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RISK REGULATION OF TISSUE ENGINEERING IN THE EU

A POLITICAL ECONOMY OF MEDICINE

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Additional declaration

The empirical data on which this thesis is based were mostly collected as part of the project Tissue Engineering Regulation and Governance (TERG), funded by the ESRC/MRC under the Innovative Health Technologies (IHT) programme. Based at Cardiff University, I worked as a research associate on this project from September 2002 to September 2004, together with Dr Alex Faulkner (Cardiff University), Dr Julie Kent (UWE, Bristol) and Dr David FitzPatrick (UCD Dublin). I was involved in the study design, organisation of fieldwork, collection of data, project-specific analysis and writing up of the data. I undertook additional data collection and analysis beyond the scope and timeframe of this project, with guidance from my PhD supervisors.

Some of the material contained within this thesis has previously been published in the following papers, and has been referenced where appropriate:

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Summary

Tissue engineering is an emerging biomedical innovation surrounded by potentiality and risk. Based on documentary analysis and expert interviews, this study discusses different constructions of risk according to main constituencies (scientists, clinicians and manufacturers), the way they prioritise and balance these risks, and how issues are framed as problematic or not. Complexity and uncertainty are the main drivers in this exercise, interpreted in terms of boundary drawing around contested risk domains. This is followed by a discussion of the translation of risk into regulatory policy, by focusing on two recent legislative initiatives by the European Commission: one to control the quality and safety aspects of human tissues and cells (DG SANCO Directive) and the other to facilitate the marketing of tissue engineered products in the EU (DG Enterprise Regulation).

These two legislative initiatives aim to overcome the current regulatory lag in Europe, where tissue engineered applications are either unregulated or subject to a broad variety in national controls. This situation is problematic for manufacturers wanting to market their products in Europe, for regulators in evaluating the risks of these technologies and defining an appropriate approval route, and for patients in terms of unequal access to potentially beneficial therapies across the continent.

Firmly rooted in ambitions to make the EU a techno-scientific and bio-economic powerhouse, regulation of this domain is troubled by competing agendas of promoting trade versus protecting public health. Social and ethical considerations about the impact of tissue engineering technology allow a reconsideration of the bio-society as alternative model, taking into account the technological as well as social character of innovation.

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List of abbreviations

ACI	Autologous Chondrocyte Implantation
BSE	Bovine Spongiform Encephalopathy
CAT	Committee for Advanced Therapies
CE mark	Conformité Européenne (Conformity with EU law)
CHMP	Committee for Human Medicinal Products
COR	Committee of the Regions
CPMP	Committee for Proprietary Medicinal Products
CT	Clinical trial
DG Enterprise	Directorate General Enterprise & Industry
DG SANCO	Directorate General for Health and Consumer Protection
EATB	European Association of Tissue Banks
EC	European Commission
EGE	European Group on Ethics in Science and New Technologies
EFTA	European Free Trade Association
EMEA	European Agency for the Evaluation of Medicinal products
EUCOMED	European Medical Technology Industry Association
EuropaBio	European Association for Bioindustries
EP	European Parliament
ESCs	Embryonic stem cells
ESC	Economic and Social Committee
EU	European Union
FDA	Food and Drug Administration (US)
GMOs	Genetically modified organisms
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
GTP	Good Tissue Practice
HTEPs	Human Tissue Engineered Products
MD	Medical Device
MDD	Medical Devices Directive
MEP	Member of the European Parliament
MP	Medicinal product
MPD	Medicinal Product Directive
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OECD	Organisation for Economic Co-operation and Development
R&D	Research and Development
RCT	Randomised Controlled Trial
SCMDMP	Scientific Committee on Medicinal Products and Medical Devices
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SMEs	Small and Medium Sized Enterprises
TE	Tissue engineering
TEMPs	Tissue Engineered Medical Products
TSE	Transmissible Spongiform Encephalopathies
OECD	Organisation for Economic Co-operation and Development
WHO	World Health Organisation
WTEC	World Technology Evaluation Centre
WTO	World Trade Organisation
XTP	Xenotransplantation

Introduction

Biotechnology policies and sciences

This thesis is about science and politics, and about the political economy of medicine. More specifically I am concerned with the negotiated boundaries between domains of risk and regulation of an emerging technological innovation called tissue engineering. These themes are studied with reference to the European Union (EU). This chapter introduces the policy scene and gives a brief outline of techno-scientific factors in the development of tissue engineered applications.

The European context: On bio-economy and bio-society

The main context to consider the policy shaping and decision-making around tissue engineering is provided by a long EU tradition to promote trade and technological innovation. Only more recently health and safety regulation has entered the equation. The European Commission plays a peculiar double role in this constellation. First and foremost the Commission functions as promoter, sponsor and facilitator of biotechnology in Europe. At the same time the Commission, as main legislative body at this level, acts as regulator of this domain. This dual objective is significant for the shaping of a regulatory regime in tissue engineering, which is why this section discusses this context in more detail.

> The bio-economy is one of the oldest economic sectors known to humanity, and the life sciences and biotechnology are transforming it into one of the newest (DG Research 2005: 2).

This wisdom sets the scene for a discussion on European policy objectives. During a high-level conference organised by the Commission's DG Research in September 2005, some 400 delegates from across the world discussed the 'knowledge-based bio-economy'. Knowledge, it was argued, has become an

extremely valuable economic resource, which would put Europe at its most competitive edge. 'In a global economy, knowledge is the best way to increase productivity and competitiveness and improve our quality of life, while protecting our environment and social model,' in the words of EU Science and Research Commissioner Janez Potočnik (DG Research 2005: 1). The main drivers for this competitiveness and growth agenda are the life sciences and biotechnology, a sector estimated to be worth over 1.5 trillion euros a year. With the United States, Japan and China already in the front seats of these bio-economies, it was declared that Europe should redouble its efforts to not lose out on the competition, to pick the 'fruits of a revolution' and bring prosperity to the citizens of Europe.

While the concept of the knowledge-based bio-economy was presented as new, the rationale behind it was not.

From its early inception, the EU has always been largely conceived as an economic unit, with a longstanding tradition of promotion of trade in a single European market. The proclaimed significance of biotechnology in fostering competitiveness is not novel either, as it has been part of the EU's long-term strategic challenge. Biotechnology has been conceived as a broad category in this respect, extending from the traditional focus on agriculture and food ('green' biotech, such as genetically modified crops) to also encompass 'red' biotechnological applications in biomedicine. Arguably this last category is becoming increasingly important for the bio-economy, where biotech applications in pharmaceuticals are joined by the 'new frontiers of medicine' such as gene therapy, therapeutic cloning and regenerative medicine including tissue engineering. This interest should be considered in the shadow of large controversy over genetically modified organisms (GMOs) as exemplar for green biotech - which the Commission typified as the weakest link in the biotech spectrum, as this controversy slowed down innovation and is held responsible for a brain drain of agricultural researchers to destinations outside the EU.

The term 'bio-society' was introduced by the 'Forecasting and Assessment in Science and Technology' programme, better known as FAST, which was initiated in 1978 to build a community method for planning and forecasting new

technologies (Abels 2002). This term emphasised the social as well as technological aspects of the applied life sciences (which included agro-food and healthcare), arguing the case for full awareness of 'life in all its forms if we are to use and manage the biosphere in a productive and sustainable way' (Green 1984: 9). Thus the bio-society was defined as:

> A society based on the conscious management of self-organising systems for the sustenance and enrichment of human life and purposes (Green 1984: 9).

FAST was the first EU programme to address long-term R&D priorities in biotechnology with the formulation of a 'Community strategy for European biotechnology' (1982) laying down the basic principles for an integrated European policy in this domain. With the bio-society notion the FAST group presented a model in which ecological modernisation of the West had to be integrated with the needs of developing countries (Commandeur et al. 1996). With its orientation on stressing social demands, the impact of the FAST message was initially limited because it clashed with the general enthusiasm for biotech potential among conservative governments in the 1980s (Abels 2002). It did have a significant influence though on the initiation of European biotech programmes over the next decades.

From these early developments the dominant frames of biotechnology became clearly visible. Biotech was seen as the driving force for innovation and a fundamental tool for socio-economic development. The economic base of contemporary society would be considerably boosted by the scale and potential of biotech applications, providing incentives for the new accumulation of investment capital to re-establish economic growth. It was also envisaged how biotechnology leads to increased competition between industries involved, both over expanding domestic markets in EU Member States and to capture export markets. The international division of labour was to be shifted within the Community and on a global scale. Finally biotechnology was presented as solution to global problems, where especially third world countries would benefit from the new applications to ease deficiencies in food production, health, energy and environmental problems (Green 1984: 10-12).

This vision was also evident from another early initiative, a report on international trends in biotechnology compiled by a group of experts for the Organisation for Economic Co-operation and Development (OECD). This report is drenched with statements on the future value of biotechnology to society and industry, where especially the financial benefit of biotech applications for the healthcare market is emphasised (OECD 1982). Furthermore the advantages for developing countries are exemplified, where 'it should be pointed out that research and development in industrialised countries of the North can be applied *mutatis mutandis* in developing countries to confront the major strategic problems of energy, food, fertilizer and health' (OECD 1982: 20-21).

The OECD report furthermore outlined the need for more R&D investment and for education and manpower in biotechnology, while substantial changes were predicted in industry-university relations and in the ways in which research is funded in the light of a growing venture capital market. Finally, and interestingly, the issue of safety regulation is addressed. The OECD states how 'public safety must be a prime concern, of course' and how all countries should have regulations for health and safety at work and for the protection of the public and their environment. Typically, the economic and innovation objective should not be hampered in this endeavour:

> Increasingly demanding legislation and excessively restrictive regulations must be avoided as these will impose major constraints on developments in biotechnology (OECD 1982: 55).

Thus the emergence of biotechnology was presented as of significant value to the global economy and world well-being. Some critics review this development in terms of 'competing images of science', most notably in relation to advances in genetics and biology which were expressed as a second industrial revolution that would transform economy and societal futures at large (Kearnes et al. 2006: 17). Projections of future imagined worlds, driven by both scientific and social imaginaries, were dominant – and for that matter continue to shape new scientific fields. It was at a time, in the 1980s, when Monsanto was still going to provide environmental friendly solutions to world hunger and poverty, and the new genetics would overtake traditional modes of production. Signs of the early rise of technocapitalism were acknowledged later (Suarez-Villa 2001; Suarez-Villa 2003).

It was in this context of an economy of hope (Helen 2004) that the European Commission kept faithful to its mission for biotech support. Since the early 1980s the EU has invested heavily and increasingly in the promotion of biotech, with major research funds and European framework programmes put in place.[1] While the initial funding programmes focused on agricultural applications and food, in the late 1980s biomedical applications could count on increasing EU support. This coincided with an extended involvement and remit of the EU in public health research, which was previously largely based at individual Member State level. For example BIOMED 1 was launched in 1990 to provide Community support and training in human genome research, disease prevention and a range of therapeutic applications (including cancer, cardiovascular and mental disorders). With a budget of US$ 166 million this programme ran till 1994, when it was followed up by BIOMED 2 (1994-1998). In these years an important shift took place, reflected in the substantially increased budget to US$ 415 million under this research programme, where public health was considered a new market for the proliferation of European competence in biotech. Under BIOMED 2 more research activities were funded and new priority areas identified, including pharmaceutical research and biomedical technology and engineering (Commandeur et al. 1996).

Notwithstanding these 'good intentions' for EU biotechnology support and facilitation, the envisaged sustainable bio-economy was not a reality yet towards the turn of the century. Competition on a global level was more difficult to achieve than originally envisaged and 'just delivering basic agricultural

[1] For example the Biomolecular Engineering Programme (BEP) was established in 1982 as the first biotechnology programme, mostly focused on agriculture and food, with a budget of US$ 20 million. This was considered low in comparison to budgets of individual governments in EU Member States, which totaled some US$ 200 million for biotech R&D over the years 1982-1983. Over the same period the USA invested US$ 335 million. The BEP was continued as the Biotechnology Action Programme (BAP). Implemented in 1985, with a four-year budget of US$ 74 million, BAP was established to stimulate a European research network between universities, other publicly funded institutes and industry, and extended its research areas to enzyme engineering and bioinformatics. The BAP was unsuccessful due to limited funding and lack of industry involvement (largely due to conflict of interest on confidentiality rules). Next was the Biotechnology Research for Innovation, Development and Growth in Europe (BRIDGE), which ran from 1990-1994 with a total budget of US$ 123 million, focusing more on industrial applications. BIOTECH 1 (US$ 229 million) running between 1992-1994 as a supplement to BRIDGE, and BIOTECH 2 (US$ 681 million) as the follow-up for the period 1994-1998 were additional examples of specific programmes for biotech R&D funding (source: Commandeur et al 1996).

commodities' had to be complemented with 'a sound institutional and financial framework' (DG Research 2005: 3). A holistic approach was needed where the bioscience sector was supported with investment, while all stakeholders involved – including industry, regulators and consumers – were called upon to make the bio-economy work. The rise of counter-movements against nuclear energy and biotechnology in the 1980s had to be channelled towards the economic growth agenda. For a long time these critical voices were considered to be based on insufficient (if not lacking) knowledge about the benefits of biotechnology, and the EU's technology policy was hardly touched by popular dissatisfaction in these days. This technocratic attitude changed significantly after the BSE crises, the controversy over GMOs and the discussion on biotechnology patents (Borras 2003). Only during the last decade the innovation agenda has opened up to include questions of risk and social sustainability. Social and ethical considerations became instrumental in creating a common vision; science had to deliver what 'the people' need in compliance with an acceptable ethical consensus.

The new millennium brought a new impetus to the competitive knowledge-based bio-economy. In March 2000 European leaders met in the Portuguese capital to set the goals of what became known as 'the Lisbon Strategy'. The European Union set itself the ambitious strategic goal 'to become the most competitive and dynamic knowledge-based economy in the world' by 2010 (Commission of the European Communities (CEC) 2001: 3). As part of its aim to make the biotechnology sector in Europe more competitive and to foster research in this area the Commission adopted the 'Life Sciences and Biotechnology Strategy' in January 2002. By stressing the benefits of biotechnology the Commission hopes to promote a revival for European industry, arguing how prejudice against biotechnology could be contra-productive for Europe by missing out on jobs, growth and prosperity. While recognising public debate and ethical concerns in this domain – the document speaks of the need for 'responsible governance' in harmony with societal values - the strategy is interlarded with actions that underline the commercial potential and need for economic growth.

Because after Lisbon the EU was still lagging behind its major competitors in terms of R&D investment, EU leaders agreed in Barcelona in 2002 to increase the financial support from 2 to 3% of the EU's collective gross domestic product by 2010. A few years later, in March 2005, a mid-term review of the Lisbon agenda led to a relaunch of the strategy where 'knowledge for growth' became the focus of European research policy (DG Research 2005).

These developments accumulated in the latest European Framework Programme (FP7), the main EU programme for Research, Technological Development and Demonstration (RTD) which will run between 2007 and 2013 with an overall proposed budget of 72.5 billion euros. The main aim of this programme is to contribute to sustainable development within the context of promoting high level research (CORDIS 2005). The EU's annual research budget was proposed to be doubled in order to achieve the strategic goals for a knowledge-based bio-economy. As such, FP7 explicitly reflects the importance of biotech in the health domain.[2] Once again the healthcare market was declared a strategic part of the bio-economy.

Against this background of a strong EU push for biotechnology and life sciences in order to make Europe a world-leading economic and scientific powerhouse, we can consider the other responsibility of the Commission, namely in controlling the safety and marketing requirements of the fruits of biotechnology. While chapter two provides the European regulatory context for tissue engineering, where tensions become visible between the long standing trade objectives and the more recent EU involvement in health and safety regulation, the next section discusses the scientific background of one particular exemplar of biotech: tissue engineering. The EU context is crucial for understanding both the development and regulation of tissue engineering, and is important for any discussion of biotechnological innovation. It flags up issues of risk and safety, of commercial endeavours and technological innovation, and relates to many of the social and ethical considerations that have become

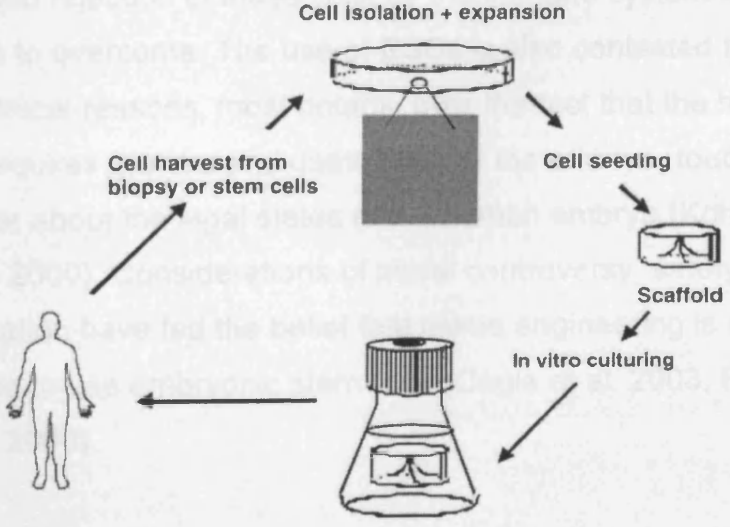
[2] The bulk of the funding goes to so called collaborative research, which is divided in thematic priority areas, the first two of which include health (€8.3 billion) and Food, Agriculture and Biotechnology (€2.4 billion). The health priority has as objective the improvement of health of European citizens as well as increasing the competitiveness of European health-related industries and businesses. Biotechnology is mentioned as first strand of research for project funding under this heading (CORDIS 2005).

central to discussions about European biotechnology. The focus of the next section is on 'the science' of tissue engineering, while also introducing broader issues of a socio-political nature to lay the groundwork for my further analysis.

