve liver cells.

Selecting this pathway would require confirmation that the combination of hepatocyte cells identified and the components of the BAL device best coincide with large scale, centralized manufacture. Also, instead of scaling up production in-house, an alternative option may be to scale-out production of hepatocytes to a Contract Manufacturing Organization.

This first business model is potentially the most desirable from a commercial point of view due to economies of scale and revenue potential. It would create a certain amount of consistent turnover for Newco and its partners, and would more likely fit the initial market penetration and revenue projections expressed in the Newco business plan; therefore it would likely be easier to resolve initial partnering selection decisions.

Second Business Model – Path B

A second business model critical path would involve Newco in Scotland becoming a centre of excellence for the production of stem cells for differentiation. The business arrangement would involve potential clients (e.g. hospitals and clinics) acquiring a BAL device unit and also setting up laboratory facilities to differentiate their own hepatocytes from Newco cells using Newco approved processes and quality standards based on a licensing agreement. In this manner, The BAL device and bioreactor cassette partners would manufacture and provide the equipment to the client, but the actual cells would be made at client facilities as needed. This kind of set-up would require logistics partners able to provide quick delivery of the stem cells from Newco to the client and long-term storage *in situ* of a working cell bank.

This business path would offer the possibility of licensing revenue for Newco with a lower cost in manufacturing. However, because of the likely smaller scale of BAL unit production and sales, potential partners may either hesitate to participate or the cost of a BAL unit may increase to the point that potential clients may consider alternate therapies. One possible solution would be to include BAL device maintenance and servicing opportunities for Newco partners, increasing possible revenue and making the endeavour more attractive.

Third Business Model – Path C

A third option would be for Newco to collaborate in establishing a Hospital Centre of Excellence in Edinburgh, where a more limited production capacity would be used for local or visiting patients, with the possibility of later licensing the procedure to other centres in different markets; or contracting out the manufacturing process. This third option would probably require lower capital expenditure, but it would also generate lower profits. A hospital partner would have to be selected, along with the BAL device and bioreactor cassette partners. The facilities for the hospital in terms of number of machines, and patient intake facilities would also have to be determined and organized. The main challenge will be either to set up an adequate “just-in-time” delivery structure from Newco’s local production facilities to the hospital zone, or to establish a system that allows efficient stockpiling and delivery, again requiring cryo-storage facilities.

Even more so than Path B, the small scale of BAL device production may make it difficult to attract partners for device manufacture.

A notable aspect of the BAL device case study is the low involvement that Newco wants to maintain in regards to the regulatory process. As the green boxes illustrate in Figure A2.1, most of the involvement by Newco with regulatory measures will be in the provision of efficacy data and the adherence to clinical grade quality standards for all of its manufacturing and processing activities. The regulatory burden would be borne mainly by the partner responsible for the final manufacture and distribution of the BAL device. This arrangement would most likely be evident in the first partnering

and business scenario with centralized manufacture and BAL device distribution, with the attraction of large scale sales relative to the other two scenarios.

A2.3 Scenarios and Critical Points for the BAL Device Case Study: Impact of Manufacturing Decisions on Product Delivery

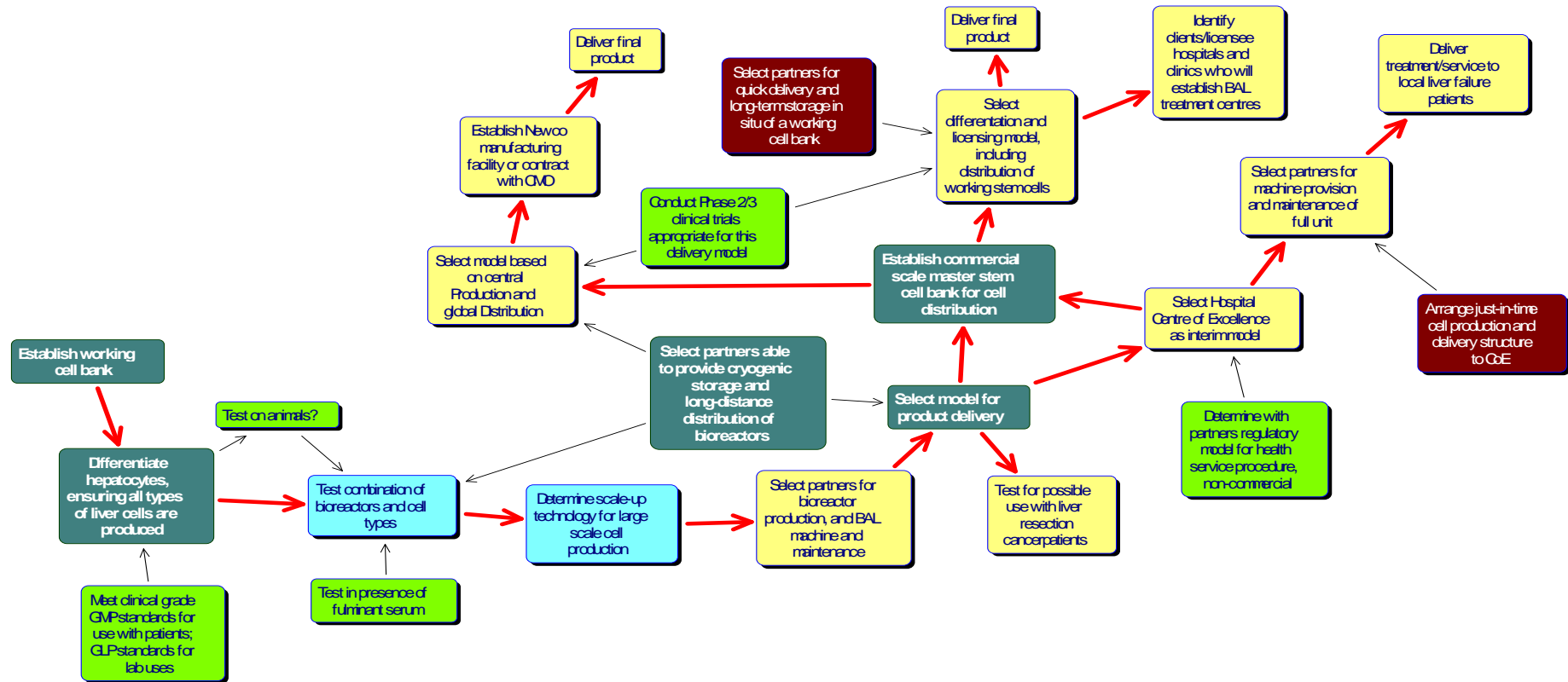
Newco's BAL Device strategy is to provide a therapy for chronic liver disease and/or liver failure. The company would produce GMP grade hepatocyte-like cells incorporated into a cassette (bioreactor) which can then be incorporated into a larger BAL Device. The combination of cells and bioreactor determines BAL device functionality. There are different ways of producing cells in different types of bioreactors, so manufacturing and scale up is a major issue for this business model.

