

The difficulties of supplying new technologies into highly regulated markets: the case of tissue engineering

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Abstract

This study provides an insight into the difficulties companies encounter in transposing basic science into commercially viable healthcare technologies, focusing on the issue of establishing a dominant supply model within a highly regulated market. The core issue is how to scale-up customized scientific processes into products able to supply wider and possibly mass, markets. In tracing the development of approaches to scaling-up, the paper highlights the influence regulatory regimes have on high technology regulated products and services. The paper details the implications of two contrasting supply initiatives towards operationalizing tissue engineering, based on differences in regulatory regimes between Europe and the US.

Introduction

The role of supply chains or networks in supporting the process of technological innovation and new product development is becoming increasingly recognised and supply networks or chains are being used more frequently as a unit of analysis¹. However the majority of existing research focuses on the private sector and is dominated by studies of the automotive, IT and electronics industries^{2,3,4}. Studies of highly regulated public sectors, such as the UK healthcare sector, have failed to ignite the same level of interest, despite growing recognition by British policy-makers and the healthcare industry of the need to improve and accelerate the supply of new technologies into this sector^{5,6}.

Empirical analysis of existing chains, identify different methods for managing different forms of supply chains, distinguishing between the management requirements of innovative products from those that are more routinely produced ^{7,8,9}. For example, if the primary objective is the reduction of cost and there is little variation in supplier performance, traditional contractual relationships may be the best approach. Where lead time and quality is important and there is a differentiated supply market, close supplier relationships as propounded by the “lean” paradigm may be more suitable. If the focus is on innovation and there is an indeterminate supply market, the appropriate pathway may involve the development of loosely coupled relationships. For example, in an influential article Fisher⁷ discusses the supply chains of three firms; Sports Obermeyer, National Bicycle and Campbell Soup. By examining the individual companies chains he assigns responsive supply chains to innovative products, and sees efficient (low cost, process oriented) chains as mismatched if the intention is to supply innovative products.

This paper addresses a supply market – tissue engineering - that is still embryonic, and therefore where supply issues, particularly how future supply networks will be structured, are still to be decided. Although there are some products on the market, it is on small scale. Until a dominant supply model is created that will support the mass production of tissue engineered products (TEP), the delivery of TEPs into the healthcare sector will be limited. However, as this paper will show, regulatory issues are inhibiting the design of suitable supply networks; without a supportive regulatory environment TEPs will fail to deliver their full market potential.

Previous studies of healthcare supply networks¹⁰, have highlighted the need to consider the regulatory environment. Although regulations can reduce uncertainty ¹¹, their failure to keep apace with technological advances can be inhibitive ¹², stimulating a need for realignment of

regulation with practice¹³. The contribution of the paper is in its analysis of the role of regulation in deciding the shape of this nascent supply network-a perspective missing from studies that emphasize the role of the supply chain alone in innovation generation¹⁴. The analysis and findings presented here will be highly relevant to procurement work in areas that explore taking innovations from pure science and technology environments into commercial environments. The paper highlights contrasting supply initiatives towards operationalizing tissue engineering between Europe and the US.

Background

Tissue engineering is poised to revolutionise the healthcare sector, offering a novel approach for the repair and regeneration of diseased or damaged tissues and organs. Spanning both the medical device and the biopharmaceutical industries, tissue engineering is an emerging interdisciplinary field with the potential to improve the quality of life for millions of patients. Globally, the market for tissue engineered products (TEPs) stands at over \$25 billion¹⁵ and analysis of the US market predicts revenues of \$1.9 billion by 2007¹⁶. Since 1990, more than \$4 billion have been invested in worldwide research and development¹⁷. Products such as Myskin (treatment for burns) by CellTran and Carticel (cartilage) by Genzyme are starting to enter the market, although within Europe this tends to be on a named patient basis, or via clinical trials as opposed to mainstream clinical practice.

According to many experts in the field of tissue engineering^{17, 18, 19}, the industry is experiencing a paradigm shift similar to that experienced by the automotive industry at the beginning of the Twentieth Century – the move towards mass production. Without significant scale-up and

automated manufacturing processes, tissue engineered products will fail to fulfil their full potential.

