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An Analysis of Supply Chain Strategies in the Regenerative Medicine Industry – Implications for Future Development

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Abstract

The pharmaceutical, biotechnology and life sciences industry was worth approximately US\$1 trillion in 2010, of which 73.2% was attributed to pharmaceuticals, 25% to biotechnology and the remainder to life sciences. Regenerative medicines, which use live cells to cure previously incurable diseases, are a small, but growing sector of the life sciences industry. Product development here is long, the industry highly regulated and scaling up from lab to volume oriented dispersed production has many challenges. In contrast to most manufacturing environments, it is not possible to change manufacturing processes or supply chains ad hoc, as the entire supply process is specified as part of regulatory approval. It is therefore prudent to plan for the integration of production processes and supply chains during development, as the cost ramifications will seal the success or failure of a therapy at start up. This paper presents a taxonomy, which decomposes regenerative medicine into exemplar cellular therapies that then enables the characterization of their supply chain strategies and structures. Using a case study methodology, we explore the supply chains of five cellular therapies to provide insight into how regenerative medicine supply chains could be configured and managed to get cell therapies to more markets faster, and within an acceptable cost regime.

Keywords: Supply Chain, Effectiveness, Cross Industry, Regenerative Medicine, Umbilical Cord Blood, Pharmaceutical, Cell Therapy, Allogeneic, Autologous, Case Study.

1. Introduction

The pharmaceutical industry and the development of therapeutic medicines have evolved over the last century. In the 1930s and 40s synthetic organic chemistry and soil microbiology generated significant opportunities for pharmaceutical innovation. In the 1940s and 50s advances were made in virology. In the 1960s there were developments in microbial biology and enzymology (Galambos & Sturchio, 1998). The model was based upon the development of small molecules that effect specific targets (proteins, cells and other entities that play a role in biological pathways) to regulate some medical disorder. These were chemically derived medicines. This was followed by the development of 'large molecule' biopharmaceutical drugs that were proteins derived from living material such as cells or tissues (Food and Drug Administration, 2012b). The majority of current pharmaceutical medicines seek to alleviate symptoms or retard progression of a disease/illness (Teo & Vallier, 2010), thereby providing time and assistance (e.g. via antibiotics) to aid the immune system to do its work. As such, pharmaceutical medication do not repair damaged tissue nor restore physical and/or cognitive functions, but act to promote cell function. Together the pharmaceutical, biotechnology and life sciences industry was worth approximately US\$1 trillion in 2010 and is expected to grow to US\$1.4 trillion by the end of 2015 (Datamonitor, 2012).

The most recent medical developments have been in regenerative medicine, which is a field that “encompasses a spectrum of technologies and approaches ranging from cell, biomaterial, and drug therapy for the promotion of endogenous regenerative capacity to whole organ/ tissue replacement with laboratory grown organs or biomimetics” (Corona, Ward, Harrison, & Christ, 2010:849). The use of stem cells is critical to the field of regenerative medicine. Stem cells have the ability to not only renew themselves but also to differentiate into other tissue types (Nirmalanandhan & Sittampalam, 2009). Regenerative medicine is a novel approach because it seeks to stimulate growth, repair and restoration of tissue and function (Corona et al., 2010), but also replace and/or regenerate form and function at a cellular level. These cellular therapies may be classified in two ways. **Allogeneic**, where the donor and recipient are different individuals (British Standards Institution, 2012). **Allogeneic** therapies can be therapies where a single cell source is used to generate cells for many patients (1:n model), or for a particular unrelated patient (1:1 model). Therapies may also be classified as **autologous** where cells are taken from a patient, expanded, potentially manipulated and then returned to the same patient (1:1 model). The development of one to many (1:n model) **allogeneic** therapies are conceptually similar to the traditional pharmaceutical model, where a drug consisting of an active substance(s) is combined with inactive excipients into a consistent and stable dosage unit (e.g. tablet), which can then be dispensed to a wide segment of the affected population. In contrast, the one to one (1:1 model) **allogeneic** and **autologous** therapies are based upon a service model (Whitaker & Foley, 2011a) such as bone marrow transplantation. Despite its 40-year history¹ the regenerative medicine industry has had marginal impact on the product development process, bio-pharmaceutical industry structure, regulatory regimes or supply chain requirements. However, there is evidence to suggest that unless steps are taken in each of these areas, the regenerative medicine industry may never deliver on its curative promises.

The first bone marrow transplant in 1968 was the first time that (hematopoietic) stem cells were used as a therapy to reconstitute similar cells in a patient (Kemp, 2006). This was a radical departure from the organ transplant model in which full functionality was assumed by the replacement. However, the potential wider use of stem cells in regenerative medicine was realised in 1998 when cell masses were successfully isolated from human embryos and stimulated with growth factors to differentiate them into multiple cell types (Nirmalanandhan & Sittampalam, 2009). As regenerative medicine is relatively new, many of its cell therapies are currently in the experimental stages or undergoing clinical trials. Hence little research has been carried out to characterise the nature of supply chains for commercial production of these therapies (Nordstorm & Nahri, 2009).

The development and delivery processes for these therapeutic medicines (to the patients) are unique compared to other industries (Rossetti, Handfield, & Dooley, 2011), i.e. a pharmaceutical company has to clearly specify production and distribution processes, packaging, labelling and storage of their drugs. There is onsite (manufacturing facility) verification by a regulatory inspector to ensure that the company is capable of manufacturing the drug consistently and that there is compliance with ‘Good Manufacturing Practices’ GMP (Food And Drug Administration, 2012a; Rago & Santoso, 2008; Stepp, 1999). After a manufacturing facility has been registered as an approved manufacturing site, there is a legal commitment to the manufacturing process for that particular drug (Food And Drug Administration, 2012a; Rago & Santoso, 2008; Stepp, 1999).

The industry is highly regulated to ensure that products are clinically safe before they are introduced to the market, and provide assurance regimes that products are not contaminated or altered from the approved form at any point in the supply chain (Maruchek, Greis, Mena, & Cai, 2011). This is particularly challenging as drugs and their active pharmaceutical ingredients (APIs) are increasingly being manufactured in a global network of facilities, and delivered by multi-tiered international distribution networks.

Several authors have noted the importance of enabling technologies alongside new therapeutic breakthroughs (Deans, 2009; Willetts & Milton, 2011). Their feeling was that without the ability to manufacture, store, transport and distribute regenerative medicine products, the therapies could never

become mainstream clinical practice. Hence, existing therapeutic supply chains such as umbilical cord blood (an alternative to bone marrow), pharmaceutical and biopharmaceutical products offer related working examples (Rossetti et al., 2011) that may contribute as appropriate starting points.

¹ Since the 1950's bone marrow has been used to treat cancer patients with conditions such as leukaemia and lymphoma. During chemotherapy, most growing cells are killed by the cytotoxic agents. These agents, however, cannot discriminate between the leukaemia/neoplastic cells, and the hematopoietic stem cells within the bone marrow. It is this side effect of conventional chemotherapy that the bone marrow stem cell transplant attempts to reverse. That is, a donor's healthy bone marrow removed prior to chemotherapy, is injected post treatment to regenerate functional stem cells and replace the cells lost in the patient's body during treatment.