In this section, we consider scenarios related to the impact of different manufacturing issues on the viability of the business model and delivery of the device to particular target markets (Figure A3.2). Two points will be discussed regarding their impact on different manufacturing and delivery mechanisms: number of cells required to treat the patient and implications for scale-up; and cell survival and transportation requirements.

A2.3.1 Issues regarding the type and number of cells required for the BAL Device

As described above, three possible business plan paths have been considered for the BAL device. Common to all three is the need for the best combination of hepatocytes to be determined in conjunction with the bioreactor design in order to ensure a high level of efficacy for the targeted patient group. Taking into consideration the number of cells required to treat the patient, if it is found that the ideal therapy requires a range of hepatocytes to be used in conjunction with one or another of the bioreactor designs for the ideal therapeutic results, this may create some new challenges for manufacturing scale up. Depending on the technology used and how different types of hepatocytes are produced (whether in the same manufacturing structure or in different structures), a broader array of hepatocytes may require more infrastructure and up-front capital and manufacturing costs than single cell type hepatocyte therapies. The reasoning here is that some hepatocytes may be more difficult than others to produce. If one set is more difficult, then depending on the different proportions needed to create a functioning bioreactor, the difference in pace of hepatocyte production may impede the pace of BAL unit production and ultimate delivery. For the licensing scenario in business model Path B, it may be difficult for on-site laboratory workers to reproduce particular hepatocytes which may either nullify this path as an option or require either on-site training/Newco staffing to overcome the initial difficulties adding to costs and logistical difficulties.

Figure A2.2 – Level 3 Value System Map - Critical Points in the BAL Device Value System Model (print on A3 paper for legibility)



Furthermore, effective and sufficient scale-up of cell manufacture is still to be achieved. Initially it was expected that this would be the major hurdle for hepatocyte production. Creating large enough cell batches for use in bioreactors would require a minimum estimated number of cells of 6×10^{10} , based on 20% of an endogenous liver. Total production based on a projection of 2500 to 5000 potential patients suitable for treatment by the BAL in the US/Europe is thus a major challenge. To achieve this, it is believed necessary to move beyond the current suspension culture methods of production to new high density suspension cell cultures (testing both two-dimensional and three dimensional types). While scale up technology has not yet been perfected, there have been advances in scale up technology using new materials and polymer surfaces. However, until this technology is established, and until the costs, infrastructure requirements and ability to create different hepatocytes is confirmed, manufacturing ability will remain an open question, with uncertainty regarding the cost and feasibility of different business plans.

It may be that, in a high cost, high hepatocyte varietal scenario, where a sufficiently large scale-up technology has not yet been achieved, either the Scotland-based hospital centre of excellence scenario, or the multiple site licensing scenario would be the most practical path to a market. Small batch production may be the solution in these circumstances.

A2.3.2 Cryogenic preservation and logistic issues

A technological factor with an equally important impact on the BAL Device business path is the effectiveness of cryogenic storage and the ability of cells to function after storage. This may be a major obstacle for BAL device development as all three scenarios involve some logistical hurdles based around hepatocyte storage. The two most obviously affected options are the large scale manufacturing and distribution path (Path A, above) and the Scottish hospital-based path (Path C, above). Path A requires the logistical step of cryogenically preserving and shipping hepatocyte cells manufactured either by Newco or by a contract manufacturing company, and delivering them to clients already possessing the BAL device. Path A requires that the cells be produced and placed in the bioreactor and then either stored at the manufacturing site until clients order them for therapy, or shipped to the client once they are produced and stored at the client's facilities. Either way, without cryogenic storage and cells robust enough to recover their capacities after freezing, effective therapy delivery in Path A will not be possible.

For Path C, while the geographic distance is much smaller, the question of storing and delivery cells to the treatment centre must still be solved. Ideally, with effective cryo-preservation either the hospital centre or Newco can stockpile bioreactor cassettes until required by patients, allowing for quick and efficient delivery of the therapy.

If effective cryo-preservation is not possible, alternative solutions would be either the continuous production of stem cells and storing for the limited life span, ensuring that active cells would be available when the need arises, or the production of needed cells as a patient is identified. The challenge of the first solution is that there would be a large amount of waste involved, increasing costs. The second solution's feasibility would depend on how quickly the adequate number of cells could be produced, given that patients in acute liver failure have a very short life expectancy.

Path B, licensed production of cells in globally distributed locations, would also be partially affected by these concerns. However, here the cost and burden of finding acceptable solutions would fall to the licensee. Furthermore, having production

facilities in the location where the therapy is provided, and managed by the same team of personnel, may make “just-in-time” production a feasible solution.

