INNOVATIVE HEALTH TECHNOLOGIES PROGRAMME

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

KEY FINDINGS

The research investigated regulatory policy relating to the emerging technology of tissue-engineering (TE) in Europe and the UK. It examined the divergent activity, discourses and values of stakeholders contributing to regulatory policy for TE in the context of different regulatory regimes pharmaceutical, medical device, and biological. National differences in regulation were surveyed. Alternative views of risks and benefits were elicited. Regulatory movements focusing on (a) sourcing of human tissues, and (b) production and therapeutic application were analysed. We assessed the implications for public health, health services and industry. We sought theoretical innovation in our analysis.

RESEARCH FINDINGS

- Variation in national approaches to the regulation of TE and conflicting expectations about the technology, some stakeholders believe, limits innovation and diffusion of TE.
- The European Commission policy process in this area has promoted transnational technical and procedural standards over certain substantive ethical standpoints.
- Regulatory harmonisation on human tissue sourcing/procurement issues in the EU took the form of a framework which allows for national variation on important dimensions.
- There was tension and convergence between the institutions and activities of tissue banks and tissue engineering industry.
- The major stakeholders negotiating human tissue regulation have been industry, regulatory policymakers, and tissue banks. Specialist ethical advice was influential but public representation has been lacking, in spite of the alleged move toward more inclusive policy formation in the European Commission.
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- Increasing stringency in the EU in accountability, surveillance and standards for quality and safety was noted, focusing on procurement and storage of human tissues and cells.
- Debate on appropriate controls for production and approval of TE products has been contentious and the development of new regulation for these products has yet to be agreed.

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The current regulatory environment

The majority of TE-active companies in Europe are SMEs. Countries most active are Germany, UK, Sweden, Italy, Switzerland. TE as a field is unstable. Its viability and scope are contested. Regulatory policy varies greatly between nation-states of Europe, some favouring use of existing pharmaceutical and/or tissue bank regulation, others promoting a new TE-specific approach. In Italy autologous (donor and recipient are the same) TE falls under the legislation of services; in France TE companies have to be registered with a tissue bank; Spain and Belgium also have strong tissue bank-based systems. Germany and Sweden see TE as within medicinal jurisdictions. In the UK there is voluntary guidance for manufacturers since 2002. Other countries dealt with TE products case-by-case. Regulatory variation is seen by industry and EC industry regulators as impeding innovation. Emerging regulation referred to the notion of a 'regulatory vacuum' in building the case for new TE-specific regulation.

R&D and funding in Europe shows a strong bias toward autologous products/services, probably due to perceived safety and ethical problems with allogeneic (donor and recipient are different) tissue-sourcing.

TE technology enters a regulatory environment comprising a fluid, evolving collection of inter-related and overlapping measures, with jurisdictions at local, national and EU/EC levels. This includes a variety of EC directives covering technologies such as medicinal products, blood products and medical devices, guidance on the quality of organs, tissues and cells, and voluntary codes of practice.

Certain stakeholders attempt to define a clear regulatory terrain for TE technology, but market-building is characterised by uncertainty. Projections of potential market size vary enormously, and business models are unclear. Information on market size of existing products was difficult to obtain. Uncertainty also exists around reimbursement and appropriate evidence for risk/benefit assessment.

Since 2002 the EU/EC adopted a new directive 'Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells' (TCD - 2004), and developed different versions of a 'Proposal for a Harmonised Regulatory Framework on Human Tissue Engineered Products' (TER 2004/5), the latter still under consultation at the time of writing. Most recent draft proposals would bring TE and cell therapy products under medicinal product legislation.

Stakeholder participation, values and interests

A plurality of interests of different stakeholders negotiate around TE. The primary interactions were 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 had weaker representation. Institutionalised bioethics opinion (in the form of EGE the European Group on Ethics in science and new technologies) had a formative influence on regulation for tissues and cells procurement. However, apart from matters of donation, the not-for-profit principle and consent, the ethical positions on the acceptability of certain human tissue technologies of concern to many MEPs were excluded from TCD under the subsidiarity principle.

In the UK, members of the British Association of Tissue Banking played a strong part in the development of the Code of Practice on Tissue Banking together with the Department of Health and regulatory agencies. Some UK scientists expressed concern about their lack of involvement in consultations on its implications. The voluntary 'Code of Practice on Humanderived Therapeutic Products' (2002) emerged from consultation at national, European and world-wide level, with the (then) Medical Devices Agency and representatives from industry playing a leading part. These policy initiatives embody a regulatory distinction between the 'banking' issues of sourcing and storage, and product approval and market issues. However, this distinction is not clearly defined. This template has been reproduced in the EC approach to regulation of tissues and cells and TE.

TE did not have a controversial general public profile. We observed a 'partitioning' process that can be regarded as a strategy to inoculate

TE against the infection of controversy. A 'technocratic' model of the regulatory process would suggest the predominance of a discourse of technical safety. While such concern is paramount in TE, this does not do justice to the complex dynamics of TE governance

Key interests of stakeholders existed in tension. Commercialisation and market-building, human rights and public health ethics, disease risk-aversion, national regulatory institutional tradition, evidentiality and regulatory policy progress, are core interests. Public health and commercialisation/promotion of trade represent pivotal values which inform much regulatory discourse and between which policymakers try to negotiate. The impact of public health crises such as BSE and HIV blood-contamination has been weighty in EU debate.