Thus in order to develop an understanding of the supply chain management of the emerging regenerative medicine industry, research was undertaken to characterise, compare and contrast the supply chains of several current cellular therapies. The research was undertaken collaboratively between the Newcastle University in the UK and Monash University in Australia, spanning UK/Australia regenerative medicine jurisdictions. The research centred on four (4) key priorities; firstly, establishing a generic starting point for regenerative medicine supply chains; secondly, developing supply chain structures associated with current regenerative medicine therapies; thirdly, comparing supply chain uncertainties across these structures; and fourthly, proposing solutions to these supply chain uncertainties (and in doing so providing risk reduction pathways for therapy development).

The paper is structured as follows. Section 2 describes the product development lifecycle within the pharmaceutical industry and the purpose/impact of a regulatory regime. An outline of the regenerative medicine industry is provided and a taxonomy of cellular therapies is presented. Section 3 outlines the research method adopted. This is followed by a case study analysis (Section 4) and discussion (Section 5). The paper ends with concluding remarks, limitations and suggestions for future research (Section 6).

2. Medicinal Product Development Lifecycle

Each year over a million patients die from terminal diseases such as cancer (World Health Organisation, 2011), while millions more suffer the effects of others such as Parkinson's disease (Parkinson's Disease Foundation, 2011). In search of a cure, billions of dollars have been spent on stem cell research (Passier, van Laake, & Mummery, 2008). Unfortunately, little research has been done on the development of the systems required to support the management and delivery of such innovative medical therapies, e.g. the supply chains for the large-scale use of regenerative medicine have yet to be determined. This means that their widespread adoption into routine healthcare practice will pose serious challenges and delays to market when such therapies have been proved safe and efficacious in clinical trials.

The strict regulation of medicinal product development and its supply chain has major influences on the viability and profitability of the company. Major investments must be made upfront to discover and prove the efficacies of new chemical compounds and many of those compounds are funnelled out through the compulsory preclinical testing and clinical trial processes (Heracleous & Murray, 2001). Even when the therapy is approved, there is no guarantee that the therapy will be successful if the company had not designed a good supply chain and business strategy.

2.1 Development Pathway

All therapeutic medicines are medicinal products and are thus subject to a stringent development lifecycle. The regulation of medicinal product pathway serves many aims. Firstly, it ensures that the drug is safe for clinical use (Maruchek et al., 2011; Rago & Santoso, 2008; Stepp, 1999). Drug safety implies clinical efficacy, the absence of adverse side effects and the minimization of interactions with other

medication that the patient might be taking during the same period (Maruchek et al., 2011). Regulatory approval for a drug is a process by which the drug must be proven safe and efficacious in fulfilling its medical intent. The process consists of medical and scientific reviews as well as clinical trials to empirically prove the drug's efficacy within the population (Stepp, 1999). As shown in Figure 1, there are three (3) core phases of clinical trials (ClinicalTrials.gov, 2007; Heracleous & Murray, 2001; Rago & Santoso, 2008). Phase 1 focuses on safety and involves a small number of healthy volunteers (less than 100) to determine a range of dosage as well as early indications of effectiveness and side effects (ClinicalTrials.gov, 2007; Heracleous & Murray, 2001). Upon successful completion of Phase 1, Phase 2 then introduces the drug to a larger number of subjects (between 100 to 300) comprising of patients and volunteers with the disease. The aim of Phase 2 is fine tune the therapeutic dosage, identify side effects and effectiveness of the drug (ClinicalTrials.gov, 2007; Heracleous & Murray, 2001) Phase 3 introduces the 'double blind' testing of a large number of patients (more than 1000) to determine long-term efficacy, side effects, and comparison to common treatments to provide a risk benefit analysis (ClinicalTrials.gov, 2007; Heracleous & Murray, 2001). It is a legal requirement for medicinal products to go through these escalating clinical trials before they are approved. The approval is via a national body e.g. the European Medicines Agency in the EU and, Therapeutic Goods Administration in Australia. Secondly, regulation also serves as a set of governing procedures to reduce patient safety risks, limit liability (Maruchek et al., 2011; Stepp, 1999), and create accountability and transparency within the whole supply chain (Faulkner, 2012; Rago & Santoso, 2008; Rossetti et al., 2011). That is regulated procedures aim to improve the governance of quality by reducing opportunity for drug counterfeiting, contamination, ingredient substitution, mishandling, and exploitation such as stockpiling and price gouging (Maruchek et al., 2011). These deviations can occur at multiple stages of the supply chain and if allowed can have detrimental effects on a firm's reputation, public confidence in the product and return on investment (Maruchek et al., 2011).

It is thus not merely the final product that is approved, but also how the product is manufactured in accordance with Good Manufacturing Practices (GMPs) that are relevant for a particular drug (Food And Drug Administration, 2012a; Stepp, 1999). Information specifying the manufacturing and supply chain needs to be submitted to the regulator after the completion of phase 3 clinical trials. This includes a number of considerations including the manufacturing equipment, production process, packaging, labelling, storage and distribution (Rago & Santoso, 2008). The processes then fall under strict audit regimes where any deviation from the approved process will be considered as an 'adulteration', and deemed different from the approved (regulated) product. If that happens, a regulator such as the Food and Drug Administration (US), is able to seek a court injunction to stop the sale of the drug and order its recall (Food And Drug Administration, 2012a; Gupta & Losordo, 2010).

Figure 1 The FDA development lifecycle of medicinal products

Therefore, pharmaceutical and biopharmaceutical companies agree to commit to the manufacturing process it proposes during the regulatory approval stage, and the process must be consistently followed throughout the lifetime of the drug. Often the challenge faced, especially by regenerative medicine companies, is the industrialisation of their product. During the clinical trial phases, where volunteers could number up to 5000, ‘doses’ can be served by small-scale decentralised laboratory manufacturing and dispensing. However, not all companies understand the designed capacity constraints imposed by the transition to large scale production and distribution post regulatory approval (Plagnol, Rowley, Martin, & Livesey, 2009). Given the viability of final products can be influenced as early as Phase 2 Clinical Trials, changes made post regulatory approval adds expense and time for re-approval. It is thus critical for cellular focused researchers to incorporate product/process designs that have industrial scalability and efficiency built into the manufacturing processes and supply chain prior to regulatory approval, as errors will affect the success of the product throughout its lifetime.

2.2 Cells as Therapeutic (Regenerative) Medicines

There has been extensive research on the use of cells as therapies to treat diseases such as heart disease (Menasche, 2009), diabetes (Ryan, Lakey, & Shapiro, 2001) and limbal stem cell transplantation (Kolli, Ahmad, Lako, & Figueiredo, 2010). Although these treatments show considerable promise, only a small number of products have progressed through to clinical trials and obtained market approval (DeFrancesco, 2010; Hegde & Schmidt, 2010).