Tissue engineering technologies

This section gives insight into the technological and scientific aspects of tissue engineering technology, which is relevant for understanding the issues around risk regulation and the expertise needed to evaluate the technology. Particular definitions of risk and safety, and the drawing of boundaries around criteria of efficacy and cost-effectiveness feed into the debate on regulatory policy formation in this domain. The expression of social and ethical concerns in this context is based on techno-scientific factors in the ongoing development of tissue engineering technology. To get to grips with these underlying issues, some understanding is needed of the making of tissue engineered applications, and the associated risks in the trajectory from cell sourcing and culturing in the lab to logistics and final implantation into the patient.

The basic premise of tissue engineering is to combine appropriate cells with a material under conditions that lead to tissue formation (Lavik and Langer 2004). The figure below shows the general principles of the technology (Stock and Vacanti 2001):



Living cells are critical components of any tissue engineered application, and much ethical and social debate is driven by the cell sources used to build tissue engineered constructs. Cells sources for tissue engineering fall into three categories: autologous cells (patient own), allogeneic cells (from a human donor, but not immunologically identical) and xenogeneic cells (from a different species, e.g. animal). Applications currently in clinical use are mainly based on the first two sources, where cells are harvested by either taking a biopsy to obtain autologous organ-specific cells or by the isolation of stem cells. Experimental use also exists of the implantation of animal cells in humans, although debate is ongoing in how far this approach comes under the umbrella of tissue engineering. Chapter 10 discusses this issue in more detail.

Scientists are still struggling to define what exactly stem cells are (Lewis 2005), but they are generally considered to be the 'master' cells of the body, that have the capacity to multiply and differentiate into many different types of specialised cells and tissues. Stem cells exist at all stages of human development, from early embryos to foetuses to adults. In the context of regenerative medicine, two main categories of stem cells have attracted attention: adult and embryonic stem cells. Much research effort goes into finding ways to understand how a stem cell differentiates into a tissue-specific cell (Nerem 2000; Prelle et al. 2002; Sottile et al. 2003). On the clinical and safety level, the use of embryonic stem cells (ESCs) might be limited because of associated risks of developing tumours if the differentiation of the cells cannot be controlled appropriately (Ho et al. 2005). Also rejection of these cells by the immune system is a major scientific issue to overcome. The use of ESCs is also contested for socio-political and ethical reasons, most notably over the fact that the harvesting of this material requires the use and destruction of the embryo, touching upon the ongoing debate about the legal status of the human embryo (Koh and Atala 2004a; Young 2000). Considerations of moral controversy, safety, efficacy and resource allocation have fed the belief that tissue engineering is still a long way from being able to use embryonic stem cells (Cogle et al. 2003; Richards 2000; Royal Society 2000).

But scientific and public debate continues. In tissue engineering the boundaries between embryonic and adult stem cells are of major relevance for marking out the regulatory domain. Because of the legal constraints and ethical objections in many countries towards human ESC research, the use of adult stem cells has gained revived interest, because it is seen as a less controversial option (Henon 2003; Moreno-Borchart 2004). Illustrative of this development is the political rhetoric used by George W. Bush, threatening his first veto in May 2005 over the expansion of federally funded research on stem cells, where the US president announced: 'I'm a strong supporter of adult stem cell research, of course.' (Jasanoff 2005: 147). In July 2006 the President did indeed deploy his first veto in moral rejection of federal funding for human embryonic stem cell research.

Thus the consideration of which cell source to be employed is of key concern for tissue engineering technologies. There needs to be a sufficient quantity of supply and one that needs to be free of pathogens and contamination. One of the technological factors inhibiting progress in tissue engineering research in the past was the difficulty of growing cells in culture in quantities that are sufficient for transplantation (Koh and Atala 2004a; Koh and Atala 2004b). Furthermore, it has been demonstrated that immune acceptance is a critical factor, together with the biocompatibility (not causing any harm to the bodily environment, such as an inflammatory response). Autologous cells have the advantage of being immune acceptable, but are not readily available ('off-the-shelf') as the culturing of patient-own cells usually takes a few weeks. Allogeneic cells do not have this disadvantage, but may cause problems with immune acceptance. Also xenogeneic cells require engineering immune acceptance and carry a risk of transmitting animal viruses that needs to be overcome to provide a safe alternative – not to mention the ethical sensitivities around the use of animal sources. Traditionally the biological materials in tissue engineering are limited to autologous and allogeneic cells, generally of adult origin, which take different processing routes. This research demonstrates that the distinction between allogeneic and autologous cells is of key importance in the debate on risk regulation of tissue engineering, and has implications for clinical use and commercialisation of the technology.

Tissue engineering would provide an alternative for the treatment of end-stage organ failure and tissue loss (Langer and Vacanti 1999) and has been labelled 'second-generation organ transplantation', although the theories and techniques behind it differ substantially (Hogle 2003: 63). As with many upcoming fields, the technology is surrounded by promises and future potential:

> Tissue-engineered products open up a new way of treating diseases. The hope is that they deliver superior treatments, improving the speed, extent and duration of healing compared to conventional treatments. The overall aim of on-going research is to improve the performance of tissue-engineered products and to enlarge application areas (European Commission (EC) 2004).

But while the principles of tissue engineering have been applied to virtually every organ system in the body, to date only a handful of products have actually reached the market (Atala 2004; Bonassar and Vacanti 1998). Most advanced applications include skin systems for wound care (burns and diabetic and venous ulcers), cartilage repair (sports injuries) and bone regeneration (for orthopaedic and dental applications). Examples of specific product categories and their associated risks are provided in the chapters to come. In the pipeline are more experimental applications that may provide clinical solutions for diseases which could not be treated in a satisfactory manner so far, such as cardiovascular diseases (tissue-engineered heart valves, vessel grafts and heart muscle tissue) or neurodegenerative diseases (e.g. Alzheimer's and Parkinson's) and damaged nerve fibres and spinal cord injury (European Commission (EC) 2004). Other potential applications include whole organ replacement, such as kidney, bladder and liver, although this is thought to be even further down the R&D line.

It should be noted that under the generic definition of tissue engineering a broad range of different applications are developed and marketed, from relatively simple constructs in skin and cartilage to more complex tissues and organs. This diverse product portfolio has far reaching implications in terms of risk and safety classifications and demands different ways of evaluating clinical efficacy. Furthermore this hierarchy of multiple outputs affects commercialisation strategies. Tissue engineered products with life-saving properties are still in early phases of development, while products currently available have to compete with alternative conventional treatments, many of

which are more cost-effective and have already conquered a steady position in the market. Issues around clinical effectiveness of these applications have a direct link with the potential reimbursement of individual tissue engineered products, and are relevant for the broader discussion about regulation and governance of this technology.

Summary

This introduction has illustrated three main points. First of all, the EU has a longstanding tradition of promoting innovation and commercial development of biotech. Notions of the bio-economy and bio-society have become central to this understanding, illustrating emerging social demands for a sustainable future and the Commission's aim to integrate these in ambitions to make the EU a global competitor in science and technology – with the life sciences and biotechnology as main weapons in this combat. Finally, tissue engineering as one exemplar in this context allows the opening-up of this long-term discussion. This research shows how policy making in this domain is increasingly dominated by broader concerns about the appropriate tools for risk assessment and management, guiding expertise to evaluate this technology and in channelling the social and ethical implications of technology. The impact of biotech applications on society at large is renegotiated, while simultaneously the EU struggles with the inheritance of years of technocratic decision-making in this domain. The remainder of this thesis explains these processes and provides a context for considering tissue engineering as technological and social innovation.

1 Product cycles, boundaries and regulatory science

The life cycle of a typical tissue engineered product constitutes the opening section of this chapter, in order to demonstrate the key issues of engagement in this thesis. The conceptual approach to these issues is discussed next, followed by a statement of my research questions and an overview of the structure of the thesis.

1.1 Apligraf ® a case study

After the terrorist attacks on the World Trade Center in 2001, all available supplies of the living skin equivalent Apligraf® were donated to New York hospitals to treat the large number of burned and wounded victims (McIntire et al. 2002: i).

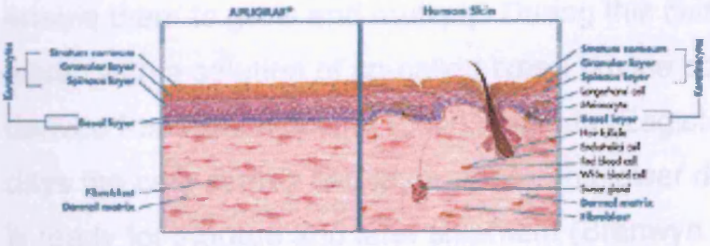
Apligraf entered the healthcare market in April 1997, when the Canadian Health Products and Food Branch (HPFB) was the first major regulatory body to approve the human skin substitute for use in healing venous leg ulcers, which are wounds caused by poor circulation in the legs (Branwyn 1998). In the summer it was launched by Novartis Pharmaceuticals Canada (Persidis 1999). In May 1998 the product received marketing clearance by the US regulatory authority FDA as a medical device for the treatment of the same condition. In June 2000 the company got approval to use the product for treating diabetic foot ulcers; chronic wounds that can take years to heal and sometimes lead to amputation. Several countries in Europe followed. Currently Apligraf has been used in 100,000 patients in the US alone, for the treatment of both venous leg ulcers and diabetic foot ulcers, and is marketed in a number of countries worldwide. In 2004 the reimbursement for the product in the US almost doubled, and not much later that year the company announced large-scale clinical trials to get regulatory approval for an additional three indications, including the treatment of bed sores (pressure ulcers), the improvement of skin

repair and reduced scarring in patients with deep second-degree burns and finally for cosmetic surgery (Organogenesis 2005a).

So what is new? Apligraf was the first mass-produced product containing living human cells and the first tissue engineered skin product commercially available for clinical application; a so called 'off the shelf' application for immediate use as a permanent dressing for non-healing ulcers. It consists of artificially-grown skin developed by the biotech corporation Organogenesis based in Canton, Massachusetts - and until mid 2003 licensed to marketing partner Novartis which also covered the European market. Also, Apligraf was the first mass-produced engineered body part to have been granted regulatory approval (Eaglstein and Falanga 1997, 1998; Trent and Kirsner 1998).

1.1.1 The lab

Years of research and development preceded the marketing approval. Apligraf, formerly known as Graftskin, is a bilayered living skin construct consisting of a dermis and an epidermis (Falanga 2000). The upper layer contains keratinocytes, the dominant cell type in the epidermis, which has protective properties and covers the dermis. The lower layer contains collagen and fibroblasts, the main constituents of the dermis, which is important for healing. Because the skin construct does not contain immunogenic cell types it is generally not rejected by the recipient (McCartney 1996).



Source: Apligraf website 2005

Apligraf is prepared from skin cells harvested from the foreskins of circumcised newborns (Waymack et al. 2000). A scientist involved in the development of Apligraf recalls how some hundred neonatal foreskins were collected from a Jewish hospital and how cell banks were set up in the US, with separate banks for the two skin type cells (fibroblasts and keratinocytes) that make up the bilayered human skin equivalent (M-EU6, 2003).

The baby's foreskin is considered an ideal starting material as young skin grows better, and is a readily available source obtained during routine circumcision. A commercial provider explains the technological benefits as follows:

> This starting material reduces variability by being derived from tissue that is the same age, sex, and anatomical location, and provides a fibroblast source with great proliferation potential, with one foreskin being able to produce starting cells for at least 250,000 feet of final tissue-engineered product (Naughton 2002: 374).

The amounts of skin to be produced in this way reach imaginary heights, although exact figures vary. According to manufacturer Organogenesis the cells from a single foreskin can produce 200,000 units of manufactured skin, enough to cover about 250 people (Branwyn 1998). Or translated into more marketable vocabulary:

> [I]t turns out that a small, postage-stamp-size piece of foreskin is enough to actually expand out to seven football fields worth of skin. (Brownlee 2001: 36; see also Van Valkenburgh 1996).

But the foreskin needs excessive processing before it can be used on the patient. First, the foreskin is decontaminated with antibiotics, antifungals, and an ethyl alcohol rinse. Next the cells are fed with nutrients and growth factors to enable them to grow and multiply. During this culturing process the cells are mixed with a solution of so-called type I bovine collagen, which is a material derived from foetal bovine (cow) placenta (Eaglstein et al. 1999). In about 20 days the cells form a two-layer upper and lower dermis and the skin construct is ready for storage and later shipment (Branwyn 1998). Over time, the donor cells from infant foreskins are replaced by the patient's own cells, and after several months none of the original graft DNA should be present anymore (Drug information online PDR 2002).

In order to provide an 'off the shelf' solution, the cell stocks are frozen in cryopreservation vials and stored in master cell banks for later use. After request by the physician Apligraf is packaged and sealed, and shipped via overnight courier for final use as permanent dressing on the patient (Organogenesis 2003). Once the production of a batch begins it cannot easily be halted so timing of the process is critical and has to be determined by planned delivery dates. The shelf life of the product is limited; the manufacturer refers to a '7 day shipping window', and advertises with a 'new 10 day shelf life' from the time of packaging. To maintain cell viability, Apligraf should be kept sealed and at the right temperature (20°C-23°C) until use. The manufacturer had to develop special 'shipping technology' to maintain the product quality; a small heavy gauge polyethylene bag with a heating plate to control the temperature in the container and to monitor the conditions during the transit of the product. The bag is sealed and comes with a so-called agarose nutrient medium, a gel-like solution that protects and nourishes the product, and a pH colour chart to check the pH of the nutrient medium upon arrival ('if the pH is yellow, return the product in a biohazard bag via overnight delivery'). The final product is supplied as a circular disk of approximately 75 mm in diameter and 0.75 mm thick, and each disk is intended for single use. Each piece of Apligraf can cover an area between 44 and 66 square centimetre (Thuesen 2001).

1.1.2 The clinic

Clinical use of Apligraf requires precision. The physician has to use a sterile instrument to remove the sheets from the container, in which Apligraf is packaged with the epidermal layer ('dull with a matt finish') facing up and the dermal layer ('glossy') facing down on a membrane. It should be applied to a clean wound bed with the dermal layer in direct contact with the wound surface. Air pockets or wrinkled edges have to be eliminated and extra product trimmed away. On top of that goes a dressing and gauzes as usual. Additional applications of Apligraf can be necessary, but should not be applied over areas of adherent product. As pointed out in the package insert, the safety and

efficacy of Apligraf have not been established for patients receiving more than five applications (Organogenesis 2003, 2005b).

The envisaged benefits for the patient of this technology are that Apligraf is not rejected and does not trigger an immune response. Other available alternatives are to transplant the patient's own skin (autograft) or to use donated skin (allograft), usually from cadavers (donor organs and bodies donated for science upon death) or animals that are anatomically close to humans such as pigs (xenograft). But not all patients have enough intact skin for autografting, and despite immunosuppressant drugs donated skin sets off an immune reaction in the recipient, which means the donor skin has to be replaced at some point and is only a temporary solution.

Apligraf is not indicated for use in all chronic wounds though, and currently only approved for the treatment of venous leg ulcers and diabetic foot ulcers - although it is also available in some countries for experimental use as part of a clinical trial, for example for burn wounds. These indications are specified in much clinical detail. A handful of clinical studies show the clinical effectiveness of the product for these particular applications. In addition to being immunologically inert (not clinically rejected), Apligraf is said to be easily applicable, to induce rapid healing, be less painful to the patient and particularly effective in hard to heal wounds.[3]

Also several studies show the effectiveness of the treatment compared to other alternatives available: Apligraf combined with standard treatment heals more diabetic foot ulcers faster than standard treatment alone, and Apligraf combined with compression therapy, heals more venous leg ulcers faster than compression therapy alone (Apligraf website, 2005). On the economic level, it has been argued that the use of Apligraf for treating hard-to-heal venous leg ulcers resulted in lower overall treatment costs (Schonfeld et al. 2000) and that the skin substitute is increasingly cost-effective over a longer analytic horizon (Sibbald et al. 2001).

[3] For reports on clinical effectiveness see amongst others: Alvarez et al. 1998; Banta and Kirsner 2002; Curran and Plosker 2002; De et al. 2002; Eaglstein and Falanga 1998a, 1998b; Fahey 1998; Kirsner 1998; Shen and Falanga 2003; Streit and Braathen 2000; Trent and Kirsner 1998; Waymack et al. 2000.

Apligraf is thus seen as example par excellence of technological superiority, as 'one of the most advanced organ constructs developed to date' and 'the most advanced bioengineered skin product' (Falanga 2000).

1.1.3 Outside the lab and clinic

So far the story of Apligraf has been a story of scientific endeavour and technological innovation. But there are also concerns, not the least in terms of risk and safety of products containing living cells. As one industrial scientist explains, who was involved in the development of Apligraf in the United States:

> I think it's because it's all so new, there are certain things that... well I mean we can go through the sort of hurdles that we had with Apligraf, because it was brand new and the Drug Administration [FDA] had big difficulties with it. Their main issues are that these cells will be harbouring some pathogen. And another issue was that these cells, because they are living and can reproduce themselves, could reproduce themselves without control, you know become a tumour and go everywhere and grow without limits. And kind of related to the pathogen one, was the fact that you can't sterilise these things, because you would kill them. So by definition you can't terminally sterilise them. (...) So there were these inherent risks, which is kind of unique for living products. (Manufacturer in tissue engineering M1, 2003)

Apligraf works by the grace of its living cells. To maintain cell viability, the product is aseptically manufactured, but not terminally sterilised. According to the manufacturer, Apligraf is shipped following a preliminary sterility test with a 48 hour incubation to determine the absence of microbial growth. The so-called USP sterility tests, which are considered the industry standard for final testing against contamination, are not performed on this product though because they require a 14-day incubation period - which is beyond the shelf life of the product. Thus the product is shipped just in time and implanted at a certain risk. For the same reason of time restraints, the testing on uniformity of the biochemical and biomechanical characteristics of the tissue from one lot to another often cannot be performed, which implies more rapid and less reliable testing than the standard.