Tissue engineering is defined as “an interdisciplinary field that applies the principles of engineering and the life sciences towards the development of biological substitutes that restore, maintain or improve tissue function”²⁰. Three dimensional (3D) tissue structures are synthesised from cells derived from either the patient (autologous cells), or from a donor (allogeneic cells) and the growth, organisation and differentiation of the cells is guided through the use of biomaterials²¹. There is increasing interest in the use of stem cells for use in tissue engineering. Currently, however, there are many scientific, legal, and ethical barriers to utilising stem cells; particularly that they may be sourced from embryos. Given that the use of stem cells in tissue engineering is still a long way from fruition, and current commercial products do yet use stem cells, we have not pursued this line of inquiry and we did not collect data upon, and therefore do not report upon, stem cell approaches.

The emerging tissue engineering industry has spawned a small range of products based on the following common source materials:

1. Autologous –cells derived from the patient
2. Allogeneic - cells derived from a donor
3. Xenogeneic – potential use of cells other mammalian sources.

As the pressure to eliminate animal-derived products grows due to fears of the cross-over of animal borne viruses brought about by high profile cases such as bovine spongiform

encephalopathy BSE and avian flu, autologous and allogeneic products have become the dominant business models. However, each type of tissue engineered product supports a very different route to market; the allogeneic route has the potential to support an automated, high volume manufacturing process akin to “Make to Stock” (MTS), whereas the autologous route is highly customised, low volume and more in keeping with the “Make to Order” (MTO) approach. The following sections describe these two contrasting approaches.

Make to Order – the Autologous route

<Insert Figure 1 here>

Unlike the allogeneic route, the autologous route is offered as a dedicated, single therapy to individual patients it includes skin, but has a broader range of applications including nerve repair and the recreation of musculoskeletal tissue such as cartilage and bone. Genzyme’s Carticel, a cartilage replacement, is currently the most widely adopted autologous procedure. The autologous route involves the removal of cells from the patient which are cultured in the laboratory before reintroduction into the patient (see Figure 1). The procedure must be undertaken in a validated clean room facility, transported to an authorised laboratory, which could be within the same clinic or hospital, another country or even at the patient’s bedside. The cells must then be recombined with appropriate biomaterials and this can take several hours, days or weeks before a viable tissue construct is ready for implantation into the patient. The regenerated tissue is transported back to the clinic and is reintroduced into the patient¹⁹.

The main advantage of the autologous route lies in the origin of the cells; since these are derived from the patient there is no risk of rejection and a lower risk of contamination and infection. The disadvantages are mainly commercial: the specificity of the procedure does not lend it to scale-up as there are a limited number of biopsies that can be manipulated at any one time. The risk of contamination is still present and, without full traceability, there is a danger of mix-ups up in the lab, which could lead to the insertion of tissues that are not derived from the patient. Finally, the limited viable window from the point of extraction to reintroduction allows for little flexibility, particularly with respect to the transportation of cells to and from the laboratory.

Make to Stock - the Allogeneic route

<Insert Figure 2 here>

The allogeneic route has the potential to support mass, off-the-shelf manufacturing at a single site. However, existing products have yet to succeed commercially and are limited to skin replacements such as Apligraf, which is produced by Organogenesis. Generally, donor cells are cultured, sorted and expanded, providing a ready supply of cells of a specific type and of a standard quality ¹⁹. The cells are manipulated and scaled-up in a bioreactor at a local, regional or national accredited laboratory, giving rise to a large volume of regenerated tissue, which can be implanted in multiple recipients. The resulting tissue can be transported to many different clinical facilities and implanted into patients (see Figure 2).

As well as the ability to scale-up and scale-out (parallel, small scale manufacturing) the process, resulting in economies of scale and enabling quality control; one cell line can give rise to 10,000

units of a standard type and quality. Also, the allogeneic route is simple inasmuch that it is one-way and more robust: the “one-size-fits all”, regenerated tissues can be produced at an accredited laboratory and transported to many different clinical facilities.

However, there are many disadvantages associated with the approach, which include contamination from the source materials, necessitating careful selection of not only the donor cells, but also the growth media and biomaterials employed during the manipulation of the cells. Consequently, sourcing is limited to a handful of suppliers and measures must be put in place to ensure full traceability of all the materials employed. Immunological rejection by the recipient is a major issue. An alternative approach is the use of stem cells, which may be immunologically neutral and therefore reduce the risk of immunological rejection.