One such product was Genzymes Carticel for treating cartilage damage (Hentze, Graichen, & Colman, 2007), which was followed by a second generation product, MACI (Matrix- Induced Autologous Chondrocyte Implant) (De Bie, 2006). Wound dressings thus became the most common cell therapy with both Dermagraft (Smith and Nephew) and Apligraf (Novartis) approved in 1998 (Mansbridge, 1998). However, both products were market failures as a result of high costs associated with their supply chain, and the direct effect on healthcare reimbursements (Ginty, Singh, Smith, Hourd, & Williams, 2010). Both Apligraf and Dermagraft were expensive to produce, have shelf life limited to a few days (Apligraf) or required specialized equipment for thawing the cryopreserved product (Dermagraft) and needed the

support of a sophisticated sales force (Kemp, 2006). Such factors increased the cost of the therapy and coupled with a lack of track record (Nirmalanandhan & Sittampalam, 2009), risk-averse insurance agencies and healthcare reimbursement organizations were reluctant to subsidize or pay for such treatments (Ginty et al., 2010). Even when treatment is approved, the reimbursement agencies restrict the use of Apligraf or Dermagraft to severe injuries or limit the number of treatments the patient can have. This had a negative spiral effect because the low demand meant that both products were not able to attain the economies of scale necessary to bring down the cost of treatment. As a result both companies filed for bankruptcy protection in 2002 (Kemp, 2006). Subsequently both products were relaunched under new brands (Organogenesis and Advanced BioHealing respectively, Parson, 2008). The rebranded products have been very successful; mainly due to a restructuring of their business models and supply chains (Kemp, 2006).

In summary, supply chains are an important input to the success of cellular therapies because processes are tightly regulated from end-to-end, which in turn has an impact on the availability and ultimately the price/affordability of the regenerative treatment. If the treatment is costly to produce, it will be difficult to prove cost effectiveness compared to alternative forms of therapy (Ginty et al., 2010; Plagnol et al., 2009). This invariably leads to reimbursement issues from insurance and public health payers (Ginty et al., 2010; Plagnol et al., 2009). We anticipate that the characterisation and analysis of existing supply chains here will inform future process design, such as providing best practices in supply chain management.

2.3 Stem Cell Sources and Delivery Mechanisms

The most publicized method of regenerative medicine is the use of human embryonic stem cells as a cell source. Though this shows good scientific promise, clinically it is a long way from routine use, partly due to its lack of availability and the stigma of destroying a human embryo. The major clinical benefit of human embryonic stem cells is their pluripotency (i.e. the ability to develop into all types of stem cells, British Standards Institution, 2012). At the other end of the spectrum are fully differentiated or mature stem cells, which have limited expandability and are usually committed to a final cell type (i.e. not pluripotent, Korbiling & Estrov, 2003). Umbilical cord blood transplantation has been one of the forerunners of therapeutic advancement in terms of availability as a stem cell source. The additional benefits of using stem cells from umbilical cord blood is their multipotency (i.e. ability to produce a range of cell types, Broxmeyer et al., 1989), and reduced ethical concerns. They are immature, which means that there are lower rates of rejection, less need for strong/costly immunosuppression drugs, and thus increased chance of cellular take-up.

For the purposes of this research cell source therapies are grouped into two types, *autologous* and *allogeneic*. **Autologous** cell therapies can be closely compared to personalized medicines, and are more commonly developed in clinical practice rather than industrial settings and are used to treat relatively uncommon indications e.g. chondrocyte implantation (Vavken & Samartzis, 2010). With *autologous* treatments, there is no need to suppress the immune system, as the treatment does not introduce foreign cells. *The supply chain can be viewed as a service starting and finishing with a specific patient.* *Autologous* therapies are similar to current practices in stem cell transplantation; they are one-to-one treatments (see Figure 2). **Allogeneic** cell therapies are treatments where a single donor is used as the cell source for providing treatments to many patients. The production and supply of *allogeneic* cell therapies is similar to the biopharmaceutical and pharmaceutical industries (Papageorgiou, Rotstein, & Shah, 2001; Shah, 2004). *Allogeneic* cell therapies expose the patient to mismatched tissue types that make it necessary to use immunosuppressants to prevent graft versus host disease (where the graft attacks the host's cells). It is also necessary to keep the cells alive so that they remain a safe and efficacious therapy when large amounts are produced, stored and shipped (Preti, 2005). Whilst there are *allogeneic* cell therapies in clinical trials (King, 1980; King & Nakornchai, 1982), *allogeneic* therapies that are commercially available are limited to wound healing. These products have faced *supply chain challenges* particularly related to limited product shelf life (Mason, 2005).

In order to understand the different types of cell therapy and segment them into groupings with similar characteristics we use Whitaker and Foley’s (2011b, figure 1, p.15) cell source network diagram as a starting point. It has been extended in Figure 2 to include multiple examples of therapies either in Phase 3 clinical trials or on market. We use it here to define a precise location for a cellular therapy within a complex hierarchic structure encompassing cell source (donor), therapy complexity (e.g. patient number), disease/prevalence, and delivery mechanism. It is thus a theory driven classification system that enables the organization of a set of information for a particular purpose, and as such conforms to the requirements of a **taxonomy**. The structure of the taxonomy starts with a **cell source**, where there is one donor (cell source) and one patient, here the **cell therapy** may be *autologous* or *allogeneic*. However, as with the most common and cost effective supply chain model (i.e. pharmaceuticals), there is also the possibility, as cell expansion is occurring, to use one donor (cell source) to treat many patients with a **therapy** (*allogeneic model*). **Disease prevalence** refers to the number of disease incidents within a given population in a particular period. Examples of high prevalent diseases include heart disease and hepatitis, where millions of people are afflicted annually. In **delivery mechanism**, procedures are represented by multiple visits to the physician or hospital, for example in *autologous* therapies, there are at least two rounds of treatment. In the first visit, cell samples are collected, and in the second, the therapeutic dose is administered via various means including surgery. Treatment via products can be visualised as either a cell based stock item (*allogeneic*) or a made to order cell item (*autologous*).

Figure 2 Therapeutic Cell Source Taxonomy

In deriving the **taxonomy**, we decided that our investigation should focus on cell therapies that are commercially available or are in late stage (Phase 3) clinical trials, because supply chains here are already documented as part of the regulatory submission and form the basis of the subsequent approval. Using this inclusion criterion, we found examples of 10 cell therapies that fit into the 12 possible supply chains shown in Figure 2. There are two delivery mechanisms (**indicated by #**) for which we could find no

examples, due to the current inability to deliver a fast and efficient donor to patient supply system. In the following sections, we use this **taxonomy** to provide a basis from which to compare existing cell therapies and their supply chains. We note that the location of therapy examples should be relatively unaffected by classification techniques or sample type. However, in informational taxonomies (such as here) examples might also overlap taxonomic categories in the formative stages of development (see e.g. Bozarth & McDermott, 1998).

