Medical Device Governance: Regulation of Tissue Engineering in the UK and EU

A. Background

It has been suggested that European Union public policy is witnessing a shift from a technocratic toward a more socially inclusive form of governance, that policies are becoming ‘precautionary’ and risk-based regulation is gaining ground. These shifts in bio-politics, it is claimed, are associated with advances in bio-technologies (Abels 2002; Vogel 2001) which hold out the promise of improving human health but are complex and risky. Study of innovative health technologies can throw light on the changes in science & technology governance processes, on transnational market-building, and on the implications for public health risks and benefits and the dynamics of innovation in healthcare systems. While some analysis of regulatory processes, risk and innovation has been carried out for pharmaceutical, genomic and to a lesser extent medical device regulation, the nascent field of tissue-engineering in Europe has not previously been studied in this way.

‘Tissue engineering’ (TE) is a contested term but may be understood to be a form of regenerative medicine’ that aims to restore and repair human tissue. TE may be taken to apply engineering and life sciences to create therapeutic human implant technologies. One influential definition (SCMPMD, 2001) describes the ‘regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules’. Such a definition excludes xenogeneic cells, organ transplants, bioactive biomaterials and cell therapy. The techniques are being applied in a variety of technologies. The focus of our research is on skin systems, bone and cartilage repair, and blood vessels. The product types that account for the majority of the current market are in cartilage, skin and to a lesser extent bone applications (IPTS-JRC, 2002). A key distinction important for the understanding of risk discourse and regulation in this field is that between autologous tissue/cells (donor and patient are the same, e.g. cartilage transplantation) and allogeneic (different donors, e.g. skin systems).

There is an established regulatory framework for pharmaceuticals and medical devices (Abraham & Lewis, 2000; Kent & Faulkner, 2002). Tissue engineering may be seen as representing new challenges to regulators, situated at the boundaries of earlier regulations, in what can be construed as a ‘regulatory vacuum’ (Faulkner et al 2003). Regulation and governance of tissue engineering technologies is thus characterised by uncertainty and instability. A new regime or regulatory order is being negotiated and continues to evolve, and the boundaries between tissue engineering, tissue banking, and medicinal product and medical device regulation are blurred.

In our research we draw together theoretical approaches to risk regulation and biotechnology governance, and political science/public policy understandings of policy and policy networks in the context of the regulatory state (e.g. Rhodes, 1997). We also recognise the value of sociological and anthropological work on the shaping of technology (MacKenzie & Wajcman 1999), on human tissue collections (tissue banks), pollution concepts and the political economy of bodies, tissues and cells (cf. Waldby, 2002; Scheper-Hughes & Wacquant, 2002).
B. Aims and Objectives

B.1 Overall Aims

- To analyse trends in regulation, governance, and evidential processes in relation to the challenge of TE technologies.
- To investigate the implications of trends in TE technologies for regulatory environments and healthcare governance, and vice versa.

B.2 Objectives

1. To map the activity of groups contributing to the regulation of tissue engineering at the EU level and describe their interface with UK manufacturers, scientists, regulators, clinicians and patients/citizens.

2. To elicit perceptions and values of these groups regarding the factors influencing the evolution of HTEP regulation.

3. To survey differences in national regulatory approaches to TE technologies in the EU.

4. To analyse and compare risk/benefit considerations of stakeholder groups as they relate to the 'assessment' of the safety, efficacy, effectiveness, ethical, legal and social aspects of HTEPs.

5. To analyse the implications for public health, health services and innovation/competitiveness.

The Objectives of the research have been met. Objective 1 informs this report generally. Objective 2 is addressed especially in Section D. 4.0. Objective 3 is illustrated especially in Section D 1.0. Objective 4 is covered in Sections D 3.0, 4.0, 5.0. Objective 5 is assessed (only briefly here) in the Conclusion below.

C. Methods

Our research focused on the application of TE technology to skin systems, cartilage and bone repair and regeneration/repair of blood vessels. These applications were in the most developed stage with either products already on the market or close to being marketed. They also employ different approaches to source material and production, thus offering the opportunity for comparison of regulatory response across technologies. Far less data was available than expected about vascular applications because the technology is less developed.

**Documentary materials**

An extensive archive of documentary materials has been collected and a bibliographic database has been established (noted as Datasets in the reporting form).