Comparison of the autologous and allogeneic routes

For both routes, there is a need for increased acceptance by both the public and clinicians. For patients this relates to apprehension surrounding the use of TEPs. Also, although a patient/insurer may be willing to pay for a manufactured device, they may question paying for tissue derived from their own body ²³. For clinicians, barriers to acceptance include the risks involved in using a new procedure, an unwillingness to move away from familiar approaches and the threat posed to existing career pathways. Finally, transportation and storage of regenerated tissue is problematic and, as yet, an expensive process. The cells must be stored within a specific temperature range, in some cases at temperatures of -32°C; developing or sourcing a suitable means of transportation and storage is, hence, both costly and challenging.

The aim of this study is to investigate the supply implications of a market on the cusp of both massive expansion and a critical paradigm shift. Having presented the background to the two approaches, we turn to the influence of regulatory environments in shaping the delivery and uptake of TEPs into the healthcare sector. As the technological frontier advances, existing regulatory frameworks are failing to keep pace with developments, which is not only restraining advances in healthcare treatments, but also preventing the development of an appropriate supply model, inhibiting a move towards “off-the-shelf” products. The contribution of the paper is to demonstrate how the regulatory environments has led to the allogeneic model dominating in the US, whereas in the EU, the dominant model for the majority of firms appears to be the autologous route.

Theoretical Background

Innovation theory increasingly focuses on the need to understand innovation as a process of interaction that take place *between* rather than within organisations^{24, 25, 26}. Work by Ragatz²⁷, Wynstra²⁸, Wynstra and ten Pierick²⁹ have highlighted the importance of supplier involvement during the process of innovation. Thus, an understanding of supply issues is essential if an understanding of the problems facing emerging healthcare technologies healthcare are to be developed.

Customer-supplier interactions can be analysed on a one-to-one, or dyadic, relationship level, for example within customer-supplier dyads. Indeed, the majority of supplier involvement in product development literature falls within this level of analysis³⁰. However, dyadic relationships are embedded in wider networks of relationships, which may enable and/or constrain innovation

processes ³⁰. Thus, it is the networks of relationships that may present the greatest innovation resource to healthcare providers. The challenges facing healthcare suppliers highlight the need for managerial and policy responses that are based on understanding both the factors enabling and constraining innovation within healthcare supply networks and also the nature and structure of these networks.

The growing interest in supply networks reflects the increasing need for organisations to utilise resources that lie beyond the internal boundaries of the individual firm. Factors such as increasing product/service complexity, outsourcing and globalisation and the need for ever decreasing time to market cycles ³¹ both individually and collectively lead organisations to rely upon the external resources of their networks of suppliers. Companies increasingly realise that it is impossible for them to possess all of the technologies and competencies that are the basis of the design, manufacture and marketing of their offerings ³², whilst at the same time being flexible enough to cope with – and thrive on – the inherent business uncertainty present in most industries. By forming inter-organisational networks with a myriad of partners, individual firms join forces and obtain competitive advantages they would not be able to gain on their own ^{33, 34}.

The interactive nature of innovation supports the development of relationships between actors; these relationships act as valuable bridges enabling the accessing of resources between actors ^{32, 35}. There are many benefits associated with developing such partnerships such as accessing expertise that lie beyond their core capabilities and the long-term development of a broad range of competencies that support innovation ^{36,37}, the spreading of risk amongst the partners, and, in some cases, the establishment of bidding consortia and joint research pacts ³⁸

The enabling role of institutions such as regulations in supporting these activities, must not be overlooked. Regulations have three major functions³⁹: to reduce uncertainty; manage conflicts and co-operations, and to provide incentives. Regulations are particularly important during the early stages of technological development or with technologies that have an ever-changing knowledge base ⁴⁰. Here, organisations look to regulators to create stability and support the co-ordination and reproduction of knowledge.

As technologies develop, however, there is a risk that regulations may become “locked-in”, regulators then look to organisations to keep them abreast with the latest technological developments. A responsive regulatory environment that can effectively redistribute the costs of change and compensate the victims of that change also supports fast rates of innovation ³⁹.

Approach

The focus of our research is on the impact of the regulatory environment. Specifically, we examine its role in shaping technological paradigms and the effect this has on the development of supply models. Looking to the EU and the USA, this study investigates how two differing regulatory regimes have given rise to two very different “dominant designs”. Based on our findings, we describe how these alternate regulatory environments have given rise to two contrasting supply initiatives and discuss the advantages and disadvantages posed by each.