2.4 Classifying Cell Source Therapy Supply Chains

Supply chain strategies are often categorized in terms of their supply and demand uncertainty using the framework designed by Lee (2002) with earlier work by Fisher (1997). The framework has been used as a reference point in a variety of applications for example, supply chain uncertainty in manufacturing (Sun, Hsu, & Hwang, 2009), in retail supply chains (Oke & Gopalakrishna, 2009), and in transport operations (Rodrigues, Stantchev, Potter, Naim, & Whiteing, 2008). Using Figure 3, we explain these strategies and suggest how they could be used to further inform the Therapeutic Cell Source Taxonomy of Figure 2.

		Supply Uncertainty	
		Low	High
		(Stable Process) (Hi-EOS) Push	(Evolving Process) (Lo-EOS) Pull
Demand Uncertainty	High Pull (Innovative products)	Responsive SC Decentralized Customization Eg: <i>BioPharmaceutical</i> AUTOLOGOUS / ALLOGENEIC	Agile SC Centralized Flexible Customization Eg: <i>One-One Therapies</i> AUTOLOGOUS
	Low Push (Functional products)	Efficient SC Lowest Cost Eg: <i>Generic One-Many Therapies</i> <i>Traditional Pharmaceutical</i> ALLOGENEIC	Risk-Hedging SC Pooled Sharing of Resources Eg: <i>Cell Banking</i> ALLOGENEIC / AUTOLOGOUS

Figure 3 Therapeutic Medicine Supply Chain Uncertainty Framework

In a *push-push* based supply chain strategy, production and distribution decisions are based on long-term forecasts with *efficiency* in mind. Typically, the manufacturer bases demand forecasts on orders received from the retailer's warehouses, and then pushes these goods through the supply chain. It therefore takes much longer for a push-based strategy to react to the changing marketplace, which often leads to inability to meet changing demand, and often leads to obsolescent inventory. The *push* strategy is characteristic of traditional 'over the counter' pharmaceuticals where the aims are to produce the large volume (Hi-Economies of Scale-EOS) drugs as efficiently as possible so as to ensure maximum availability at minimum cost. This strategy is symptomatic of the one-many allogeneic cell therapy model.

In *pull-pull* based supply chains, production and distribution are driven by true customer demand (e.g., real time point of sale data) rather than forecast. Retailers typically hold little inventory, preferring to

respond only to specific orders. These systems are attractive because zero inventory forces decreases in lead times, decreased system variability, and in particular, reduced inventory at the manufacturer. This situation forced the whole supply chain to be *agile and flexible* in response to specific real time demand. In the *pull* strategy, products include experimental drugs for clinical trials or anti-cancer drugs that represent the last line of defence against aggressive cancers. Due to their high price and short shelf life, such low volume (Lo- Economies of Scale-EOS) products are typically not stocked but are made and shipped upon clinical request. This strategy is symptomatic of the one-one autologous cell therapy model.

In a *push-pull* strategy, the initial stages are operated in push mode, while the remaining stages employ a pull mode. The interface between the push-based stages and the pull-based stages is known as a decoupling point. It is at these points where materials are accumulated (pushed-in) and the location where the customer's order is acted upon and customization takes place (pulled-out). Products that follow the *push-pull* strategy include base medical devices that are produced efficiently and shipped to decentralized points where a *fast customised response* to physician's request can be made. This strategy is symptomatic of the biopharmaceutical autologous / allogeneic cell therapy model.

In a *pull-push* strategy, the initial stages are operated in a pull-based manner, while the remaining stages employ a push-based strategy. This is an unusual combination in which common resources are shared and inventory is pooled (pulled) into decentralised locations (hence the *risk of poor fulfilment is hedged*). Retailers call this strategy *continuous replenishment* where point of sale data is used to prepare shipments at previously agreed-upon intervals to maintain specific levels of inventory (with short lead-time and Lo-EOS). This strategy is used by Cardinal Health (USA) and Australian Pharmaceutical Industries to provide contract manufacturing, wholesale and distribution services, and similarly by various blood and cell banking organisations. This strategy is symptomatic of the cell banking autologous / allogeneic cell therapy model.

It thus appears that Lee & Fisher's supply chain modalities are equally applicable to Pharmaceutical, Biopharmaceutical and cellular therapies. The next section highlights the study's design to collect information from these unique supply chain structures in this emerging field.

3. Methods

A qualitative research design was deemed appropriate for this exploratory paper due to the lack of research into the supply chains for cell therapies (Nordstorm & Nahri, 2009). Furthermore a qualitative research design allowed us to ask 'how' and 'why' questions during the data collection process. The qualitative methodology also allowed for in-depth understanding and analysis (Tharenou, Donohue, & Cooper, 2007) of the regenerative medicine supply chain phenomena, especially in the under-explored area of cell therapies. Here the structural themes, rather than established theories, are of primary importance (Yin, 2009). We thus chose purposeful sampling of contrasting information rich cases for in-depth study. This type of comparative sampling involves two or more population groups with distinct theory based characteristics. Finding manifestations of our theoretical constructs of interest was necessary to establish, elaborate and examine which factors are associated with or interact with them.

3.1 Qualitative Selection

The case selection was made with the aim of identifying a sample of firms that had developed cell therapies, were involved in a significant segment of the supply chain, were interested in participating in the research project, and were available to share information. We adopted Lee & Fisher's (2002) Supply Chain Uncertainty Framework as the theoretic lens to view cell therapy supply chains. In so doing, theoretical replication in case selection was assured by ascertaining that differences existed among the cases regarding the characteristics of supply chain structure (type, number, scope of elements) and their developmental progress (efficient, responsive, risk-hedged and agile). In accord with McCutcheon and Meredith (1993), we have more confidence in generalizing the case study's findings (i.e. analytical

generalization) because the cases selected differ widely in their key characteristics. The framework also provides a grounded explanation for the attributes of different supply chains by comparing and contrasting different supply chain models from different countries against structural criteria informed by the framework.

The selection process resulted in the identification of one (1) generic supply chain environment (see Figure 4) and four (4) examples of commercially available therapies operating within cell therapy supply networks. The four (4) companies identified as case exemplars are indicated by * in Figure 2.

The first is the hematopoietic/umbilical cord blood product to treat diseases such as hematopoietic cancers (e.g. leukaemia) - low/medium disease prevalence. It is a **one-one, allogeneic** product based supply chain. This has been selected as a case study because hematopoietic stem cell transplants are regarded as one of the first cellular therapies, and as such their supply chains are relatively mature.

The second case study is Relinethra, a product to treat limbal stem cell deficiency in the eye - low/medium disease prevalence. Relinethra is a **one-one, autologous** procedure/service supply chain. We have selected this as a case study as it is in phase 3 trials, and Reliance Life Sciences have begun to question their supply chain strategy, structure and viability.

The third case study is Apligraf (from Organogenesis), a product to treat Diabetic foot and venous leg ulcers that are not healing – low/medium disease prevalence. Apligraf is a **one-many, allogeneic** product based supply chain. Apligraf was one of the first cell therapies on the market. It subsequently suffered from financial problems due, in part, to its supply chain configuration. Reviewing a supply chain that now works would also inform the evolving industry.

The final case study is that of cadaveric islet transplantation to treat severe hyperglycaemia in type 1 diabetics – low/medium disease prevalence. It is a **one-one, allogeneic** procedure/service supply chain. The cell therapy was chosen because it relies on a donor becoming available (much like an organ transplantation), has an underdeveloped supply chain, limited process knowledge and low level control of the shipment steps.