A2.4 Conclusions

As has been outlined above, the effective delivery of a BAL device to patients/clients still faces many key uncertainties based on technological development. These questions will have an impact on the type of business model selected, the costs involved and the potential revenue streams possible for Newco and partners.

Four main challenges were identified:

1. finding the combination of hepatocytes necessary for effective therapy, and establishing a successful method to consistently differentiate cells to match the needed hepatocytes;
2. establishing and confirming the necessary partnership arrangements to manufacture and deliver the BALdevice;
3. finding the appropriate scale-up technology to mass produce hepatocytes in the necessary numbers;
4. developing the cryogenic technology necessary for cell storage and delivery.

The third and fourth of these challenges formed the basis of two scenarios that were discussed in more detail. Regarding the first scenario (third challenge above), progress is being made on polymer based scale-up technology, potentially increasing the capacity of cell production by several orders of magnitude, although still not to a sufficient scale to deliver a therapy.

The second scenario (fourth challenge above), significantly affects the BAL device delivery logistics and hence delivery of any form of therapy across the three projected business models. Using the BAL device in a non-commercial hospital centre-of-excellence model where cell production could be maintained on a continuous basis with an expected degree of waste raises some interesting possibilities. This may be justifiable on the basis of health service treatments and patient care, even though it does not have such an attractive profit model for the company.

As with all regenerative medicine therapies based on stem cells, regulatory uncertainty will play an important part in the eventual delivery of the therapy. Because of the extra-corporeal nature of the device, the regulatory system was expected to be less onerous in this case study than for RBCs (8 years instead of 10-15 years). However, regulatory constraints do not feature heavily in the value system environment of Newco’s business plan because of the company’s early decision not to become involved in regulatory aspects of the eventual value chain for delivery of the BAL device to its end markets.

ANNEX 3. RED BLOOD CELLS CASE STUDY

A3.1. Background

The development of industrial scale cultured red blood cells (RBCs) from stem cell lines aims to meet the growing need for new sources of blood products as a result of problems in the current supply chain, risks of contamination and risks associated with immune responses for patients that require repeat transfusions.

Previous attempts to develop artificial blood products to replace donated blood have been largely unsuccessful, mainly due to problems with toxicity and manufacture. However, advances in stem cell science have opened up the possibility of manufacturing in vitro produced RBC replacement products containing cells that perform at least as well as, and perhaps better, than conventional donor blood.

In this case study, the company and the scientists involved are using stem cell science and technology for the differentiation of enucleated RBCs for clinical use derived from clinical grade GMP human embryonic stem cell lines. In future, as the technology for differentiation and scale-up of iPS cells matures, they will probably be used as the source cell lines.

The current challenges in development of this product from HESCs are (i) improving RBC differentiation and (ii) achieving the required scale-up in manufacturing processes to satisfy a niche patient group (thalassaemia). The potential to satisfy larger markets for blood transfusion products will be explored in future stages of product development.

In the short-term the business model is based on establishing proof of concept, getting into phase 1 and 2 clinical trials and becoming an innovation leader in the development of cultured blood products, including the associated technologies and processes. In the longer term further clinical development, probably with commercial and non-commercial partners, will be required to get the product to market. Along this complex and largely uncertain product development pathway there are major scientific, manufacturing and regulatory challenges, and also opportunities to capture value by exploiting other applications of the discoveries, products and services that will be generated at different points on the value chain.

A number of key factors will drive the demand for cultured blood, building on the already well established supply and distribution chains in the UK.

1. There needs to be an established market for the product.
2. The quantities required for commercial scale-up will to a large extent require parallelisation of production, without fundamental change in the production process itself.
3. There is a clear and compelling need for the product to replace current donor supplies, provide a better matched product for those needing repeat transfusions (such as thalassaemia patients), and also to meet the growing needs of developing countries, which could be an important and growing market in the future.

The following sections describe the value system maps (Figures A3.1 and A3.2) for the development of red blood cells from SCs and the related challenges, bottlenecks and opportunities for product development. We consider some of the critical points in the value chain and discuss scenarios that have important implications for this product.

A3.2. Description and Analysis of the Level 2 Value System Map

The Level 2 Value System Map (Figure A3.1) (see Main Report, section 4.2) illustrates the steps, options and decision points along the business model critical path (the red arrows) from a starting stem cell line to delivery of a therapy to patients, in the context of the value system related factors (e.g. regulation, IP, markets) that influence this business model positively or negatively. As noted in the main report, beyond the early starting points on this map, most of the decision points and inputs are speculative – the map can be seen as an exercise in technology foresighting, rather than a description of current reality.

Reading Figure A3.1 from left to right, the critical path for product development has two main branches following acquisition of the starting cell line: (i) manufacturing and scale up processes and (ii) actions to meet regulatory requirements.

A3.2.1 Cell line procurement and differentiation

The critical path begins with a series of science and technology-related issues, first obtaining the starting cell line and developing a starting master cell bank. The company is currently working with HESC lines but plans to base future developments on IPS cell lines once the science and technology issues with these cells have been resolved. The starting cell line should ideally be type O-negative but currently no HESC lines of this type are available. It would be easier to obtain an IPS cell line of this type. Even more useful would be an immortalised progenitor cell line that is expandable and can only differentiate into RBCs.

