

Scientific Report on Exploratory Workshop

'Regulation and Governance of Human Tissue Engineered Products in Europe'

held at the University of West of England, Bristol, UK. June 23rd-24th 2004
(EW03-189)

1.0 Executive Summary

This workshop brought together participants from eight countries with expertise and interests in the areas of sociology of health, science and technology studies, political sociology, political science, bioethics, health economics, political economy, social history, regulatory affairs and tissue banking. The aims of the workshop were:

- To share information about technological changes in the area of human tissue engineered medical products and markets for these products,
- To explore current understandings of regulatory policy as it relates to these products and regulatory activity in this area,
- To identify appropriate theoretical tools that may be used to analyse regulation and governance of human tissue engineered products in Europe,
- To develop research questions and methodological approaches for further exploration of the relationship between regulation, governance and innovation of human tissue engineering in Europe.

The workshop sought to address these aims through three paper sessions. The first, *Regulation and innovation in human tissue engineered products*, comprised presentations on a UK funded project looking at the regulation of tissue engineering in the EU (Alex Faulkner et al), and *The Regulatory history of a tissue engineered product* from an industry perspective (Phil Brown). This set the scene for a discussion of the relation between innovation and regulation, analysis of current policy initiatives to prepare new EU legislation for human tissue engineered products and factors shaping the emerging regulatory order. Tissue engineering technologies may be seen as at the borders of current regulation of healthcare products. Industry has lobbied for new regulations to assist in bringing innovative products to market and to reduce obstacles which arise as a result of national variation in policy. While market projections are uncertain, and the potential therapeutic benefits of these products are yet to be assessed on a large scale, the initial success of a small group of products has been seen as inhibited by the absence of pan-European regulation and associated with this, difficulties in securing reimbursement through national healthcare systems. This is a highly contested area, in so far as there is an unclear definition of what is tissue engineering, diverse predictions about the potential of the technology to address public health needs and lack of successful business models for the industry.

The second session sought to develop an analysis of regulation and governance in different sectors. Extensive research carried out by Abraham, was presented in a talk on

Pharmaceutical regulation in the EU. The ways in which political interests lie at the heart of regulatory science were highlighted, for example how the work of EMEA as the regulatory authority mediates national interests as part of the regulatory decision making process. This in turn raises doubts about the claims to a universalistic science, and challenges conventional models of regulatory science. Inter-agency competition for regulatory business creates a climate where there is a pressure away from increased stringency in drug assessment and lowering of standards. In an analysis of *Medical device governance in the EU* Altenstetter explored the different history of device regulation, the move to a harmonised approach during the 1990s and importance of post marketing surveillance systems in different national contexts. Her study of adverse incident data highlights differences in implementation of the harmonised approach, and she identified specific ways in which the UK medical device governance is distinctive.

In the third session the focus of the workshop shifted to think about the procurement and banking of human tissues and ethical aspects of tissue engineering. In a presentation by Loty on *The impact and results of the authorisation procedure for tissue banks in France* the regulation of tissue banks was explained. This illustrated growing attention to the regulation of human tissues and how national regulatory frameworks have been set up to regulate tissue banking. This is alongside the emergence of new EU legislation on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (the Tissue and Cells Directive) (Directive 2004/23/EC). In France ‘tissue engineering’ is not a recognised concept, and there is a strong view that all tissues and cells are now well regulated and with minor adjustments the existing medicinal product, medical device and Tissue & Cells Directive is a sufficient basis for control over all ‘tissue engineered products’. Distinctions between autologous and allogenic products according to such a view can be addressed within this framework without the need for a further EU directive or regulation. Continuing the theme that these technologies are based on the manipulation of body parts, the final presentation by Derksen on *Remaking the Body* pointed to important ethical and philosophical issues. Specifically an ‘engineering’ approach sees bodies as made rather than born, and boundaries between human and machine, human and animal may be seen as challenged by such developments. In the laboratory setting scientists seek to produce bodily norms and may be seen as engaged in a form of ‘body politics’.

In a wide ranging discussion many questions and issues emerged with scope for further research and investigation. These included consideration of the relation between ethics and regulation, comparison of pharmaceutical, medical device and tissue engineered product regulation, how national and supranational interests are represented in different sectors, the accountability and transparency of regulatory systems, public involvement in regulatory policy debate, the privatisation of knowledge and commercialisation of body parts and an economic analysis of tissue engineering product markets. As a group of researchers important links were established and a special edition journal issue is planned to help set out more comprehensively the research work currently being undertaken in this area and potential avenues for further inquiry.

2.0 Scientific Content

2.1 *Background*

The emergence of innovative technologies using human tissue is the subject of much scientific discussion and debate. Scientific journals report on the development of new techniques for manipulating and processing human tissue and the potential for new therapeutic applications. According to some commentators expectations for such therapies are high and the promise of tissue engineering as a form of 'regenerative medicine' which assists and enables the body to repair itself represents a new and exciting era that builds on recent developments in cellular biology, material science, chemical engineering and medicine. The field of tissue engineering therefore brings together new disciplinary alliances and the new expertise is being built up in academic and commercial environments.

Based on this promise investment in research & development has been substantial (Lysaght & Hazlehurst 2004) and commercial enterprises have promoted products in order to open up new markets worldwide. A recent study of today's markets funded by the European Commission identified the main areas of application for the technology as skin, cartilage, bone, cardiovascular substitutes, organs, nervous system and soft tissue (Husing et al 2003). However as the authors point out existing products on the market are limited to skin, and cartilage (and to a limited extent bone) (2003:10). Despite methodological difficulties in defining what counts as 'tissue engineering' and accessing market data this study provides the most comprehensive analysis of today's markets for these products in Europe available. They note that in Europe greater emphasis has been placed on the development of autologous products compared to the US where allogenic products have been marketed. The value of products relates to 'quality of life' rather than patient survival, and tissue engineering product markets are more focused than those for pharmaceuticals (2003:15). Moreover, in the most developed market, for skin systems as treatment for chronic wounds and burns, profitability of products has been a key issue in the face of reimbursement difficulties leading to bankruptcy of two US companies (Advanced Tissue Sciences and Organogenesis) (see also Bouchie 2002). Current evidence suggests that the tissue engineering industry is in very early stages of development and that economic environments are contributing to difficulties in growing markets as well as new products, though some analysts remain optimistic about long term prospects (Lysaght & Hazlehurst 2004).

