Chapter 20

Early Public Procurement Involvement in Emerging Technologies? The Case of Tissue Engineering

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INTRODUCTION

Research on the innovation process and its effective management has tended to focus on incremental innovations or "good practice." In other words, "doing what we do, but better" (Phillips, Noke, Bessant & Lamming, 2006, p. 1). Such practice is well suited to stable product and market, but is not appropriate when new technologies emerge that challenge existing modes of practice and call for significantly adapted approaches (Day & Schoemaker, 2000; Leifer, McDermott, O'Conner, Peters, Rice & Veryzer, 2000).

Within the public sector there is a growing realization for the need to address the challenges posed by disruptive innovations. In the past, increased accountability and the move towards clear audit trails have been instrumental in ensuring decisions are made using standard and traditional, tried and tested approaches (Lindblom, 1959). However, new pressures from within the public sector appear to downgrade the importance of conservative decision processes in favour of more creativity, particularly the role of public procurement in evaluating new technologies (Marceau & Basri, 2001). For example, within the UK, the Healthcare Industries Task Force (2004, p. 84) has highlighted the need for methodologies that "recognize[s] the different approaches necessary for evaluating 'disruptive/ transformational' compared to 'incremental' innovations."

Conventional assessment techniques may act as a barrier to emerging technologies since it is difficult to understand or evaluate their potential (Lynn, Morone & Paulson, 1996; Moreau, Markman & Lehman, 2001; Veryzer, 1998). Analytical procedures for evaluating new product opportunities, such as return on investment (ROI), are

based on projections of future performance that consider variables such as acquisition cost and established reimbursement rates which, in the context of disruptive technologies, do not yet exist. (Utterback, 1994; Coye and Kell, 2006). It has been shown that, for healthcare, purchasing decisions have a significant impact on the uptake of new technologies and that pressures to cut cost and meet targets have promoted the adoption of "tried and tested" technologies as opposed to emerging technologies (Marceau & Basri, 2001; McKelvey, 2003).

Elsewhere, we have argued that current customer-supplier models fail to consider the degree of industrial maturity, highlighting the need for public procurement to better understand the positioning of a technology/industry on the innovation life cycle (Johnsen, Phillips, Caldwell & Lewis, 2006). Also, we proposed a focus on the development of the wider infrastructure; for instance, the institutional aspects, rather than the development of single new technologies or product applications (Phillips, Johnsen & Caldwell, 2006). This would shift attention from simply the development of product applications to the development of the product/service offering and the creation of new value propositions.

This chapter explores the challenges confronting an emerging healthcare technology, tissue engineering. Focusing on the influence of reimbursement, we pose the question: "Does reimbursement influence the adoption and use of new technologies?" Reporting on the findings of an in-depth study, the chapter discusses how differences in reimbursement mechanisms have contributed towards the development of starkly contrasting initiatives for the operationalization of tissue-engineered products (TEPs) within Europe and the US, resulting in major differences in their adoption and use. Drawing on our findings, the chapter calls for public procurement involvement earlier on in a technology's life cycle and closer engagement with relevant stakeholders.

The selection of public procurement as the basis for the study is deemed particularly relevant. First, in evaluating studies on the differences between public and private organizations, it has been found that only in the areas of personnel and procurement are there consistent empirical findings to support the public sector being "different" (Rainey & Bozeman, 2000). Second, public procurement has in recent years achieved some prominence, principally as it has increasingly been seen as a mechanism for delivering government

policy, rather than a rule-based clerical function (Fee, Maxwell & Erridge, 1998). Not only has the combined power or leverage of public sector spending been recognized, but also how public sector spending patterns can affect markets, sectors and technological change (Caldwell, Walker, Harland, Knight, Zheng & Wakeley, 2004).