The analysis draws on a programme of interviews and meetings with organisations actively engaged in tissue engineering. Between August 2004 and March 2006, we conducted over 130

hours of semi-structured interviews and meetings with over 35 key individuals including practitioners, government agencies, trade associations and researchers (see Table 1). The interviewees were selected by means of reputational sampling whereby experts in the field highlighted appropriate personnel. This reputational sampling resulted in interviews with nine companies with operations in Europe, six of which were European, one Australian and one from the US. Globally, there are around 90 firms actively engaged in tissue engineering, twenty-three of which are based in Europe. Hence the study is representative of approximately 10% of the world tissue engineering industry and over 25% of the European tissue engineering industry. A theoretical sampling approach was adopted, whereby semi-structured interviews were conducted until theoretical saturation had been achieved i.e. until no new or relevant data appeared to be emerging^{41, 42}.

Tissue banks are also active in tissue engineering, although their primary focus is on research, or production for in-house treatments. Currently, the majority of tissue banks are public, non-profit organisations that do not produce any TEPs, although, strategically, this could be avenue that the larger tissue banks could pursue in the future. Consequently, the minor interest that these organisations displayed in commercial activities resulted in our decision not to include them in this particular study.

The data were analysed using NVivo, combining interviews and identifying generic themes. A powerful and comprehensive software package, NVivo is designed to support qualitative research and analysis in a wide range of fields and qualitative methodologies. Generally, qualitative data are relatively unstructured and dynamic and cannot easily be subjected to quantitative methodologies. Across the disparate array of methodologies (such as action research, grounded

theory and phenomenology) there are common themes associated with all approaches to qualitative data analysis. In each case, the researcher must explore data in a sensitive manner without quantifying the data *a priori*. As understanding develops, the researchers must record their findings by means, for example, of field notes, annotations, and models. All such records are considered to be data.

The analysis involved the formation of categories, concepts and ideas in a manner that allows thorough and effective exploration of the data. NVivo enables this, most commonly by using nodes. Free nodes are used for ideas or concepts that cannot be easily categorised; tree nodes are used for those topics that may be grouped and sub-grouped. In this study, the nodes were chosen through discussions within the research team and through consultation with an expert panel, comprising of established academics and practitioners in the areas of supply chain management and tissue engineering. Node selection was based on concepts, ideas, and themes that the research team (including practitioners) felt would be of relevance and interest to the project (thus combining the benefits of the literature, prior conceptual work and the experience of the practitioners).

Given the sensitive nature of some of the issues relating to tissue engineering, the interviews were conducted within a mutually established framework of confidentiality that went beyond the standard requirements of much management research. No labels have been attached to individual organisations beyond categorisation of their role in the supply network (as displayed in Table), and no direct quotations have been attributed. The majority of organisations interviewed were in the stages of pre-commercialisation, resulting in fears relating to the protection of IP (intellectual property). Also, concerns were raised regarding public perception, although the study did not

focus on stem cell research, interviews often strayed onto this topic, particularly with respect to regulation and hence there was a fear of “trial by association”. Consequently, we have faced restrictions on how we may present our findings, although it is important to mention that all the interviewees highlighted the impact of regulation in determining which technological trajectory to pursue and its influence in shaping future supply initiatives. Differences arose in how different organisations perceived how these supply initiatives would be structured and managed.

<Insert Table 1 here>

The regulatory environment: the EU context

Across the EU a patchwork of regulatory approaches exist; non-regulated areas such as Holland, Denmark and Sweden, specific regulations for the handling and storage of tissues in France, Italy and Spain and codes of practice in the UK. Switzerland is the only European country with regulations that factor for TEPs. The lack of consistency and clarity can be attributed to various issues such as national regulatory preferences, stakeholder pressure and cultural and ethical concerns relating to TE. However, the key factors are the lack of a clear and unified regulatory framework at an EU level, stemming from a fundamental problem – an inability to classify TE products as a medical device or as a pharmaceutical. To be marketed in Europe, TE products must be issued with either a CE mark (medical devices) or a product licence (pharmaceuticals), to do so manufacturers must achieve quality, safety and performance standards.

The lack of harmony across the EU can be traced back to the exclusion of human tissues, human tissue products and human tissue derivatives from the medical devices directive (93/42). The

exclusion arose from an inability to reach a consensus regarding the status of human tissue products. The pharmaceutical directive did not prevent the use of human tissue; however, products must be medicinal. Many TEPs are more structural and device-like in function and do not demonstrate a pharmaceutical, metabolic or immunological mode of action e.g. bone void fillers; as such, they fall under the medical devices directive, which excludes human tissue. Consequently, these products are unable to apply for a CE mark and cannot be marketed freely throughout the EU.