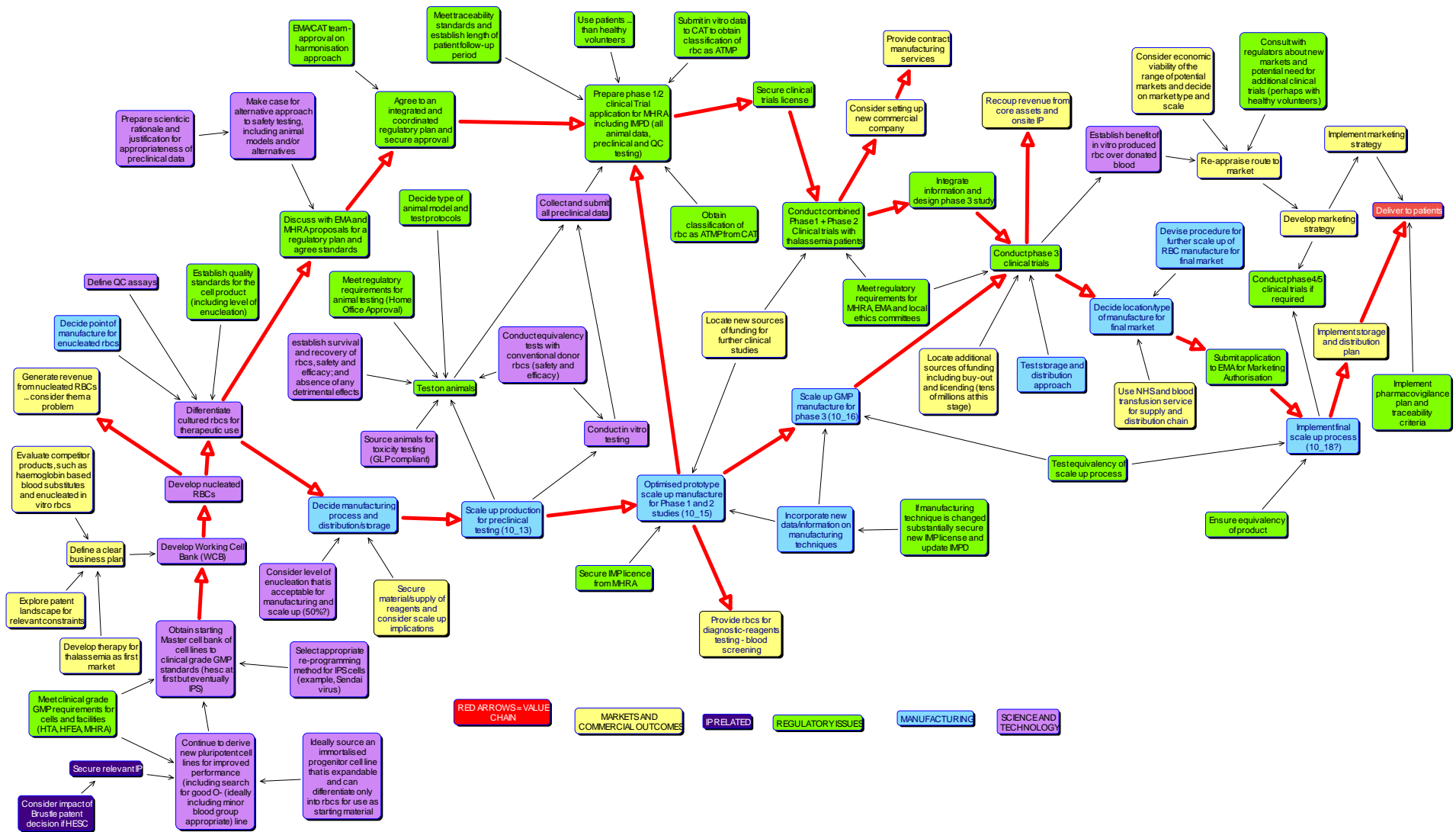
Whatever the starting material, it will be crucial to secure relevant IP and to meet clinical grade GMP requirements for cells and facilities. The recent Brustle decision on patenting of embryonic stem cell lines means that IPS cells are likely to form the starting material for the final clinical product. For IPS cell lines, selection of the re-programming method is important (currently Sendai virus but this will be regularly reviewed to check on scientific developments).

The next key step in the business plan is to develop a Working Cell Bank, including a comprehensive exploration of the IP landscape to identify relevant constraints and evaluate competitor products, such as haemoglobin-based blood substitutes and other methods for developing enucleated RBCs in vitro.

It is also important at this point to define the initial target market, in this case beta-thalassaemia, a niche market that will enable proof of concept to be established, and may also be amenable to regulation as an Orphan Medicinal Product (with benefits of extended market exclusivity, fee reductions and protocol assistance). For beta-thalassaemia (affecting 1 in 100,000 globally and 1 in 10,000 in the EU), the only current treatments are frequent blood transfusions combined with chelating medication, or bone marrow transplant from a suitable donor.

Considering blood for routine transfusion as a future global market, the demand is likely to be high. Donation figures were 92 million units in 2007, 55 million of these in developed countries. World demand is estimated to be around 200 million units per annum, requiring approx 5×10^{20} RBCs. In the UK, approximately 2.2 million units are procured and processed per annum at a cost of around £140 per unit (NHSBT tariff price, 2008/2009 – real cost is more). In the United States, approximately 16 million units are processed per year (approximately 40,000 units/day).

Figure A3.1 Level 2 Value System Map – Summary Model of RBC Development (print on A3 paper for legibility)



The next step in the map is to develop nucleated RBCs, then differentiate cultured, enucleated RBCs for therapeutic use as a viable alternative to conventional blood transfusion. The differentiation process must achieve a RBC product that exhibits: definitive erythroid lineage cells (including globin switching); oxygen carrying capacity; morphology that resembles normal RBCs; a deformability profile that matches the natural product; and output scale-up of approx 10^{11} with 50% fully matured cells.