Re-configuring regulation

The distinction between autologous /allogeneic technologies was key to the regulatory debate in Europe in 2002-4. The definition of 'engineering' the degree and type of manipulation applied to tissues or cells was crucial as new configurations of regulatory authority were negotiated (developments in 2005 emphasize the scale of production). Possible institutional arrangements for marketing authorisation and production quality assurance include the central European Agency for the Evaluation of Medicinal Products (EMEA), or linked 'centres of excellence' located across Europe. The availability of limited technical expertise was a concern in these debates.

There was convergence and tension between tissue banking and tissue engineering. While originally envisaged as regulating tissue banks the scope of the TCD was extended to include all 'tissue establishments' thus widening the reach of the regulation and promoting 'a level playing field' as desired by the industry sector. The tissue bank community lobbied strongly to resist convergence with commercial tissue engineering, disputing the need for a 'third pillar' of TE-specific product regulation.

Support for a new TER was 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.

National interests and different state institutional arrangements for managing healthcare products were 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 UK Committee for the Safety of Devices has TE on its agenda.

Overall there is increasing stringency in accountability, evidence, reporting requirements and standards for quality and safety, extending from collection, procurement and storage of human material to manufacture and global distribution.

Conclusions and Implications

TE comprises hybrid technologies evoking complicated regulatory activity which tries to balance a variety of national, transnational and sectoral interests. There remain major uncertainties in market-building, health risk and in the technical profile of TE technologies. It 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 cultures of existing regulatory agencies.

The European Commission promotes transnational technical standards over ethical standpoints. Regulatory harmonisation in Europe is taking the form of a framework which allows some national variation. The emerging governance distributes accountability between national and EU authorities while in principle tightening control over sensitive matters. There is increasing 'purification' of regulatory standards.

The effect of regulatory variation in the EU upon innovation and competitiveness of the trade area is negative but is difficult to assess in detail. EU actors perceive lack of competitiveness in

Comparison to the US. Lack of consensus on appropriate evidence bases for TE technologies means that public healthcare systems are not yet, in general, eager to adopt them.

The regulatory identity of TE technologies was unclear. Blurred boundaries between tissue banks and manufacturers means tension between public sector collection and donation of tissues and cells, and commercial exploitation of TE technologies. Lack of regulatory expertise is a block to innovation. A regulatory patchwork and conflicting expectations lead to a perceived limited, skewed and delayed diffusion of TE.

The new regulatory developments are protective of public health, in principle, but as always this is balanced by the motivation to promote technical innovation and markets. The regulatory process for TE technology continues to evolve. Further study is needed to capitalise on the findings summarised here.

About the Project

The study focused on knee cartilage regeneration, skin systems, bone and blood vessel applications, and the broader range of TE encompassed by formal regulation. This includes technologies not yet in the healthcare system. It was necessary to understand technical aspects of the sourcing and mode of production of different applications. Factors affecting the participation of diverse stakeholder groups, and their discourses, values and interests were identified. Analysis of how projections of risk and benefit shape regulatory policy, product testing and evaluation, standards, and clinical practice was carried out. We explored the implications for healthcare practice, public health and innovation.

The study took place during 2002-4 and lasted 27 months. The research team members combined the disciplines of sociology, science & technology studies, and bio-engineering. An advisory group included clinical, industry and political science viewpoints. We undertook: (a) a Europe-wide questionnaire survey of regulatory agencies (12 out of 17 countries responded); (b) 63 interviews amongst strategically placed regulators, EC/EU officials, expert policy advisors, scientists, industry regulatory affairs and other staff, trade associations, consumer organisations, and clinicians; and (c) the collection of documentary materials including drafts of EC regulatory texts, EU parliamentary debates, position papers, UK and other codes of practice and professional guidance, industry marketing material, and scientific accounts. All members of the team undertook some interviews. Apart from the UK, interviews were conducted in countries including Denmark, France, Germany, Italy, Sweden, Belgium and the Netherlands. Some were conducted with members of the European Commission and European Parliament. Few 'consumer' interviewees were identified, pointing to the low public profile of existing products. We also observed meetings of regulatory policy networks, including an industry-sponsored 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 procurement directive; British Association of Tissue Banks Annual meeting; European Commission 'Stakeholder Conference' on proposed product approval regulation.

An extensive bibliographic database was constructed including policy-relevant documents, clinical research reports, commentaries on regulation and the TE field, and theoretical material. Interview transcripts and associated fieldnotes made by the research team for each interview were entered into Atlas-ti qualitative data analysis software, forming a dataset that continues to be used for further analysis and dissemination work. The project team made valuable contacts with a wide range of the stakeholders in TE-related regulatory policy formation in the EU and UK, the project became widely known amongst these networks, and acknowledged as making a valuable contribution to the debate in the field. We made numerous conference presentations to diverse audiences, and continue to produce publications based on the research.

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