TEPs that fall under the pharmaceutical directive also face major obstacles. All pharmaceutical products must demonstrate efficacy: how the product performs in a controlled clinical setting e.g. drug trials. For TEPs this is difficult to undertake, conventional drugs can be subjected to large-scale randomised trials, but TEPs are limited by their specificity, especially if they are autologous, and problems related to the identification and quantification of active ingredients. Further vagaries arise over defining TEPs as a product or a service, some nations, such as Switzerland, view autologous products as a service, a biopsy is taken from the patient, scaled-up and then reintroduced. However, since manufacturing procedures must be applied to expand the cells, many argue that it should be classified as a product.

Without harmonisation, EU states apply their own rules, for instance, in Germany any product derived from human tissue must be regulated as a pharmaceutical whereas in the UK it tends to be on a case-by-case basis. Other member states, fearful of the potential impact of TEPs, appear unwilling to take a firm stand. Steps are being taken to establish a clear regulatory framework. With a focus on patient safety, the Directorate General for Health and Consumer Protection (SANCO) has drafted a directive for the banking of tissues. The SANCO directive, commonly

referred to as the “procurement” directive covers the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells and is set to be in force in April 2006. It was developed in response to fears regarding the source of human cells, particularly following high profile events such as infection of human material with HIV (France) and BSE (UK). Once in place, the procurement directive will apply, in whole, to the supply of any human tissue to a patient, regardless of existing regulation and relates to both pharmaceuticals and devices.

Another directorate, DG Enterprise, is looking at promoting the freedom to access TEPs; however DG Enterprise only covers pharmaceutical directives. Following two consultations, steps are being taken to harmonise rules for all TEPs and to produce a regulation as opposed to a directive, preventing any variation in transposition into national law.

The regulatory environment: the US context

Unlike the EU, the US has developed regulations that address TEPs. In 1996 the FDA introduced legislation covering cellular based therapies, which was followed, in 1997, by the development of formalised approaches to cellular and tissue-based products ¹⁶. In 2001, rules for good practice were proposed and rules for the registration and listing of those engaged in the production of TEPs were made final.

The confusion regarding TEPs classification as either a medical device or pharmaceutical has been overcome through the FDA’s creation of an “Office of Combination Products” in 2002. Decisions regarding a TEP’s status are based on the product’s primary mode of action. If the

product has a direct biological activity the regulatory lead is taken by the Center for Biologics Evaluation and research (CBER). If it is predominantly structural in nature it is overseen by the Center for Devices and Radiological Health (CDER). Some therapeutic products have since been referred to the Centre for Drugs Evaluation and Research (CDER). In some cases, products may be evaluated by all three centers, consequently, during the development of a product it is important for firms to consider which regulatory route would be more appropriate, which may necessitate accentuating or playing down some features. The FDA also encourages dialogue, allowing firms to develop a clear understanding of the steps that must be taken to meet the regulatory requirements.

Comparison of the EU and US

As a result of EU regulatory vagaries, we found that firms will either invest heavily in understanding the regulatory environment of each nation or adopt a more selective approach. Accordingly, the existing situation appears to favour smaller companies, operating in highly localised areas as opposed to multinationals that wish to export and import products throughout Europe. In addition, in marketing their products, firms “cherry-pick” EU nations, selecting regulatory environments that are amenable toward the marketing of TEPs.

The regulatory environment also impacts on reimbursement mechanisms. Without a CE license, European procurement agencies are unable to purchase those TEPs categorised as a medical device. Consequently, the EU market for TEPs is, as yet, restricted to the private sector and unregulated areas, or the über-rich and super-elite athletes who can afford to pay for the treatment. Alternative routes firms employ to market their products involve employing existing

products as a means of accessing clinicians, who may be willing to trial or champion a TEP; firms frequently cited clinicians as the route to market.

The most notable contrast between the US and EU is the EU preference towards the autologous as opposed to allogeneic route. The ability to circumnavigate regulations by classifying an autologous procedure as a service and the lower risks involved relating to infection, rejection and contamination have made this the preferred route, despite the associated high costs. Also, firms are unwilling to establish costly production facilities, hence, the current regulatory climate appears to favour a specialist, low volume, MTO approach, which if conducted on a patient-by-patient basis can be undertaken using contract labs or within a clinical setting.