Enucleated RBCs are expected to carry little or no risk of adverse immunogenic response, although there is not yet evidence to support this. However, cell enucleation is currently the major challenge in this case study - It is not clear how long it will take and how much it will cost to develop enucleated RBCs. Achieving 50% enucleation would probably lead to a viable product, using physical methods to separate nucleated from enucleated cells (100% enucleation is unlikely to be achievable and 10% enucleation would be unviable).

At this point there is a possibility to explore the potential market for nucleated red blood cells, for example for researchers working on malaria vaccines. This could provide a revenue stream to help to support continuing research and development on the primary product, rather than treating nucleated RBCs entirely as a problem.

Once successful enucleation has been achieved, the company must define the quality control assays and establish quality standards for the cell product, including the acceptable level of enucleation. This will be a key regulatory requirement further along the future implementation of the business model. At this critical point of differentiating enucleated RBCs, the map splits into a regulatory path for clinical testing of the product and a manufacturing path. Both need to be progressed in parallel up to the start of phase 3 clinical trials.

A3.2.2 Manufacturing path

The decisions on manufacturing location and processes will have an impact on future options related to storage and distribution of the final product. This manufacturing decision for initial production of enucleated RBCs requires the developer to secure a reliable, cost effective supply of reagents for scale-up of cell production and to consider the acceptable level of enucleation. These factors are all likely to change over the future timescale of the product development. For example, many researchers globally are working on development of enucleated RBCs and one or more future breakthroughs may alter the extent of this challenge; likewise, the cost of goods is likely to decline in later stages of manufacture as reagent suppliers face an increasingly competitive environment (currently, to develop one unit of blood it could cost £50,000 for the stem cell factor alone).

The next step is to scale up RBC production for preclinical testing (see 3.2.3) likely to require approx 10^{13} RBCs. Achieving this degree of scale up is another major and currently unresolved challenge.

The preclinical phase will include animal testing, requiring decisions about: the type of animal model and test protocols; meeting regulatory requirements for animal testing; sourcing GLP compliant animals for toxicity testing; establishing survival and recovery of the RBCs; general safety and efficacy of the product; and a substantial amount of in vitro testing. Although many of the details of these regulatory requirements are currently uncertain, they will enable equivalency tests with conventional donor RBCs and provide the required preclinical data for a phase 1 clinical trial application.

Animal testing is a continuing area of uncertainty for this product. Some animal testing will be required for regulatory purposes (section 3.2.3), but it is unclear what relevance the animal data will have for product safety and efficacy in humans.

Nevertheless, basic small animal toxicity testing is likely to be a minimal requirement and total cost for the animal work will likely be in the region of £250,000 and take approximately 6-12 months to complete.

The next major manufacturing step is to optimise prototype scale up manufacture for a combined phase 1/2 clinical trial, which will require in the region of 10^{15} RBCs. This will require a manufacturer's Investigational Medicinal Product (IMP) license from the MHRA. The description of this scale-up process will also make an important contribution to the clinical trial application to MHRA. The developer should also at this stage incorporate any new data or information on improving manufacturing techniques. However, it is important to note that if the manufacturing process is changed substantially, it may be necessary to secure a new IMP license and update the Investigational Medicinal Product Dossier (IMPD). Again, it will be important to consider cost of goods. At this stage of development, 1 unit of the cultured blood could cost anywhere from £10,000 to £100,000, depending on costs of media and stem cell factor.

At this point in the manufacturing critical path, there is an option to provide cultured RBCs for diagnostics/reagents testing and blood screening. This could be a lucrative market and enable the developer to derive some additional commercial value whilst continuing to develop the clinical product. At this stage, it is also important to locate new sources of funding for further clinical studies and manufacturing scale-up. Getting to phase 1 studies can probably be funded by public sector grants (£5-10M approx) but further clinical studies will require a substantial investment (tens of millions GBP).

The next major step in manufacturing is to scale up for phase 3 clinical trials, which will require approximately 10^{16} RBCs. This again represents a significant step change in manufacturing capacity and will require industrial scale technologies that have not yet been developed.

A3.2.3 Regulatory path (up to Phase 2 Clinical Trials)

Once cultured RBCs can be successfully differentiated for therapeutic use, the next stage on the regulatory critical path is to initiate discussions with EMA and MHRA about proposals for a regulatory plan and to agree standards. At this point one might begin to make a case for alternative approaches to safety testing, including use of animal models and/or alternative in vitro testing. The crucial element here is to prepare a strong scientific rationale and justification for the appropriateness of the preclinical data to be collected.

In consultation with the regulatory authorities, the developer will need to agree to an integrated and coordinated regulatory plan and have it approved. The Committee for Advanced Therapies (CAT) within the EMA will also provide advice/approval on the relevant harmonisation approach within the EU.

The next major step is to prepare the phase 1/2 Clinical Trial Application for MHRA, which will include the IMPD (which contains all the information on the animal data, preclinical and QC testing). As part of this application, it will also be important to agree traceability standards with regulators and to establish the required patient follow-up period; to specify subjects for the clinical trial (with patients rather than healthy volunteers) and to obtain from CAT classification of the end-product as an ATMP.

Once a clinical trial licence has been secured, a combined phase 1/2 clinical trial with thalassaemia patients can begin. This trial will require up to 50 patients, and the developer will need to have considered issues of cost and time to recruit patients and conduct the tests. Regulatory requirements for MHRA, EMA and local ethics committees will also need to be met for all clinical trial phases.

The phase 1/2 trial is a crucial step in the value chain. If the trial is unsuccessful, one option might be to establish a new commercial company and provide contract manufacturing services and expertise based on the science, technology and manufacturing competencies and capabilities that have been acquired during the product development process. If, however, safety of the product, and perhaps some efficacy, has been demonstrated through the clinical trial, all the information and data should be integrated and used to design a phase 3 study. If the parallel activities around manufacturing scale up have also been successfully achieved, phase 3 studies could then begin.