Another safety concern is related to the clinical effects. Tumour formation, and carcinogenicity more general, has been addressed as a risk for many tissue engineered products. Tests on Apligraf have not revealed a tumorigenic potential of the cells contained in the device, but at the same time the manufacturer warns that 'the long term potential of skin cancers from these cells is unknown' (Organogenesis 2005b).

Furthermore, because Apligraf is made from human neonatal foreskin tissue, the foreskin donor's mother needs to be tested for human viruses. Currently these tests include antibodies to human immunodeficiency virus type 1 and 2 (HIV-1 and HIV-2), human T-lymphotropic virus type 1 (HTLV-1, which is associated with leukaemia cancer), hepatitis C virus (HCV), hepatitis B surface antigen (HbsAg), and syphilis. The screening of donors is to prevent microbiological contamination associated with the sourcing of the tissue, to control the possibility of viruses causing infectious diseases. But to prevent disease transmission, safety checks are also critical during the process of production and storage of the cells. The skin cell banks which are the source of the cells from which Apligraf is derived, are tested for human and animal viruses, retroviruses, bacteria, fungi, yeast, mycoplasma, karyology, isoenzymes, and tumorigenicity (Apligraf website, 2005). This is to make sure no contamination takes place during the production process, although the risk of this occurring is considered lower than associated with the source material. This mostly relates to personnel working in the laboratory handling and processing the cells, and the availability of a controlled environment with standard operating procedures and all kind of quality systems to prevent process-related contamination.

Next there is the safety control of the final product; according to the manufacturer, the final product is currently tested for 'morphology, cell viability, epidermal coverage, sterility, mycoplasma, and physical container integrity' before shipping (Organogenesis 2005b). This cannot rule out any adverse reactions at the receiver's end though, which made the manufacturer send out the warning that Apligraf is contraindicated in patients with a known hypersensitivity to any of the components of the Apligraf shipping gel.

As far as documented in the public domain, the company had at least one recall a year due to risk of contamination of Apligraf (Jette 2004).

One specific concern with Apligraf, and with tissue engineered products based on cell culturing more general, is the use of animal-derived material during the product manufacturing process. To create Apligraf, the human foreskin cells are mixed with a connective tissue protein derived from cow tendons (type I bovine collagen). All animal-derived products need to be tested for micro-organisms, and the bovine material can only be obtained from countries free of bovine spongiform encephalopathy (BSE). Because of this specific animal component, Apligraf is contraindicated in patients with known allergies to bovine collagen. Adverse reactions associated with this material are considered 'patient specific responses'. Social and ethical sensitivities around the sourcing and donation of these cells have not been publicly addressed in this respect.

1.1.4 Onto the market

These social issues are paramount. One example is the trade in foreskin ('the foreskin resale industry is a multi-billion dollar a year business!') and ownership of human material. The manufacturer needs to obtain informed consent from patients, or in this case their parents, for the donation of neonatal foreskin to be used for the commercial production of Apligraf (Enoch et al. 2005). Concerns have been expressed over the fact that companies make profit on bodily material against the background of a long tradition of unpaid voluntary donation of tissues and organs in Europe. Interesting in this respect is that originally many commercial developers of these skin products classified the foreskins as clinical waste, while the 'added value' would lie in the processing and manufacturing process.

Also economic issues are important for understanding the development and use of tissue engineering technologies. On the broader horizon of the rise and fall of biotechnology, the business climate has not been favourable to the Apligraf producer, and Organogenesis gained bad press after negotiations failed with marketing partner Novartis about profits of Apligraf lagging behind. The company had to briefly stop the shipping of Apligraf in September 2002

and filed bankruptcy under US chapter 11 not much later after debts had reached the amount of $32 million. Organogenesis made a new start in 2003 and claims to be profitable now after further improving its 'flagship product' Apligraf.

1.1.5 Into the regulatory arena

But in Europe Apligraf is not widely available. Some point to the complex and uncertain regulatory climate in the European Union, with approval routes for 'hybrid' products such as Apligraf differing per country. This seems a universal issue. Because Apligraf was the first in a range of novel therapeutic products, gaining regulatory approval by the Food and Drug Administration (FDA) for the US market proved difficult initially. The combination of different product characteristics and jurisdictional overlap between biologics, drugs and devices caused uneasiness about which existing regulatory route to follow. As one of the developers of the product explains:

> Apligraf is a device, but because it is alive it also has biologic activity. We therefore worked with FDA officials to determine the standards of approval, safety testing and manufacturing by which we would be judged (Parenteau 1999: 84).

After many negotiations Apligraf was labelled as a medical device in the States and in the end the only issue for the manufacturer was to prove that the product was not contaminated. Unlike approval procedures for medicinal products, there was no need to demonstrate safety, no toxicology testing was required nor evidence of efficacy (M-EU6, 2003).

But while the US and Canada approved Apligraf under their medical device regime, the European market remained unstable. Initially the only European markets where Apligraf was available were Ireland and Austria, because these countries did not have any regulation at the time, and therefore no product approval was deemed necessary. The product was also available in Switzerland for some time.

With EU-wide regulation still under development, currently great variability exists in approval routes across Europe. In the United Kingdom for example

Apligraf is officially 'unregulated' but covered by a voluntary code of practice, Ireland has put the product under its medicinal product regulation, just like Germany and Austria, while Denmark takes a 'case by case' approach for tissue engineered products more generally, and in Switzerland Apligraf is classified under the transplantation regulation for products of human or animal origin, because it contains viable cells (TERG survey 2003).

At EU level tissue engineered products are excluded from the Medical Device Directive (Directive 93/42 EC article 1 par 5.f), which means they can not be classified as devices. In 2001 manufacturer Organogenesis, back then still in collaboration with Novartis, submitted an application at the European Agency for the Evaluation of Medicinal Products (EMEA) to get centralised approval for Apligraf as a drug in Europe. An industrial scientist involved in this regulatory procedure explains the difficult process of getting Apligraf on the market via this route (M-EU6, 2003). Against the background of the BSE crisis in 2001 and several other recent health scares, many European countries expressed concerns about the dangers of disease transmission. Pressure was put on the evaluation agency EMEA to consider Apligraf as a medicinal product – mainly because of the more stringent controls for drugs in comparison to medical devices. The pharmaceutical dossier for Apligraf was thus submitted to the centralised procedure of the EMEA, and two European member states (the UK and Denmark) had to act as rapporteur in the expert meetings of the Committee for Proprietary Medicinal Products (CPMP) that is responsible for approval of new medicinal products. The EMEA could not decide initially what to do because Apligraf was such a different 'unusual' product.

The product is complex because it has three active ingredients - two types of human skin cells and the bovine extract - and in preparing the pharmaceutical dossier the company got assistance from external reviewers. One of the key issues was batch control, as explained by another scientist involved in the approval process for Apligraf:

> Other issues they [the regulatory agency] had were from a definition point of view, of defining the composition of what a batch was. These really weren't safety issues, but more regulatory issues. The composition they had a big issue with because it changes all the time, because of the use of living cells made into a product. But these cells were responding

> to their environment, and what they made changed, so what you actually put on the patient from a clinical point of view is different. I mean you have to explain to them what it is, the recipe that we put together. And also the batch size, because the amount of testing you would need to do on a batch of biologics for example - you couldn't do on this because the batch size is too small. So there was this specific thing that they had to change the definitions of, and regulations for, but those were more bureaucratic rather than safety or quality issues (M1, 2003).

In addition to problems with the analysis of different batches, and the batch size, tests had to be defined and applied, for example for cell mutation and to show that Apligraf was not carcinogenic. In other words the requirements for the pharmaceutical approval procedure had to be interpreted in a way to fit a complicated combination product such as Apligraf. Organogenesis got the green light for submitting its application during a pre-submission meeting with the EMEA in September 2000. Over 200 questions were asked, many more than usual for a pharmaceutical product, mainly addressing quality control and viral safety of Apligraf. The company had to be able to test for all human viruses, which was not considered undoable but an expensive and time-consuming process – especially as it had to be done within the six months as dictated under the approval procedure. According to a company insider the safety testing was not problematic from a technical point of view, but more funding and equipment were needed to conduct the tests. But at the background another struggle took place. During the regulatory approval stage the professional relationship between producer Organogenesis and marketing partner Novartis broke down. The company landed in a financially precarious situation; restructuring in an attempt to survive the organisational crisis led to many redundancies and considerable downsizing (M-EU6, 2003). The bankruptcy of the company was claimed to be partly due to this 'unproductive relationship' (Jette 2004). Organogenesis pulled out of the negotiations and failed to get centralised regulatory approval for Apligraf on the European market.

1.1.6 To the exodus

The lack of a clear regulatory approval scheme resonances in the reimbursement of the product by national healthcare systems. Contrary to the US, which has a healthcare insurance system in place which covers Apligraf (CIGNA 2005), in Europe problems persist in obtaining reimbursement authorisation. According to some critics this is a direct effect of the unbalanced cost-effectiveness of the product. The price of human skin equivalent ranges between under a few hundred US dollars to over a thousand dollars per square foot – and depending on the wound more than one application is needed. Apligraf costs about US$1000 per unit, which comes in a circular disk of 75 mm (Thuesen 2001). In comparison, cadaver skin costs only a little over $2 per square inch (and usually comes in much larger sheets). Especially with the limited shelf life of Apligraf, there is a risk of wasting the product after the expiry date has gone.

But high product cost is just one issue. Others point out the limited clinical evidence available for the long-term evaluation of tissue engineered products such as Apligraf. Clinical trials would be needed to provide information on the cost-effectiveness of the treatment compared to conventional alternatives, and it is exactly the lack of cost-effectiveness data which makes insurance companies reluctant to reimburse treatment with tissue engineered products.

Currently Apligraf is no longer available anywhere in Europe, except as a special request by a surgeon for a named patient on compassionate grounds (M-EU6, 2003). According to Organogenesis, the reason for withdrawing from the European market in 2001 was 'not related to lack of reimbursement or regulatory hurdles'. Rather, it was the animal-derived component of Apligraf in the aftermath of the BSE crisis in Europe that triggered the exodus:

> The European Commission doesn't want anything with bovine collagen on the market, so we stopped shipping it over there.
> (Customer relations officer Apligraf helpline M4, 2005)

1.1.7 Why Apligraf matters

Apligraf is a good product example, as it demonstrates many of the underlying issues in tissue engineering that are relevant in a social scientific analysis of the technology. The sourcing and handling of cells, their culturing and processing in the lab, the subsequent preservation and storage in cell banks, the testing, the distribution of the product and the final implantation into the patient are all associated with risk and safety issues. The donation of tissue covers a broad area of safety concerns including the suitability of donors, the screening of donated substances, and the traceability from donor to patient and vice versa. Also the ethical and health implications of the use of human tissues and cells have provoked debate, for example about voluntary unpaid donation versus commercial use of human material, gaining true informed consent in a highly uncertain application, and not the least about the tissue and cell sources, including the use of animal derived material. These issues are of transnational importance when human tissues and cells are imported and exported within the European Union and beyond.

In addition to risk and safety issues during the development of a tissue engineered product, the example of Apligraf also highlights the concerns related to marketing of the product. Here, issues to do with regulation, reimbursement and clinical evidence for these therapies come to the fore, and the expertise needed to assess clinical and scientific data as part of a broader risk management approach. With the proceeding commercialisation of the technology, also issues of an ethical and social nature become relevant and justify a social scientific analysis. As such, Apligraf is a case study example of a technological innovation that raises a range of social and ethical questions in a globalised society.

These developments are analysed in the context of boundary-work, where different sets of actors define and articulate perceptions of risk in order to demarcate what becomes part of the regulatory domain. The next section provides the underlying analytical framework for my research, followed by the main research questions. The last section is a general overview of the structure and argument in this thesis.

1.2 Negotiating boundaries of science and regulation

This section outlines my conceptual approach in terms of boundary work and regulatory science, drawing on strands of theory developed in social studies of science and technology (STS) and the sociology of scientific knowledge (SSK).

1.2.1 Boundary issues

> 'Science' is no single thing: its boundaries are drawn and redrawn in flexible, historically changing and sometimes ambiguous ways (Gieryn 1983: 781).

For some time, sociologists of science have struggled with the question how to identify unique characteristics of science that distinguish it from other activities. The demarcation of science from non-science is rooted in a long-term tradition of reasoning and thought – from Popper's falsifiability via Mertonian ideas of certified knowledge and social norms to Kuhn's paradigmatic consensus (Gieryn 1995; Guston 1999). In 1983 Thomas F. Gieryn introduced the notion of 'boundary-work' as one way of dealing with this dichotomy. The process of constituting a boundary concerns in the first place attempts by scientists, where boundary-work is described as the 'attribution of selected characteristics to the institution of science (i.e., to its practitioners, methods, stock of knowledge, values and work organization) for purposes of constructing a social boundary that distinguishes some intellectual activity as non-science' (Gieryn 1983: 782). Furthermore, 'boundary-work occurs as people contend for, legitimate, or challenge the cognitive authority of science – and the credibility, prestige, power, and material resources that attend such a privileged position. Pragmatic demarcations of science from non-science are driven by a social interest in claiming, expanding, protecting, monopolizing, usurping, denying, or restricting the cognitive authority of science' (Gieryn 1995: 405). The notion of 'science' here is that of a kind of spatial marker for cognitive authority, a space with flexible and contextually contingent borders and territories that are continuously negotiated. In other words the boundaries of science are themselves ambiguous.

In previous work on the development of tissue engineering as an interdisciplinary research field (Geesink 1998), I have demonstrated the discursive strategies of boundary-work in which tissue engineering is considered as a specialised field which can be separated from other specialised areas. The drawing of boundaries around a professional field can be interpreted as means of a professional community to gain legitimacy and credibility for its activities and to get access to the privileges that are connected to this demarcated domain (see also: Gieryn 1983, 1995). By defining what tissue engineering is and is not about, different groups with varying (scientific, clinical, commercial etc) stakes in the technology claim a particular professional domain for reasons of expansion, monopoly, expulsion and protection.

This research takes this boundary-work concept one step further by analysing more recent attempts within the tissue engineering field to discriminate science from such non-sciences as technology, policy, politics and regulation. My aim is not to determine if tissue engineering is a science, or what kind of science.[4] Rather, I am concerned with the perceptions of professional actors (the 'inhabitants' of the social world of tissue engineering, see also later) on demarcating the domain over several important issues including risk, regulation, expertise and ethical concerns. I demonstrate how 'the science' of tissue engineering constitutes many differentiated boundaries *within* and *across* each of these domains, most notably in relation to ambiguous definitions of risk, negotiated boundaries of uncertainty and in carving out what is considered the regulatable domain. The boundaries of tissue engineering are not just ambiguous, flexible and dynamic – as argued in Gieryn's original account – but also continuously reconstructed by different actors, often inconsistent and heavily contested.

Useful additional concepts for my analysis – all easily identifiable by the prefix 'boundary' - are those of boundary objects and boundary concepts, boundary organisations, boundary ordering devices, and finally boundary evolution and

[4] Although, admittedly, in earlier work I argued how tissue engineering has some interesting 'mode-2' characteristics of knowledge production, such as transdisciplinary work in a market-driven environment (see for more detail also Gibbons et al 1994).

transgression (see for other categories, such as boundary talk, also: Glasner 1998). These are discussed in some detail next.

'Boundary objects' were introduced in 1989 by Star and Griesemer as 'objects which are both plastic enough to adapt to local needs and constraints of the several parties employing them, yet robust enough to maintain a common identity across sites... They have different meanings in different social worlds but their structure is common enough to more than one world to make them recognisable, a means of translation' (Star and Griesemer 1989: 393). Boundary objects travel between different social worlds, previously defined by Strauss (1978) as groups and organisations committed to a particular activity, and thereby building up certain shared ideologies. The use of boundary objects between various social worlds is an important notion for this research, as it underlines the different organised interests between domains and the ways in which its inhabitants engage with the objects and each other. Firmly rooted in traditions of symbolic interactionism, social worlds have been interpreted in the literature in terms of different academic disciplines or specialties (see for example: Amsterdamska 2005; Duncker 2001), while Gieryn, in later work, has argued how 'science itself may be a social world, made up of many social worlds, or part of a more encompassing social world' (Gieryn 1995: 412). However defined,[5] all social worlds share three main characteristics: segmentation (division into subworlds), intersection (where social worlds meet) and legitimation (defining and enforcing the boundaries of the social world).

As such, the notion of a social world can also be adapted to analyse professional spheres that are not wrapped up in traditional disciplinary boundaries (which is of major relevance for an interdisciplinary and hybrid science domain such as tissue engineering), but also it does not have to be limited to 'pure' science in itself. In this research a social world can be understood in terms of practices and shared beliefs between actors within and between different stages of innovation. For example R&D actors constitute one such social world, further differentiated in technological, clinical and commercial

[5] For example Gerson (1983) discriminates between three kinds of social worlds: production worlds that make something (science produces facts); communal worlds that pursue community values; and social movements that compete for change in society (see in Gieryn 1995).

'subworlds', while regulatory policy activity can be conceived as another dominant social world, where technical and ethical frames represent different ideologies and activities that it is made up of. The boundaries of these social worlds are set by temporary and thus fluent or hybrid understandings of the issues at stake, and are negotiated and at many times contested. This is where the concept of boundary objects proves useful.

Boundary objects organise shared but also distributed cognition among these various heterogeneous groups, which do not necessarily fully share the definition of an object. Boundary objects are concrete or conceptual objects which are flexible enough for different social worlds to read their own specific meaning in them (and manipulate them at hand), while at the same time they are robust enough to allow for a common identity across sites to maintain unity and to give the different actors the opportunity to share some interpretations across social worlds (Löwy 1992; Star and Griesemer 1989). They can be anything from people and ideas to projects, texts and maps – as long as these objects are relatively stable to facilitate articulation between different actors and social worlds (Shackley and Wynne 1996). These objects have an important task in understanding how the heterogeneous interactions may be efficient; how 'work can be done' across different viewpoints and goals.