The US regulatory system has not only been established for over ten years, but also it has managed to evolve and is perceived as the epitome of “good tissue practice”, encouraging several of the key players to establish production facilities in the US. Once firms are registered and their products licensed they are entered into the “red book” which basically, is a database of products eligible for reimbursement by private health insurers and is the gateway to the US healthcare market. Consequently, the straightforwardness of the US regulatory environment appears to have created a large and, more importantly, viable market that firms can envisage supporting MTS products.

Furthermore, the clear regulatory framework has encouraged multinationals to invest in the US as opposed to EU. Without the need to wrangle with a myriad of different regulations and regulatory agencies and with reimbursement mechanisms in place, such organisations see the

potential of large-scale manufacturing facilities; the size of the US market is seen as being large enough to carry the cost of development.

Existing Supply Models

The supply market for TEPS is in its infancy, with only a few allogeneic dermal (skin) products and several autologous procedures in production. For the allogeneic products there are a number of routes to market. The predominant route involves the production of tissue at a central facility. The TEP is produced from a carefully selected cell line which, once expanded to increase cell numbers, is packaged and distributed to clinics or hospitals. Difficulties arise in the transportation of these products which have to be kept within a specific temperature range and must be applied within a certain timeframe. In some cases, up to 60% of products are lost once the product leaves the manufacturing facility due to issues such as time delays at the hospital, or large fluctuations in temperature during transit. To cover these losses, such products come with a high price tag that could be reduced if the production volume could be maintained. Some allogeneic products can be frozen and stored for future use, but make the product a more expensive option relative to existing therapies.

For autologous procedures, a number of different supply models exist. In all cases a biopsy must be taken from the patient, the cells from this sample are then isolated and expanded prior to reintroduction into the patient. Generally, the biopsy is taken to a clinical facility and transported back to the patient within a period of 48 hours. There are capacity restraints – only a limited number of biopsies that can be manipulated at any one time. The laboratory facilities are also costly employing highly skilled, graduate level staff. However, the key issue surrounds

transportation, first the biopsy must be transported to the laboratory, again at a controlled temperature and within a specific timeframe, once manipulated, the tissue must be transported back to the patient under the same controlled conditions. Genzyme's Carticel, is currently the leading autologous procedure and its manufacturing facility in the US has produced over 10,000 units. With over 20 biological safety cabinets, around 20 samples can be processed every month and the whole procedure can be conducted within a period of 48 hours.

Other autologous procedures can be carried out within the hospital and in one case, within the operating theatre. Innovative modes of application have been developed that, for a particular dermal replacement, involve spraying the dermal tissue on to the patient. This procedure avoids the high costs of transportation but requires skilful application by the clinician who must first be trained in its use. Cosmetic procedures for the removal of wrinkles are becoming increasingly popular; biopsies are removed from the patient at a private clinic, expanded in a laboratory and reimplanted into the patient upon their return. This approach has been successful on account of public demand and a willingness to pay.

According to some specialists, lessons could be learned from other industries such as the food industry, where the demand for ready meals in the 1980s necessitated the development of temperature controlled distribution mechanisms. However, within the field of tissue engineering, the focus is still on the basic science and there appears to be an unwillingness, particularly on the part of the scientists, to other sectors may be a rich source of new ideas.

Future Supply Models

During the interviews there was some consensus regarding the shaping of future supply models. The majority of interviews agreed that the allogeneic route was the most commercially viable option but that developments, particularly in the EU, were being held back on account of regulatory uncertainty. Consequently, the market potential currently lies in the US. Also, issues surrounding public acceptance need to be surmounted.

Providing the market for allogeneic products was sufficiently large, the majority of individuals envisaged a large-scale, automated manufacturing facility where cells could be expanded in industrial fermenters. If transportation issues could be overcome, and the cells could be maintained within a constant environment that could support constant production, these facilities could be located nationally or even regionally and provide off-the-shelf products. A number of units could be purchased by hospitals and stored in freezers until required by the clinician.

With respect to autologous tissues, it was envisaged that patients could bank tissue for future use; however, the shelf-life of autologous tissue would need to be increased if this were to be viable. It was suggested that specialist centres may be created, whereby patients fly in from all over the world in order to receive treatment. The underlying rationale for establishing a number of centres stems from the losses incurred during the transportation of cells/tissues which would be overcome if the patients travelled to the centres. Major world centres of expertise could be developed akin to today's science parks, with companies, scientists and hospitals working together in a specific field.