A3.2.4 Phase 3 trials and final product development

As described above, many uncertainties will need to be resolved before this stage is reached and the timescale to reach this stage is also uncertain. The business model beyond this point is therefore even more speculative and liable to future changes than the earlier parts of the critical path.

Additional sources of funding, and perhaps licensing or partnership arrangements, will be vital for phase 3 studies and beyond. It will be important to devise commercially and medically viable storage and distribution options for the final product. For example, if thalassaemia disorders are the chosen market, a multi site phase 3 trial in different international locations may be required. Choice of market might also affect funding opportunities, particularly from public sources. Phase 3 studies will be much larger and more costly than phase 1/2 and will require efficacy data and comparative testing with conventional transfusion.

If the phase 3 study is unsuccessful, the developer could recoup revenue from core assets and onsite IP and/or go back to a previous exit strategy, setting up a new company to provide contract manufacturing services.

In demonstrating equivalency of the product to regulators, the developers believe that it will have many advantages over conventional donor blood, particularly in that all the cells will be of the same age and therefore less may need to be transfused to get the same clinical benefit. If the phase 3 study is successful, and demonstrates benefits of in vitro produced RBCs over conventional donated blood, two potential paths could be pursued, as alternatives or in parallel.

The developer could take the final product to the thalassaemia patient market. This will again require a decision on the location and type of manufacture for the final market, which is dependent on devising a procedure for final scale-up of cell production to meet the needs of the selected market. Centralised manufacturing would seem the most appropriate option, using the NHS and blood transfusion services in the UK for the supply and distribution chain. In this case, an application should be submitted to the EMA for a Marketing Authorisation. The final scale-up process can then be implemented (requiring approx 10^{18} RBCs), the storage and distribution plan can be implemented, and the product delivered to patients. The final requirement is to implement the pharmaco-vigilance plan and meet the traceability criteria agreed with the regulators.

After a successful phase 3 study, the developer could re-appraise the route to market and consider the economic viability of a range of potential markets beyond the niche thalassaemia market. This would depend on the market size and the scale for which there are sufficient financial resources and manufacturing capabilities. It may require consultation with regulators about the need for additional clinical trials, perhaps involving healthy volunteers. If it is the case that different blood markets will require new clinical trials, this would add significantly to development costs, but would also open up new value propositions and commercial opportunities. A marketing strategy

would then need to be developed for each new market, following phase 4/5 clinical trials if required, before delivering the product to patients in the clinic.

As described by those developing the business model for this product, reflected in Figure A3.1, the critical path in the cultured blood business model is split between a manufacturing and a regulatory path, with cross-over points at various stages of the product development pathway. The total time and cost to get to scale up to phase 2 studies from the starting material is expected to be in the region of £10M (not including clinical trials) and to take 10 years. The phase 1/2 clinical trials will probably add around £2-3M to that figure. Beyond that, the product will require tens of millions GBP to go to phase 3 trials and beyond, requiring commercial company involvement for final delivery of the product.

A3.3. Scenarios and Critical Points

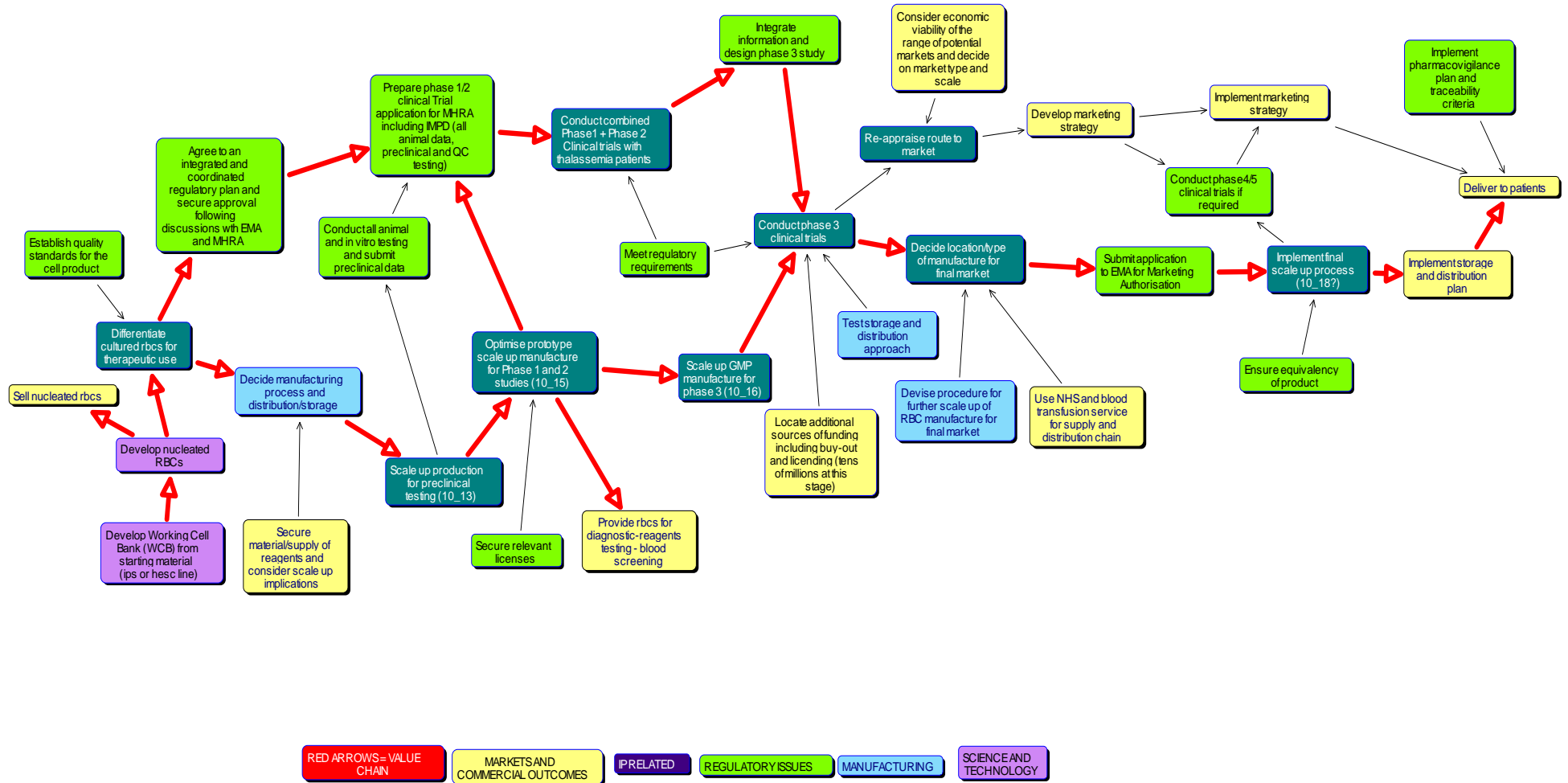
In Figure A3.2 (Level 3 Value System Map) (see Section 4.2 in the main report) the dark green boxes highlight the development stages that present significant challenges for the proposed business model, for example requiring step changes in scale up or meeting some of the projected regulatory requirements, with the potential to make or break the product. The viability of the business model, and availability of some options for product development and value creation, are determined by these critical points. The yellow boxes illustrate the broader market and commercial outcomes, showing where alternative sources of value may be secured at different stages of development (and potential exit strategies should the main product fail at any point). They also demonstrate when additional sources of funding will need to be secured or supply chains maintained.