The metaphor of boundary objects was adopted and adapted by several other sociologists of science. Ilana Löwy for example developed a typology of boundary objects and boundary concepts, the latter of which are ideal-typical and loosely defined concepts, the vagueness of which makes them adaptable to local sites in order to facilitate communication and cooperation (Löwy 1992). Both types are multifunctional in that they make interaction of distinct scientific cultures easier on the cognitive level, while at the social level specific social interests are advanced via the development of inter-group alliances. In her study on immunology, Löwy demonstrates the relevance of loosely defined boundary concepts in the construction of scientific knowledge and their effectiveness in forging professional inter-group alliances. Interesting parallels with tissue engineering can be drawn here in terms of the ability of these boundary concepts as tools which further the development of so called 'trading zones' or 'pidgin zones' between different and distinct professional groups.

While Löwy praises the strength of loose and rather vague concepts for easier interaction between social worlds, Fujimura underlines the need for more stable means of establishing the same goal. By bringing together several boundary objects with common methods into a 'standardised package' Joan Fujimura presents researchers a tool which is 'less abstract, less ill-structured, less ambiguous and less amorphous' to get their work done (Fujimura 1992). In this way interfaces are created between multiple social worlds where actors can cooperate but still maintain their integrity in their respective social worlds (Guston 1999).

These interpretations of boundary objects limp between flexibility and robustness, or between 'looseness' and stability of the objects that travel between different social worlds. This is an important notion for the demarcation of these domains and the ways in which the participants of the defined spaces interact which each other and their broader environment. At the same time it has been argued how not only objects are subject to boundary work. This is where the notion of the 'boundary organisation' entered the equation. It has been described how organisations can become boundary objects, reconfiguring the relation between science and politics. David Guston presents the boundary organisation as one route to stabilisation of 'the potential chaos of the science/politics boundary' by internalising its contingent character (Guston 1999: 90). These contingencies are continuously being negotiated but within the confines of the boundary organisation. This provides a relevant insight for our case of tissue engineering, but not for reasons of reaching stability (see also below). In this study I argue how the European Commission can be considered a boundary organisation which mirrors the division between politicians and scientists. At the same time this division is more complicated and only unproblematic as long as science and politics do not act in 'co-production'. Guston speaks of a 'combined scientific and social order' in this respect, where cooperation across domains is required to achieve a shared objective, and with the boundary organisation as organised space for the creation and use of boundary objects (1999: 105). Organisations enrol actors in certain routinised processes and create sets of rules that stabilise social relations within and beyond these organisations (Kelly 2003).

The relevance of this approach, then, lies in the institutionalised context of boundary work, where consensus over boundary objects (which according to the original contribution by Star and Griesemer is a matter of local agreement) becomes subject to a slightly more complex set of dynamics. However, the preoccupation of several critics with reaching stability is – though understandable in the practical world - rather unproductive in the case of tissue engineering. This is for the following reason.

Tissue engineering represents a domain, call it a social world in itself, which is surrounded by technological, political and social uncertainty. This uncertainty is reflected in the boundary-work exercises taking place across the multiple social worlds. Simon Shackley and Brian Wynne modified the boundary object notion to describe 'boundary-ordering devices' that allow actors to negotiate uncertainty across many domains (see in this respect also their concept of 'anchoring devices' in: Van der Sluijs et al. 1998). While these boundary-ordering devices are less durable and reproducible than boundary objects, they point towards the important issue of uncertainty which also features largely in tissue engineering. Furthermore, these authors focus on the authority of scientists as policy advisors, which is another important strain in this research. Advisory scientists are faced with negotiating uncertainty both within their scientific domain (with their scientific peer groups) and with policy actors – in other words across different heterogeneous groups with their own institutional affiliations, practices and ambitions. Where science and policy meet, advisory scientists perform boundary-work on the dominant representation of uncertainty to sustain the authority of science but to allow for negotiation of uncertainty, thereby spanning the boundary between science and policy, to define a common discourse and culture. As the authors explain:

> Compared to boundary objects, which emerge over an extended period of focused interaction... uncertainty discourses are a quicker, more appropriate means to reconcile heterogeneity and cohesion; they are 'shorthands' for achieving some understanding among actors involved in highly fluid institutional and epistemic sets of relations. They allow the actors to define their interests, build alliances, map out futures, and construct identities rapidly and across many domains. We suggest the term 'boundary-ordering device' to describe discourses that have these sorts of effects (Shackley and Wynne 1996: 280).

We return to this notion of uncertainty and of expert knowledge for policy purposes later. It should be noted here that the discourse of uncertainty is an important underlying frame for assessing and managing risks of tissue engineered applications. As discussed in more detail later, the social construction and definition of risk constitutes the drawing of boundaries around particular risk domains and vis-à-vis the social world of regulation. Of significance in this respect is that boundaries evolve over time and can be transgressed. As described by several authors, the introduction of new technologies into society represents a particular relevant development where, for example, the boundaries between public and private are not simply given; 'rather, we might speak of evolving boundaries that are created, maintained, and changed during the process of introduction and development' (Stemerding 1996 in: Glasner 1998). The involvement of different interest groups gives boundaries a 'temporal' dimension, where boundary objects go through an elaborate process of articulation, translation, negotiation, triangulation, debating and, sometimes, coercion (Fujimura 1992; Fujimura 1996). Furthermore the risks associated with boundary transgression are a feature of society in late modernity (Beck 1992; Giddens 1990). New knowledge coupled with new reflexivity reconsiders the authority of science, and the role of expert knowledge in fields of science and medicine. As also pointed out by Glasner, the boundary between laboratory and society is necessarily transgressed when the risks of new technologies only become knowable in the future, with the new genetics being an example in place (Glasner 1998).

Tissue engineering science and the politics of regulation are shaped by boundaries and demarcations between science and 'non-science' (e.g. policy), between risk and safety, risk and uncertainty, public health protection and promoting trade and innovation, and between techno-scientific and moral concerns... The identification of the appropriate boundary objects that are translated and articulated between different social worlds of R&D and regulatory policy (and all its subworlds) is of major relevance in this study. Definitions of risk as one way of boundary drawing are a dominant framework for the main analytical chapters in this thesis across the R&D domains of techno-science, clinical practice and market respectively, while the reconstruction and renegotiation of these risk boundary objects takes place in

the regulatory world with its own measures of protection and expansion. Within and across these worlds the sort of biological material on which tissue engineered applications are based becomes an important boundary marker. Furthermore, tissue engineering can be considered a boundary concept in itself, allowing a range of conflicting interests (between different professional groups, developers and regulators, states and industry, experts and bureaucrats, national Member States and the EU, DGs within the Commission, technical and ethical frames etc) to enrol each other and work towards a desired outcome. One set of boundary objects here refers to the need for regulation, which unites the various agendas of regulators and commercial developers to some extent, while another set of interests is expressed over risk and safety issues, and over the inclusion of socio-political and ethical concerns versus techno-scientific approaches to regulation. Thus not the aim but the scope of regulation serves as contested domain and explicit opportunity for boundary-work by various actors.

The margins of crossing or transgressing the boundaries become interesting in this respect, because at these intersections concerns are expressed and possible controversies arise. It is also here that boundaries can become permeable rather than fixed.

Social and ethical concerns are especially 'vulnerable' for operations at these crossroads. The boundary conditions are defined by the social negotiations of different interested parties over, amongst others, which risks start to establish the regulatory envelope around the boundary objects. In the political debate on the articulation and translation of (particular forms of) risk into regulatory policy, boundaries of 'legitimatisation' are raised to 'solve' ethical disputes.

Gieryn considers scientists' attempts to demarcate their field as strategy to assert or reclaim contested authority. This is mainly present when implicit social consensus breaks down and conventional distinctions or divisions become challenged, which are then forced to be made more explicit. Thus boundary-work is activated where credibility is contested and 'where regnant assumptions about boundaries suddenly appear murky or inapplicable' (Gieryn 1999: 24). Gieryn places a strong link here between boundary-work and the long tradition

in the sociology of scientific knowledge (SSK) of studying controversies. During controversies scientists have to articulate and reconstruct assumptions about the unique characteristics of science and the distinction with other institutions. While my research is not a controversy study as such, the element of conflict in boundary-work is important. Furthermore, several diverging interpretations from Gieryn's contribution need to be discussed here.

First, the author sees boundary-work as motivated by territorial ambition over authority and credibility, where scientists demarcate their field. My study acknowledges the role of conflict in this endeavour, but is not based on the assumption that an (external or actual) enemy or competitor needs to be in sight in order to revive the demarcation exercise. Second, scientists (but also other actors, see later) may have other motivations for their boundary-work than expansion, monopoly, expulsion or protection of autonomy. The complex configuration of tissue engineering regulation, with many different agendas across domains, necessarily constitutes very pragmatic boundary objects, where not the authority of the field or its diverse 'subworlds' are at stake, but the need 'to get work done' in a situation of conflict over how this work needs to get done. Furthermore, as also demonstrated by Kelly in her study on public bioethics bodies, when science controversies are framed as a moral dispute, rather than merely technical or political, the boundaries between science and politics are subject to different forms of boundary-work: 'where disputes critical to science lie outside its domain of authority, scientists may seek to blur rather than demarcate boundaries among political, ethical and scientific spaces' (Kelly 2003: 344). The claiming of territories and conflict over boundaries between most notably technical versus ethical stances are important drivers for the debate on tissue engineering regulation. The question of blurring rather than demarcating these boundaries is an empirical one addressed in this research.

Boundary-work theorists have argued how scientists have a significant stake in maintaining exclusive control over expert knowledge and autonomy, employing different tools in their boundary struggles (Kelly 2003). As demonstrated in this section, these tools include objects and concepts, organisations and devices. However, boundary-work is not the exclusive domain of scientists, but can be extended to analyse the activities of other groups. In this research I am

concerned with the 'narrow' techno-scientific actors, but also with clinicians, manufacturers, regulators, politicians, patient groups, advisors and other experts with a stake in tissue engineering. This means I move away from Gieryn (and other)'s exclusive focus on science as domain of demarcation. A particularly relevant expression of boundary-work takes place in the interaction between what I label the social world of R&D actors (broadly conceived as scientists, clinical professionals and commercial developers) and the social world of regulation (including the former and the rest). The notion of regulatory science is of major significance in this respect, and is discussed next.

1.2.2 Regulatory science

During boundary-work, actors struggle over defining the contested boundaries that separate science from policy. The domains of science and policy are defined and distinguished, while at the same time the interaction between these social worlds is negotiated. The boundaries between these domains are important because whether a question is classified as scientific or political shapes judgements about who should resolve it (Hilgartner 2000).

Regulatory science refers to 'forms of knowledge and understanding developed in response to the requirements of government and industry in the context of the regulatory process' (Irwin and Michael 2003: 45). As such, regulatory science brings together the relation between regulatory policy and scientific expertise, and the role of scientific evidence and uncertainty in decision making. It also highlights, according to some interpretations (see for example Jasanoff 1987 and 1990), the boundaries between science and politics, of academic science as opposed to regulatory science. Also the relation between innovation and regulation, and the operation of science in 'separate' areas (academic, government, industry – see also Leydesdorff (2001) in this respect) are implications of regulatory science.

As pointed out in an authoritative account on regulatory science (Irwin et al. 1997), many terms are used to discriminate between academic science and such things as 'trans-science', 'mandated science' (Salter 1988) and 'regulatory science' (Jasanoff 1990). Jasanoff draws a particular contrast between what

she calls research science, with the aim of seeking 'truths' of originality and conducted by universities, and regulatory science which is driven by policy relevance and usually takes place in an industrial or government setting. This stresses the significance of scientific advice for the policy process.

Scientists are prominent actors in providing knowledge and input into the policy process. Given the complexity and range of scientific uncertainties of tissue engineering technology,[6] scientists necessarily get engaged in wider debates about policy and regulation and are called upon to provide advice or an expert opinion in all kinds of committees or commissions. The role of scientific experts is sometimes seen as a fifth branch of government (Jasanoff 1990).

Regulatory agencies are a pool of (scientific and technical) expertise and much decision-making is left to these regulatory bodies. The relevance of these agencies for politicians lies in their continuous concern over a set of issues, whereas politicians usually do not have the time or knowledge to build up and maintain specialised skills and expertise. The complexity of technological and scientific changes has led to an expansion of regulatory agencies. This has created a situation where an increasing part of government is conducted by technical experts, who are contrary to their political executives not elected. This in turn has raised issues of accountability and credibility, especially when it concerns supranational regulatory institutions in the EU that operate on an even more distant level of democratic participation (Abraham and Lewis 2000: 18). While recognising the importance of expert knowledge in policymaking, especially in complex science domains, at the same time these bodies have been criticised for their 'closedness' and being shielded off from external scrutiny (Irwin and Michael 2003).

Issues of legitimacy of expertise are considered more pressing when the products being regulated are science-based. Examples include the regulation of pharmaceuticals, GMOs, chemicals, nuclear waste and, of course, tissue engineering. Here a strong link exists between expertise and risk. Potential risks and benefits of a product are assessed by experts for the purpose of

[6] This also applies to biotechnology in a broader sense - see for example Scoones (2001), Salter and Jones (2002), Irwin et al (1997) and Jasanoff (1995a, b).

decision and policy making. This also includes industrial scientific practices that aim to comply with regulatory requirements (risk-benefit assessment, testing), which has led some to believe that political decisions about risk in society are increasingly dominated by networks of scientists in industry, government and industry-funded academic experts (Abraham and Lewis 2000).[7]

But the notion of expertise is also problematic for other reasons. First, 'objective science' has gone bankrupt. Images of objective, policy-free expertise have been undermined by several public health crises, culminating in the 1996 BSE disaster (Levidow and Carr 2005). It is considered common knowledge that scientists do not limit their judgements to purely scientific matter. Expert knowledge is not value-free but conditioned by the social context of research that gives limitations in their technical assessment (Krimsky and Golding 1992). Especially biotechnology has raised moral and ethical issues which call for more than purely scientific understanding. Controversy and disagreement amongst scientists have demonstrated not just the contested nature of objective science, but also the normative assessment in which scientists engage. Under the influence of social, political and professional considerations expert advice is coloured and not necessarily free of interests. This is increased by uncertainty and controversy where lack of sufficient knowledge or contested advice brings the assessment of risk into the political domain. For regulators and decision-makers this means that they have to judge the acceptability of risk based on conditions in which it is not always clear how to interpret scientific data and risk assessments. This has led some to argue that scientific risk assessment cannot be done independently of policy judgements or political agendas (Levidow and Carr 2000).

[7] An interesting take on this is provided by Frank Fischer, who analysed the relations between technocracy and the politics of expertise. According to this author, technocracy is about the adaptation of expertise to the tasks of governance, with a decision-making system that is designed to promote technical solutions to political problems. In order words a different kind of expertise is referred to here, that of technocrats as experts in public and private organisations with important decision-making functions. Especially in modern bureaucratic states this form of expertise is strong and increasing, as many decisions are left to policy experts within the administration. Experts, according to this theory, are thus at the heart of political power. This poses broader questions about the relation between expertise and democratic politics. Technical experts might not be in political control themselves, but their information becomes an important resource in the governance of modern society (Fischer 1990: 28).

This is especially pressing in the health and safety domain, where experts are increasingly and more explicitly uncertain about the model on which to base regulatory action – or this uncertainly is reflected by the variety of expert opinions on the subject. This uncertainty is also evident from the increasing recourse to precaution.[8] The precautionary approach has become one of the central principles that guide decision-making involving the protection of human health and safety, where risk and uncertainty (and uncertain risks) are key notions. This influence is also felt in the regulatory domain of tissue engineering. Where Community legislation for the safety of human tissue was science-based, the decisions on specific applications were based upon the precautionary principle.

Regulatory initiatives can thus no longer be taken as once and for all political decisions based on expert advice, but must take into account expert and social judgement, with an understanding of the dynamics and complex interdependent problems of the issues faced. This would also imply a blurring of the classical separation of powers between actors (or institutions more specifically), highlighting the need for a new approach to regulation in and by the EU (Lebessis and Paterson 1997). As also pointed out by Salter and Jones:

> The traditional reliance of that [EU governance policy] community on technocratic networks as the mainstay of policy formation and implementation is no longer a sufficient mechanism for maintaining the legitimacy of the process. New policy networks imbued with different value systems are rapidly making inroads into the previously impermeable policy community of EU governance. Recognising the limitations of the existing means for securing agreement to regulatory change, the institutions of the EU are adapting their stance, or stances, and seeking new methods of engagement... (Salter and Jones 2002b: 325).

[8] One of the key principles shaping the regulatory context is the precautionary principle, which relates to the management of risk. The precautionary principle covers 'those specific circumstances where scientific evidence is insufficient, inconclusive or uncertain and there are indications through preliminary objective scientific evaluation that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the chosen level of protection' (CEC 2000: 9-10). Although originally only mentioned in relation to environmental issues in the Treaty, the precautionary principle covers a broader range of circumstances to be covered by EU policy. According to the Commission, recourse to the precautionary principle presupposes that potentially dangerous effects deriving from a phenomenon, product or process have been identified, and that scientific evaluation does not allow the risk to be determined with sufficient certainty.

Studying human genetics, the authors speak of an increasingly recognised need to broaden the circle of participants in European governance, such as NGOs and 'the public at large', in order to accommodate the not always compatible demands of different interest groups (including science, industry and civil society). An important observation in this respect concerns the role of ethical advisory bodies in the EU regulatory process, where bioethicists become the new regulatory 'experts' (Salter and Jones 2002b: 330). Thus expert advice is not limited to techno-scientific actors, which the case of tissue engineering will also demonstrate.

But risk regulation via the EU expert system also raises more complicated issues. In the context of calls for 'more than just technical advice', and the proclaimed need to also take normative, political and ethical considerations into account when deciding on the social acceptability of risks, the EU expert system is put in a difficult position. Given that social acceptability is not a straightforward European notion, but rather negotiated at national level, it is unlikely that one single expert body at EU level will be able to come up with uniform decisions that are acceptable within the whole Community. Therefore, if risk assessment is to include normative and political considerations, the EU committee system has to balance between universal European-wide agreed criteria and national concerns (Joerges and Neyer 1997). We return to the specifics of this EU committee system in chapter 2.