BACKGROUND

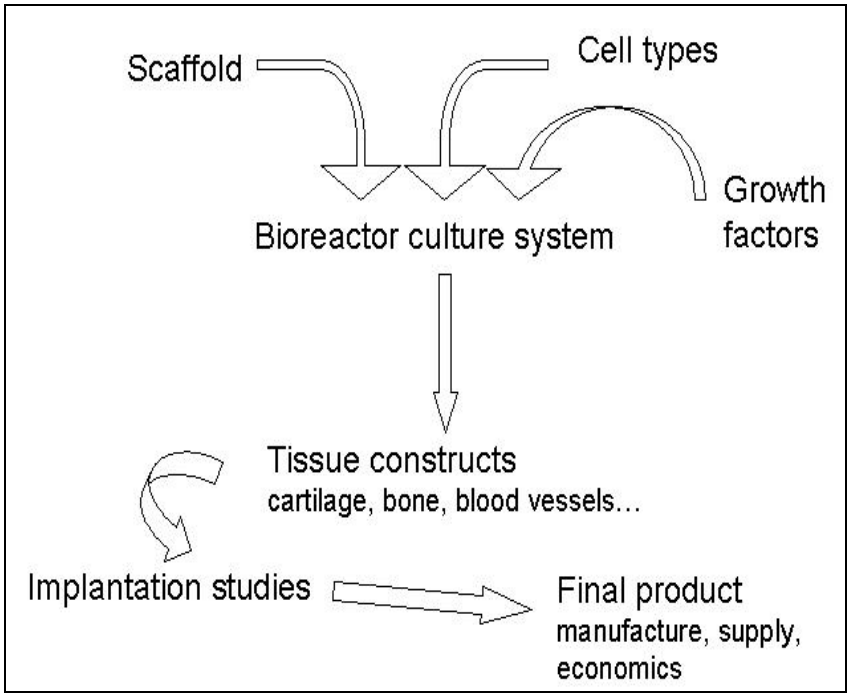
Tissue engineering is set to transform healthcare delivery, potentially replacing conventional therapies for the repair and regeneration of diseased or damaged tissues and organs. The global market for tissue-engineered products (TEPs) is estimated to be in excess of $25 billion (Bassett, 2004), and analysis of the US market predicts revenues of $1.9 billion by 2007 (IPTS-JRC, 2005). Over $4 billion have been invested in worldwide research and development since 1990 (World Technology Evaluation Center, 2002), and TEPs are slowly emerging onto the market; e.g., Myskin (treatment for burns) by CellTran and Carticel (cartilage) by Genzyme.

Tissue engineering is "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" (Langer & Vacanti, 1993, p. 921). Three dimensional (3D) tissue structures are synthesized from cells derived from either the patient (autologous cells), or from a donor (allogeneic cells) and the growth, organization and differentiation of the cells is guided through the use of biomaterials (Griffith, 2002) (see Figure 1). There is increasing interest in the use of stem cells for use in tissue engineering, but many scientific, legal, and ethical barriers prevent their use, especially since 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 investigation and have not gathered data, and hence have not reported upon, stem cell approaches.

A range of TEPs has been developed on common source materials and are categorized accordingly:

1. Autologous – cells derived from the patient.
2. Allogeneic - cells derived from a donor.

FIGURE 1
Outline Process of Tissue Engineering



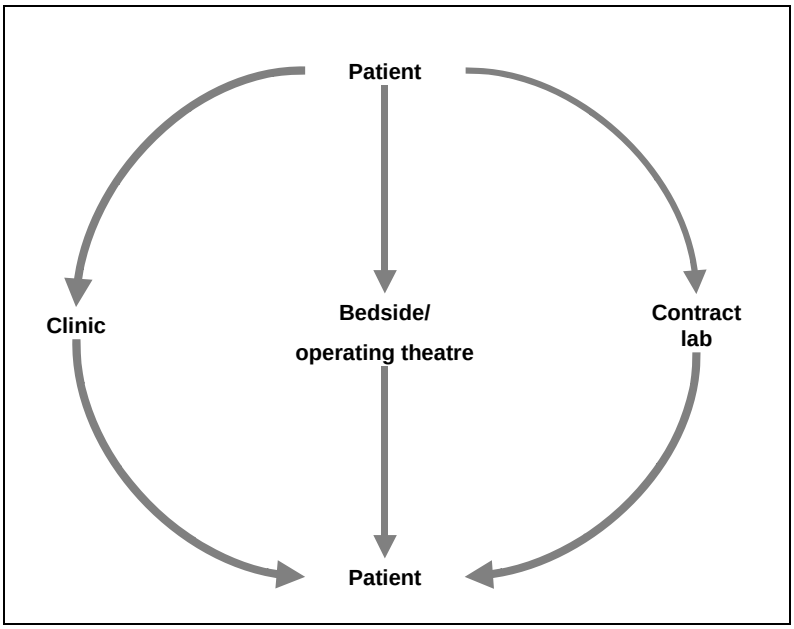
- Xenogeneic – potential use of cells from other mammalian sources.