**Survey of EU regulatory authorities**

A survey of regulatory authorities across the EU was carried out in order to find out about current regulatory policy and practice relating to ‘human tissue engineered products’ (HTEPs) (referred to in this report as TE technologies). It was difficult to identify appropriate authorities and individuals. We combined websearches of official government sites, snowballing and cold calling. 38
questionnaires were distributed to regulatory authorities and experts in 17 EU member states. After followup we received responses from 12 countries, two incomplete, and some with additional documentation. Most survey respondents were regulators, who were willing to be interviewed. Contact details of additional potential interviewees were identified.

*Interviews with relevant actors (‘stakeholders’)*

Sixty three in-depth, semi-structured interviews were carried out in the UK and across Europe (classified in table below).

<table>
<thead>
<tr>
<th>Category</th>
<th>UK</th>
<th>Rest of EU</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulators</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Manufacturers</td>
<td>3</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Clinicians</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Scientists</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>‘Consumers’</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>EU advisory</td>
<td>0</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>29</td>
<td>34</td>
<td>63</td>
</tr>
</tbody>
</table>

Sampling - Interviewees were sought who were active in the ‘field’ of tissue engineering regulation, or engaged in scientific/clinical/manufacture of TE technologies for skin, bone or cartilage, blood vessel repair, or members of consumer groups who were/might be users of such products. They were identified via the scientific literature, internet searches of professional organisations, consumer organisations, official and government web pages, personal contacts, attendance at relevant scientific and regulatory affairs meetings and through snowballing. In particular we sought individuals occupying strategic intermediary positions such as representatives, advisors, officials and committee members.

Invitation and consent procedures followed ethical guidelines. Fewer ‘consumer’ interviewees were identified than expected. Few consumer organisations claimed knowledge about TE products. This pointed to the low profile of these products amongst the wider public.

The interviews were designed according to a broadly similar topic guide which aimed to explore aspects of professional and institutional activities, participation in regulatory policy making, views of TE technologies and relations between stakeholder groups.

Most interviews were face to face but fourteen were conducted by telephone. All interviews were tape recorded (except five where interviewees declined) and were fully transcribed and coded with the assistance of ATLAS-ti software. Fieldnotes summarised and highlighted features of each interview.

*Attendance at fieldwork conferences and meetings*

An additional rich source of data was fieldwork conferences. These generated extensive fieldnotes, and materials relating to TE science, industry activities,
regulatory issues, and ethical debates. Team-members attended meetings including: an industry-sponsored regulatory workshop; meeting of Regulatory Affairs Professional Society; scientific meeting on TE applications; conference on Commercialisation of TE; EU Parliamentary Hearing on proposed Tissues and Cells directive; British Association of Tissue Banks Annual meeting; EC Commission ‘Stakeholder Conference’ on proposed regulation for TE products.

D. Results

1. TE as a regulatable zone: market uncertainty and anticipatory regulation

It can be seen as politically and economically important to establish clear regulatory fields in order that the resources and expertise necessary for a novel commercial technology might be mobilised. The notion of a technological ‘zone’ (Barry, 2001) with its connotations of boundary-definition captures this concept. We conceive of the development of regulation and the development of technological zones as inextricably interwoven. Regulatability interacts with commercialisation and social acceptability.

Our research shows that TE as a field is unstable and its viability and scope are contested. The regulatory approach varies greatly between nation-states of Europe (see section 2). While certain actors attempt to define a clear regulatory terrain for TE technology, market-building is characterised by uncertainty. Concerns were expressed about investment, appropriate business models, and difficulties securing reimbursement in the absence of regulatory approval. While industry stakeholders project stable images of a TE zone, other national authority representatives (for example in the tissue-banking sector) maintain that TE is ‘only chondrocytes and keratinocytes’ (cartilage and skin cells). Two of the major early (US) TE companies were forced to cease trading and one of the largest Europe-based companies re-located most of its activity to the USA. In a European Commission’s ‘impact assessment’ projections of the potential market for TE, varied widely: estimates for market value from different sources range from 3.9 billion by 2007 up to 400 billion worldwide (IPTS-JRC, 2003:35).

Our survey of national authorities highlighted the difficulty of establishing detailed information about the current availability of individual products in healthcare systems in the EU. R&D and funding in Europe shows a strong bias toward autologous products/services. This is felt by many members of the policy/issue networks to be due to the greater perceived risk associated with allogeneic applications. This view contrasts with the USA where allogeneic applications are at least equally widespread especially amongst the larger companies (IPTS-JRC, 2003; WTEC, 2002).