Companies engaged in autologous procedures also perceived tissue banks as a potential competitor. In most countries, tissue banks already have a national scope or regional scope of activities, which means, relative to companies, accessing markets is not as difficult. It was suggested that, in the future, larger tissue banks might create national networks for the manufacture and distribution of TEPs.

For both routes, it was recognised that a big facilitator for the future would be the sourcing of a serum or animal free methods of culturing cells and this would be an area that could be developed in partnership with specific suppliers. It was also recognised that, if TEPs were to become a commercially viable product, research into the management of the supply of TEPs needs to be undertaken.

Conclusions

The challenge posed by innovative health technologies (IHTs) suggests that the creation and constitution of new networks does not necessarily follow a rational, planning led process. Whereas the importance of supply chain relationships has been recognised in the field ¹⁴, this paper has contributed by highlighting the additional challenges posed by regulation.

The two dominant business models appear to support two types of market. The autologous route serves the consumer market composed of individuals who are willing to pay for immediate results e.g. elite athletes or recipients of cosmetic surgery. The allogeneic route appears to have the potential to serve an industrial market. Industrial markets are characterised by interdependent relationships between professional buyers and the suppliers ⁴³, resulting in complex

organisational networks. Currently, the nascent market of tissue engineering does not display these characteristics, yet these may require active management if the allogeneic route is to succeed commercially.

This study has found in line with many other studies that the regulatory environment contributes towards the shaping of innovative products/services. This paper has demonstrated, by examining an emerging science based innovation, how the US and EU regulatory environments have shaped the *delivery* of innovative products/services. However, regulation is not the only issue, reimbursement adds to the issues confronting firms wishing to market their products in the EU but, until regulations are developed that embrace all TEPs, this issue looks set to remain for some time. As a result procurement agencies are unable to support the uptake of TEPs into the healthcare sector, highlighting one of the many difficulties associated with the introduction of IHTs. This also raises another issue: the prospect of a tiered approach to medical treatment; e.g. treatments available only to those rich enough to afford customised autologous treatment.

Looking to the US, it is evident that a coherent and straightforward regulatory route supports the development of a uniform market, encouraging firms, particularly multinationals, to invest in manufacturing facilities and look towards the development of large-scale automated MTS processes. The result is the emergence of the allogeneic route as a dominant business model. The fragmented nature of the EU market has created uncertainty and hesitancy and until harmonisation is achieved, firms are unwilling to establish costly, hi-tech production units. With markets limited to handful of member states, firms have looked towards small-scale, low risk, MTO approaches and hence the autologous route has become the preferred approach which has been fuelled further by a consumer market willing to pay for autologous procedures.

The apparent scope for TEPs to revolutionise healthcare treatment looks set to threaten established modes of practice and suggests potential obstacles may arise in delivering TEPS downstream to hospital and clinicians. Due to the early nature of the products this paper has not been able to comment, in any depth, upon any resistance that might come from established medical professions (or suppliers), but there is evidence to suggest the medical professions often take very active steps to prevent disruptive technologies that threaten their status.

The study has also highlighted a phenomenon common across many sectors, the blurring of a stark distinction between products and services⁴⁴. The new technology of tissue engineering is an example in the medical area of how new and innovative treatments will increasingly combine product and service. At present it appears that the regulatory system in the EU is less equipped than its American counterpart to assess innovations that are both product and service based. We conclude that there is a real need for those responsible for regulation to grasp the nettle of servitisation and adapt regulatory frameworks to take account of the increasing service element in many major innovations. It is beyond the scope of this paper to address why the US environment has been more conducive to the emergence of service/product hybrid innovations, but highlights the area as an important one for future research.