Currently, xenogeneic products have limited potential due to the risk of cross-over of animal borne viruses. Consequently, autologous and allogeneic products have emerged as the dominant business models, although their routes to market are very different. The allogeneic route follows a "Make to Stock" (MTS) approach and promises to employ an automated, high-volume manufacturing process. Similar to the "Make to Order" (MTO) approach, the autologous approach is highly customized and low volume. The next section describes the two contrasting routes.

The Autologous Route

A dedicated, single therapy, the autologous route is provided on an individual patient basis and supports a wide range of applications such as skin and nerve repair and the restoration of musculoskeletal tissue (e.g., cartilage and bone). The procedure must be undertaken in a validated clean room facility and involves the removal of cells from the patient. The cells are transported to an authorized laboratory, which could be within the same clinic or hospital, another country, or even at the patient's bedside (see Figure 2). The cells must then be recombined with appropriate biomaterials. This can take several hours, days or weeks before a viable tissue construct is ready for implantation into the patient. The regenerated tissue is shipped back to the clinic prior to its reintroduction into the patient (Williams, 2005).

FIGURE 2
The Autologous Route



The advantages and disadvantages associated with autologous procedures are shown in Table 1. Sourcing the cells from the patient negates the risk of rejection and lowers the risk of contamination and infection. However, the procedure is highly specific, resulting in a limited market and little opportunity to overcome economies of scale through mass production; capacity is bounded by the number of biopsies that can be manipulated concurrently. Contamination remains a risk, as does implantation of cells from another patient. Also, throughout the process there is little flexibility; the cells remain viable for only a short period of time and often must be maintained under extreme conditions (e.g., -42˚C), making transportation both problematic and expensive.

TABLE 1
Advantages and Disadvantages Associated With the Autologous Route

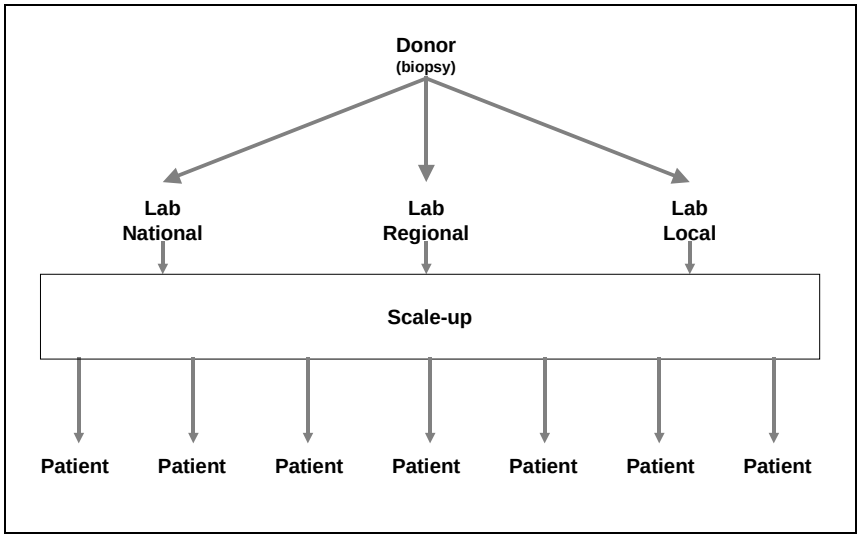
Advantages	Disadvantages
Minimal risk of rejection Lower risk of contamination Patient specific Broad range of applications	Economies of scale Limited market Risk of mix-up Acceptance –patients/clinicians Limited capacity Limited window