Regulation must be flexible to allow for technical innovations which are not wholly predictable. The regulatability of TE technology contends with uncertainty about the definition of TE, potential markets, the reimbursement environment, evidential needs in the face of unknown risks, and scientific and ethical framings of risk and benefit.

2. National variation, regulatory jurisdictions and strategies

Very wide variation in the national approaches of different EU Member States to the market approval of TE technologies was documented through our regulators survey and in interviews. Our survey illustrated the difficulties that industry might experience in locating sources of authoritative advice. In Italy autologous TE falls under the legislation of services; in France TE companies have to be registered with a tissue bank and Spain and Belgium also have strong tissue bank-based approval systems.
Germany and Sweden see TE as falling within medicinal jurisdictions. In the UK there is voluntary guidance for manufacturers (MDA 2002). Other countries also deal with applications for approval on a case by case basis. Setting up clinical trials has been a further strategy for introducing a product into national healthcare systems.

This national variation reflects underlying histories of healthcare product regulation, and embedded relationships between producers and regulatory bodies which can show a preference for one or other regulatory route. The important question for regulatory policy is the significance which is accorded these variations by different stakeholders. The concept of a ‘regulatory vacuum’ was used rhetorically to problematise this inter-national variation, especially by industry representatives and by agencies in the European Commission itself.

TE technology enters a regulatory environment that can usefully be conceived of as a fluid, evolving collection of inter-related pieces, with jurisdictions at local, national and EU/EC levels. We have mapped the detail of this in Europe and the UK (see annex 1). The UK’s development of codes of practice and guidance has anticipated developments in the EU/EC. UK regulatory policymakers saw them as influencing the shape of EC policy, and providing a template for the separation of ‘banking’ issues of sourcing, storage, distribution and testing of tissues from issues of product approval and marketing.

Two major European Commission initiatives in regulatory policy have/are being formulated. The ‘Tissues and Cells’ Directive (EC DG Sanco, 2004 - TCD) and a forthcoming Regulation on market approval of TE products (EC DG Enterprise 2004a - TER) These are discussed further below. We have observed a strategy of regulatory ‘partitioning’ in the negotiation of this regulation which seeks to clear the terrain for promotion of a transnational tissue engineering zone. The partitioning of ostensibly similar therapies from tissues and cells and TE products is observed in relation to ethically or technologically ‘risky’ technology. For example a senior UK regulator stated at a Europe-wide regulators/industry conference that ‘Realpolitik dictated the exclusion of stem cells’.

3. Regulatory policy network participation

The material composition, sourcing and production processes of TE technology are crucial in understanding the mobilisation of ‘relevant actors’. TE has become an arena in which a plurality of interests of different stakeholder constituencies is being negotiated. We assessed our findings in terms of the alleged shift in the social organisation of policy formation, in relation to technocratic/inclusionary models, interest pluralism or ‘regulatory capture’, social closure, and neo-corporatism. Findings of colleagues (in the ESRC Innovative Health Technologies programme) indicate that while relationships between regulatory policymakers and industry exhibit social closure in pharmaceutical regulation (Abraham, 2000) in human genetics a more inclusionary form of governance responsive to bioethical constituencies is emerging (Salter & Jones, 2002). Our analysis of network participation in TE suggests that while bioethics does inform the development of regulation, the primary governance network interactions are between regulatory policymakers and industry representatives, and a small number of influential scientific research actors. The voices of public health bodies, consumer groups, and clinicians currently have relatively weak representation.

In Europe, consultations were held for both the TCD and the forthcoming TER. It is undoubtedly the case that specialised, institutionalised bioethics opinion (in the form of EGE – the European Group on Ethics in science and new technologies) has had a
formative influence on regulation for tissues and cells. However, apart from matters of donation, the not-for-profit principle and consent, the ethical positions on the acceptability of certain human tissue technologies that many MEPs sought to include during the passage of the TCD through the EU Parliament were excluded. A principle of subsidiarity emerged as a means of bracketing out some ethically controversial issues.

DG Enterprise conducted a web-based consultation exercise on the proposed TER and held a follow-up ‘Stakeholders Conference’. While the participation principle was inclusionary, it was clear that apart from EC officials the strongest and most organised contribution came from industry, together with a small number of key scientific research representatives. A patient association contribution was minimal. (EC DG Enterprise, 2004b).