It has been argued that these human tissue engineered products currently fall outside existing regulatory frameworks for medicinal products and medical devices and that in the absence of pan-European regulation national approaches to them are diverse and complex. They present new challenges and issues for regulators. Specifically these include issues relating to the sourcing, traceability, storage, testing, and safety. Current discussion amongst policy makers, regulators, industry and others, suggests ways in which risk management and quality systems may be adapted to provide quality assurance and protect public health. The recently adopted EU Directive on *setting standards of quality and safety for the donation, procurement, testing and processing storage and*

distribution of human tissues and cells provides a new framework for the regulation and management of ‘tissue establishments’ including not for profit tissue banks, for profit banks and commercial manufacturers (Directive 2004/23/EC). This legislation, to be implemented by April 2007 in all member states, may be seen as representing a tightening of controls over the procurement and storage of human tissues. Its passage through the parliamentary process was relatively smooth aided by the decision to allow member states authority to implement additional restrictions on the collection and use of specific cell types. This principle of subsidiarity sought to address differences regarding ethical concerns. Its scope and application to ‘manufactured’ or highly manipulated human tissue engineered products remains somewhat contentious and has fuelled debate about the need for further pan- European legislation directed at such products.

A new EU Tissue Engineering Product Regulation is currently under preparation. Following a consultation exercise in 2002 (DG Enterprise 2002) DG Enterprise have been engaged in the drafting of a new regulation which is expected to focus on the manufacture and distribution of human tissue *engineered* products. At a stakeholder meeting in Brussels in April 2004 an outline of the regulation was presented and further web-based consultation took place over subsequent weeks (DG Enterprise 2004). The proposals were for a regulation to cover both autologous and allogeneic human tissue engineered products and for standardised products, products for a limited number of patients or for a single patient. *Engineering* in this draft “means any process whereby cells and tissues removed from a human donor (source materials) are substantially manipulated, so that their normal physiological functions are affected” (2004:7). On the demarcation between this proposed regulation and Directive 2004/23/EC it proposed that the latter would apply only to the donation, procurement and testing of cells and tissues and that a clear borderline between these two pieces of legislation “requires that the term ‘engineered’ be precisely defined”(p8). Proposals to transfer some products from the somatic cell therapy annex of the Medicinal Products Directive (2001/83/EC) were also outlined and where human tissue engineered products are used in combination with a medical device the Medical Devices Directive will apply to the device. With respect to market authorisation suggestions were for a two tier approach. A centralised procedure centred around the EMEA for allogeneic products and nationally based approval for autologous products with the option to seek centralised approval if desired. Common guidance for all member states was proposed and a role for EMEA as providing scientific expertise, inspectors and a clearing house.

There are a variety of tools within the social science which may be useful to assist in analysing and understanding the emergence of a new regulatory regime for human tissue products. As Kent et al note in a forthcoming paper (Kent et al forthcoming) Vogel (2001) and others have suggested that we are witnessing changes in the political culture of biotechnology governance in the EU and that relationships between EU institutions may be characterised by competitiveness. Suggestions that we are moving away from a model of technocratic decision making based on regulatory science towards ‘a participative ethos’ have identified changing relationships between science, industry and state regulation. For example, Salter and Jones argue that ethical concerns and the role of the consumer-citizen, rather than a focus on promotion of innovation and industrial

development, have been increasingly influential in the area of human genetics. They suggest that the rise of bioethics may be seen “as a countervailing force to the imperatives of economic progress in the political culture of EU regulation, its embodiment in international agreements and its expression in institutional arrangements, raises some intriguing questions regarding its capacity to act as a political broker in governance disputes” (2002:338). On the other hand, Abraham and Lewis (2002) argue that in the area of pharmaceutical regulation, despite consumers’ growing activism, there is minimal decline in producer power or medical authority and that Europeanisation of regulation has led to a form of highly organised neo-liberal corporatism. Based on an analysis of recent events surrounding the use of breast and hip implants, Kent and Faulkner (2002) suggest that (at least in the UK) we may be witnessing a more user-oriented, if not socially participative, approach to medical device regulation. Thus it appears unlikely that a single unified trend in the societal structures of contemporary biomedical governance, across different types of technology, risk or industrial sector, can be identified. This makes it particularly important to analyse the association between governance formations and specific technological fields. The workshop was directed towards assisting in this regard, to provide an opportunity for researchers to engage directly with questions around the regulation and governance of human tissue engineered products, to share information and work towards developing a research agenda for further social scientific investigation.

2.2 *Regulation and Innovation in Human Tissue Engineered Products*

In this session **Alex Faulkner** (Cardiff University) presented an UK Economic & Social Research Council funded collaborative project (with Julie Kent, Ingrid Geesink & David FitzPatrick) which aims to:

- analyse trends in regulation, governance and evidential processes in relation to the challenge of TE technologies;
- explore the implications of trends in TE technologies for the regulatory environment and healthcare governance and vice versa;
- and examine the implications for healthcare practice, public health, innovation and competitiveness.