The Allogeneic Route

The allogeneic route appears to have the potential to serve an industrial market, although currently only a handful of products have managed to break the market. Cells are sourced from a donor and manipulated in a bioreactor, giving rise to a large volume of regenerated tissue of a specific type and of a standard quality, which can be implanted into numerous beneficiaries (Williams, 2004). The process can be undertaken at a local, regional or national accredited laboratory and shipped to multiple clinics (see Figure 3).

Table 2 highlights the advantages and disadvantages relating to the allogeneic route. Clearly, the main advantage is the possibility for scale-up, supporting the production of thousands of units from one

FIGURE 3
The Allogeneic Route



cell line of a standard quality. A more robust model, the allogeneic route supports the transport of a uniform product to many different clinical facilities.

The allogeneic route also has many disadvantages, such as microbiological or viral contamination from the source materials (e.g. HIV, BSE), resulting in a limited number of approved suppliers, and the need for full traceability of all materials used during the process.

TABLE 2
Advantages and Disadvantages Associated With the Allogeneic Route

Advantages	Disadvantages
Market size One-way model (lab to patient) Economies of scale (mass production) Greater quality control	Limited applications Infection/contamination Rejection of host cells Sourcing suitable cell line Transportation & storage Traceability Acceptance –patients/clinicians

Also, unless immunosuppressants are administered throughout the patient's lifetime, the range of TEPs is limited to immunopriveleged tissues such as skin and brain, which are not readily attacked by the recipient's immune system. Stem cells may have the potential to overcome this, but are not within the remit of this study.

Both routes are subject to resistance from both the public and clinicians. Clinicians' resistance relates to the potential of TEPs to disrupt existing healthcare treatment and threaten established modes of practice. Fear of an unknown is the main basis of patients' resistance.

The aim of this study is to investigate the influence of reimbursement upon public procurement in terms of the uptake and use of an emerging technology, contrasting the alternative approaches of the US and Europe towards the delivery and uptake of TEPs into the healthcare sector. Within the US, the allogeneic route is the dominant model, as opposed to the EU where the autologous route is preferred.

APPROACH

Between August 2004 and January 2006 we conducted over 130 hours of semi-structured interviews and meetings with over 35 key individuals engaged in tissue engineering. Using reputational sampling, interviews were conducted with key individuals from academia, industry, government, consultancies, funding bodies and trade associations (see Table 3). Nine companies participated in the research, six of which were European, one Australian and one from the US. Worldwide, around 90 firms are active in tissue engineering, of which 23 are European. Therefore, our study represents approximately 10% of the world tissue engineering industry and more than 25% of the European tissue engineering industry. Semi-structured interviews were conducted until theoretical saturation had been achieved; i.e., until the researchers deemed that the interviews were no longer delivering any new or relevant data (Strauss and Corbin, 1998; Bryman, 2004).

Due to sensitivity regarding some aspects of tissue engineering such as protection of IP (intellectual property) and fears of being linked to stem cell research, strict confidentiality was adhered to. Consequently, individual organizations have not been identified

except in terms of their role in the supply network (as displayed in Table 3).

TABLE 3
Classification of Interviews

Category	Number of organizations	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**

FINDINGS

Tissue Engineering in the EU

Currently, TEPs lie beyond the scope of existing reimbursement policies, yet without reimbursement TEPs will not fulfil their full market potential. To be marketed in Europe, healthcare products must be issued with either a CE mark (medical devices) or a product license (pharmaceuticals). However, since the EU has been unable to agree on their classification as either a pharmaceutical or a medical device, there are no uniform regulations for TEPs. The existing pharmaceutical directive does not prevent the use of human tissue, but requires rigorous and often costly drug trials to be undertaken. TEPs that are structural, as opposed to medicinal, must follow the guidelines for quality, safety and performance as laid down by the medical devices directive. However, the medical devices directive excludes human tissue; consequently, such TEPs cannot apply for a CE mark.