In the UK, members of the British Association of Tissue Banking played a significant part in the development of the Code of Practice on Tissue Banking together with the Department of Health and regulatory agencies. The voluntary Code of Practice on Human-derived Therapeutic Products emerged from consultation at national, European and world-wide level, including representatives from industry, research, regulatory professionals, professional associations and Royal Colleges, research councils, competent authorities, tissue banking and biological standards groups, ethical and patient groups. The group that produced the guidance document comprised regulators, industry representatives and scientists. Several key individuals occupied strategic intermediary positions in the EC consultative and advisory networks, influencing both UK and the EU regulatory frameworks.

Thus evidence of a structural shift away from technocratic decision making or neo-corporatism appears weak, in spite of the ascendancy of bioethics (Kent et al forthcoming – see Outputs below). There are strong links between industry and the European and national regulatory state. Industry has been well organised in lobbying for regulation. Scientific opinion has been sought and included in the drawing up of proto-regulatory measures.

4. Stakeholder values and interests

We have been able to analyse the framing of risk and benefit positions, alternate and new forms of risk, the influence of ‘precautionary’ principles, and the deployment of social values in the assessment of TE and promotion or opposition to it amongst different groups.

TE does not have a controversial general public profile. Our analysis suggests the deployment of strategies which inoculate TE against the infection of controversy. A technocratic model would suggest the predominance of a discourse of technical safety in its regulation, however while such discourse is important our analysis shows that such an account does not do justice to the complex dynamics of the ‘values-assessment’ (Webster, 2002) that is displayed in the multiple strands of its emerging governance.

Very broadly, public health and commercialisation/promotion of trade represent pivotal values which inform much regulatory discourse and between which policymakers try to negotiate. In Europe, these values are enshrined in separate articles of the ‘Treaty of Rome, and also embodied in separate Directorates of the EC. Thus the TCD is a ‘protection of public health’ initiative, while the forthcoming TER ‘belongs’ to DG Enterprise. The bias toward autologous technology in Europe is seen to be associated partly with the impact of public health crises such as BSE and
the French HIV blood-contamination scandal, reference-points that are consistently referred to in our interviews and in EU parliamentary debate.

Industry advocated a ‘level playing field’ with the tissue banking sector (see section 5) and harmonisation of regulatory routes for TE products across Europe and globally (e.g. Eucomed 2002). They support the principle of proportionality of level of regulatory control to degree of risk. They invoke the needs of ‘the European patient’ and advocate consideration of Human Rights in regulation and in formal statements acknowledge bioethics (EGE) principles.

EGE principles have been a major impetus behind the Commission’s drive to create regulation: they noted in 1998 an ‘urgent need to regulate the conditions under which human tissues circulate within the European Market’ (EGE, 1998). The ‘Explanatory memorandum’ prefacing the TCD, emphasises body integrity, donor consent, protection of identity and the social solidarity of donation. EGE has recently produced an Opinion on TE products (EGE 2004). This notes social variation in stances on ethical principles without commenting upon the implications. There are signs that subsidiarity will again be brought into play to manage ethics conflicts. This requires further investigation.

The discourse of evidentiality reaches into the technological appraisal of the sourcing and material safety of TE and testing of efficacy through clinical trials and cohort studies. Ethical perspectives are frequently articulated by clinicians and scientists, although their voice as organised participants in ethics discourse about regulatory policy at EC-level in this area appears to be weak. An ethics of evidentiality (clinical efficacy and effectiveness) has been notable amongst clinician representatives. In the UK it has been powerful in determining the NHS policy of confining autologous cartilage technology to clinical trials. TE can be depicted as presenting novel risks which in turn make new demands upon evidence in areas such as toxicology testing and clinical trials. We have noted perceived shortcomings in evidence such as lack of appropriate biological outcome measures, and in testing for presence of unknown contaminants in tissues manipulated in animal-derived culture media.

The idea that ‘autologous tissue engineering is an ethics free zone’ (Scientist EU-6) was a widespread position. A discourse of risk/safety of disease transmission underlies it. By contrast a key UK scientist representative argues that some autologous applications may be as risky as allogeneic technology not because of safety but because of functionality, for example in the case of potential engineered heart tissue, a vascular application where the consequences of failure are more severe than in the case of skin or cartilage technologies. The consultation proposals for TER (EC DG Enterprise 2004a) show ambivalence about the respective risks of autologous and allogeneic technologies, invoking subsidiarity for autologous applications by proposing that they be the responsibility of member states.