The data collection involved targeted interviews with senior executive officers from umbilical cord blood banks and cell therapy companies in Australia and the UK. A conscious decision was made to interview executives who have in-depth business knowledge of their field and were able to provide sound opinions about the supply chains and their structure for future cell therapies.

3.2 Qualitative Technique

The conceptualisation of words being condensed into content categories (M. Weber, 1987:7) has been a central idea in qualitative data analysis. This content analytic technique is reliant on the grounded examination of qualitative data to enable the identification of patterns, the development of categories, and the aggregation of content into constructs (Insch, Moore, & Murphy, 1997). While this grounded inductive theoretic technique has been used extensively in the discovery and exploration of theoretic and conceptual structures, it has also been used as an adjunct (as in this case) to the explanation and extension of relative organisational dispositions (Glaser & Strauss, 1967:45) and their interconnections.

The qualitative collection technique here comprised a semi-structured interview schedule that was used in face-to-face interviews. Consistent with the overall purpose of this study, the adaptive cycle dimensions from Conant et al. (1990), and Choe et al. (1997) strategic orientation work, the interview structure broadly addressed the external and organisational factors that influence supply chain strategies. The questions within the interview schedule were open-ended and were designed in the first instance as a guide for discussion and secondly to demonstrate the value of the supply chain strategies in terms of therapeutic delivery. In this research, recordings of interviews were transcribed in preparation for manual

assembly into coded segments. Analysis allowed review and comparison of categories and their content, and sought to achieve parsimony of categories in simple structures (Richards & Richards, 1994). The interview structure and responses also allowed some limited numerical data to be gathered about the linkage between structures.

3.3 Qualitative Coding

The qualitative coding aimed to synthesise data elements into the categorical structure provided by the literature. Hammersley and Atkinson (1989:168-169) made an important distinction between the allocation of data to categories in ethnography, compared to coding in quantitative research. That is, with the richness of meaning in ethnographic data, there is little to be gained from an analytic strategy that classifies responses to one and only one category. In contrast, Weber (1990) recommended a single classification schema where categories are mutually exclusive and data can be categorised according to suitability.

In the current study, multiple classifications were appropriate to enable the multi-dimensional nature of the supply chain constructs to be considered. Therefore, the responses here were integrated into multiple categories via manual techniques. The techniques outlined by Miles and Huberman (1994) were drawn on to arrange empirical evidence into structures in the form of words and tables rather than numbers. By looking at these structures, within group similarity, and across group differences could be established and subsequently ordered into supply chain categories for comparison.

The following sections are designed to analyse the unique supply chain structures of four (4) examples of cellular therapies (plus a generic baseline example). We do this by seeking answers to the following Research Questions:

- RQ1. What is the generic starting point for the development of regenerative medicine supply chains?
- RQ2. What is the structure of supply chains associated with current (core) regenerative medicine therapies?
- RQ3. What are the comparative supply chain uncertainties?
- RQ4. How might these supply chain uncertainties be resolved (to reduce therapy developmental risk)?

In doing so, the paper contributes to the existing knowledge of therapeutic medicine by providing an integrated taxonomy of known cell therapy supply chains. With this knowledge, we then unpack the supply structures (RQs 1 & 2) to inform the development of future supply chains in the regenerative medicine field (RQs 3 & 4).

4. Cell Therapy Case Studies

In this next section, we start the analysis with an overview of a generic cell therapy supply chain. The overview describes the activities and issues faced at each step the supply chain. To examine the structure of cellular therapy supply chains we have undertaken core case studies from the cell therapy matrix in Figure 2. We then proceed to detail four (4) of the most prominent examples, starting with the product that has the longest history in this domain namely; Hematopoietic stem cells (Allogeneic - Product), followed by Relinethra (Autologous - Procedure), Cadaveric Islet Transplantation (Allogeneic - Procedure), and Apligraf (Allogeneic - Product). The section then concludes with a brief summary.

Figure 4 Generic cell therapy supply chain

4.1 Generic cell therapy supply chain

In answer to RQ1, which asks; *What is the generic starting point for the development of regenerative medicine supply chains?*, we undertook discussions with several companies regarding their supply chains². We combined this data with our knowledge of the processes involved in cell therapy production, and developed a generic cell therapy supply chain (Figure 4) based on the initial assumption of a centralised laboratory / production facility within e.g. a quaternary hospital. This generic supply chain is also representative of a chain with multiple laboratories or production facilities where inventory and shipping issues are present whenever cells are being transported from one clinic/location to another. The generic supply chain shown describes all the possible steps in the production and supply of a cell therapy, the associated issues and potential links to the regenerative medicine industry. It is made up of twelve (12) discrete steps.

The supply chain begins with the identification and **Collection** of clinical quality cells. Identified cell lines are then screened, verified and stored/**Banked** in a cryopreservation environment until they are needed. This creates the first *decoupling* point. In preparation of the patient's therapy, cells are drawn from the bank and **Expanded** to volumes necessary for mass production or at least to the required volume for a prescribed number of therapeutic doses. In the case of pluripotent or multipotent stem cells, they need to be **Differentiated** into the required type of cell/ stem cell specific to the patient's therapy (second *decoupling* point). Subsequently, the biomaterial is **Purified** to remove undesirable elements and the cleansed biomaterial is **Formulated** into therapeutic doses according to the patient's specifications (third *decoupling* point), such as body weight. The doses are then **Tested** and **Stored** according to conditions required for long-term storage (fourth *decoupling* point), or to survive 'live' **Shipment** to the healthcare facility where they can be administered to the patient. The patient is subsequently **Monitored** for adverse reactions, control doses are sent back to the releasing laboratory for quality assurance, and in both cases, data collection is used for scientific knowledge building. As in conventional supply chains the four (4) *decoupling* points in this generic chain depict places where change of state occurs, inventory accumulates, customisation occurs, and/or transfer to other laboratories (eventually industrial entities) could take place.

Typical structures for manufacturing oriented supply chains are often depicted having storage points (i.e. cell **Banks**) as the first node of their chains, particularly for efficient (*push-push*), responsive (*push-pull*) and risk hedging (*pull-push*) strategies. These strategies seek to develop an inventory of raw material or product that enables varying degrees of customisation and modes of delivery to an end user (patient). These strategies are distinct to an agile (*pull-pull*) strategy where virtually no stock is available (e.g. for autologous treatments), where the raw material (cells) are taken from the patient to be processed into therapy that is specific to that patient.

In answer to RQ2 concerning the supply chain structures of current regenerative medicine therapies, and RQ3 requiring a comparison of supply chain uncertainties, we now construct the supply chains of four (4) different types of cell therapies and compare the uncertainties of each to the generic supply chain shown in Figure 4. RQ4 will be addressed in Section 5.1.

² Companies we have had multiple discussions with include: Reneuron, Tissue Regenix, Cell Medica, Genzyme, Neotherix, Smith and Nephew, Intercytex, and Athersys.