He explained the difficulties in defining what is ‘tissue engineering’ and how different definitions have different meanings and champions. Examples of TE products such as skin systems (eg Apligraf, Dermagraft, Transcyte, Vivoderm), knee cartilage regeneration (eg Carticel, OsCell), bone regeneration (eg Healos) and potential applications for vascular prostheses, organ-assist device and others were briefly outlined. In mapping out ‘the EU regulatory jigsaw’ and ‘UK regulatory jigsaw’ Faulkner et al elaborated on the existing regulatory framework and recent initiatives at both EU and UK level to develop new regulation and controls for human tissue and tissue engineered products. Most importantly at EU level, Annex 1 of Medicinal Products Directive 2001/83/EC for cell therapy medicinal products, the CPMP Points to Consider on xenogenic cells, gene therapy, the TSE Directive, and Tissue and Cells Directive (2004/23/EC), provided a background for discussing the positioning and governance of TE technologies. In the UK context, the UK Code of Practice for Tissue Banks (Medical Devices Agency 2002), Code of Practice for Human Derived Therapeutic Products and other guidance documents characterise a regulatory environment that is in a state of change and flux.

In reporting on work in progress to analyse the project findings Faulkner et al identify a range of key points which included:

1. Contested definitions of ‘TE technologies’ as a regulatable zone with blurring of sectoral boundaries.
2. Conflict over ‘regulatability’ for example in relation to the Tissue & Cells Directive the exclusion of ethical positions on grounds of subsidiarity.
3. Variation in national policy positions regarding tissue based products, a ‘regulatory vacuum’ and absence of pan European controls.
4. Boundary issues of *supply* of human tissues and cells and *engineering* products/services.
5. Tension between ‘banking culture’ and ‘commercial standards culture’; blurring of public and private.
6. Autologous/allogeneic distinctions: contested projections of market and risk.
7. Fluctuating market projections
8. Unclear public image of TE.
9. Regulator/industry affiliations and limited pool of expertise relating to TE in regulatory institutions and some member states.
10. Scandal landmarks in TE policy discourse around BSE, HIV blood.

11. Ethics – participation of specialist publics’ and industry ethics voices.
12. Growing recognition of the policy neglect of the hospital sector as a site of ‘engineering’ activity.
13. Regulatory reach includes ‘the fridge’ (in hospital clinics), the ‘garage’ and the world ie from small laboratories and tissue banks to global manufacturers.
14. UK quality systems approach and regulatory framework of EU
15. Pre-emptive influence of UK actors
16. National vs transnational (EU) interests and regulatory infrastructures (cf autologous vs allogeneic).
17. Tension between public health/competitiveness agendas evidenced by the roles and activities of different EC Directorates.

Identification of these key points led to a discussion of the approaches to analysis being developed within this project, using data to illustrate insights gained. These focus on the need to analyse the role of the regulatory state and governance, how issue and policy networks and strategic alliances shape the regulatory environment, the politics of participation and representation of different interests. Faulkner also illustrated ways in which TE regulation is ‘co-constructed’ as a regulatable field in the discourses of trade organisations (eg EUCOMED), regulatory professionals, national representatives and others. He briefly outlined approaches to analysing risk and benefit of TE technologies and the implications of regulatory change for public health, healthcare systems and innovation/competitiveness.

Phil Brown (now at Quintiles Consulting and formerly Regulatory Affairs Manager Genzyme Europe) gave a view of industry’s experience. He described the first generation autologous tissue engineering product for repair of focal defects in knee cartilage- Carticel. A surgeon takes a biopsy from the knee and sends it to Genzyme in the US where cells are isolated, cultured, returned to the surgeon and implanted in the same patient. This technique, known as Autologous Chondrocyte Implantation (ACI) requires training for surgeons and is dependent on the expertise and skill of surgeons using it. It is a costly procedure. Genzyme was the first company to develop the technique following the earlier work of the Swedish group led by Lars Petersen. Good Manufacturing Practices (GMP) requirements were applied and since 1997 when Carticel first became available industry has worked with the US regulator, the FDA, to develop Good Tissue Practices (GTP).

In Europe, he suggested that rather than a regulatory vacuum there are lots of national regulations. This is labour intensive for industry to understand and requires companies to negotiate with national regulators to get products to the market. From an industry perspective there is a need for harmonisation and pan-European regulation. Consumer protection legislation applies to all such products. Genzyme, like other multi-nationals, needs nationally based regulatory expertise to assist in effective marketing of its products. The different levels of information and requirements work against multinationals developing services for autologous products.

In his view cell culturing is not rocket science and has been widely practiced for many years leading to what he described as ‘cottage industries’ that are located within local hospitals often funded by government grants and subject to few regulatory controls. This has a detrimental effect on multinational companies such as Genzyme who currently have to compete on rather different terms.

Regarding clinical performance of ACI, data produced can not be presented in traditional ways as for medical devices or drugs and industry has had to work with regulators in developing an understanding of what might be accepted as evidence of clinical efficacy. TE products are frequently regarded as ‘development’ products. This in turn makes reimbursement via national health care systems difficult to obtain. Industry therefore, including Genzyme, have lobbied strongly through trade associations such as EUCOMED for new regulation and have sought to educate regulators about the prospects for tissue engineering. Specific patient groups have lobbied for access to TE products. However such products remain expensive compared to more traditional treatments though Carticel, if compared to costs associated with knee replacement is very competitive.

Emerging issues and questions

1. The new Tissue and Cells Directive being implemented over the coming two years will rely on the comitology procedure for the development of technical standards. Such a committee process may be regarded as a ‘closed shop’ – there are issues about who gets to participate in this process and appropriate expertise is needed.
2. In the context of post-normal science how are the benefits of TE applications to be assessed? Is it in relation to therapeutic effect with clinical benchmarks? Is efficacy and effectiveness at the population level?
3. To what extent does it make sense to talk of a regulatory vacuum rather than regulatory freedom, why is regulation seen as helpful and necessary – to open up markets?
4. While hopes and expectations for TE seem high how can the market for TEPs be assessed and how far does the regulatory environment inhibit innovation, development and marketing of such products?
5. Are products or processes patentable given the reliance on surgical competence for example? What does this tell us about the privatisation of knowledge, the patentability of human tissues and the claims by industry to ‘add value’ to tissues through the processes of manipulation and cell culturing?
6. In what ways is risk reallocated from the public to private and how are risks understood in relation to TEPs?