In summary, the influence of public controversies relating to disease transmission is important. Relations between ethical concerns and regulatory policy making emerged strongly. Indeed we suggest that in the case of TE we see evidence not only of risk-based regulation, but also of selective ethics-shaped regulation. The predominant discourse on risk is focused upon safety and quality rather than efficacy.

5. Convergence and tensions between tissue banking and tissue engineering

With the emergence of TCD we found that the boundaries between tissue banking and tissue engineering have become blurred and there is convergence between them. Debate in the EU Parliament, at hearings, in policy documents and interviews
pointed to controversy surrounding the scope of the directive and its application to different sectors and communities. While originally envisaged as regulating tissue banks the scope was extended to include all ‘tissue establishments’. The effect of this has been to widen the reach of the regulation (see below) but also to promote ‘a level playing field’ for tissue banks and tissue engineering companies. It is apparent that activities in the public and private sector overlap. Tissue banks may be both non-profit and for-profit.

Tissue engineering companies were keen to be able to be licensed tissue establishments to prevent reliance on tissue banks and avoid their charges. Tissue banks were perceived as wanting to distance themselves from industry and commercial interests by rhetorically asserting a distinction between ‘traditional’ tissues and ‘engineered’ products. Such a distinction though is controversial and difficult to sustain (section 2). As noted TE is subsumed under tissue bank regulation for example in France where no distinction is made between tissue banking and TE. Hence political debate turns on the technical distinction between tissues and the degree to which they are manipulated. Positions within this debate reflect interests of the two communities.

Of primary concern to many was a conflict between public service values and commercialisation. The TCD took many key industry stakeholders by surprise and appeared to be in isolation from the work of DG Enterprise. Tissue banks within hospitals and health care systems were seen as representing values more commonly associated with organ donation and transplantation, based on ideals of altruism and gifting of tissues for the benefit of others.

The tissue bank community have been a strong lobby group in relation to emerging regulation (section 4). They have resisted convergence with commercial tissue engineering, disputing the need for a third pillar for product regulation and arguing that existing medicinal product regulation be adapted. Attitudes and practices relating to quality and safety of tissues and those pertaining to product testing and marketing of tissue engineered technologies differ. Much regulatory debate has centred on potential alignments and convergence between them. This tension is central to the reconfiguration of regulatory authority.

6. Reconfiguring regulatory authority

We see “relationships between expertise, authority, credibility and control being negotiated and contingent” (Hogle 2002: 276) and constituting the boundaries of jurisdictions. The arrival of TE challenges numerous boundaries of authority and expertise: national/European, medicine/device, human tissue/animal tissue, tissue bank/industry, commerce/public health, and the bounded structures and habits of existing regulatory agencies.

National interests and different state institutional arrangements for managing healthcare products are evident. In the UK the merger of the Medical Device Agency and Medicines Control Agency in 2003 was represented as a response to the growing number of ‘combination products’ (combining attributes of drug and device), and it is notable that the Committee for the Safety of Devices is considering TE technologies. Accreditation of tissue banks by inspectors from the medicine unit of MHRA is in progress, but the role of the proposed UK Human Tissue Authority is yet to be formally defined. Some UK scientists expressed concern about their lack of involvement in consultation about implementation of the tissue bank new requirements.
The material technology is important to negotiation of regulatory jurisdictions. Our interviewees noted that source materials needed to be stringently characterised if therapeutic effects were to be clinically tested. Therefore for the manufacturer clinical grade materials were needed at the research stage if a marketable product was envisaged, also necessitating product safety data. The effect of this is unclear - the potential exclusion of research and development trials from the TER was seen by some as de facto excluding clinical trials (DG Enterprise 2004b).

Within the EC’s DG Enterprise, boundary disputes between drug and device groups shape debate around the TER. Strained relations between the jurisdiction of DG Enterprise and DG Sanco (public health) regarding the scope and interface between the TCD and TER were evident. Medical device regulation (MDD) has had wide support from the device industry, and is seen as relatively liberal and light-touch compared to medicinal product regulation. Proponents of a third pillar of product regulation regard this regulation as unsuited to the governance of TE technologies. However others believe that revisions to the Medicinal Products Directive (MPD - such as its annex on cell therapy) provide a basis for regulation (Kent et al forthcoming).