As such, the EU has an institutionalised and organisational structure in place to canalise expertise, to 'make it work' in regulatory decision shaping and making. Certain routines and procedures are developed to guide this process, with standardised ways and protocols which shape the division of labour between science and policy. It has been suggested that by embedding boundary-work in organisational structures, the demarcation between policy and science, and between different fields of expertise, lead as such to institutionalised boundaries (Halffman 2003: 3). The notion of the boundary organisation, as discussed before, covers this process.

Thus expertise plays a significant role in regulatory science, and the strategies used by experts to influence regulatory policy making. The division of expert

labour, in defining what counts as expertise in one field and not another, is of key concern. Regulatory expertise, then, is about competed science and policy domains over different regulatory and institutionalised settings.

The notion of regulatory science is relevant for the analysis of tissue engineering regulation, as it highlights the significance of scientific advice for the policy process. Moreover, it makes explicit the division of labour between scientific experts and policy makers, and the ways in which they negotiate the conditions of their interactions (Halffman 2003; Jasanoff 1990). In addition, the kind of knowledge that is relevant in regulatory activity is being discussed and demarcated. This concerns the question of expertise as such, but also the kind of expertise that is relevant for regulatory decision-making. It includes knowledge claims about what applies to the particular domain or activity subject to regulation, about what is in and out. In tissue engineering these claims are being contested on a 'multi-governance level', where knowledge has different meanings and interpretations on national and EU policy-making level.

An important observation in this respect is the increasingly global character of regulation and innovation (Irwin and Michael 2003). Regulatory requirements are not limited to national boundaries, and as also demonstrated in the case of tissue engineering, national governments have to harmonise their frameworks in line with EU level regulation. With companies targeting global rather than local markets for their products, national governments become part of a larger and international network of trade and exchange, which means that also regulatory systems become globalised. This also affects the content and level of expertise needed, and the scientific evidence to underpin regulatory decisions.

This is a useful starting point for analysing tissue engineering regulation, given the prominent role of scientific experts in this complex domain that is surrounded by uncertainty, to gain insight into the strategies used to influence regulatory policy-making. First of all, the definition of what needs to be regulated and what is considered problematic in tissue engineering (for example in terms of risk) is structured along the lines of what knowledge is relevant for decision-making in this particular area. To analyse and understand

in what way tissue engineering is regulated in Europe implies an insight into what 'the problem' is and how this is framed and defined within the different domains of science and policy (but also in its diverse subworlds). It is about which arguments and what information is used in the process of regulatory decision-making, what is included and excluded, which assumptions are made and how these are translated into policy. In short, this is about defining what is problematic and what is relevant for policy.

This boundary drawing in competing fields of knowledge also has consequences for the way in which policymakers and experts interact with each other and what value is assigned to the scientific knowledge that is catapulted into the decision-making. With policymakers looking for practical advice and juggling with uncertainty of scientific knowledge (Levidow et al. 1997), boundaries of regulatory science dictate the structure of this encounter. The way expertise is used can become political by for example presenting uncertain scientific information as objective claims in policy, or by referring to the expert status of knowledge in controversial or contested political decision making. Another implication of boundaries in regulatory science is the question of who has access to the regulatory decision-making process. In their study on the control of agrochemicals, Rothstein and colleagues demonstrate how regulatory science is a restricted domain, where wider public groups are effectively excluded from discussion (Rothstein et al. 1999).[9] Most regulatory

[9] A vast body of knowledge has focused on the role of laypersons as experts and the participation of citizens in regulatory science. Irwin developed the democratic concept of 'citizen science' (Irwin 1995) and 'scientific citizenship' while looking at the relationship between science policy and public engagement (Irwin 2001). He argues for more contextual forms of knowledge and understanding. Other critics in this tradition have studied 'lay expertise' as authoritative source for decision-making and the role of laypersons as experts in defining risk (Wynne, 1995, 1996). Moreover, 'social movement' theorists have pointed towards the role of for example consumer groups and environmental organisations in recruiting their own scientific experts to challenge the established regulatory regime. An example of this perspective includes the much cited study by Steve Epstein on lay activist pressure groups in HIV/AIDS becoming experts themselves, and as such reaching the heart of regulatory science with their direct involvement in drug testing for this particular medical condition (Epstein 1995).
The 'intrusion' of lay people into the expert system has led some commentators to argue that technical policy decisions need not necessarily be left to professional experts as the sole source of technical specialist knowledge, and that regulatory agencies should be more open to citizen participation (Funtowicz and Ravetz 1993). The relevance of these perspectives, then, lies in drawing attention to the role of other than the 'usual suspects' (i.e. professional experts or technocrats) in regulatory science. The notion of democratic regulatory science usually underlines the benefits of direct public participation in regulatory activity, especially where it concerns public health issues or technologies of which the risks and benefits directly affect the population.

science is conducted in the private sector, and with limited peer review also external scrutiny becomes restricted. Furthermore, without the appropriate skills and expertise, the significance of participating in this domain is limited (Irwin and Michael 2003). Thus different actors have uneven access to the domain which is restricted to 'experts only', and excluding those without the needed resources or credentials to take part in the activity of regulatory decision-making. (Halffman 2003: 4). For example in tissue engineering this refers directly to the role of commercial providers and industrial lobby groups who have the (technical, scientific and financial) resources to become part of the policy shaping and making process, while on the other hand clinicians and perhaps more so consumer and patient groups might lack these means. In this way the shaping of distinctions between the science and policy domain leads to inclusion and exclusion of particular stakeholders in the regulatory setting.

My research does not involve 'a public' though and is not concerned with 'citizen science' (Irwin 1995), citizen-consumer participation or 'active citizenship' (Abraham and Lewis 2000), nor with the role of what one could call non-professional experts. Hereby it moves away from the literature on public understanding of science and social movements. In this way, my analysis is limited to small groups of techno-scientific, commercial, clinical and regulatory actors in the inner circle of tissue engineering regulation. As such I have a narrow take on regulatory science.

1.3 Research questions

From the key issues described in the case study and conceptual elaboration, four critical research questions emerge that inform the rest of my analysis. The first of these concerns the context of studying tissue engineering as exemplar for biotechnological innovation, with the shaping of a regulatory regime in this techno-scientific area as explicit focus of attention. This context is drawn from understandings in the political economy of medicine, and analyses implications for conceptual discussion within science and technology studies (STS). I adopt these approaches as initial orientation for the analysis of my empirical data, while I am also interested in the significance of my tissue engineering case study in reconfiguring understandings within the STS literature, i.e. in terms of boundary issues across domains and notions of regulatory science. This leads to the following over-arching set of research questions:

- **How can the shaping of a regulatory regime in tissue engineering be understood from perspectives in the political economy of medicine? And what is the significance of this approach for the reconfiguration of notions of boundary work and regulatory science as tradition within the STS literature?**

From this broader context, this research is concerned with, firstly, perceptions of risk and, secondly, the transition from risk to regulatory policy. These developments are analysed in terms of boundary drawing and the articulation between differentiated domains of risk and uncertainty, expertise and regulatory policy making. More specific research questions drawn from this overall concern include:

- **How and to what extent are risks articulated in tissue engineering R&D and in which ways are they framed and differentiated?**

Insight into these issues is needed to analyse how different risk discourses translate into regulatory policy making in this area. In particular I am interested in how the boundaries between these domains are drawn and reconstructed,

what the role and interest representation of participants is in these activities, and finally what the implications are for the shaping of a regulatory regime in tissue engineering, which brings us back to the broader concern of this thesis. Thus two follow-up research questions are:

- **How and to what extent are risk perceptions reproduced in EU regulatory policy of tissue engineering?**

- **Who are the participants in regulatory science of tissue engineering and what are the implications of a possible shift between the boundaries of techno-science and socio-politics in this particular domain?**

These questions are fuller elaborated and answered in this thesis.

1.4 Brief chapter by chapter overview

Chapter 2 introduces the EU policy context of tissue engineering regulation, from national differentiation in regulatory pathways to tensions at Community level between public health protection and the promotion of trade. Key policy concepts are presented that inform my analysis of the two legislative initiatives discussed from chapter 8 onwards.

Chapter 3 contains my analytical approach to risk, the empirical focus and boundaries of my research, and an account of the research process and methods used.

The following chapters discuss the main empirical data and analysis of my research. Adopting a tripartite analytical model for the classification of risk perceptions, domains are explored of technological risk (chapter 4), clinical risk (chapter 5) and commercial risk (chapter 6). The last section of this part draws these together and analyses perceptions in terms of a risk hierarchy and risk balance (chapter 7). The framing of risk perceptions is the main starting point for my discussion. From a social constructivist perspective I analyse how risk

discourses in tissue engineering are framed by different constituencies involved in the front-end of tissue engineering R&D: scientists, clinicians and manufacturers.

Chapter 8 makes the transition from risk to the social world of regulation. Here a new set of actors is introduced: policy makers, expert advisors, manufacturers and other groups involved in EU policy shaping. I consider this in terms of boundary drawing and the articulation of particular powerful or dominant risk discourses, where certain arguments are fore grounded and others 'boxed out' in favour of what is perceived to be belonging to the 'regulatable' domain.

This chapter also introduces the two main regulatory initiatives that are explored more fully next: the SANCO Directive on quality and safety aspects of human tissues and cells (chapter 9) and the DG Enterprise Regulation for the marketing of these products in the Community (chapter 10). These chapters discuss the role of ethical concerns in EU regulation and how this relates to broader stakeholder participation in regulatory science.

Chapter 11 briefly reflects on current and future regulatory developments, followed by a general conclusion.

2 EU regulatory structures

This chapter provides the context for EU policy making in tissue engineering by analysing the main drivers for regulation and pointing out the problematic nature of current structures to manage the increased need for regulatory policy in this domain. I do this by, first, focusing on national regulatory pathways, while then shifting attention to attempts at European level to develop Community-wide regulatory policy. This leads into a broader discussion about legitimacy of Community action and the specific structures put in place to govern complex biotechnologies such as tissue engineering.

The regulatory climate for tissue engineering is shaped by three main and interrelated developments. First is the observation that until very recently no EU-wide controls were in place to cover products based on human tissues and cells, effectively creating a regulatory lag. One effect is that individual Member States have started adopting their own interim solutions, leading to a regulatory patchwork of approval routes and a confusing situation for manufactures and regulators in how to deal with complex tissue engineered products. Patients are subject to different systems for controlling the risks of these products, while availability of tissue engineering therapies differs per country. A second main development is the 'quest for equivalence' at European level for existing Community legislation (e.g. for medical devices and pharmaceuticals) to incorporate tissue engineering. For years the EU has sought to extend the scope of these legislations, which was accompanied by heated and still ongoing debate over the appropriate ways for risk regulation of tissue engineering. When this deemed unsuccessful, the development of a specific Community-wide framework for tissue engineering was the main focus of effort and attention. My research is concerned with these policy developments. A third main observation though is that specific legislation is bound by years of EU struggles to integrate the original aims of competition and trade with more recent involvement in Community health and safety regulation. The introduction to this thesis has illustrated the EU context of biotechnological innovation, with key understandings of bio-economy and bio-society. This chapter focuses on the role of the Commission as regulator in this context, demonstrating how

continuous boundary drawing takes place between conflicting aims and institutional ambitions. Furthermore technocratic versus democratic stances provide the background for considering the role of expertise in the EU decision-making system, where 'government by committee' has become a dominant but problematic means for gaining legitimacy for Community actions.

2.1 A patchwork of policies and a regulatory lag

One main driver for the development of Community wide legislation for tissue engineering is the current diversity in regulatory pathways at individual Member State level. Bio-economies in the United States, Canada, Australia and Japan have some regulatory classification system in place (Lloyd-Evans 2004). In contrast, the current control situation for tissue engineered products in Europe is diffuse and diverse. The EU situation has been referred to as a 'regulatory vacuum' (Faulkner et al. 2003) and a 'regulatory gap' (DG Enterprise 2005a) and is discussed in terms of 'regulatory barriers' for product marketing (Schutte 2002). This situation can be understood as caused by a 'regulatory lag', referring to the delay between technological, economic and political change and the response of regulators. Although often used in an economic context, this term is an appropriate depiction of the European situation for tissue engineering, as it takes into account the 'developing' character of regulatory activity.

None of the existing European regulatory frameworks covers tissue engineered products adequately (Bock et al. 2003). There is wide variation amongst product developers and national regulatory bodies as to the appropriate approach for a given product type. Tissue engineered products are considered hybrid or combination products at the borderline of existing regulation of medical devices, medicinal products and biologics. With the first tissue engineered products on the market already, and in the absence of European-wide regulation, some EU Member States have started developing their own regulatory framework, resulting in a patchwork of regulatory systems and routes.

The following overview is copied from a study conducted by one of the Commission's research centres (IPTS-JRC), and gives a good impression of the regulatory status in different countries. The green dots (on the left) represent autologous applications, while the red dots (right) are for allogeneic products.

	Country	Austria	Belgium	Bulgaria	Cyprus	Finland	France	Germany	Ireland	Netherlands	Poland	Slovakia	Spain	Sweden	UK
framework	not at all			●●	●●				●●	●●	●●	●			
	as medicinal product (MP)	●●	●●			●●		●●							
	as medical device (MD)														
	as MP or MD, decided on case-by-case basis												●●	●●	●●
	specific national guidance						●●								●●
	other regulations	●●										●			
authorisation	by product authorisation (PA)		●					●							
	by manufacturing authorisation (MA)	●●	●					●●							
	by accreditation... of the tissue establishment		●●									●			
	by PA and MA						●●	●					●●		
import	from EU MS mandatory through accredited... tissue establishment in your country		●●				●●					●	●●		
	from non-EU country mandatory through accredited... tissue establishment in your country		●●				●●					●	●●		

Source: IPTS, 2004

As also became clear from a project survey carried out in 2003 (TERG 2003), in some countries tissue engineered products can only be imported via authorised tissue banks (Belgium, France, Spain), while in other countries pharmaceutical regulation must be followed (Austria, Finland, Germany). In a third category of countries (Italy, the Netherlands, Denmark, Ireland) tissue engineered products are considered outside the scope of either medicinal product or medical device legislation, and are as such considered unregulatable. Formally this is also the case in the United Kingdom, but this country has issued voluntary codes of practice for quality management in the processing and storage of human tissue (Department of Health (DoH) 2001) and for the safety and quality of human tissue and cell-derived products (DoH Medical Devices Agency (MDA) 2002). The lack of a specific framework for tissue engineered or combination products does not imply that products are not available on national markets. Some countries work on a case by case basis. For example Ireland and Italy have applied the medicinal product legislation for a small number of products to enter their respective home markets (Kent et al.

2006). Finally, some countries have 'partial' controls or standards. Austria and Germany require Good Manufacturing Practice (GMP) for all cell based products, while the Netherlands has developed legislation for procurement and quality (Lloyd-Evans 2004). Often these controls are not complementary though. For example the lack of a mandate to inspect production sites by the Dutch government has resulted in a trade barrier with Germany and Austria that both request GMP compliance certificates (Schutte 2002). Finally, some countries ask for clinical trials.

The tissue banking route has been particular influential in Europe. It implies licensing tissue or cell banks, and imposing quality and safety measures for the sourcing and donation on the banks, which then function as gatekeepers to the market. In France accredited tissue banks manage medical devices that contain human tissue, while in Spain the starting materials for tissue engineered products have to be sourced from approved tissue and cell banks which see to quality control. Thus manufacturers have to liaise with authorised banks, which often charge fees for their services, in order to access the national market. This system is similar to that of medical device regulation, where decentralised notified bodies control market authorisation on national level. But while commercial developers have long been in support of a decentralised system à la medical devices as a possible route for tissue engineered products, the monopoly of tissue banks in some countries has been highly criticised. Because of their gate-keeping and intermediate role, these tissue banks protect the domestic market from outsiders by requiring contracts with tissue banks, whereby only imported products are subject to regulation and not those manufactured in the home country. Furthermore, while manufacturers have to comply with more or less strict quality and safety controls, many hospitals and university laboratories are exempt from regulatory oversight for their cell culturing activities taking place at a small scale. This illuminates tensions between profit and non-profit activities, and between institutional actors representing these stances, while also the level of activity from local to global is of key concern.