4.2 Umbilical Cord Blood (Hematopoietic) Stem Cells

Using live cells as therapies is an old concept, with successful blood transfusions dating back to 1901. Hematopoietic stem cells are usually derived from bone marrow, peripheral blood, or umbilical cord blood (UCB) to treat a variety of diseases, e.g. leukaemia and lymphoma. Transplantation (dating back to work by E. Donnall Thomas in the 1950s), is now routine practice with more than 50,000 hematopoietic stem cell transplantations completed worldwide each year (Chustecka, 2010). Using interviews with executives at UCB banks in Australia and the UK we have constructed the supply chain for hematopoietic stem cells (Figure 5).

The preference is to use stem cells from an UCB bank as opposed to bone marrow or peripheral blood because the number of nucleated stem cells is higher and the immaturity of the cells means lower (better) immune responses. Except in very rare cases, organ donation and stem cell donation are from *unrelated* donors (i.e. the cell source is *allogeneic*), and means that the patient receiving the donation will typically require immune suppression to prevent the grafted cells attacking the host tissue (graft versus host disease) post-transplant. However, this risk can be minimised if the donor is a closely matched tissue type.

Where there is a national health service there are national UCB bank, bone marrow and peripheral blood stem cell banks, which service and regulate the supply chain. Public UCB banks don't charge a fee to bank cells from a child's UCB because the donation is made with altruistic intent and the donor relinquishes all claims to the UCB. In contrast, private banks and hybrid banks (e.g. Virgin Health Bank) provide a fee based guarantee to store the UCB, to be cultivated to produce therapeutic stem cells for treatment in case the same child becomes ill in the future. We consider this to be an example of a *pull-push (risk hedging)* strategy, where the demand for UCB is considered to be functional with stable and growing demand (e.g. leukaemia in children), while supply is uncertain and variable due to various cultural factors.

Figure 5 Hematopoietic stem cell supply chain

Once an accredited collector collects and sends the donated blood to the nearest affiliated UCB bank, a series of tests are conducted to determine if the cord blood unit is free of infectious diseases and of

clinical quality. Parameters such as stem cell count and tissue type are noted and the UCB cryopreserved for future clinical use. When a clinician/patient with similarly matched tissue type makes a request to the UCB, the bank performs a set of release tests prior to shipping the cord blood for transplantation. The bank subsequently requests patient information post transplantation as part of quality accreditation and scientific knowledge building.

4.3 Relinethra

Relinethra is a cell therapy developed by Reliance Life Sciences to treat limbal stem cell deficiency that causes blindness. Through discussions with executives at Reliance Life Science, we have learned that it is a procedural, *autologous* (one to one) therapy to treat a low prevalence disease. The supply chain for Relinethra is shown in Figure 6.

Figure 6 Relinethra supply chain

Being an *autologous* cell therapy, Relinethra’s supply chain is ‘supply to demand’ and an example of an agile (*pull-pull*) strategy. As with most autologous therapies, the decoupling point is at the beginning of the supply chain, when the patients donate their own cells for culture. The supply chain uses only eight (8) of the steps outlined in Figure 4, with shipment occurring at two (2) points; shipment of the biopsy for culture, and then the final product back to the patient.

A biopsy is taken from a patient at the hospital where they are to be treated. It is shipped at 2-8 degC to Relinethra’s production site where the limbal stem cells are isolated, expanded and formulated into two (2) therapeutic doses. Both doses are shipped back to the hospital in a customised container (designed by the company), that is validated to keep the cells alive for 24 hours and incorporate technologies needed to pre-treat the cells before the operation. Sending two (2) separate therapeutic batches to the hospital limits risk in scheduling, so if one of them is lost or damaged the other will be used. If this is not the case then the other is returned to Reliance Life Sciences, unopened and they perform extensive testing on this batch to ensure the patient received safe and efficacious treatment.

The shipment of a live stem cell transplant has raised issues for Reliance Life Science, especially since they mainly operate in hot climates. The customised container can maintain its contents at a low temperature but for only 24 hours. Shelf life in this instance is a major constraint on the supply chain and, though a solution is in place, it is not optimised.

4.4 Apligraf

Apligraf is a product from Organogenesis and is a living skin substitute to treat foot and leg ulcers that do not heal with conventional dressings. Through conversations with executives at Organogenesis and various corporate resources, we have determined the structure of their supply chain. It is an *allogeneic* (one-to-many) product to treat a low/medium prevalence disease, the supply chain for Apligraf is shown in Figure 7.

Figure 7 Apligraf supply chain

To produce Apligraf a vial of fibroblast cells are removed from a working cell bank, where they are stored at -70 degC and thawed. The production process involves three (3) steps; one to produce the dermal layer (6 days); a second to produce the epidermal layer (4 days); and the third step is a 14-day procedure where the combined layers go through cornification. The whole process therefore takes 20 days for the expansion, formulation and testing. After this the product is individually packed for use in nutrients and sealed, and shipped overnight by courier. Apligraf has a shelf-life of 10 days from the point of shipment and must be maintained at 20-23 degC during both shipment and storage.

Referencing Figure 3, Apligraf has characteristics quite similar to that of a biopharmaceutical and as such has a responsive (*push-pull*) supply chain strategy. This is because the product cannot be 'supplied to store' (efficient: *push-push*) in the same way as a pharmaceutical drug due to its shelf life. Market coverage also means that a 'supply to demand' agile (*pull-pull*) model does not suit either; leaving a patient waiting 20 days for treatment is neither safe nor suitable especially when cost demands for

Apligraf are high. However, the responsive supply chain is by no means efficient due to the mismatch between varying demand and production forecasts. To ensure availability and prevent loss of sales, the forecast scenario would inevitably have to be a slight oversupply of the product. Where supply is greater than demand, this will lead to the loss of substantial amounts of product that are not used within the nominated shelf-life. Such losses are ultimately a cost reflected in the price of the treatment.

4.5 Cadaveric Islet Transplantation

People with Type 1 diabetes take insulin to control their blood sugar levels, but people who are not aware their blood sugar is high often suffer a hyperglycaemic attack and trigger a medical emergency. It is possible to negate hyperglycaemia by transplanting a patient who is glucose unaware with cadaveric islet cells (i.e. cells that control blood sugar). Through conversations with senior researchers (at Newcastle University), we have determined the structure of the supply chain. Cadaveric islet transplantation is a procedural, *allogeneic*, one to one, low prevalence cell therapy; its supply chain is shown in Figure 8.

Islet transplantation is dependent on a donation of a pancreas from a deceased person. If the pancreas is not suitable for whole organ transplantation, it is ambulated to a central production facility (e.g. Oxford or London). The islet cells are then isolated from the pancreas in a manual, highly variant process and formulated into a therapeutic dose. The cells are tested before release and then transported in a cool box to a transplantation hospital by ambulance. On arrival, the cells are prequalified to validate the results from the production facility and are then transplanted in a surgical procedure to the patient.