Support for a new TER has been mobilised across medicinal/device boundaries and new alliances have emerged. For example, relations between different industry sectors have been strengthened. 'Big pharma’, biotechnology and medical device companies have developed joint ventures at company level and between trade associations.

The appropriate institutional arrangements continue to be discussed, including the potential role of EMEA, which is seen negatively by many SMEs. Suggestions for alternate structures for marketing authorisation and production quality assurance include a proposal for a limited number of ‘centres of excellence’ across Europe, a compromise between a wholly centralised model and a member-state based system. Such discussions turn on questions about who has the appropriate expertise and authority, mutual recognition between member states, and the appropriate levels of control for different levels of public health risk. Two key technical and political questions are highlighted in this debate:

1. What might be regarded as significant differences between autologous and allogeneic products?

2. What constitutes a ‘tissue engineered’ product and how might the concept of ‘engineered’ be defined?

We have indicated some of the range of different positions regarding these questions. The institutionalised answers to them will represent the development of new ‘hybrid regulatory institutions’ (Brown & Michael forthcoming).

7. Regulatory reach: from the fridge to global manufacturing company

In reconfiguring regulatory institutions the reach of these initiatives extends from the fridge in a hospital department or university laboratory to production facilities belonging to a company with global distribution networks. Tissue and cells may be stored for the use of a single patient or a larger group, they may be used locally or exported across Europe or to the US and elsewhere.

The long history of storing and using tissues in surgical procedures has been integral to the everyday practices of plastic and reconstructive surgery, which it has been
suggested is the earliest form of tissue engineering (JK fieldnotes, TE conference 9-10.04.03). But the lack of regulation for tissue banking activities has been a concern for the Council of Europe and Department of Health since the early 1990’s and a review in the UK was carried out in 1995 that found that ‘some areas that were very well run… there were a lot of other questionable activities going on…, bits of bone, skin and things in fridges… without very much quality control at all’. (Regulator R3) According to manufacturers, on the basis of conformity to regulations and quality assurance standards the risks associated with locally based tissue banks engaged in tissue and cell therapies is greater than those for industry bodies. Therefore they take the view that industry is ‘cleaner’ than tissue banking. The risks associated with ‘batch size’ also figured in policy debate as another possible basis for connecting risk classification to new regulatory structures.

So stakeholders deploy two diverse characterisations of the production of tissue engineered products. One is that it is a relatively low tech activity that can be carried out with minimal resources and in an uncontrolled environment (or at least less well developed quality systems and management). In contrast, the same activities are characterised as being highly technical and specialised and requiring strict controls, risk management, safety standards and quality assurance. We highlighted the different perceptions of risk associated with the donation, storage and processing of tissue and cells, and the positions of different stakeholders in relation to this policy debate as it is being played out in the formation and implementation of new regulation.

Taken overall, the proliferation of new codes of practice and regulation shows trends in the arenas of technical and healthcare system innovation toward increasing ‘purification’ in response to, and in interaction with, the perceived dangers and promises of TE. These take the form of increasing stringency of technical standards as well as the introduction of pan-Europe and national monitoring and accountability frameworks.

8. Conclusions and Implications

The research has fulfilled its overall aims. Crucial regulatory developments are still under way. We have focused primarily on skin systems, bone and cartilage repair, and blood vessels. The distinction between autologous and allogeneic applications has emerged as crucial to developing regulation.

**Neo-corporatism.** We have identified influential core (though not cohesive) policy networks comprising EC policymakers, national regulators, industry representatives, key scientists, tissue bankers and specialist technical consultants. Looser and less organised ‘issue networks’ interact with this, composed of parliamentarians, clinician groups, patient groups, and other scientists. Institutionalised bioethics appears to occupy a distinct place in the policy network structure, with high selective overall influence (no doubt aided by broad sociocultural shifts) but low levels of interaction, and positioned outside the pressure-cooker of EC-based regulatory negotiations. There is no general public presence.

**Key interests impacting on TE governance exist in tension to produce the dynamic of regulatory development. We identified these as commercialisation and market-building, human rights and public health ethics, transmissible disease risk-aversion, national regulatory institutional tradition, evidentiality and regulatory policy progress.**
**Implications of regulation for innovation.** Given the lack of harmonised regulation the regulatory identity of TE technologies is unclear. Blurred boundaries between tissue banks and manufacturers mean that the commodity status of TE technologies also is contested. A regulatory patchwork and conflicting expectations lead to a perceived limited, skewed and delayed diffusion of TE. Lack of regulatory expertise is a block to innovation.