Thus tissue engineered products are either uncontrolled or regulated via different tracks in Europe and a regulatory space exists between different types

of existing legislation (Kent et al. 2006; Kleijwegt 2003). In the absence of national regulatory oversight, manufacturers can freely market their products without any form of approval, apart from import licences (Brown et al. 2001). Although this has been perceived as favourable by some, overall the strongest drive for harmonised regulation has come from industry. This has several reasons, most of them related to perceived negative effects on commercialisation of products, as 'the process of obtaining marketing approval can appear to be inconsistent or uncertain' (Smith and Hellman 2003). According to one regulator, industry is currently in a vulnerable position and in support of measures to overcome the current regulatory vacuum:

> The industry equally abhors a vacuum. Industry likes to have certainty, likes to know where it's going to. I think the industry prefers in a way to have some framework within which to operate. It's always rather uncomfortable when there's no framework on there. Equally if you're bringing forward a product, you worry that suddenly two years down the track new regulations come in and you'll get caught by them. So I think they do like certainty, they do like framework... they would welcome a regime. On the other hand they don't want a regime which is unhelpful to them; they want something which is balanced and proportionate in there. (Regulatory professional in national government agency R2, 2003)

Furthermore, there is also an argument of 'fairness' in good practice towards different developers currently trying to market their products. As described in the excerpt below, patient safety has to rely on responsible behaviour from companies as long as no formal control mechanisms are in place:

> Complicating this whole equation in Europe are the products that have been marketed and sold for a number of years in the current pan-European `regulatory vacuum'... Responsible companies pursue a course, allowing for sufficient development data to be generated, that will ensure public safety and health, while also looking at the ethical issues at stake. Furthermore, these companies clearly respect the need for regulation in this area, and make every reasonable attempt to discuss issues with the relevant regulatory authorities. Presently, without legislation, there is the potential for less responsible players to abuse the regulatory vacuum. (Brown et al. 2001: 296)

This argument also relates to unequal competition between companies that have good intentions in commercialising their products and developers that merely take advantage of the situation, for example by only targeting 'easy' unregulated markets. But the main imperative for a commercial push towards regulation lies in the harmonised nature of controls. The current market for

tissue engineered products is very heterogeneous and highly segmented. This means that companies operating outside their home market have to meet a wide spectrum of regulatory requirements for bringing their product to the market, as the single market concept does not apply. It also means that the same product is subject to different controls across Europe. Multinational industries would benefit from uniformity in the '25 different legislations' that are currently dominating the EU landscape (Veulemans 2005), as their activities are typically not limited to national markets. But also the many smaller and medium sized enterprises (SMEs) that dominate this field are helped by harmonisation. The current regulatory uncertainty affects these companies' investors' confidence and cash flow:

> Given that there's a lack of clarity in the law you have to take a case by case approach. And that is wonderful for the regulatory authorities, to take a case by case approach, but the unfortunate thing is that companies who are relying on - most of them are small start-up companies, whatever they're doing will have to satisfy the investors. They can't take a view based on a regime which has no clarity, no certainty.
> (Legal professional in regulation of biotechnology O2, 2003)

This also relates to the lack of expertise and experience of many of these small companies. As repeated by many officials, EU-wide regulation would mean clarity for industry as it becomes known which criteria and rules to comply with. While larger companies have the manpower, expertise and resources 'to do whatever is necessary' to wiggle their products into any of the existing legislative frameworks, the various smaller companies do not (A-EU3, 2003).

One influential European trade body in this domain has pointed out how the current regulatory impasse negatively affects innovation and patient access:

> The regulatory vacuum that exists today in the European Union leaves the door open to inconsistent practices in the field of human tissue technologies and an uncertain environment for manufacturers and regulators. At the same time, it has a negative impact on R&D investment and availability of innovative technologies, and ultimately, prevents patients in a critical condition from acceding to life-saving treatments. (EUCOMED 2002)

As a major commercial developer explains, manufacturers are faced with the effects on lacking regulation on commercialisation of their products, while according to the same discourse patients are put at risk:

> The lack of pan-European regulation is making the commercialisation of tissue products very complex, as no centralized approval or marketing strategy can be developed. This results in either delay in availability of such products to patients, or puts their safety at risk, where no regulations are applicable. The picture is made even more complicated by the requests for evidence of cost-effectiveness by some reimbursement authorities: 'unregulatable' does not exclude a review from a pharmaco-economics perspective (Brown et al. 2001: 289)

The lack of regulatory product approval has a negative effect on considerations, by national health systems and insurance companies, for potential reimbursement of treatments and products. While manufacturers and commercial developers conceive the regulatory lag as problematic for commercialisation purposes, regulators and government bodies point out the effects for (access to) public health and patient safety. In the absence of unified controls patients are subject to different treatment regimes, which implies they do not have equal access to potential beneficial treatments. It also means patients in different Member States are exposed to varying degrees of risk. Thus both benefits and risks are diffuse and unequally divided between countries. Furthermore, issues of public trust in these technologies are put to the test, and public confidence might be undermined when the same product is subject to different degrees of risk and safety control. Thus one reason for regulation is to build or maintain trust in products irrespective of their country of origin. As one official in a national regulatory body explains, several European Member States have developed their own legislation for just this purpose:

> Everybody's afraid that if something happens and this type of products are unregulated then we create public interest and for not saying public criticism why a national authority has waited too long. If something comes up in one country nobody can point or will point the finger to the Commission. It will only be a national problem. So everybody's interested to have something settled and its own territory to show to his minister and to the public that it's a little bit controlled. It's better controlled than nothing.
> (Regulatory affairs professional in government R-EU5, 2003)

With more and more tissue engineered products being developed and entering the European market, and increasing diversity in national systems with Member

States developing their own regulatory (interim) solutions, the EU has recognised the need for some form of pan-European legislation to cover this new category of products. The details of this legislation are the subject of the final chapters of this thesis. The first question though was what this new regulation should look like.

2.2 The quest for equivalence

In good EU tradition, the initial impulse was to look at the possibility of extending existing Community legislation. Resembling the quest for 'substantial equivalence' as found in environmental regulation, the idea was to use 'experience from elsewhere' and 'analogues as predictors of future risk' (Scoones 2001). Substantial equivalence refers to the similarity or likeliness with conventional products with the same end use, even though different means of production and processing were used to create these products. The special or unique status of products (their 'novelty'), and of specific types of risk assessment to evaluate these products, is thus of main concern.

In tissue engineering we observe a quest for equivalence in terms of both defining the technology (what is a tissue engineered product?) and in identifying which legislative options are available to fit this definition. As such, substantial equivalence has been sought in technological and regulatory frameworks for medical devices and pharmaceuticals, also known as the two regulatory pillars of the EU health domain, while also national tissue banking regulations were taken into account. Efforts to identify and adjust relevant legislative measures at European and Member State level can be considered in the light of demarcation and boundary drawing, which has led to the conclusion that a unique regulatory space had to be created for tissue engineering regulation in the EU.

A traditional starting point for regulation of any healthcare product in Europe is the existing framework for medicinal products and medical devices. Of most relevance in this respect are the Directives on Medicinal Products (2001/83/EC) and the Directives on Medical Devices (93/42/EEC), which together constitute a

well-established framework of the European regulatory system to cover the safety, quality and performance or efficacy of many healthcare products.

The general Medical Devices Directive (MDD 93/42/EEC) was implemented in Member States in 1998 (European Commission (EC) 1993). This Directive defines the 'essential requirements' that devices must meet before being placed on the EU market. Conformity to these requirements is needed before market approval is granted, when the device gets a CE-mark.
Overall, the medical device regime is considered less stringent than that for pharmaceuticals. This relates amongst others to the testing of devices, and more specific to the need to perform clinical trials. An important distinction is that for medical devices, unlike for pharmaceuticals, demonstration of *performance* is required rather than *efficacy*. Clinical trials are seldom performed in the medical device world.

The question whether quality and safety demonstration should be supplemented by data on clinical effectiveness has divided parties in the tissue engineering debate. Where the medical device regime mostly relies on pre-clinical data collection and the monitoring of devices after marketing, the pharmaceuticals legislation has more specific and stricter requirements for clinical testing.

Indeed, medicines regulation was one of the earliest areas of Community control in the health domain, with the first Directives on pharmaceuticals being introduced in 1965.[10] From its early inception, the aim of the EU medicines legislation lies in the dual purpose to protect public health and support free movement of products, the principles of which underlie the entire harmonisation process in Europe (EMEA 2006).

[10] This was Directive 65/65/EEC. The current relevant legislation is covered in the Medicinal Products Directives (2001/83/EC) or MPD, where criteria of quality, safety and efficacy are laid down for medicinal products for human use (European Commission (EC) 2001a). This Directive governs the market authorisation, manufacture and distribution of medicinal products in the Community. In October 2001 a review of the Medicines regulation was announced. Directive 2001/83/EC was amended by Directives 2002/98/EC, 2003/63/EC, 2004/24/EC and 2004/27/EC. See for earlier developments of the EU medicines legislation Abraham and Lewis (2000).

Since 1995 a pivotal role in this legislation is played by the European Medicines Agency (EMEA), an EU regulatory body headquartered in London. The EMEA is part of a centralised system, supported by a mutual agreement procedure, where all medicines in Europe are subject to a single evaluation. Companies submit their request for marketing authorisation to the EMEA, which then goes to one of the scientific expert committees dealing with either human or veterinary use. For application in humans this concerns the Committee for Medicinal Products for Human Use (CHMP). This Committee has also been influential in advising on tissue engineering regulatory pathways. After a positive opinion from this expert Committee on criteria of quality, safety and efficacy, the Commission gives single market authorisation valid throughout the EU (Abraham and Lewis 2000: 113). The EU medicines regulation has been described as very complex, and the Europeanisation process as shifting from a weak to a strong regulatory state in the pharmaceuticals sector since 1995 (Elmalem 2002).

In the context of tissue engineering regulation it is relevant to point out some of the difficulties in defining products under particular regulatory regimes. The technology and its diverse applications are novel and largely experimental, and complexity and uncertainty around risks and benefits make it difficult to predict the impact and outcomes of the technology. This puts regulators in a difficult position, but at the same time this phenomenon is rather typical for technological innovations entering the regulatory domain. In the first place, this is a matter of contested definitions, and in boundary drawing around including or excluding products in a certain technological and legislative domain. The demarcation between drugs and devices is relevant in the light of many new products being developed that do not easily fit in either of these categories. In order to institutionally and legally deal with controversy around these new so called borderline or combination products (such as drug-device or device-biologics combinations) the European Commission published guidelines (DG Enterprise 2001). As a general rule it was stated that products are regulated by either the Medical Devices or Medicinal Products Directive, and that the procedures of both Directives do not apply cumulatively.

Generally borderline issues are discussed between manufacturers and regulators during the approval stage, which means a lot of informal discussion takes place before the actual approval is granted. This also implies room for negotiation. Originally many commercial developers of tissue engineered products have a background in medical devices. Classification of a borderline product as medical device serves their interest, as they have the necessary expertise and experience in gaining marketing approval for these types of products. Moreover, the medical device regime is less strict in terms of demonstrating clinical efficacy, while this process is much more complex and lengthy when a product falls under the medicinal product regime. More clinical trials and more elaborate clinical evidence is needed on not just performance but also effectiveness of a product, with longer review times, higher fees and more documentation required upon submission of a dossier to the EMEA. Gradually more borderline products are being developed by pharmaceutical companies now. In the US this has led to inter-institutional tensions between the different centres of the regulatory body FDA that are dealing with medical devices, medicinal products and also biologics (Altenstetter 2004). While there is one European regulatory agency for pharmaceuticals, the responsibility for medical devices at European level lies with two EU bureaucracies, namely DG SANCO and DG Enterprise. In the literature tensions have been described between different goals and institutional aims of public health and industrial policy. Sources of conflicts, economic interests, and a 'clash in cultures' have been found in the different policy sectors (Williams 2003: 10-11). As demonstrated later, these tensions are also real for tissue engineering.

Thus borderline products pose specific problems to manufacturers and regulators alike. Especially in the light of the different safety criteria attached to medical devices and medicinal products regimes, the specific risk assessment process for tissue engineering becomes important in determining the effects for public health. The main issue with tissue engineering is the fact that many of these products contain human tissues or cells of some form. Even though part of these products could be classified as medical device, the final product excludes them from the classical definition of a device and as such from the Medical Devices Directives. Equally, the mode of action of some of these products resembles a pharmaceuticals approach, but the Medicinal Product

Directives do not (fully) apply. As also pointed out in the following fragment, this has created a regulatory lag:

> The uncertainties and risks associated with tissue engineering...have caused regulators to delay the introduction of clear pathways to regulatory approval, since they have been used to dealing with drugs or devices, and tissue engineering products are neither, but do involve both (Lloyd-Evans 2004).

For a while, it looked like the pharmaceuticals framework would be the most appropriate solution to cover tissue engineering. Gene and cell therapy products were already covered under the Medicinal Products Directive (MPD), since 1998, and the scope of this Directive could be extended to also include tissue engineering (European Commission (EC) 1998). This was indeed the purport of an important document adopted in May 2001, which suggested that all Member States should regulate human tissue products as a medicinal product via the centralised procedure (EMEA: CPMP 2001: 3).

Industry was not undivided in its enthusiasm: definitions in this document were vague, and it was unclear whether products for orthopaedic and wound care applications, in other words the skin and cartilage products closest to the market, would be covered under this legislation. Also autologous applications would not fit the definition of medicinal product, and manufacturers were concerned about strict and inappropriate requirements of preclinical safety and clinical effectiveness. Furthermore, with a background in the medical device sector, most companies were uneasy about the application of pharmaceutical legislation. Especially smaller companies would become victim of this approach:

> I think any pharma-like legislation is survivable for some of the big companies because they have a whole organisation in place because if they are big pharmaceutical companies, all their products go through that process so for them it's not a big issue but for the smaller companies it is... I mean this is biotech, people from biotech fields, it's an innovative field, you're speaking about high technology and so one would be stopping innovation if there is just no proper legislation that would take into account all these elements.
> (Corporate affairs manager in multinational company M-EU5, 2003)

But the first steps towards filling the regulatory lag in tissue engineering were made. As also discussed in the Apligraf case study, early experiences from a company actually following this track were negative though.

Discussions about the exact requirements and definitions continued, and not much later the Medicinal Product Directive was updated to accommodate a more restricted definition. This was an important legislative move, as it directly concerned certain tissue engineered products. Moreover, under the influence of a growing number of products on the borderline between medicinal products and other frameworks, in the new EU medicines legislation of 2004 (Dir 2004/27) also the very definition of a medicinal product was expanded. The status of borderline products was clarified: it was decided that when a product's status is unclear or when in doubt, regulators will default to medicinal products status to protect public health (Article 2.2. Dir 2004/27).

To sum up, both the medical device and medicinal product Directives have been influential in discussions how to regulate products containing human tissues or cells. The scope and potential extension of the borders between these different legislative bases has been debated extensively over the last decade or so, in order to find substantial equivalence, at least in legislative terms, to fit tissue engineering. While several attempts have been made to include tissue engineering under either of these existing regulatory pillars in the EU health domain, these frameworks could not be stretched. One underlying motivation was that tissue engineered products were considered to pose substantially higher risks than medicinal products and the highest risk class III medical devices (European Commission: EESC 2002: C 85/46).
In the meantime more products were entering the fragmented European market, which meant that manufacturers had to fall back on national legislations and frameworks, if any. It also meant that patients throughout the Community were subjected to different levels of risk (Indech 2000).

One effect of the absence of appropriate European controls was that national legislations became more influential. Most notably tissue banking provisions, and perhaps more so the tissue banks that act as institutional gatekeepers to home markets in several influential Member States, have become dominant

players in the EU domain. Tensions exist between these national provisions vis-à-vis EU level initiatives. But also cultural differences were influential. Most tissue banks operate on a not-for-profit basis, which has led to conflicting views with commercial developers over the nature of donation and commodification of human tissues and cells. Also important in this respect is that formal regulation of these tissue banks, both at national and at European level, is by and large lacking. This is perceived as problematic because of associated health risks, especially given the growing market for human tissues. At European level this led to several initiatives and calls for action. In the summer of 1998 the European Group on Ethics in Science and New Technologies (EGE), an authoritative Commission advisory group, published an Opinion on the ethical aspects of human tissue banking. EGE speaks of an 'urgent need to regulate the conditions under which human tissues circulate within the European market' (EGE 1998: 7).

These developments provide the context for developing a specific Community framework for tissue engineering, which became considered the third pillar in the EU health domain (Bock et al. 2003), taking into account the complexity and uncertainty around the technology, its evolutionary or developing character, and the differentiated risks of its diverse applications. Gradually but with increasing urgency the suggestion arose that because of the specific nature of tissue engineered products, a separate framework had to be developed. Of major significance was the EU experience with mad cow disease (BSE) and several food and blood contamination scandals, which provided a push for stricter health and safety requirements.

This thesis is concerned with the specific legislations that have been developed for tissue engineering most recently. What can be considered as the emergence of a regulatory regime, two main tracks dominate the EU regulatory landscape. One of these concerns the European regulation of human tissues, and mostly covers tissue banking activities such as the donation, procurement, testing, processing, storage and distribution of human tissues and cells. In this research I refer to this as the SANCO Directive, by its initiator DG SANCO, the Health and Consumer Protection Directorate General of the European Commission. The SANCO Directive covers all tissues and cells of human origin

intended for application in the human body, and introduces quality and safety standards across the EU. In addition to this process based approach a second track covers the marketing requirements for tissue engineered products. For this a proposal for a specific Regulation has been developed by DG Enterprise, responsible for the promotion of trade in a single European market, which is currently still going through the legislative cycle. In this study I refer to this as the Enterprise Regulation.

Before discussing these two regulatory tracks in more detail, it is important to consider the legal basis of these initiatives, as they are rooted in different value systems underlying Community action. The next section looks at the context and tradition of health regulation at EU level, and the scope of Community intervention more generally, pointing out implicit discrepancies arising from the very aims of EU controls. Background is provided into the gradual shift of Community action from an exclusive focus on economic imperatives towards broader concerns with health and safety of its citizens. It is argued how this extended involvement has been influential in considerations of the particular ways and legislative means to control tissue engineering technology, and provides insight into the current conflicts between public health and competitiveness agendas in this domain.

2.3 Risk regulation in the Community

Regulation is often understood as a fundamentally political-economic concept, interpreted as a way in which governments attempt to manage the tension between protecting the public and allowing producers to trade and make their products profitable.[11] They do so by issuing rules to control the manner in which these enterprises behave and conduct their operations. From this normative perspective regulation is seen as a state intervention to correct 'market failure' (such as monopoly power or inadequate provision of public goods) and is justified out of the neoclassical economic argument that an

[11] A much cited definition refers to regulation as 'a sustained and focused control exercised by a public agency, on the basis of a legislative mandate, over activities that are valued by society' (Selznick 1985 in Majone, 1996: 3). I am not so much concerned with the etymological development of the term regulation and the historical conceptual roots. For an account of this see Jessop (1995). See Ogus (1994, chapter 1) on historical development of regulation.

unregulated market is inadequate and undesirable (Abraham and Lewis 2000; Hancher and Moran 1989a; Majone 1996).