Without a CE license, European procurement agencies are unable to purchase those TEPs categorized as a medical device. TEPs classified as pharmaceuticals must prove their efficacy or performance in a controlled clinical setting. Although conventional drugs can be subjected to large-scale randomized trials, TEPs are

limited by their specificity; it is difficult to identify and quantify the active ingredients. A "Catch 22" situation has arisen; lack of reimbursement for clinical trials acts as a barrier to many of the smaller manufacturers, but without the clinical data, reimbursement cannot be achieved: "Small tissue engineering spin-outs can't do studies that involve 100s of patients not unless they have received really massive investment" (Personal communication with the Company CEO, October 6, 2005).

Reimbursement is often denied on the basis that TEPs are still experimental:

> To make money from them (TEPs) you have to be reimbursed for your products. Now that's almost like an order of magnitude that becomes increasingly more difficult to get reimbursement for your product if it doesn't have a product license because it's seen as a development product and therefore either private insurers or the NHS won't touch it (Personal communication with an industrial consultant, September 20, 2005).

Consequently, TEPs are not sold using a formal or conventional route. During the interviews, several organizations admitted to using the "compassionate use route" whereby the product is supplied to an individual doctor on a named patient basis. Other routes adopted by companies include "second line treatment," where conventional therapies have failed and few alternatives exist.

Clinical studies are another popular route, providing a means of receiving some reimbursement for TEPs during the clinical trials stage and had generated significant sales for one particular product. Such studies provided clinicians with a research project with the potential to deliver the requisite journal publications for career progression. For the TEP manufacturers, the studies not only enabled clinical access, but also gave rise to valuable feedback on the performance of their product. It also generated knowledge capital, developing pools of experience within clinics. Clinicians were seen as central in promoting the uptake and adoption of TEPs. Many interviewees described clinical champions as instrumental in ensuring the diffusion of TEPs into the healthcare system, their opinions and preferences having an influence on procurement:

> They're [clinicians] more able to influence a purchaser to start spending money on it, they understand how to work the reimbursement systems, so it's forced us as a business to look into different channels and different customers (Personal communication with the R&D Manager, June 28, 2005).

Currently, the industry has little understanding of how much national agencies would be willing to pay for TEPs. Many interviewees suggested there is a need to go beyond addressing the scientific issues to consider the development of feasible business models. Without a target price to work towards, there is a risk that TEPs will be unaffordable and beyond the reach of most patients. However, it was also pointed out that it is very difficult to acquire such information. Few studies exist that compare the cost-effectiveness of TEPs to conventional therapies. Informed discussion between national procurement agencies, healthcare insurers, clinicians, industry and scientists needs to be undertaken to develop an understanding of what steps need to be taken to develop products that are economically viable and likely to be reimbursed:

> If you don't know what the target price is you don't know where you stand, so that's the kind of issue because it's a systems problem rather than a specific technical problem and it involves lots and lots of disciplines working together in a structured and organised way which is not the norm (Personal communication with the Biotechnologist, September 23, 2005)

It was felt across the tissue engineering industry that the inability of healthcare professionals, namely finance directors and procurement, to see beyond the TEPs' upfront costs, or "sticker price," acted as a major barrier to adoption. Significantly, all referred to the need to consider the whole life cost of treatment as opposed to the initial outlay. For instance, in the case of wound treatments, not only should the cost of the dressing be considered, but also the need for repeat treatments and associated costs such as transport, nursing and homecare. With an aging population, the whole-life costs of treating age-related conditions such as diabetes and venous ulcers were often highlighted, particularly in relation to the potential of TEPs to combat spiralling costs:

> I did an ulcer clinic twice a week and there are hundreds of the things [ulcers] and they never get better. These people are housebound so they need an ambulance to collect them, to bring them to hospital. They have meals-on-wheels; somebody to do the shopping for them and then you have all the bandaging costs and everything else. They never get better, these people are incredibly depressed by it all, so then you chuck out a load of Prozac to go with it. Then you have other complications. The whole thing is a shambles and if you add up all those costs. I can't believe that *** [a TEP] isn't cheap. The trouble is it's the way we cost it, because the meals-on-wheels comes out of other budgets" (Personal communication with the Clinician, September 19, 2005).

The most significant outcome is the EU preference towards the autologous as opposed to the allogeneic route. Without reimbursement there is no commercial justification for firms to invest in the large-scale production and marketing of TEPs:

> The reimbursement side is a challenge from a commercial aspect and I suppose when you think about it over the space of the last 10 years if a major company has developed a [allogeneic] product and has got very limited sales on it it's very unlikely that that company is then going to say well shall we develop it further. That could be one of the reasons why it hasn't happened in Europe because companies are saying well we're not selling that product in Europe, why should we develop the market in Europe? (Personal communication with the R&D Director, September 29, 2005)

Currently, access to TEPs is limited to extreme cases: "heroic" treatments where conventional therapies have failed, or the affluent classes and super-elite athletes who can afford to pay for treatments such as collagen implants and cartilage replacement. Consequently, a customized approach is a more attractive proposition, making the less risky autologous procedures, which can be provided using a "make to order" approach, the favored option within the EU.

Tissue Engineering in the US

In contrast to the EU, the US has regulations that are specific to TEPs. Initially, an assessment is undertaken by the Office of Combinatorial Products, which determines, according to the TEP's

primary mode of action, the regulatory pathway it should follow. TEPs that are biologic in nature are under the administration of the Center for Biologics Evaluation and Research (CBER). The Center for Devices and Radiological Health (CDER) looks after TEPs that are more structural. The Centre for Drugs Evaluation and Research (CDER) oversees some TEPs considered to be therapeutic in their actions. The Food and Drug Administration (FDA) promotes regular industry-regulator interaction as a means of encouraging understanding and synergy. Consequently, interviewees saw the US approach to regulation as more straightforward and progressive than the EU's.

Unlike the EU, clinical trials can be reimbursed in the US. Facilities must be registered, but once products have been licensed they can be recorded in the "red book," a database of products eligible for reimbursement by private health insurers and the first step into the largest healthcare market in the world. The result has been the emergence of the allogeneic route as the dominant business model and the production and marketing of allogeneic products:

> We passed a milestone last year as a company - we sold 10,000 implants of that particular cellular product. I would say that probably 90% of that or more occurred in the US where there's a clear reimbursement structure, but I look at this and say there are 10,000 who have been treated in the US and if you looked to the UK you'd find 2 or 3 over the 10 years (Personal communication with the Director of Regulatory Affairs, September 16, 2005).

The tissue engineering industry, especially the MNCs, are keen to invest; with reimbursement mechanisms in place and a clear-cut regulatory framework, firms can visualize the potential of large-scale manufacturing facilities and the size of the US market is seen as being large enough to carry the cost of development:

> Adoption in the US market was always the first for us because 1) it's the biggest and 2) the reimbursement healthcare system works to the benefit of these types of technologies. With the US system of reimbursement once you've got that it's for the whole patient episode (Personal communication with the Technical Director, June 29, 2005).

In comparing tissue engineering in the US and EU, we found that EU appears to favor smaller low-scale manufacturers, whereas the US supports the major companies. Without widespread reimbursement, larger organizations perceived little value in exporting and importing products throughout Europe, although they had located business units in nations where there was perceived to be significant market demand in the future.

As a result, there was a general consensus that the first commercially viable products would appear in the US. Reimbursement mechanisms for both the whole patient episode and also for clinical trials creating an environment conducive for the development and adoption of innovative products.