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Table 1 Classification of interviews

Category	Number of organisations	Number of interviews conducted
Firms	9	17
Universities	6	9
Consultancies	3	3
Funding bodies	3	3
Trade associations	2	4
Regulatory bodies	2	2
TOTAL	25	38

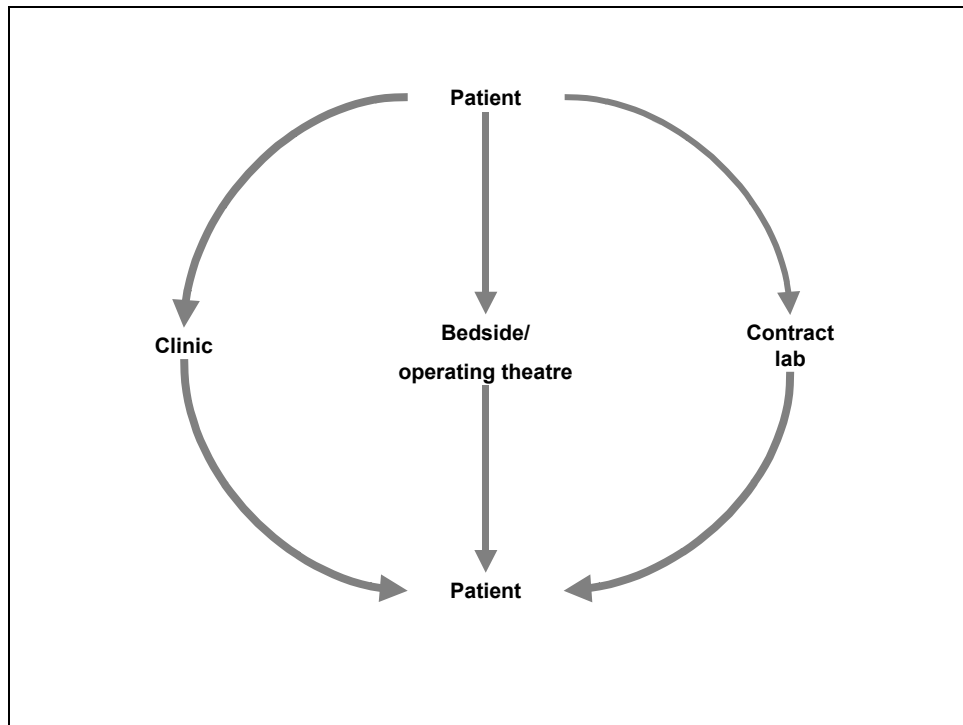


Figure 1 The Autologous route

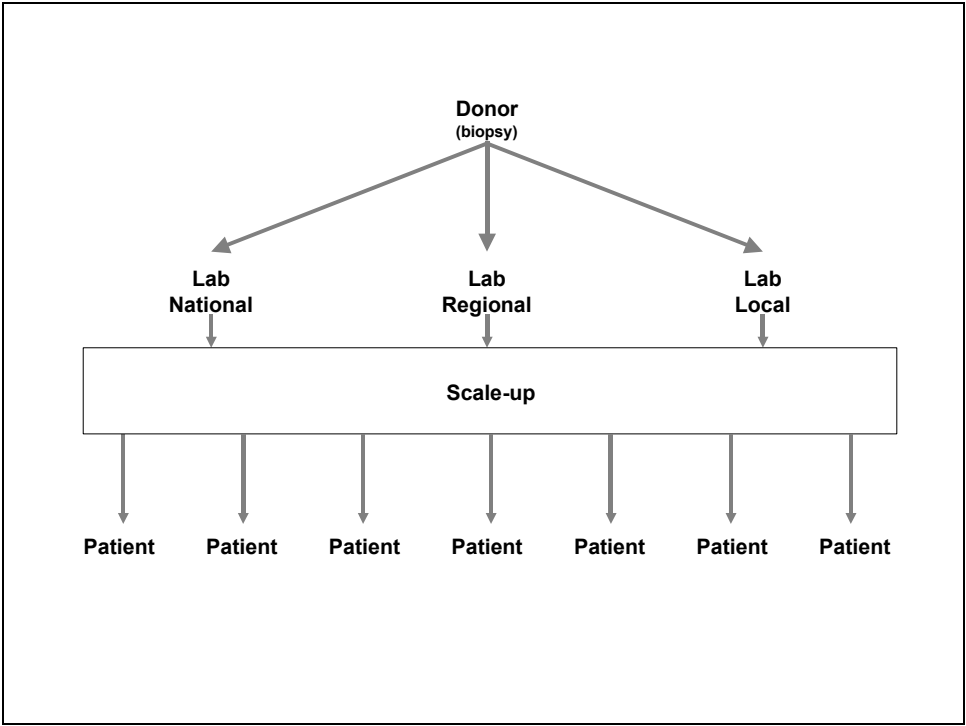


Figure 2 The Allogeneic Route