A broad but for this research useful distinction that is often made, concerns the difference between economic and social regulation (Ogus 1994). Economic regulation is concerned with controlling the terms of entry to a particular market, and primarily applies to monopolist positions in industry that need counterweight. This understanding is too narrow in focus for this research. Social regulation has a wider range and aim, and is not about regulating a specific industry or sector, but tries to protect whole populations against social discrimination and risk (Moran 2001). As such it covers issues of health and safety, environmental and consumer protection.

Although originally the Union was primarily seen as an economic community, with free movement of goods within the internal market as its main aim, it has gradually become more involved in health and safety regulation – so much so, that consumer health and safety protection has been widely recognised as an independent community objective in its own right (Vos 1999). As is also evident from the case of tissue engineering, the Community is now one of the key actors in European health and safety regulation.

To understand the underlying dynamics of this involvement, we need to discuss the legal basis of Community action. The Treaties represent the constitutional law of the European Union, laying down the basic policies and institutional structures and covering the legislative procedures. Of this primary legislation the Treaty of Amsterdam (1997) is the most important one for tissue engineering, as it is in this piece that the need for community wide legislation on human tissues and cells was first made explicit. Also, it was in this Treaty that the dual objective of the Community became clearly visible, in trying to unite the aim of creating a single European market with considerations of public health and safety. Two Treaty articles are of particular relevance in this respect, namely the one on public health (art 152) and the one covering completion of a single European market (art 95). These different articles are discussed next.

Increasing involvement in public health protection

In addition to securing free movement within the European Union, which has been covered in Community law since its early inception, the Amsterdam Treaty was the first piece of communal legislation that made public health protection a formal Community objective. With the new article 152 (ex Article 129) of this Treaty the EU became able to adopt strategies to ensure 'a high level of human health protection in the definition and implementation of all Community policies and activities', rather than just supporting the efforts of Member States (Article 152, al 1).[12] Of particular significance in this respect is the explicit statement in this article that the Community will adopt legislation on human tissues and cells:

> The Council... shall contribute to the achievement of the objectives referred to in this article through adopting: measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures. (European Commission (EC) 1997: art 152, al 4(a))

The development of quality and safety measures for human tissues and cells can be considered the first formal reference to an explicit Community obligation in the public health domain. Following this Treaty, which entered into force in May 1999, action was initiated to control human tissue and cells. This was one the one hand born out of concerns with increasingly globalised trade and exchange of human body parts within and outside the Community, and safety threats this would pose in terms of cross-border disease transmission and equal access to scarce goods. In other words, the Community felt a need to develop quality and safety measures on a European scale rather than leaving this to Member State level. On the other hand this article was addressing a current regulatory gap in that no EU wide regulatory controls were in place to cover these human body parts. Out of similar safety concerns, and in addition

[12] Covered by this article is cooperation between Member States in fighting disease and more general causes of danger to human health, while also objectives of improving health are listed. Importantly, amendment of this particular Article was driven by a strong lobby from Member States and EU institutions alike to not repeat the errors that were made during the BSE crisis, where the Commission was accused of following a too strong market-influenced policy. The health and safety of persons in relation to products featured large in this debate. Thus a high level of consumer health and safety protection has become a widely recognised aspect of Community activity, and a legitimate goal in itself.

to public pressure and concern after contaminated blood scandals in one influential Member State (France), for blood products a separate track was followed which led to Directive 2002/98/EC, and which falls beyond the scope of this research (European Commission (EC) 2003b).

It is also here that tensions become visible between two dominant guiding principles of EU action, namely public health protection and promoting trade. A more original aim of the Community refers to the marketing of products based on human tissue and cells: 'to guarantee patient safety and to ensure that tissue engineered products can be marketed without obstacles throughout the European Union to those who need the innovative therapies' (European Commission (EC) 2004).

Promoting trade and a single European market

As discussed in the introduction to this thesis, the EU has a long tradition of promoting trade and stimulating biotechnology innovation to make the European bio-economy a global competitor. This objective is reflected in discussions on the regulation of tissue engineering as one promising exponent of the life sciences and biotechnology sector.

Economic goals of Community action are covered by several Treaty articles (e.g. Articles 28-30). The most influential one is Article 95 of the Amsterdam Treaty, which has as objective the establishment and functioning of the internal market, including the adoption of harmonisation measures in the EU. The majority of secondary community legislation for the placing of biotechnology products on the market is based on this Article (Sheridan 2001). Important exceptions to the rule apply though in how far Member States have the 'right' not to follow the harmonised approach of the Community, as the possibility was created for Member States to adopt more stringent measures than those laid down in Article 95 to protect the health of their public, as long as these are compatible with the Treaty (and in particular are not used as a trading barrier). As furthermore expressed in this article, its objective is not to replace the public health goals:

> The Commission, in its proposals... concerning health, safety, environmental protection and consumer protection, will take as a base a high level of protection, taking account in particular of any new development based on scientific facts (European Commission (EC) 1997: art 95, al 3).

In other words the health and safety agenda cannot be compromised with completion of the single European market. This does not prevent ongoing itchiness though between the public health and trade objectives. Community structures for risk regulation have a dual basis, where on the one hand tensions arise from the opening up of markets, while on the other regulatory concerns of consumer health and safety need to be addressed. Moreover, it has been argued how the internal market objective led to an increased involvement of the Community in health and safety regulation, and as such the implementation of a greater number of rules at this level, because of the trade barriers on these issues that have been created at national Member State level. Some speak of a 'spill-over' effect in this respect, arguing how the Community involvement in public health was an accidental consequence of the market integration objective (Vos 1999).

To sum up, it is argued that although the Community's involvement in regulation of health and safety can be mainly understood as stemming from its commitment to achieving an internal market, after the BSE crisis a specific legal basis and commitment was provided for the protection of human health and safety. Two Articles of the Treaty of Amsterdam are of particular relevance to tissue engineering; one on public health (Art 152) and the other on completion of a single European market (Art 95). These dual objectives provide the basis for secondary legislation of tissue engineered products, which are discussed later on in this research.

With this observation the last of three main developments has been illustrated, leading to the need for specific Community wide regulation of tissue engineering. With large diversity in national regulatory pathways, and failing efforts in stretching existing EU frameworks in the health domain, the current development of tissue engineering policy needs to be understood in the context of tensions between health and trade objectives, which is also visible in the institutional arrangements and structures in place to obtain this goal.

Furthermore, as also described in the introduction, a strong economic and innovation-driven framework forms the backbone for these regulatory efforts. As integral part of the EU ambition to establish a solid knowledge-based bio-economy, the Commission plays a double role of both promoting and regulation biotechnology. The implications of this complex constellation determine the process of regulatory decision making in this domain, and with that the impact of tissue engineering on the bio-society.

With the increasingly dominant role of the EU in regulating biotechnology, also other tensions arise. The next section describes issues of legitimacy in Community policies and the complicated and technocratic system of expertise originally developed to make EU governance processes more transparent and democratic.

2.4 More responsibilities and more complex configurations

The scale and scope of regulation covering the European community has grown substantially over the last decade, in some cases outnumbering the legislation with domestic origin in Member States.[13] According to some, the EU can be characterised as a 'European regulatory state' (Majone 1996). One of the practical problems of the extended involvement in Community regulation is that the European Commission, as the most important executive agency of the Union, is not equipped to take on the massive task of collecting and evaluating scientific data for regulatory purposes, as it is lacking expertise and manpower to carry out these tasks.[14] Therefore the incorporation of scientific expertise into decision-making has become extensive part of many of the regulatory initiatives

[13] For an indication of the number of Regulations and Directives produced in Brussels over the last years, see Majone (1996: 56-59). Especially in European environmental law a fair number of regulatory instruments have been produced, with a shift from initial Directives concerned with product regulation to more and more legislation covering processes (Sheridan, 2001).

[14] As described extensively by Majone (1994, 1996, 2003), unlike nation states, the EU does not have a large bureaucracy at its disposal to implement its policies, nor a large budget for redistribution. The European Commission only has indirect means of exercising power and influencing Member States, and regulation is one such means. The EU can promulgate regulations, while the costs in terms of money and staffing are borne on the national level: 'constitutional ideologies such as subsidiarity allow institutions like the Commission to expand ruling domains while pushing the responsibility, and the cost, of regulation down to national and sub-national levels' (Moran, 2003: 17). Thus by expanding the scope of its regulatory activities, the Commission can increase influence over its Member States.

of the Commission, including those on tissue engineering. It is also in the Treaty of Amsterdam where the Commission has explicitly inserted the obligation to base its internal market proposals on new scientific evidence, thus underlining the importance of scientific expertise. The implications of this construction have been outlined elsewhere (see under regulatory science in chapter 1).

The regulation of tissue engineered products can be situated in the context of a larger discussion about the position and methods of the EU, and the effectiveness and legitimacy of European policy. Several principles have been adopted to deal with the increasingly complex problems the EU faces, especially in the face of further enlargement. Proportionality, subsidiarity, transparency and flexibility reflect a concern to respect a certain autonomy at Member State level, to leave scope for national decision-making and legislation, to only act insofar as needed for achieving Treaty objectives, to keep the consultation and decision making process open and accessible to the citizen, and to recognise diversity in arrangements between different Member States (Lebessis and Paterson 1997: 5).

With the increased interference in health and safety regulation on Community level, EU institutions are faced with conducting risk assessment and risk management tasks that were previously decided upon in the national context. This poses several regulatory difficulties, most notably in the relationship with individual Member States, as also addressed in the White Paper on European Governance (European Commission (EC) 2001b). One such issue concerns the impact of regulation in the light of the transfer of powers from national to European level, and the Community competence in dealing with risk and safety of innovative technologies. This includes legal questions about rule implementation and highlights most notably the principles of subsidiarity and proportionality, which have been particularly influential in tissue engineering regulation.[15] The subsidiarity principle was introduced in the Maastricht Treaty,

[15] In Community speak proportionality and subsidiarity are described as follows: From the conception of policy to its implementation, the choice of the level at which action is taken (from EU to local) and the selection of the instruments used must be in proportion to the objectives pursued. This means that before launching an initiative, it is essential to check systematically (a) if public action is really necessary, (b) if the European level is the most appropriate one, and (c) if the measures chosen are proportionate to those objectives (EC, 2001a: 10-11).

reflecting the Member States' reluctance to accept the Community's assumption of greater powers (Vos 1999). By limiting its powers and competence to Treaty objectives, room is left for national decision-making and legislation, where subsidiarity dictates that Community action is only possible if the objectives of the proposed action cannot be achieved sufficiently by the Member States and for reasons of scale or effects can thus be better achieved by the Community (European Commission (EC) 2001b).
Given the closely tied links between health protection and market integration, Community action is generally required for issues of health and safety, which would provide the subsidiarity principle with a straightforward approach. As demonstrated later though, in the case of tissue engineering particular retreat is done on this principle, most notably to prevent contested ethical issues from entering the Community legislation.

With this context in mind we will return to Community policies in chapter 8. The next chapter outlines my analytical framework and includes a methodological account.

3 Analytical and methodological approach

The purpose of this chapter is threefold. First it serves as conceptual introduction to my understanding of risk, which is a key theme of engagement in this thesis. I discuss risk perceptions as socially constructed and hence contingent notions, and give insight into the way in which I have organised my data and structured my argument. I provide a model for discussing different perceptions of risk across three distinct but interrelated domains, structured along different phases of the innovation process. This provides the background for chapters 4 till 7 in which these domains are further explored and interpreted. A second aim of this chapter is to introduce the main players, while also setting the empirical boundaries of my research. This is relevant for the transition into the third part of this chapter, which includes my methodological engagement. It contains a description of the research process and methods used to unravel perceptions of risk and dimensions of tissue engineering regulation in the EU.

3.1 Perceptions of risk and boundaries of risk domains

Risk is a hot topic of political debate in the EU, and represents in many ways the much wider political and social concern about the governance of science in the EU (Borras 2003). Risk technologies have become a key strategy over the last decades, exemplified by developments in genetics and the creation of the human genome project, where the human body has been redefined as a field of risk (see also: Gabe 1995; Rose 2001). Political discourse has focused on risks associated with new biomedical technologies, with various strategies developed to control risk, where regulatory efforts were targeted at tackling potential hazards while at the same time problems arose of lack of scientific knowledge about these new sciences and technologies.

> Risk is a way of ordering reality, of rendering it into a calculable form. Risks come into existence through complex and multiple processes of inscription, interpretation and boundary work carried out by a variety of actors. Risk is a strategy of making events and situations governable and introduces a calculative rationality for governing the conduct of individuals, populations and collectivities (Gottweis 2005: 183).

Risk is presented here as a 'strategy' for governance, and particular definitions of risk determined by technology have led to a regulatory system. Importantly, the very existence of risk is considered part of a complex process where different actors negotiate the boundaries of the notion of risk and its diverse appearances. This is an important underlying assumption in my research.

3.1.1 Constructing, framing and categorising risk

One conceptual notion of risk departs from the politics of risk definition, based on the assumption that 'whoever controls the definition of risk controls the rational solution to the problem at hand '(Slovic 1999: 689). In tissue engineering there is no such thing as 'the definition of risk' though, as broad variability exists between different professional groups on how to frame risk issues, highlighting 'the contested nature of who is defining what as risk and how' (Adam et al. 2000: 4).

My study discusses different interpretations of risk as *frames* as a means of 'shaping, focusing and organising the world around us' (Lewicki et al. 2003: 11). Framing, then, is the activity and process of creating and representing frames; of interpreting and making sense of what is going on. These frames are no static entities and not permanent, but are fed by new experiences and information which can lead to 'reframing'. I prefer to label this process in terms of 'reconstructing' frames and boundaries, to denote my interpretation of frames as social constructions as a meaningful way of discussing different interpretations of risk (see also later). Furthermore, and typically, frames are used to 1) define issues as problematic or not, 2) shape what actions should be taken and by whom, 3) protect oneself by recourse to legal or other rights, 4) justify a stance taken on an issue, and 5) mobilise people to take or refrain from action on issues (Lewicki et al. 2003: 15-19). Risk frames in this case stem from differences in how various stakeholders view the type and level of risk associated with a particular phenomenon.

As such, frames become most explicit in situations of conflict and controversy. Risk controversies have been described extensively in the literature, where Vaughan & Seifert (1992) take the stance that disagreements about risk can be

traced back to substantial variation in underlying belief and value systems. The authors present three themes that dominate debates about public health and environmental risks, which are of particular relevance to tissue engineering: the definition of risk (and related concepts), the weight or value attached to different dimensions of risk, and the issue of framing or structuring the decision or policy problem (Vaughan and Seifert 1992: 120-121).

The first one relates to the issue of how to define risk. For example, the concept of risk tends to embrace broader dimensions for lay populations than for experts. However, this study demonstrates how the debate on risk also reveals broad variability in perception and assessment of risk within and between different professional groups involved in R&D in this technological domain. In my research I use a typology of risk assessment over three distinct but interrelated dimensions, based on scientific risk (safety), clinical risk (efficacy) and commercial risk (marketability). A model depicting this classification is described later on in this section.

Furthermore, interested parties disagree about the factors that determine the (un)acceptability of risk, most notably regarding the value of health considerations relative to economic benefits or technological advances, but also in how to weight the amount of uncertainty in scientific risk estimates or the importance of immediate versus long-term consequences. I argue how risk debates in tissue engineering are driven by a broad range of considerations, extending the health versus economic nexus and also including more differentiated concerns. In my research I demonstrate how a hierarchy of risk is constructed based on two dimensions: first in terms of risk domains (safety, efficacy, marketability), but across sections based on the particular engineering route and cell source used in tissue engineered applications (autologous versus allogeneic).

Finally ongoing debate exists over how to conceptualise or frame risk issues. One important question addressed under this heading is whether the management of (public health) risks is about fairness regarding the distribution of risk and benefit in society, or belongs to scientific and economic domains. Another question is about the population affected, and if risk estimates should

be targeted at particular vulnerable groups (such as children) or expressed in terms of average risk to the entire population. Finally the levels of aggregation and the time-scale involved are critical. In my research I use the concept of 'balance of risk' to demonstrate different perceptions of (levels of) acceptable risk in a given context at one point in time and for particular groups affected. Thus the balance of risk determines the level (e.g. in terms of individual versus collective) of risk management approaches, but also takes into account acceptability over time ('inter-generational risk').

These different frameworks of risk are important because they dictate which 'solutions' are constructed in the policy process, e.g. which risk management strategies are considered valuable and feasible, and what information is needed and useful in reaching a decision. It also has implications for the legitimacy of different viewpoints in the policy process. By analysing the key dimensions of the construction of risk in tissue engineering, and the different dimensions and values attached to variations in risk, risk framing is linked to policy implications. The construction of risk discourses is tied in with the expression of a technological, political or social acceptable solution. Thus the definition of risk is at the same time the definition of a solution.

A main concern for the conceptual use of the term 'risk' in my study relates to the understanding of risk perception as a socially constructed concept,[16] but it also includes an interest in the policy implications of (differing) conceptual approaches to risk. By adopting a social constructivist perspective on risk, I move away from the view that scientific knowledge is composed of objective facts that can be explained, predicted and controlled, and as such provide the basis for decision-making.[17] A technical approach of risk does not take into

[16] As advocated by amongst others Tom Horlick-Jones (1998). Also other authors have pointed out how risks are necessarily socially constructed, with 'risk construction as a practice of manufacturing particular uncertainties that may have harmful consequences to 'life' in the broadest sense of the term' (Adam et al. 2000: 2).

[17] At the same time the limitations of this approach should be noted here. Social constructivists deny the existence of an objective material world and as such problematise the notion of objective truth. Instead they emphasise the contingent basis of social reality, where social facts are contested and subject to diversity of interpretation. The strength of this approach is its focus on broader social processes and the importance of the social, political and economic context. One criticism though is that social constructivism still involves objectivism because it assumes that the processes through which social problems are constructed are themselves objective facts which can be studied as such. Also social constructivism has been criticised for its

account the complex and socio-political nature of phenomena, including political dimensions (such as conflict or discrepancy over definition of what risks are and how they should be managed) or ethical concerns (including values in judgement of risk). By focusing on underlying values in risk assessment and risk decisions, the starting point of analysis is a concern with the perceiver of risk, rather than with risk as a phenomenon in itself (which, in technical terms, is usually expressed as probability in one way or another). Perceptions of risk, as has been argued, differ over place and time and per social setting, depending on the frame of reference or the social and cultural context is which risk is assessed and managed. While acknowledging that the notion of objective facts versus more subjective concepts of risk are in practice often blurred, and as such represent extremes in the ideal-typical spectrum, by understanding risks as value-based entities that cannot be separated from the policy-related science context, the door is open to analysing diverse belief systems that underpin different notions of risk. This provides a context for the shaping of a risk regulation regime, which is the focus of later chapters.