Figure 8 Cadaveric islet transplantation supply chain

Though the supply chain for islet transplantation looks similar to that of UCB in Figure 5, supply uncertainty is higher here (i.e. a willing donor who has recently deceased), and unlike UCB, storage of islets for therapeutic use is not currently viable. It is also dependant on; a suitable recipient being available; the donor source and recipient being geographically similar; and fast and effective shipment of the islet cells via use of scarce resources i.e. ambulances/helicopters. In the UK, the process is validated so as the cells can be on the road for no longer that eight (8) hours and there are concerns that even this is too long. The uncertainty of the supply raises the risk that when the cells arrive for transplantation they may no longer be viable. This uncertainty and risk has meant that only approximately 12 cadaveric islet transplantations have been completed in the UK in the last year. As the procedure's *agility* is focused on

the patient, the current supply chain strategy is *pull-pull*, but in reality the supply of the biomaterial is a matter of chance. If it was possible to store the islet cells then this would limit the risk in the shipping procedures, negate the need for duplicate testing, and move the supply chain strategy towards a more *efficient* model, where there is a bank of cells that a clinician can turn to should a patient require an islet transplantation.

4.6 Summary

Though not exhaustive, we have been able to identify some of the issues associated with each of the core cell therapy supply chains. An example of these is the issue associated with shipment. If the cells are to be shipped live, then strictly controlled conditions are required and need to be expeditious due to limited shelf life. If cells are to be stored (or banked), then the supply chain needs to be supported by temperature controlled infrastructure. We have shown for example, that an *autologous* cell therapy will not go through the banking steps, as it is likely to be used immediately. Steps required for cell expansion are smaller for *autologous* cell therapies that treat individual patients as compared to *allogeneic* cell therapies. The overall supply chain is also shorter where the starting cell type (here adult stem cells) are already the stem cells required by the therapy, meaning differentiation and/or purification steps are not required. Thus any changes to the starting cell type will require impacts on supply chain technology, structure and cost, but gains in responsiveness and agility.

5. Findings and Discussion

Supply chain management in the medical field already operates within strict regulatory frameworks and legislative environments. However, the design of effective supply chains for cellular therapies also overlays requirements such as; developing and maintaining quality with comprehensive traceability; fast and reliable temperature controlled logistics; scalable, robust, reliable, consistent processes; ultimately at an affordable price to clients. The following section thus seeks to answer RQ4 - How might these supply chain uncertainties be resolved (to reduce therapy developmental risk)?

5.1 Reflections from the Case Studies

The UCB supply chain does not include the processes of cell expansion and differentiation but it does contain experience in all other aspects of the cell therapy supply chain. The nature of handling live cells for use as therapies and the surrounding governance is routinely exercised in the UCB industry. However, there are limitations to the supply chain of cord blood that should be noted when creating supply chains for cell therapies. Notably the processes are labour intensive, customised and subject to high variations, which together places significant demands on process scalability and automation.

Nonetheless, the simple supply chain of UCB (Section 4.2) can be used to inform one to one *autologous* and *allogeneic* cell therapy procedures. Such is the case of cadaveric islet transplantation (Section 4.5), where cells are extracted from a donor, undergo minimal processing, and are administered back into a waiting patient. Such a model is not a 'make to store' as there exists a list of patients awaiting transplant, and as a result, the cells are not banked but shipped live. This scenario is similar to a form of sibling cord blood transplantation, where the cord blood derived from a younger sibling is used to treat an older sibling that is suffering from a disease.

Even though the case study of the cadaveric islet transplantation did not involve the banking of stem cells as per the norm in the cord blood industry, we have highlighted potential issues associated with the banking of cells for regenerative medicine. That is, as cell therapies become routine practice, stem cell banks need to be established to support the regenerative medicine industry in harvesting, testing, storing and distributing different types of stem cells such as mature, human embryonic and hematopoietic stem cells. Since such banks have not been established, the development of a stem cell banking system would benefit from the experience and best practices of the (private and public) cord blood industry. This would

shorten the time taken to build up an efficient banking system, based upon best practices that have been effective as well as legally and ethically compliant.

The traditional pharmaceutical supply chain is a Push-Push supply chain starting with the inward supply of raw materials to the pharmaceutical company/manufacturing plant. Push-Push supply chains could inform cell therapies that can be stored (e.g. cryopreserved) for *allogeneic* (one to many) treatments. In using an allogeneic cell source, the decoupling point is at shipment and patient administration. Therefore, we can postulate that the supply chain model for *allogeneic* cell therapies is a 'supply to store'. Here the decoupling point is much like that of a pharmaceutical, where treatment is customised to the patients at the point of administration. However, challenges remain as to how the process can be industrialised. Firstly, cell expansion technologies are still experimental and have not been approved for clinical use. Secondly, there will be issues pertaining to Good Manufacturing Practices, cost of running industrialised clean rooms and complexities of managing warm and/or cold supply chains, and lastly, the likelihood that cells can be stored with a reasonable shelf life is slim.

Therefore, a key decision area lies in whether or not *allogeneic* cell therapies will be a make-to-stock (supply to store) or a just-in-time model. Make-to-stock would require massive scientific advances in the ability to pause a cells' metabolism so that they can be safely stored. Though cryopreservation is the current preferred option to solving this problem, the cryopreservation formulas and the thawing techniques do result in cell losses. Additionally, using cryopreservation methods would demand highly specific and expensive storage solutions. There are thus no current commercial cell therapies that follow a pure make-to-stock or *push-push* (efficient) strategy.

As was seen from the case studies, the regenerative medicine supply chains are likely to follow either 'supply to store' or 'supply to demand' models, based on the cell therapy type (*autologous* versus *allogeneic*), and the availability of different tissue types. Referencing Figure 3, we can also establish that current regenerative medicine supply chains can follow either *pull-pull*, *push-pull* or *pull-push* strategies. Donors with rare tissue types will likely have recipients waiting, whereas the need for common tissue types is not immediate. Thus, donations of common tissue types will be stored, via cryopreservation, until a closely matched recipient requires them. Shortage of rare tissue types (influenced by ethnicity) is the reason why calls for donation are often seen. Despite the delivery of *allogeneic* treatments being similar to the products from pharmaceutical and biopharmaceutical industry, it is more prudent to assume that the regenerative medicine industry will begin with small scale and highly customised treatments. Mason (2005) highlighted that it is common for cell therapies to have varying scales and doses, which contrasts sharply against the standardised products and recommended dosage of the traditional pharmaceutical industry.

In addition, if cell therapies were to follow the supply chains of Pharmaceuticals or Biopharmaceuticals, the model would have to be wholly *allogeneic*, i.e. large-scale production from multiple cell lines to treat targeted segments of the patient population. This would result in capacity issues concerning differentiation, formulation, storage and shipment (seen in Figure 4), where there is little industrial best practice to adopt or to reference. That is, while sterility, shelf life and traceability are quality criteria in the pharmaceutical and biopharmaceutical industries, these are magnified with cellular therapies by the requirement to keep cells alive, safe and efficacious. This means therapies need to be transported quickly under sterile and temperature controlled conditions. Based on the case studies, we see cellular therapies leveraging on two possible types of supply chain in addition to being transported in cryopreserved form. The first of these is a warm supply chain that allows cells to be shipped in, or at close to culture conditions, while the second is a cold supply chain that maintains a temperature of around 2 to 8 degC.