CONCLUSIONS

As this chapter has demonstrated, reimbursement policies have the potential to influence the uptake of new and emerging technologies, particularly those that do not conform to existing business models and threaten to disrupt established modes of practice. Further, siloed budgets and target setting appear to favor the adoption of products where the initial outlay is low, but the whole-life cost of treatment may be high.

As a disruptive technology, TEPs have the potential to transform healthcare delivery., since they result in “different” ways of working as opposed to simply “better” ways of working, they are difficult to assess, either clinically or economically. Studies of disruptive healthcare technologies have found that interaction with key stakeholders is central in promoting their adoption (Straube, 2005; Coye and Kell, 2006). For disruptive healthcare technologies, a tangible market does not exist until their value is recognized by procurement agencies and healthcare providers. However, until evaluation methodologies are developed that allow for disruptive as well as incremental technologies, reimbursement will be difficult to achieve. Increasingly, new technologies, such as tissue engineering, combine both product and service innovations, and evaluation must be based on assessment of the whole product offering.

Based on the evidence, we propose that for emerging and potentially disruptive technologies, such as tissue engineering, the successful transition from basic research to successful

commercialization requires early support from key elements of the innovation system. Earlier involvement from national procurement agencies, such as earlier evaluation and comparisons with conventional treatments and reimbursement of clinical trials, could enable technologies to be developed that not only compete with existing technologies in terms of improved patient welfare, but also in terms of cost-effectiveness. Earlier involvement may also enable procurement agencies to plan and assess for potentially beneficial technologies and to justify their cost. A systemic approach would enable dialogue between national procurement agencies, healthcare insurers, clinicians, industry and scientists, supporting the development of products that are economically viable and likely to be reimbursed.

During the early stages of a new technology, the focus is often on scientific rather than commercial issues. If new technologies are to make a successful transition from basic science to commercialization, an understanding of the underlying rationale behind many purchasing decisions needs to be understood before a solid business case can be established. Such an understanding can only be achieved through closer interaction with procurement professionals sooner rather than later in a technology's life cycle. Through interaction, potentially beneficial, cost-effective technologies can be identified in a timely manner and equitable patient access facilitated.

In comparing the adoption and use of TEPs in the US and the EU, it is evident that the ability to achieve reimbursement in the US has created market potential for TEPs, promoting investment in manufacturing facilities and the development of large-scale automated processes. The potential of the allogeneic route to serve a mass market has resulted in its emergence as the dominant business model. With reimbursement undertaken on a case-by-case basis, uptake in the EU is slow and the market lacks any real potential. Consequently, companies are unwilling to invest in high-cost production units and instead have preferred to adopt the autologous approach, which is less risky and can be undertaken on an individual patient basis. Such a customized approach is further promoted by a private market that is willing to pay for autologous procedures.

The EU's wait-and-see, risk averse approach may be more pragmatic. In such a billion dollar industry, do national public

procurement employees have a chance of playing on level terms with the big biotech companies? The hype surrounding such emerging technologies could promote over-commitment of public resources. A delayed response could transfer the high costs related to the introduction of a new technology elsewhere and become the burden of the private healthcare sector, or that of a country wishing to become a national leader in the field of tissue engineering.

Clearly, regulation is an additional complication. Until a uniform regulatory route is established, the potential of the EU market will continue to elude the tissue engineering industry. Without the support of national procurement agencies and healthcare insurers, the majority of patients will not be able to access TEPs. Currently, TEPs marketed in the EU cannot compete economically with existing therapies and, hence, are only available to those that can afford to pay for treatment.

This chapter has demonstrated that the manner in which the different components of a healthcare system interact has a major influence on the rate and direction of technological change. Decisions based on conventional assessment techniques not only promote the adoption of lower risk, conventional treatments and inhibit the uptake of emerging technologies, but also impact industrial development and the development of national capabilities. Consequently, there is a need for procurement to consider the impact of their purchasing decisions not only on their immediate environment, but on society as a whole.

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