2.3 *Analysis of regulation and governance in different sectors*

John Abraham (University of Sussex) introduced his talk with a review of the conventional model of science and politics in regulatory settings. In this model politicians introduce legislation creating regulatory agencies to enforce it. Regulatory agencies develop science-based regulatory standards for risk-benefit assessment and regulatory scientists apply these standards to individual cases and recommend decisions or policies on ‘acceptable risk’. Politicians ‘rubber stamp’ or reject these recommendations. In relation to pharmaceutical regulation technoscientific systems contribute models of drug toxicity and efficacy derived from animal testing, models of drug dosage and pharmacokinetics from trials with healthy people. In addition models of safety and therapeutic effectiveness are derived from double-blind clinical trials and models of adverse drug reactions are derived from post marketing surveillance systems. From another perspective there are different interests at stake including the interests of patients and public health, commercial interests, institutional interests of regulatory agencies (both national and supranational) and professional interests of expert scientists. He argued therefore that the conventional model of the relation between science and politics is flawed since interest politics strikes at the heart of regulatory science. Interest politics can influence regulatory decisions by its involvement in the establishment of ostensibly science-based regulatory standards, the selection and construction of datasets and the interpretation of evidence.

The role of regulatory agencies (eg. EMEA, CPMP) and the structural features of pharmaceutical regulation in Europe were outlined. The CPMP while comprised of experts also seeks to represent national interests through the selection of rapporteurs. The payment of fees for services provides incentives for retention of high quality staff and both national and supranational interests compete within this arena. Claims are made for a universalistic science underpinning regulatory decisions, but in reality political processes shape outcomes. There is inter-agency competition for ‘regulatory business’ and speed of approval times is emphasised. Approval times may be seen as being given greater priority than the quality of the assessment. There is pressure to approve applications unless there ‘are grounds for supposing the authorisation may present a risk to public health’ which contrasts with comparative efficacy/benefit considerations. Abraham presented evidence that indicates that there is a pressure towards lowering of standards associated with this system. National regulators (for example Sweden, Germany) are forced to accept products which they might otherwise not have approved. This relates to the emphasis on getting products to market rather than harmonisation to promote safety standards. Inter-agency competition for regulatory business creates a climate where there is a pressure away from increased stringency in drug assessment. Abraham demonstrated how testing requirements under ICH standards have been reduced.

While there has been increased transparency of EU drug regulatory decision-making information provided is discretionary and citizens’ do not have right of access to information. European Public Assessment Reports (EPARs) on products are produced by the EMEA as an output from the centralised procedure, itself both a political and

scientific process. It can therefore be argued that regulatory science is not as open to public scrutiny as some might claim and that commercial interests dominate decisions about access to information. Science therefore may be seen as beyond the scrutiny of the community though the more vigilant citizen may be better informed. Finally a distinction must be made between regulatory standards and regulatory outcome since standards are interpreted by regulators and differences in interpretation are possible.

Christa Altenstetter (City University New York) gave an overview of the historical development of medical device regulation in Europe. Pan-European medical device regulation is younger than the more established pharmaceutical regulatory system. Implementation was across member states from 1993 but although harmonisation was promoted there was fierce competition between France, Germany and the UK who fought to defend national rights. Directives had to be transposed into national legislation and there has been a long learning process associated with the regulation of this sector. In the preparation of the directives she suggested that the Commission and industry had delayed the process of considering public health concerns emphasising trade issues rather than the regulation of risks. The directives had provoked controversy in some countries. Post marketing surveillance is a key feature of the regulatory system and her study of adverse incident data reveals interesting national differences. Notably there is higher reporting of adverse incidents in the UK and France, relatively low reporting in Germany. There is enormous diversity in medical devices which are classified using a system of risk categories (Class 1 low risk- Class 111 high risk).

In developing a comparative analysis of medical device regulation in Europe Altenstetter examined what is distinctive about the governance and regulation of devices in the UK. The National Health Service (NHS) is the largest purchaser of medical devices and healthcare provider. As a tax-based health care system with a key role for General Practitioners it is an important market for medical devices. It is also a preferred site for the conduct of clinical trials and outcome studies because of access to the national population. It is also a leader in the collection of epidemiological data and has some national registries. The clinicians and professional interest groups are well organised through the Royal Colleges and other institutions. The UK regulatory authority is relatively well resourced compared to other states, has a higher staff capacity, provides comprehensive guidance on adverse incident reporting, a high level of transparency, high volume and good quality information. Ethics committees have had a key role in the approval of clinical investigations.

According to Altenstetter national and commercial interests are mediated in a number of ways. There is a strong research base in the UK, but weak product development and marketing. Instead there is a reliance on foreign manufacturers. Good co-operation between industry, government, the NHS and private or charitable organisations characterises the UK environment which is not typical of other EU countries. She presented data to illustrate these points. Most recently a review of the work of notified bodies (which award the CE mark to products and are licensed by the regulatory authorities) has questioned their competencies (leading to the establishment of an

oversight group NEBOG). There are national variations in relations between regulators and the notified bodies in each member state. A new EU evaluation system has been set up, initiatives to promote e-labelling and a new IPR framework. Exchange of information between member states has been encouraged and the UK has been active in this regard.