**Implications of TE for regulation.** TE is hybrid technology evoking complicated regulatory activity which tries to balance a variety of national, transnational and sectoral interests. The hybridity of the material technology is associated with promotion of new regulation and resistance to it. The development of regulation must anticipate major future uncertainties in market-building, health risk and in the technical profile of TE technologies. The societal significance of human and animal tissue sourcing underlies increasing ‘purification’ of regulatory standards in TE technology (see G. Outputs: Faulkner et al).

**Implications for public health; industrial competitiveness; healthcare system innovation.** In principle, the new regulatory developments are protective of public health but as always this is balanced by the motivation to promote technical innovation. TE has managed to remain non-controversial in the public view. The effect of regulatory variation in the EU upon competitiveness of the trade area is clearly negative. EU actors perceive lack of competitiveness in comparison to the US. Prescription status, generally not yet resolved, will be important in influencing diffusion. Lack of consensus on appropriate evidence base for TE technologies adoption means that public healthcare systems are not in general eager to adopt them.

**E. Theoretical development**

As befits study of a hybrid technology we have drawn in a range of theoretical perspectives to develop this work. We have introduced the concept of a ‘regulatory order’ (in preference to the more rigid, rationalistic regulatory ‘regime’) to signify the fluid, shifting, negotiated, often non-rational contours of a complex regulatory environment. We have drawn concepts from governance theory such as the regulatory state and policy network, together with sociological understandings of risk and shaping of technology. Emerging analysis of the global ‘tissue-economy’ (Waldby 2002) has been incorporated in our approach. We have recognised the importance of evidentiality in its link to contemporary governance. Comparative analysis between innovative health bio-technology zones remains highly under-developed but we have laid down some markers for this enterprise.

**F. Activities (conferences etc)**

Conference papers/presentations:


2004 Faulkner, A., Kent, J., Geesink, I., FitzPatrick, D.
Purity and the dangers of innovative therapies: re-ordering regulation and
governance in the shaping of tissue-engineered medical technology.
'Healthy Innovations' international workshop, jointly organised by the ESRC Centre
for Research on Innovation and Competition, and the Wellcome Centre for the
History of Science Technology and Medicine with the support of the ESRC
Programme on Innovative Health Technologies. University of Manchester, 8-10 July
2004
2004 Kent, J. Faulkner, A. Geesink, I. FitzPatrick, D.
Regulation and Governance of Tissue Engineering in Europe and the UK,
presentation to the Committee on Safety of Devices, Medicinal and Healthcare
products Regulatory Authority (MHRA), 1 July 2004.
2004 FitzPatrick, D., Faulkner, A., Kent, J., Geesink, I.
Tissue Engineering – The Regulatory Domain
Presentation at the British Association for Tissue Banking (BATB) 12th Annual
2003 Kent, J. Faulkner, A. Geesink, I., FitzPatrick, D.
The Social Shaping of Regulatory Policy Relating to Human Tissue Engineered
Products, BSA Annual Medical Sociology Conference, York,
26th -28th September.
2003 Geesink, I. Faulkner, A. Kent, J. FitzPatrick, D.
Globalisation of Risk: Regulation of Tissue Engineering in the UK and EU.
SSTNET 6th European Sociological Association Conference, Murcia, Spain.
September.
2003 Geesink, I. Faulkner, A. Kent, J. FitzPatrick, D.
The Governance of Risk and Human Tissue Engineered Products
BSA Risk & Society Study Group Conference, 8-9 September 2003, University of
Plymouth
2003 FitzPatrick, D.P. Kent, J. Faulkner, A. Geesink, I.
Medical Device Governance: Regulation of Tissue Engineering in the UK and EU
Biotech Society conference, Helsinki, 29-30 September 2003
2003 Kent, J. Faulkner, A. Geesink, I. FitzPatrick, D.P.
Governance of Human Tissue Engineered Products in Europe –the case for a new
regulatory regime?
Innovation in Europe: Dynamics, Institutions and Values conference at Roskilde
University 8th-9th May 2003. For conference track ‘Risk society and the governance
of science’.
2003 Faulkner, A. Kent, J. FitzPatrick, D., Geesink, I.
Tissue-engineered human implant technologies and European regulatory policy: recent history of the regulatory shaping of technological careers
Society for the Social History of Medicine Summer Conference, 11-13 July, 2003,
Manchester.
2003 Faulkner, A. Kent, J. FitzPatrick, D., Geesink, I.
The regulatory environment for tissue-engineered implant technologies: some
implications for R&D and product innovation.
Presentation at Cardiff Institute of Tissue Engineering and Repair (CITER), Annual
Meeting, Aberystwyth, 1-3 September 2003
2003 Faulkner, Geesink, I., A. Kent, J. FitzPatrick, D.
Public Launch of CITER Cardiff Institute of Tissue Engineering and Repair, City Hall
Cardiff, 13 March 2003
Poster presentation ‘Medical device governance: regulation of tissue engineering in
the UK and EU’.