Several major scientific, technological and regulatory challenges are relevant to this product, and there are some key areas of continuing uncertainty. The ability to develop enucleated cells and scale them up to the level required for the clinic are the two major currently perceived roadblocks, but they can potentially be overcome with sufficient time and resource. Once these are resolved there are additional critical points (particularly from the regulatory side) that could fundamentally impact on the success of the product. Figure A3.2 highlights these key decision points and areas of uncertainty that need to be resolved in the critical path for RBC development. We explore two scenarios that relate to important areas of uncertainty in the future development of this product: manufacturing scale up; and the uncertainties surrounding regulatory requirements.

A3.3.1 Step Change in Manufacturing Technology for Niche market

Up-scaling of manufacturing capability is reported by those developing the business model to be the key current challenge for the commercial production of RBCs. If economies of scale can be achieved there is a well established, well regulated market with a sophisticated supply chain already in place for a business opportunity that essentially involves product substitution. However, the current blood transfusion product is cheap (National Health Service Blood Transfusion tariff price for a unit of blood is around £140) although there is insufficiency of supply. The plan to target a smaller niche market for the first marketed product is based on the perceived difficulty in achieving the scale-up required to provide an economically competitive replacement for the current product in the larger general transfusion markets. However even for this niche market, step changes in manufacturing technology will be crucial.

Figure A3.2 – Level 3 Value System Map - Critical Points in the RBC Value System Model (print on A3 paper for legibility)



This scenario focuses on the capability and capacity to scale up the manufacturing technology to meet demand at sequential stages of the business model as described above for a thalassaemia market, and to identify how this may affect the business model and value propositions.

The key variables that will impact on this scenario are location of manufacturing, number of patients required for early clinical trials, technologies of scale up and cost of goods for various media and stem cell factors. There is uncertainty, at the level of orders of magnitude, about numbers of cells required for preclinical testing, for each stage of clinical trials, and for the final market. There are also several critical points in the business model where the project is at risk of failure and alternative options may need to be pursued.

The first critical point on the map is to differentiate enucleated cultured RBCs. Beyond this point, the step changes required in scale up of cell production occur at four points: (i) scale up for preclinical testing (10^{13}); (ii) scale up for phase 1/2 clinical trials (10^{15}); (iii) scale up for phase 3 clinical trials (10^{16}); and (iv) scale up for final market (10^{18}). If at any of these points the ability to scale up to the required number of cells becomes either technologically unachievable or not cost-effective, then the project has either failed or been delayed until this technological obstacle can be overcome. The developer will probably not be able to accommodate any serious delay and must therefore consider an exit strategy. Viable exit strategies may include becoming a contract manufacturer or supplying RBCs for blood screening and diagnostic/reagent testing.

At the moment the technology for the required levels of scale-up, even for the early stages of product development, is not available. However, there are no perceived inherent blockages; given sufficient time and resource it is assumed that the required levels of scale up will be technologically feasible. Also, the cost of goods for the media and stem cell factors are expected to decline to enable a cost effective business model in the long run.

Scale up to a combined phase 1/2 clinical trial, including the required scale-up for preclinical tests, is expected to be achievable through public sector investment (~£10–15M). However, scale up for phase 3 clinical trials and the final market (even a niche one) will require commercial funding in the tens of millions of GBP. Figure A3.2 highlights the need to secure this additional funding, including the options of buyout and licensing, to enable this level of scale-up.

Serving the thalassaemia market has implications for the storage and distribution systems to be adopted as the largest patient markets are not in the UK. The business model must therefore ensure that manufacturing and distribution facilities are located so as to align with the key markets.

There is a great deal of uncertainty about the time required to get this product to a market and those involved in developing the business plan expect that it will take 15-20 years before phase 3 trials are initiated. One option for later stage product development, when the scale-up and resource requirements escalate significantly, would be a mixture of government and charitable funding (£50-100M) to develop expertise in up-scaling the production of cells to support a national endeavour to become a world leader in cultured blood production. In this case, the make or break point would be whether the technology can be made to work. This approach would perhaps be preferable to, and more realistic than seeking a conventional commercial investor.