Emerging issues and questions

1. How do interests shape regulatory decisions and what is the relation between science and politics in the different sectors?
2. Can lessons learned from pharmaceutical regulation and medical device regulation be applied to the emerging regulatory regime for tissue engineered technologies?
3. In both sectors discussed regulation is directed at building markets for drugs and devices and health and safety issues appear in tension with, or indeed secondary to this. In this the case in relation to TEPs?
4. At the national level of implementation and adverse reporting how do political cultures affect the approval and reporting process?
5. Is it the case that in relation to drug regulation there is evidence of standards going down but in device regulation standards have gone up (given the different histories of each sector) and if so what does this imply for standards for TEPs?
6. The structure of the pharmaceutical industry is different, (more multinational) from medical device sector so does this different structure impact on regulation in particular ways?
7. While there is provision for borderline products to be regulated under the current MPD and MDD how might tissue products with a scaffold for example be regarded – as a borderline between device and something else?
8. The role of EMEA is well established in the area of pharmaceutical regulation but its operation as the regulatory body for TEPs raises questions about the balance of expertise within and across member states. How far such a centralised procedure is perceived as diluting national standards could be a concern.
9. Public confidence in the market or new products may be linked to public involvement in what ways is public involvement in the developing tissue engineering regulation likely to foster such confidence?

2.4 *Philosophy, politics in tissue banking and tissue engineering*

Bernard Loty (Medical Director Etablissement Francais des Greffes) presented a discussion of the impact and results of the authorization procedure for tissue banks in France. He reviewed the legislative framework in France which includes laws on Bioethics (1994), Cell & Gene Therapy (1996), Public Health Safety (1998), Customs regulation relating to import and export of organs, tissues and cells (Law no 92-1477 art 18/19 1998; Decree April 1996). These laws set out the role and responsibilities of the regulatory agencies, protect donors, regulate procurement, promote safety, authorise importation, control transplantations and regulate tissue banks. A series of decrees to regulate tissue banks set quality standards, distribution rules, authorisation processes and requirements for adverse incident reporting. With the development of this framework there has been a decline in the number of tissue banks in France and Loty presented data on the current distribution of banks for different tissue types noting especially the shortage of skin banks in some regions. This change in the pattern of tissue bank facilities may be seen as the effect of stricter regulation and the need for authorisation and licensing of the banks leading to the closure of many smaller banks. Tissue banks are geographically spread, may be located within or outside universities and while most are public not for profit, there are five for profit banks.

In the French context tissue banks are recognised as engaged in activities which may include ‘high technicity’ products. However no distinction is made between tissues and cells and in France there is no such thing as ‘tissue engineering’ rather it makes sense only to talk of tissues and cells some of which are more complicated or have ‘high technicity’ compared to others. But all tissues and cells are regulated in the same way and according to Loty there is no need for further EU regulation since the Tissue and Cells Directive (TCD, Directive 2004/23/EC) has now been adopted. In this analysis of the EU regulatory framework, Loty recounted the history of debate within EU relating to human tissues. The lack of agreement regarding their inclusion in the Medical Device Directives meant much time was lost in debate. Article 152 of the Amsterdam Treaty set high standards for quality and safety of organs and substances of human origin and in 1998 the European Group on Ethics (EGE) stated that there was an urgent need to regulate human tissues in the EU market. A series of meetings in Paris, Porto and Malaga led to the drafting of the TCD and in a short time the directive has been adopted and is to be transposed by April 2006. Highlighting key features of this new directive, Loty pointed to the emphasis on donation, procurement and testing, and the inclusion of different tissues and cell types (including stem cells and reproductive cells). Frontiers with existing medicinal product and medical device directives are defined and he explained the relation to the MPD Annex 1 on Advanced Therapy Medicinal Products. The applicability of this annex for human cells was explored and questions asked about the need for another directive for Human Tissue Engineered Products. Such questions turn on debate about the extent of manipulation of tissues and cells, the appropriateness of the authorisation procedure (for example where autologous products are for one patient), the ‘mode of action’ and functionality of the products. Based on his experience in France, Loty argued strongly for further modification of the TCD to include a centralised procedure for

autologous and allogenic products *without* batch production, and in combination with biomaterials (that is in combination with current Medical Devices Directive MDD). For allogenic products with serial risk (batch) he would support their inclusion within the Medicinal Product Directive. In sum therefore, according to this view, there is no need for another Directive to regulate Human Tissue Engineered products separately. In the interim France authorises the importation of some ‘tissue engineered’ products through tissue banks, under its tissue bank legislation.

‘Remaking the Body’ was the title of the talk by **Mechteld-Hanna Derksen** (Eindhoven University) about her PhD research in the Netherlands. Her work is located within the broad area of science and technology studies and comprises an ethnography of tissue engineering in the laboratory. While ‘tissue engineers’ are sometimes accused of playing ‘God’ engineers stress the huge potential benefits of their technology. Derksen highlighted the dual character of tissue engineering. First its technological character which emphasises what can be made – a ‘bionic human’ with engineered mechanical parts such as heart valves (the focus of the laboratory which she is studying). Second the notion that the body is self healing – as a leading scientist says in defining tissue engineering as ‘the persuasion of the body to heal itself through the delivery to the appropriate sites of molecular signals, cells and/or supporting structures’ (Williams 1997). Derksen noted however that confusions arise from this dual character which Thacker (2002) also identifies ‘the confusions that result are that the body supposedly benefits from technical intervention, while all the time remaining a “natural” biological entity that is unmodified by technology’. The focus therefore of Derksen’s study is the question ‘how does the research practice of tissue engineering remake the human body and human embodiment?’

Her early observations of the scientists and laboratory work highlights the attention being given to improving mechanical characteristics of the scaffold (supporting structures for tissues) and mechanical stimulation (to model the function of valves). The scientists seek to identify the ‘right properties’ (eg. elasticity, stiffness, degradation rate), to use natural valves as a model and consider quality and regulatory issues. Derksen argues that tissue engineering raises questions about norms for bodies, and that the human body becomes less distinctively human. While creating an autologous substitute for a natural tissue suggests that the body does not change by tissue engineering she argues that the ‘remaking’ of tissue implies making a new version that differs from the original. The body is no longer just born but also partly made. Research practice therefore means creating norms for the body and so tissue engineering can be described as a form of body-politics. Moreover in her discussion of the laboratory work the boundaries between human and animals appear to dissolve and she draws on Donna Haraway’s notion of a cyborg to think about these processes. In important ways therefore tissue engineering may be seen as going beyond biomedical engineering and the professional responsibilities of engineers linked to their activities in ‘remaking the body’.