2002 Faulkner, A. Kent, J. FitzPatrick, D., Geesink, I.
Regulatory policy for tissue engineering.
Inaugural meeting of CITER Cardiff Institute of Tissue Engineering and Repair.

Additional activity:

2004 European Science Foundation/ European Medical Research Council Exploratory workshop:
Regulation and Governance of Human Tissue Engineered Products in Europe
University of West of England, Bristol, United Kingdom, 23-24 June 2004
Convened by: Dr Julie Kent

G. Outputs

Towards Governance of Human Tissue Engineered Technologies in Europe: Framing the case for a new regulatory regime. Technology Forecasting and Social Change.

Outputs in preparation so far

Faulkner, A. Kent, J. Geesink, I. FitzPatrick, D. Purity and the dangers of innovative therapies: re-ordering regulation and governance in the shaping of tissue-engineered medical technology. (target journal Social Science and Medicine).
PhD Thesis: Ms Ingrid Geesink, research associate to the project, is undertaking a PhD dissertation (at Cardiff University) closely connected to this research.

H. Impacts

The research has become widely known amongst the many different UK and European networks involved in tissue engineering and its regulation. Dr Kent has discussed the work in the UK Committee for the Safety of Devices (of which she is a member) in the context of the Medicines and Healthcare products Regulatory Authority (MHRA) consideration of TE regulation. Dr Kent and Mr Faulkner both contributed to the EC’s impact assessment of proposed policy in the field, being included in the EC’s Institute for Prospective Technological Studies’ evaluation. AF has joined the Research Committee of the Cardiff Institute of Tissue Engineering and Repair. Our editorial in the British Medical Journal evoked discussion in the journal about risk management of TE. Our publications have been drawn upon in recent and forthcoming books on innovation and governance in New Medical Technologies (Brown & Webster, 2004) and Genetic Governance (Petersen, forthcoming). By informing the European Science Foundation workshop noted above, the research
has brought together academics internationally with special expertise in worldwide regulation of medical devices, genetics and pharmaceuticals as well as TE, to provide the platform for comparative analysis of regulation across medico-commercial sectors. Joint work with colleagues in the Innovative Health Technologies programme (Brown & Michael) will further develop the mission of comparative analysis.

I. Future Research Priorities

The work is already expanding in a number of directions. As noted above, regulatory policy for TE continues to develop, and in fact is currently (Autumn 2004) at a crucial stage in the EC. Thus the first priority is to capitalise on the work reported here to develop the analysis further as the EC, EU and member states grapple with the regulation of the commercialisation and marketing of TE technologies. The relationship of TE to stem cell technologies has been an important feature of this study and the negotiation of this boundary in the context of ‘regenerative medicine’ deserves closer scrutiny. JK will develop an interest in foetal stem cell technology in a further project already supported by ESRC. More systematic comparison between TE and cognate sectors (pharmaceutical, medical device, xeno, blood products, human genetics/biotech) has also emerged as an important and productive area for further activity.

Additional topic areas are:

a. Investigation of the structures and discourses mediating public ethics, specialised ethics and regulation in this field;

b. International comparative analysis of tissue engineering governance in different EU countries, USA and east Asia;

c. Socio-economic analysis of tissue engineering markets including the activity of the range of small scale ‘tissue establishments’;

d. Implementation process of risk regulation of TE products in Europe and in local regulatory catchment areas as technologies develop.

ANNEXE 1. Selected Legislative and Regulatory Instruments

CPMP/CVMP Notes for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev 2. – October 2003) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal Products (CVMP).


ANNEXE 2. References