Even in that case some additional commercial funding would be required to take the product to the final market and to begin planning to target additional markets. To secure this level of funding, developers will need to have demonstrated proof of concept, safety and efficacy.

One final issue relevant to this scenario relates to the starting cell line for the cultured RBCs. This case study is based on a HESC line as the source material for the differentiation process, seen as the option most likely to succeed when this project began. However, given

new scientific discoveries, the developers are currently considering a switch to an iPSC derived source for the final product to be marketed to patients. This decision has been strongly influenced by recent problems in Europe in the potential to gain patent rights in HESC-derived products.

Current developments are continuing based on HESC starting materials but a parallel manufacturing/scale-up critical path will need to be developed based on an IPS cell line at some point in the future. The developers of this product do not consider there to be any fundamental constraints in switching cell lines. Indeed, the manufacturing and scale-up technologies developed, tested and refined for the embryonic cell lines should be applicable to the iPSC line. However, the costs of this will need to be built into the business plan, alongside the costs of the necessary clinical trials for the new cell lines.

A3.3.2 Impact of Regulatory Uncertainty or Changes During Development

This scenario considers the robustness of the business model and its value chain, given the regulatory uncertainties and potential changes in regulatory requirements, e.g. related to the use of animal models and to the scale and scope of clinical trials.

The regulatory path is even more complex and uncertain than the manufacturing path in the case study of cultured RBCs. The requirements for animal studies (type of animal model, level of testing required) are not yet clarified and, depending on future regulatory decisions, could significantly affect the viability of the product. It is unlikely that regulators will demand animal studies that are prohibitively time consuming and expensive, but developers will need to conduct some animal work and provide scientific justification for the work proposed.

Basic animal work may take 6-12 months and cost at least £250K. In addition, there is always the potential for regulators to demand further animal studies before granting a clinical trial license. A key question is whether a large animal study would be required, and what criteria for comparison in these studies would be relevant to understanding the safety and efficacy of the product in humans. For example, human RBCs would not function in an animal in the same way as they would in a human (even in an immune compromised animal), and if cultured RBCs were developed from animal cell lines, the product itself would not be equivalent.

It is therefore important, in order to avoid the negative scenario of extensive and prohibitive animal testing, for the developers of this product to engage early with regulators and to make a case for alternatives to animal testing, as indicated in Figure A3.2. This will include establishing good in vitro data and presenting a strong scientific justification for its relevance in the clinical trial dossier.

The other significant area of regulatory uncertainty concerns the nature of future clinical trials and whether new clinical trials will be required for different markets. For the thalassaemia market, the clinical trials are likely to be conducted on patients rather than healthy volunteers and the numbers required will be relatively low (~50 in total) which may enable the trials to take place in the UK. Once safety and efficacy have been confirmed, phase 3 trials will probably be required to demonstrate superiority, or at least equivalence of performance, compared with conventional donor blood. For thalassaemia patients, the cultured product is expected to perform much better than currently available donor blood, although there is uncertainty about the specific requirements for the initial clinical trials. These will need to be negotiated with regulators, but the regulatory route to the thalassaemia market is not expected to present surprises that are unduly prohibitive.

Nevertheless, the need for additional data to gain marketing authorisation for different blood markets generates a high level of uncertainty about potentially viable routes to market. The time and costs associated with these regulatory requirements will determine the viability of pursuing different markets and the marketing and manufacturing strategies that are adopted. The re-appraisal of the route to market following phase 3 clinical trials is therefore a critical point on the map.

If regulators require extensive clinical trials for the larger general transfusion markets that are seen as the ultimate target for this technology, this will need to be considered in the business plan. However, this scenario may not be as disruptive to the proposed business model as some the others we have discussed, precisely because it emerges after the product has been shown to be safe and effective in a niche market. Presumably, once the product is actually working in the clinic for thalassaemia patients, the developer should be able to attract sufficient funding to develop the product for new and emerging markets. Furthermore, the developer will have much stronger evidence of the product's performance and safety profile, from the phase 3 trials, when negotiating with regulators on the design and conduct of further trials for future, larger markets.

A3.4. Conclusions

This case study promises to deliver high commercial value if the manufacturing/scale up challenges can be overcome, and the regulatory path to a successful demonstration that the product is safe and effective in a niche market can be met. Although this case study reveals a great deal of complexity and uncertainty about the product development options, it is clear that completion of each milestone cumulatively increases commercial viability. The enucleation issue is clearly a make or break part of the development pathway, but the developers expect that this can be overcome with a level of funding that is not prohibitive. Related to the issue of enucleation, the manufacturing challenge of sorting/filtering the remaining nucleated cells when scaling up for clinical trials and final market is considered to be one that can be overcome with technologies either already available or soon to be available.

It is notable that the level of uncertainty associated with these key factors for the development of the product has declined considerably over the 2 year period of this project.

One key remaining challenge is the ability to scale up the manufacturing process to deliver the product to patients and meet regulatory requirements for preclinical and phase 1/2 studies. In this case study securing additional funding at key milestones will be crucial for the success of the product. Although the level of investment needed to meet scale-up and regulatory costs, going into phase 3 clinical trials and beyond, is substantial, the size of the potential blood products market will probably attract investors. In short, once safety and efficacy can be demonstrated for a niche market, and the scale-up challenges have been overcome, companies and private investors will probably provide the funding required to target additional markets and meet, if necessary, the regulatory requirement to conduct additional clinical trials.

In summary, the cultured blood case study, although highly complex and uncertain and subject to numerous scientific, manufacturing and regulatory challenges, could lead to a number of large and potentially lucrative markets for this product, that will attract further investment and partnership opportunities.