Emerging issues and questions

1. Is there a need for a further EU Directive on Tissue Engineered Products or can existing regulation now be modified and applied to such products? While the EU Commission (DG Enterprise) have devoted effort to preparing a draft directive can a consensus be reached on the need for further legislation?
2. What might be the impacts of tissue bank regulation and licensing in other member states compared to experience in France and will export and importation of tissue and cell products be facilitated by the Tissue & Cells Directive?
3. Will 'combination products' using human tissues be accommodated in similar ways to combination medicinal product/medical devices or under separate regulation?
4. Are tissue banks' and tissue engineering manufacturers' activities converging and if this is the case what are the implications of convergence?
5. Is public response to donation affected by emerging legislation?
6. How are ethical values shaping regulatory processes and scientific practices? To what extent are ethical issues addressed in different forum and in what ways does scientific discourse legitimate scientific practices?

2.5 *Roundtable discussion*

A wide ranging discussion amongst workshop participants explored some of these emerging issues and questions and other aspects. The extent to which we are witnessing a process whereby new regulation aimed at opening up new markets for tissue engineered products will lead to a growth in applications and therapies was debated. Pressures for regulation have largely been driven by industry efforts to bring innovative products to market, but scientific and economic issues surrounding the development of new applications, effective business models, reimbursement policies and clinical demand for products are in flux. The sector is very young and the technology while showing promise is still untested, that is applications in many areas have not yet been clinically tested or evaluated. Different time frames therefore seem important to different social groups. While scientists take a longer term view, industry and regulators are concerned about marketing and safety of products already available. Investment in product development is expected to follow, associated with growing expertise and knowledge about the technology. Public participation in debate around human tissue products has been relatively low, especially compared to the profile of debate around xenotransplantation, and the human genome project. Frequently ethical debate has been ruled out even though in other forum ethical procedures have been formally built into the political process (for example the role of EGE and ethical review of embryonic stem cell research by DG Research). Evidence from studying the pharmaceutical industry suggests that greater public accountability and stakeholder involvement reduces potential for sensationalist stories and controversy. Furthermore greater transparency and public participation can assist in defining and reallocating risk.

3.0 Assessment of the results and contribution to the future direction of the field

The purpose of this exploratory workshop was to contribute to the dialogue across Europe about the implications of these technological changes and to promote social scientific understanding of the links between regulation and innovation in this area. Our aims were to:

- To share information about technological changes in the area of human tissue engineered medical products and markets for these products,
- To explore current understandings of regulatory policy as it relates to these products and regulatory activity in this area,
- To identify appropriate theoretical tools that may be used to analyse regulation and governance of human tissue engineered products in Europe,
- To develop research questions and methodological approaches for further exploration of the relationship between regulation, governance and innovation of human tissue engineering in Europe.

Many aspects of technological changes in this field and the economic factors shaping the development of markets for 'human tissue engineered products' (HTEPs) were considered. The expertise of the workshop participants and knowledge of regulation and governance issues relating to the fields of pharmaceuticals, medical devices, tissue banking and tissue engineering together with insights from industry, clinical practice and tissue engineering in the laboratory produced a high level of exchange of information. The specific details of emerging regulatory policy for tissue banking in Europe and proposals for a new regulation for HTEPs were analysed with reference to the empirical work being carried out by a number of workshop participants funded by the UK Government, EU Commission and others. It was evident that analytic and theoretical tools employed to explore relations between the regulatory state, industry, consumers and medical practitioners in other sectors (especially medical devices, pharmaceuticals, human genetics, xenotransplantation) have potential value for explicating processes shaping the regulation and governance of HTEPs in Europe. In particular the role of interests in shaping regulatory decisions, challenging claims to a universalistic science and the dynamics of relations between the national and supranational level have utility for examining current initiatives relating to the governance of human tissues and tissue engineering. Important linkages were made between ethics, values and technology. These relate to concerns about the privatisation of knowledge, intellectual property and patenting of human tissue, commercialisation and commodification of the body and remaking bodies. The institutional incorporation of ethical review procedures and ethics groups within the EU bureaucratic process was noted. Discussion also highlighted the value and importance of a historical understanding of the development of different sectors' markets and regulatory profiles and relations between institutions and the structuring of healthcare product fields. In addition the relatively low public profile of tissue engineered products in the context of the alleged 'public confidence' role of regulation was considered important.

Finally, a number of questions for further research and range of methodological approaches were identified. While the focus of EU research funding has been in developing the technology itself scope for additional social scientific research was highlighted in a number of areas for example:

- Investigation of the relation between ethics and regulation in this field;
- A comparison of regulation and governance of the pharmaceutical, device and tissue engineering sectors;
- Comparison of regulation and governance of specific technologies;
- Analysis of policy and issue networks shaping tissue engineering;
- An socio-economic analysis of tissue engineering markets;
- An international comparative analysis of tissue engineering in different EU countries
- Study of the implementation of risk regulation of tissue engineering products in Europe as technologies develop.

3.1 *Comments from participants on the workshop:*

After the workshop all participants were invited to submit a short comment on the proceedings and workshop outcomes. The following submissions were received.