With appropriate (scalable) process and (adaptable) supply chain strategy, new cell therapy companies should be able to anticipate challenges based on the logistical requirements of their therapies and take necessary steps to control cost structures. As seen from the examples of Apligraf (Section 4.4) and Dermagraft the cost of treatment has an influence on whether or not reimbursement agencies would pay

for or subsidize the treatment (Ginty et al., 2010), and this has a direct impact on the success or failure of the therapy.

In summary, the regenerative medicine industry is in its infancy, and any moves to a *push-push* (efficient) strategy is premature, as gaps remain in clinical record tracking, technology, demand management and logistics. To improve the chances of a successful therapy, supply chains here should thus focus on building upon the best practices of the cord blood industry in the collection and banking of stem cells, distribution of the product, quality control and traceability.

5.2 Scientific Development, Regenerative Medicine and Thoughts about the Future

The rapidly developing science surrounding production of multipotent (Bushell-Embling, 2012; Deans, 2009) and induced Pluripotent Stem Cells to derive embryonic-like stem cells as feeders to therapeutic R&D, is evidence of the need to store stem cells in their undifferentiated state. The capability to culture, differentiate and store these stem cells consistently and efficiently under GMP conditions signals that significant effort needs to be undertaken to adapt best practices from environments such as cell and tissue banking, e.g. GMP/quality accreditation, patient follow-up and inventory management.

The many challenge in determining patient outcomes in cell therapies (Gupta & Losordo, 2010; Labopin et al., 2009), necessitates a patient follow-up routine (e.g. that employed at AUSCORD) as one of the ways to determine long-term efficacy and identify potential adverse reactions in patients (i.e. a pharmacovigilance routine).

In terms of inventory management, public umbilical cord blood banks such as those operating under AUSCORD, continuously compare their current stockpile of cord blood with an ideal inventory mix that balances the country's obligation of providing equitable healthcare against associated costs. Stem cell banks could also adapt forecasting and inventory management strategies from here to better align their inventory to a country's healthcare requirements.

From a commercial point of view, these future realities could lead to a reduction in the number of differentiated cell lines required by biopharmaceuticals to produce their therapies. This in turn may refocus R&D towards cell differentiation and other forms of process development as a means of deriving first mover advantage. Some countries for example Germany (Schuster, 2012) have legislated that stem cells are non-patentable if an embryo is destroyed as a result of their derivation, thus enabling faster process development. Under such scenarios, it is possible to imagine the formation of niches within the regenerative industry supply chain, where upstream organisations specialise in the production and storage of raw materials (e.g. stem cells) and because of efficient and/or patented processes become natural monopolies.

These niche providers then supply stem cells to biopharmaceuticals and biotechnology companies who will then apply their patented cell differentiation techniques to formulate therapies. This line of thought could also lead to biopharmaceutical companies adopting a decentralised business model based upon industry-shared infrastructure, and in so doing transforming the industry into one capable of delivering agile product/services.

6. Conclusions

Given the heavy investment in R&D and expectations from investors, regenerative medicine companies have significant motivation to understand the characteristic of their product and apply the appropriate supply chain strategy. In this paper we have argued how regenerative medicine supply chains could be configured and managed to reduce the risk of high treatment cost (Ginty et al., 2010), and ultimately impact the success or failure of a therapy. Cost structures can be controlled through the combination of knowing the characteristics of the therapy/product using the taxonomy in Figure 2, matching against an

appropriate supply chain strategy (Figure 3), and mapping to an appropriate supply chain structure typified in Figure 4.

We advocate that the regenerative medicine industry requires a completely new approach to supply chains and their infra/info structures if there is to be widespread adoption of cellular therapies. Our generic supply chain is an example of the challenges faced by an efficient (*push-push*) supply chain in this industry. It commences with nodes for cell collection and cell bank storage that seeks to develop an inventory of raw material that can then be efficiently processed/customised and delivered to an end user (patient). The technological and structural challenges necessary to achieve this outcome were the subject of this paper.

Umbilical Cord Blood (Hematopoietic) banking is a form of risk hedging (*pull-push*) strategy, where the demand for UCB is considered to be functional with stable and growing demand (e.g. leukaemia in children), while supply is uncertain and variable due to various cultural factors. Except in very rare cases, stem cell donor and receiver are unrelated (i.e. *allogeneic*), and this means that the patient receiving the donation will typically require (costly) immune suppression to prevent the grafted cells attacking the host tissue post-transplant. The short-term challenge here is to improve/expand inventory management techniques to more precisely match population tissue distributions. The longer-term challenge is at the cellular level.

Apligraf is an *allogeneic* therapy that is characteristic of a responsive (*push-pull*) supply chain strategy. This is because the product cannot be stored due to its shelf life. However, the responsive supply chain is by no means efficient due to the mismatch between varying demand and production forecasts. To ensure availability there is an oversupply of the product, and losses are ultimately a cost reflected in the price of the treatment. Our discussion showed that high costs resulting from a mismatch between therapy and supply chain has led to market failure. The scale of production, inventory and storage demands of *allogeneic* cell therapies means they require a different infrastructure, one not dissimilar to that of the biopharmaceutical industry. In the short-term it is thus appropriate advice for regenerative medicine companies to look to the biopharmaceutical industry for guidance on issues such as shelf life and process scalability and regulatory constraints.

Relinethra's *autologous* therapy supply chain is an agile (*pull-pull*) strategy. As with most autologous therapies, the decoupling point is at the beginning of the supply chain, when the patients donate their own cells for culture. Here there is essentially no stock is available, and raw material (cells) are taken from the patient to be processed into therapy that is specific to that patient. Cadaveric islet transplantation is an *allogeneic* procedure, where *agility* is focused on the patient. The current supply chain strategy is agile, but in reality the supply of the biomaterial is a matter of chance. If it were possible to store the islet cells then this would limit the risk in the shipping procedures, negate the need for duplicate testing, and move the supply chain strategy towards an *efficient* model, where there is a bank of cells.

Cell therapy development currently relies on differentiated mature cells as their raw material and therefore the step of differentiating cells does not feature in our case analysis. However, we envisage a future where the use of pluripotent or multipotent stem cells will dictate specialisation in banking and supply. That is, the process of cell differentiation could then play a crucial role in developing supply chains as a key competitive advantage and in shifting the regenerative medicine industry into a more procedurally based services based industry.

6.1 Limitations & Future Research

Cell therapies that are on the market or in late stage clinical trials are more often than not, developed by companies who value intellectual property. This has study limitations; principally that proprietary information of supply chains was not disclosed due to competitive conditions. This meant that our study was limited to information that was in general publicly available.

Despite the small scale of this study, we believe it can be used as the foundation to model a coherent and detailed set of supply chain routes that will undoubtedly benefit the many cell therapies still in development. We envisage that through this research, supply chain transparency (governance) will become familiar to regulators (simplifying approval), and this will in turn help cell therapies get to more markets faster, and within an acceptable cost regime.

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