Michael Nusser (Fraunhofer ISI, Karlsruhe, Germany): The future of Tissue engineering

Tissue engineering (TE) is an innovative field with a dynamic scientific-technological development. Although future developments seem promising, they are highly uncertain. At present safety standards for human Tissue-engineered products (hTEPs) differ widely in Europe with potentially harmful consequences for patients' health. A hTEP regulation in this early stage of TE development could provide a reliable and stable framework for all players in the TE innovation system. It gives a good idea of the requirements that have to be met if hTEPs are to be commercialized successfully within the European Community. Sufficiently high standards regarding safety, quality and efficacy of hTEPs could ensure patient's and public health. This will increase trust in TE and hTEPs in general, and thus contribute to increased investment in the field in the medium to long term. Given the infant stage of the TE sector the additional expenses for a hTEP specific regulatory framework and infrastructure could be understood as "an investment into the future".

With respect to the **design of a hTEPs regulation** "hTEP specificities" and "requirements depending on risk" should be taken into account in order to avoid conflicts with medicinal products and medical device regulation and prevent ineffective or inappropriately high regulatory requirements. The regulation in its present draft form specifies only the essential requirements but leaves it to the applicants how to meet these requirements. This avoids barriers for innovation activities and ensures technological flexibility. Such a framework will require guidance (developed by EMEA) which is based on scientific criteria for proving quality, safety and efficacy of hTEPs without compromising the objectives of the regulation of simplicity, accessibility and effectiveness. This guidance should be developed in a transparent process which draws on the best available expertise from science, authorities and industry. Public and ethical issues (e.g. traceability vs. patients' interests of confidentiality and anonymity) should also be taken into account.

The success of a hTEP regulation depends on the milestones and quality targets of the **implementation** plan. A true harmonisation of standards in all EU Member States and for all players (companies, tissue banks, hospitals) is important. All TE players (regulatory authorities, hTEPs manufacturers, upstream and downstream players, staff and committees involved in clinical trials, medical staff involved in TE treatments, investors and reimbursement institutions) should be informed, educated and trained in a timely and comprehensive manner about the regulation. Reduced requirements for low-risk hTEPs, measures targeted at resource-poor applicants such as small and medium-

sized companies (e.g. funds for dossier preparation, R&D programmes for clinical trials), and a service orientated "one stop shop" approach in regulatory bodies (e.g. no need to submit the same information for several regulations) should alleviate administrative burdens and costs for applicants. Effective and efficient organisational structures, procedures and instruments should guarantee good communication and direct interaction mechanisms between authorities and different TE players and should foster innovations. Continuous monitoring and evaluation of the implementation process could identify best practices and could support the initiation of effective and efficient mutual learning processes within the EU Member States.

A regulation and its implementation is only a necessary prerequisite for promoting the TE sector but is not sufficient. In addition, an active development of **attractive features of the hTEP demand and supply side** is necessary if the EU is to become a lead market for TE. Achieving fair reimbursement conditions for hTEPs (this requires assessments which show the relative benefits of hTEPs, e. g. evidence of efficacy, cost-effectiveness and superiority over conventional therapies) are of vital importance for the small and medium-sized TE companies with limited resources. Agreements between the EU and other non-EU countries (e. g. EU/USA, EU/Far East countries) and R&D, marketing and distribution cooperations between TE companies and large pharmaceutical companies are also necessary in order to exploit the potential global market volumes of hTEPs. European standards must be enforced in the whole TE value chain and an "EU TE quality sign" should be actively marketed within and outside the EU. Furthermore, a close cooperation and integration of different policies (e.g. interdisciplinary TE research programmes) which are supported by all relevant stakeholders and encompass the entire TE innovation system is a success factor for a fast growing TE industry in Europe.

Christa Altenstetter (City University New York, USA)

The regulatory regimes for pharmaceuticals and medical devices were established at different time periods internationally, and in Europe. The pharmaceutical regime has been evolving over three decades and is embedded in well-established global regulatory practices, international protocols, and institutional arrangements. In the case of the EU, pharmaceuticals were regulated prior to the creation of the single European market in 1985 and extended afterwards, and completely overhauled in 2003. By contrast, medical device regulation, which now also covers IVD-devices is fairly recent in most countries in Europe, and is entirely embedded in the creation of that market. (Historically, the few countries that regulated IVD products did so under a pharmaceutical regulatory regime.) Consequently, the institutional arrangements and regulatory causal mechanisms differ for medical devices and pharmaceuticals, but they have in common that they are unusual consumer products with a potential to harm humans which justify stricter regulation. In both sectors regulation is highly knowledge and problem-driven.

With sources of risks the focal point of regulation, rather than the facilitation of trade and access to markets, the sources of risks point to a wide range of stakeholders with different political, economic and professional interests and public and private healthcare responsibilities. Several sources of risks can be distinguished, each raising public and private issues in healthcare responsibilities and involving a range of different stakeholders, including patients, the regulators, manufacturers, medical technology representatives, scientists and clinical innovators abiding by the scientific rationality of their respective discipline. The systems for managing health risks are complex and are contingent upon the governmental, economic and political circumstances of each country and typically distinguish between effective regulatory controls in pre-market and post-market phases.

Five clusters of ideas and practices are pertinent to medical device regulation: issues of quality, safety, performance, clinical evaluation (efficacy), and the conduct of clinical investigations constituting the core agenda around which the global, regional and national regulatory discourse, decision-making, and conflict management over the prevention of risks take place.

Proposed topics for comparison:

- What does regulation and governance actually mean in various product sectors represented by the workshop participants, and what are their essential features?
- Is there such a thing as a ‘universal’ regulatory science, and what is its role?
- How to explain a few paradoxes emerging from a comparison of a two-tiered pharmaceutical regime and the medical device regime subject almost entirely to national controls, and what are their implications for public policy and research?
- With implementation the weakest link in the EU regulatory chain in most product sectors, what are the core features of *problem*-oriented implementation strategies and post-market surveillance and medical vigilance practices in different product sectors and across the member states? What characteristics should an effective implementation strategy to secure the prevention of risks?

Maarit Heinonen (Biokemian ja mikrobiologian laboratorio, Finland)

Regulation of tissue engineered products is quite challenging. At present there is no consensus on whether the products should be regulated on the same basis as medicinal products, or as medical devices. It has been suggested by the industry that the regulation should be based on the regulation of medical devices, as there are many similarities in these products. Also medicinal regulation has been considered technically and economically too challenging for TE products. However a question was raised amongst workshop participants, whether regulation based on notified bodies would guarantee a uniform regulation for these products. In my estimation a centralized regulation would be best way to guarantee harmonized regulation. Although member state regulation is based on EU directives, there are always differences in the implementation and interpretation of the directives. If autologic products are left to member state based regulation, as the current scenario proposes, care should be given to implementation of directives and education of both regulators and health care sector to guarantee uniform safety and efficacy of treatments.

Another important issue raised by workshop participants was the impact of ethical questions to regulation. It was first suggested that ethical issues should be left outside of regulation, as it is hard to find EU wide consensus in these questions. However it was pointed out that these questions can not be left without notice in the preparation of legislation. Questions about donor selection and donors rights as well as acceptability of embryonic stem cell lines and commercialization of these are of central importance in TE and should be discussed accordingly. The workshop felt that ethics should be included in legislation process and the issues should be publicly discussed. Closely related issues of patenting and reimbursement should also be discussed in this context. For development of viable commercial TE products it is highly important, that all these three – patenting, regulation and reimbursement – are functioning and predictable. To guarantee this discussion should be active and open. Otherwise future ethical assessment may be unforeseeable and diverse.

Mechteld-Hanna Derksen (Technical University of Eindhoven, Netherlands)

Reflections on the workshop suggest that the role of ethics may be even more complicated than we discussed. Ethics is portrayed as seen as a separate subject. For example the idea that ethical positions can be excluded on ground of subsidiarity. This would suggest that what is regulated at EU-level is not normative. However questions faced by the EU like whether the main concern is with markets or with public health, point to a different direction. Formulation of regulation in either terms is related to visions about the good in life (aren't most or all political questions also ethical of nature?) So how do people work around the ethics involved? Which questions are dealt with by recognising them as having an ethical component and which not?

With regard to the role of time, it was suggested people have different time frames in mind. Patients are interested in solutions today, scientists in long-term developments etc. What is the EU regulating: what is possible; what is thought to be possible in short, medium, long-term or maybe more backward looking not all that is possible, but just some parts of it? It seems to be a mixture. So a question to ask is why are they regulating what (at this point in time). For example, industry stimulates the regulation of the putting on the market of products available in short term. But are there also products regulated that are most certainly not available in say 10 years? If so, why and on whose initiative?

The distinction between transparency and access to scientific information seems very important. Transparency is related to the process. However, I understood that the people involved in the process may be little knowledgeable about the field. If we (general public including scientists) agree to the rules (process), this does not imply we also assume that the actors involved are capable of applying those rules. So access to information is not only related to issues like autonomy and informed-decision making, but also to the verification of the process (e.g. where the research results interpreted in the right way).

3.2 FURTHER OUTCOMES

A special edition journal issue is planned for 2005 which will build on the papers and discussion from the workshop and an appropriate journal is being identified for this purpose. The following workshop participants have agreed to contribute:

John Abraham

Christa Altenstetter

Mechteld-Hanna Derksen

Alex Faulkner & Julie Kent

Maarit Heinonen

Linda Hogle (unable to attend workshop)

Michael Nusser & Barbel Husing

4.0 Programme

Workshop Programme

1830hrs ARRIVAL - Wednesday 23rd June at *Holiday Inn, Filton, Bristol*.

1900hrs DINNER - at *Holiday Inn, Filton, Bristol* for participants.

THURSDAY 24th June at University of West of England, Bristol.

The workshop will cover three areas and will comprise short presentations by a number of participants around the topics identified. The roundtable discussion will draw on the expertise of the full range of the group by seeking to identify key areas for further investigation, assessing the utility of available analytic and theoretical concepts for understanding regulation and governance of HTEPs.

0900hrs Introduction and welcome by ESF representative.

0915hrs – 10.30hrs

Regulation and innovation in Human tissue engineered products (HTEPs)

(Chair Julie Kent)

- Regulation of tissue engineering in the EU

Alex Faulkner

- Regulatory History of a Tissue Engineered product

Phil Brown

Coffee

10.45 – 11.45hrs

Analysis of Regulation & Governance in Different Sectors

(Chair Julie Kent)

- Pharmaceuticals Regulation in the EU

John Abraham

- Medical Device Regulation in the EU

Christa Altenstetter

11.45-12.15hrs

Discussion

Lunch

1.15- 2.15hrs

Philosophy, Politics in Tissue banking and Tissue Engineering

(Chair Naomi Pfeffer)

- Tissue banking in France – a case study (Bernard Loty)
- Human Tissue Technologies and Values (Mectheld-Hanna Derksen)

Tea

2.30–4.30hrs

Roundtable discussion (Chair Peter Glasner)

END

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5.0 Statistical information

Gender

18 Workshop participants – 10 men and 8 women

Countries of employment¹

8 countries represented – Austria, Finland, France, Germany, Italy, United Kingdom, Netherlands, United States.

(Participants from Spain, Portugal, Norway and United States who had accepted invitations were unable to attend due to unforeseen circumstances.)

Age distribution

Data on age was not available for all participants so estimated in some cases.

Under 30 years of age – 4 participants (3 women, 1 man)

30-40 years of age - 2 participants (1 man, 1 woman)

40-50 years of age – 3 participants (1 woman, 2 men)

Over 50 years of age – 9 participants (3 women, 6 men)

Professional standing

3 Phd Students

1 Post doctoral researcher

8 Established professionals/academics

6 Professors

Acknowledgements

I would like to thank the European Science Foundation for supporting this workshop and all those who attended and contributed to this lively and productive event.

Dr Julie Kent
Scientific Convenor
University of the West of England
3 September 2004

¹ Note some participants nationality was different from their country of employment.

Annex 1

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