Against this conceptual background of framing of risk, the purpose of chapters 4 till 7 is to analyse the socially constructed or framed nature of risk in tissue engineering, including the various plural rationalities involved (compare Gabe 1995). As such, my study is not concerned with determining the accuracy of risk assessments or the success of communicating risk to the public, but rather with analysing how concepts of risk are constructed and agreed on in a broader arena. Risks are defined in particular ways that reflect the social and political setting or order, and with particular consequences for the public. Thus this research also aims to take into account the ways in which the constructions of risk shape the political debate in particular ways.

To this effect, my research analyses the wide-ranging accounts provided by professional groups involved in the front-end of tissue engineering research and development, namely scientists, clinicians and manufacturers. My focus is on how and to which extent risks are articulated in the different domains of tissue engineering R&D and in which ways they are framed and differentiated.

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selective skepticism, where Woolgar and Pawluch speak of 'ontological gerrymandering' (1985). With thanks here to Tom Horlick-Jones for pointing out these limitations.

To conceptually approach these different perceptions of risk, I adopt the demarcation approach as described in chapter 1. I analyse these perceptions in terms of boundary drawing around particular risk domains and identify the boundary objects that move within and between the different risk domains (and beyond, which is of concern for regulation as discussed subsequently). The next section provides a classification model to engage with the three dominant social worlds of risk perceptions.

3.1.2 Perceptions of risk in tissue engineering R&D: a classification

Social scientific perspectives on risk are divers, and risk typologies abundant (see for useful overviews: Horlick-Jones and Sime 2004; Renn 1992; Slovic 2000). Categorisation of risk is not novel either (see for one attempt: Sarangi and Candlin 2003).

From expert interviews (see later) different notions emerged of 'the risks' of tissue engineering, and more particular articulation and differentiation of these risks over specific spheres. I have called these risk domains. As such, a rather grounded approach was adopted where dynamic and varying interpretations of risk seemed to emerge as an important theme during the fieldwork. Initial inspiration to analytically engage with this variation came from a risk typology developed by Douglas and Wildavsky in their work 'Risk and Culture' (Douglas and Wildavsky 1982). This model is concerned with risk perception, and classifies how different social groups select risk based on their cultural characteristics. The authors define three general areas of concern with risk: *Socio-political risks* include dangers to social structure, usually stemming from human violence such as crime or war; *economic risks* are threats to the economy or risks of economic failure; and what they label *natural risks* includes ecological threats to nature and the body, which covers risk from technology (Lash 2000).

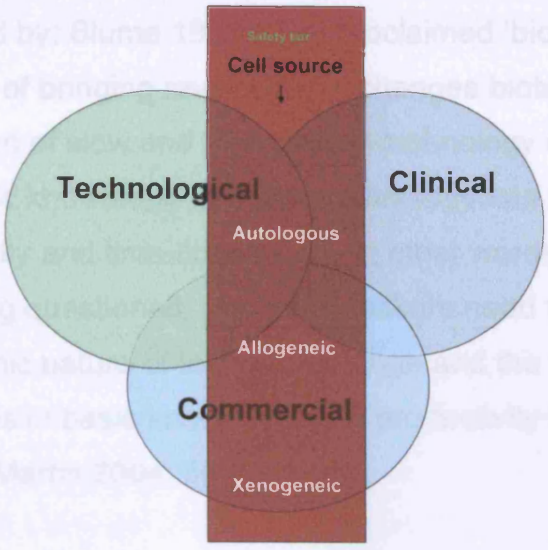
Douglas and Wildavsky use this typology not to provide a classification of 'real' risk but as a tool to link particular risk perceptions with separate risk cultures. This provided a good starting point for discriminating between different risk perceptions in tissue engineering. In my research I translate this model to different stages of the innovation process of biomedical technology, and as

such have a narrow take on risk perception as defined by actors in research and development (R&D) of this technology. The structure of this underlying innovation framework is discussed next.

My classification of risk perceptions follows the early stages of the innovation cycle of (biomedical) technologies, where innovation is simply considered as 'introducing something new' (Loughlin 2002). The innovation development process has typically been described as a linear model consisting of six phases, starting with problem or need definition which stimulates research and development, towards commercialisation, diffusion and adoption of the innovation by users to finally its consequences (Rogers 1995). My model for categorising risk perceptions is only concerned with a fraction of this process, namely the R&D and commercialisation phase, where scientific knowledge and insights of basic and applied research are further developed and converted into products or services for sale in the marketplace. Commercialisation, then, is the final station of interest in my study, where innovations are conversed into production, manufacturing, marketing and distribution of products. With respect to domains of innovation, this research speaks in simplified terms of lab, clinic and marketplace, which are each connected to certain practices and value systems. Perceptions of risk of tissue engineering technology are discussed in relation to these three domains. This leads to the following alternative risk typology:

A taxonomy of risk:

Risk domains and a safety bar based on cell source



In this model the three social worlds of lab, clinic and marketplace are visible as main domains, corresponding with the following categories of risk:

- Technological risk (safety)
- Clinical risk (efficacy)
- Commercial risk (marketability)

Technological risk covers concerns related to the processing and manufacturing of human tissue and cells, and reflects an overall concern with safety. Clinical risk is about perceptions of risk related to clinical evidence available for these products, with efficacy as key word. Commercial risk refers to concerns about the market and business climate for tissue engineering, and includes factors to do with cost and marketability of tissue engineered products.

Thus this typology is a reflection of the innovation process from lab to clinic to market. It covers the different phases in the R&D process with a focus on primary scientific work and basic research in the lab (technological risk, discussed in chapter 4), to the clinical phase in which the constructs are translated into initial clinical testing in humans (clinical risk, chapter 5), as a first transition into the market place, where the products enter the commercial cycle (commercial risk, chapter 6).

It should be noted though that these phases of innovation do not necessarily take place in a linear sequence, nor that these are distinct (a more dynamic stance is provided by: Blume 1992). The proclaimed 'biotech revolution' is one example. Instead of bringing revolutionary changes biotech has followed a well-established pattern of slow and incremental technology diffusion, where the translation of basic knowledge into new technology has been argued to be more difficult, costly and time-consuming. In other words the linear model of innovation is being questioned, and policymakers need to take into account the 'uncertain, systemic nature of technical change and the very long time scales between advances in basic knowledge and productivity improvements' (Nightingale and Martin 2004: 568).

This uncertainty has been described as notable characteristic of medical innovation. Policy debates are often based on the assumption of innovation as a homogeneous activity that follows the linear model as discussed above. But processes of innovation differ per sector and per economy, with extreme diversity of background conditions underlying the innovation process (Gelijns and Rosenberg 1995). For example technological innovation in the semiconductor industry does not resemble the process as found in fields such as tissue engineering. Even within the medical domain the conditions for successful innovation differ substantially per sector and sub-sector (e.g. compare pharmaceuticals and medical devices). In the case of tissue engineering this could be extended to even larger diversity because of the broad range of clinical applications, from relatively simple woundcare products to highly manipulated and complex constructions for whole organ replacement - that also constitute different risks.

Highlighting these limitations serves to illustrate the danger of crude reductionism in my classification of risk across three domains of lab, clinic and market. Therefore I also demonstrate the dynamic interactions between inhabitants of these domains, and the ways in which risk perceptions serve as boundary objects in negotiating what belongs to the social worlds of risk and/or regulation, and how the conditions of these boundaries are contested and negotiated. Here I rely on social constructivist notions of how 'relevant social

groups' help to shape technological innovation, acknowledging the relevance of interest groups and networks of social interaction around technical, scientific and medical innovation (Pinch and Bijker 1987). With this approach the distinct linear stage model of technological development is questioned, adopting a more dynamic view on the spread of innovative technologies (see also: Nicholson 2002). Eliciting different risk perceptions in transcending boundaries (rather than assuming these are fixed) is one way of illustrating this point.

Furthermore, the model also contains a 'safety bar' which runs across the different risk domains. This bar is based on interviewees' perceptions of the 'riskyness' of the different biological materials which form the starting materials for tissue engineered applications. Here it becomes clear how many of these risks are related to each other, but also constitute different values across risk domains. Therefore, in chapter 7 alternative dimensions are discussed in the perception of risk. One of those I have labelled the 'risk hierarchy', which is a reclassification of risk in terms of the particular source material used for tissue engineered construct. Autologous applications are generally considered 'less risky' than products based on allogeneic material. As demonstrated though, this perception clashes with another concern high on the risk list, namely the use of xenogeneic material in the cell culturing process for both the autologous and allogeneic engineering routes. Furthermore I argue how the particular cell source determines not only scientific endeavours but also drives clinical concerns and commercial strategies. It is here that the risk hierarchy becomes a more dynamic model, where risk in techno-scientific terms takes on a different meaning and value in clinical and commercial domains.

Another dimension of risk described in this chapter is what I have called the 'risk balance', which is about acceptability of risk, where perceived risks of tissue engineering are differentiated into levels and degrees of risk for particular applications (life-saving versus cosmetic, availability of alternatives), subsets of populations (e.g. children), and over time ('intergenerational risk'). The content of the balance of risk and the hierarchy of risk provide the context for risk management approaches, making the transition to the social world of regulation as discussed in subsequent chapters. The next section discusses the implications and limitations of this research.

3.2 Empirical focus and boundaries

In this section I draw the boundaries of what this thesis will include and what is excluded. The main players are briefly introduced, the timeframe and geographical limitations, and my conceptual approach to the regulatory domain. Also a note on terminology is presented, which is important for understanding the contested scope of tissue engineering regulation as discussed later.

3.2.1 Relevant actors

Community level policy development is characterised by frequently opposing views, powerful commercial interests, and social and political pressures. Tissue engineering is exemplar for an emerging innovative technology which involves a broad and growing network of actors with wide ranging interests. In the context of an increasingly urgent need for specific Community regulation for tissue engineered technologies, my main focus in this research is on two broad categories of actors. First I am concerned with interest groups in the R&D phase of tissue engineering, and their specific concerns with demarcating domains of risk. This includes discourses of technological risk and safety, clinical efficacy and marketability of products as employed by scientists, clinicians and manufacturers. Second, I describe the politicised nature of these risk domains when entering the regulatory world. Here I analyse the participation of diverse stakeholders involved in EU regulatory policy shaping and making. This entails a complex network of EU bodies and regulatory agencies, national governments, manufacturers and trade bodies, scientific experts and policy advisors, and to a lesser extent clinicians and patient groups. Of the diverse EU bodies in this domain, I limit my empirical engagement to the role of the European Commission and Parliament (and to some extent the Council). These institutions are assisted by staff at bureaucratic departments called Directorates-General (DGs) that take on specific tasks or policy areas. Two DGs are of particular relevance to tissue engineering regulation. DG Health and Consumer Protection (DG SANCO) has as goal the promotion of a better quality of life and is in charge of the public

health agenda, and proposes regulation that addresses these issues by imposing rules that assure a minimal level of quality and safety of medical products throughout the EU. DG Enterprise is mainly responsible for trade and the free circulation of products within the internal market, and its legislation is targeted at removing trade barriers. In terms of specific policy analysis a further breakdown of focus is on the regulatory efforts of these two dominant DGs, where I analyse the SANCO Directive on quality and safety of human tissues and cells, and the Enterprise Regulation in development for the marketing of tissue engineered products.

These specific regulatory initiatives are used as a vehicle to discuss the EU committee system and the role of expertise in regulatory science. Here the main participants are scientific (and other) experts engaging in policy debates, where sometimes strong links exist with industry. This adds another dimension to the circle of interest groups, as the intertwining relations and boundaries between science and policy, science and industry, and more explicit the interlinkages between science, regulatory policy and industrial practice are redefined in the arena of tissue engineering regulation.

3.2.2 Timelines and locations

One implication of my focus on these regulatory initiatives concerns the timeframe in which the specific regulatory activity in tissue engineering takes place. The phase of development of the SANCO Directive started in summer 2002 with the initial proposal, and with the final Directive being adopted in March 2004. The implementation phase for Member States is 2 years, with transposition into national legislation by 7 April 2006. The preparations for the DG Enterprise regulation date back to the same period of time, with a final proposal for a Regulation presented in November 2005. Thus the implementation phase and any weaknesses this may reveal lies beyond the scope of this thesis, which will however provide a definite account of what is being regulated, including an initial analysis of the regulatory closure achieved in the face of the tensions between market and safety central to this thesis.

A note on my use of the concept 'European Union (EU)' is needed in the context of the recent enlargement. EU is used in two ways in this thesis: when it concerns EU wide regulation the new EU-25 including accession states applies. However, the majority of the fieldwork (e.g. interviews) carried out for this research dates from the period of time (May 2004) before the enlargement. This means that in the analysis of developing regulation for tissue engineering mainly the 'old' EU-15 applies.

Furthermore, this study is a case study of tissue engineering regulation in the EU and as such limits its scope to debates and stakeholders at this level. This is not to suggest that an analysis of national stances is excluded, nor that input of Member States into the European debate or national positions towards European regulation is being ignored. In effect, a lot of discussion and agenda setting within the Commission can be traced back to national differences in aims and approach to tissue engineering regulation, and this thesis includes and unravels these interactions. Also in the discussion on expert systems, and more specific on comitology, the input of national Member States and their representatives is paramount. However, this thesis does not contain specific case studies of national legislation, and is not concerned with local policies, but is limited to the effects of national regulatory provisions on EU policy shaping.

Finally within several comparative studies of regulation of science-based products (such as pharmaceuticals, medical devices, agricultural biotechnology and nuclear power plants) reference is made to the role of the United States, or more specific that of the Food & Drug Administration (FDA). In my research the importance of the role of the US is acknowledged and explored via policy texts and literature, but data collection from fieldwork is beyond the scope of the present study.

3.2.3 Regulatory regimes of tissue engineering?

My concern with regulatory policy development is contextualised as the shaping of a regulatory regime in tissue engineering at EU level. According to Hood and colleagues, who have written extensively on the governance of risk and variety in systems of regulation over different policy settings, an analytical

distinction can be made between the 'context' and 'content' of such a regulatory regime:

> *Regime context* means the backdrop or setting in which regulation takes place, such as the different types and levels of risk being tackled, the nature of public preferences and attitudes over risk, and the way the various actors who produce or are affected by the hazard are organized. *Regime content* means the policy settings, the configuration of state and other organizations directly engaged in regulating the risk, and the attitudes, beliefs, and operating conventions of the regulators (Hood et al. 2001: 21).

In short a regulatory regime can be seen as driven by three broad features: type and level of risk, public preferences and attitudes towards risk and organised interests around those risks. The authors argue that by separating risk regulation into diverse dimensions of control and different elements of regime content, the shaping of regulation can be understood better than by analysing regulatory regimes in aggregated form (Hood et al. 2001: 139-40).

The notion of a regulatory regime is a useful starting point for my analysis, whereas I will also demonstrate the weaknesses in this approach, most notably over the assumption of a direct relationship between risk and regulation, crude reductionism to a by now infamous three-tier classification and thereby marginalising the more complex and dynamic character of the social construction of risk and the ways in which these risks are negotiated to become adopted (or not) for purposes of regulatory policy.

One relevant element of this model, then, lies in the notion of interest representation in regulatory policy shaping. This is also further developed by Hancher and Moran (1989a) with the concept of 'regulatory space', in which they identify a dominant role for large firms. This concept proves useful in the analysis of stakeholder participation in tissue engineering regulation, as it focuses on the 'inhabitants' of what the authors conceive as common regulatory space. The dimensions of this regulatory space can be understood by looking at national regulatory settings, including their specific political, legal and cultural attributes (Hancher and Moran 1989b: 277). The boundaries of this regulatory space are defined by a range of regulatory issues (such as safety), that are contested by different groups in the arena. In their empirical

investigation of the pharmaceutical industry, the rules of inclusion and exclusion are set by large and complex organisations: big firms and regulatory agencies decide who is in and who is out of the regulatory space. The way these large organisations work (via administrative hierarchies applying standard operating procedures, or simply routine) defines the content of the regulatory space, while the same goes for the organisation and prioritisation of issues (of what is 'regulatable'). The relation between large organisations is perceived to be key in understanding the shape of the regulatory space, and the characteristics of the organisations (such as cultural environment, resources available, standard operating procedures) define the conditions under which these organisations can enter the regulatory space and maintain their position.

The value of the regulatory space approach is not so much situated in the authors' plea for an analysis of the dimensions of regulatory space by studying national regulatory settings and their specific political, legal and cultural attributes. Although my research is concerned with national differences in the regulation of tissue engineering products, the main goal is not to explain different styles and outputs, but rather the effects of national divergence in the context of EU policy shaping. The concept of exploring regulatory space is useful in identifying the role of large organisations (regulatory bodies at national and supranational level and the multinational industry) and their interdependence, plus the institutional setting in which regulatory space is organised. Also the definition of regulatory issues by the different competing groups proves useful in the case of tissue engineering, as also discussed under notions of boundary-work and the European Commission as boundary organisation.

Furthermore, the notion of a regulatory space has been conceptualised in alternative but overlapping terms. For example, the notion of the 'agora' has been coined in this respect (Nowotny et al. 2001), while also an 'arena' would refer to the politicised nature of interest representation in regulatory activity. Some authors refer to a 'regulatory order' in an attempt to describe the different interlinked regulations and laws that govern certain technologies (Faulkner et al, 2006) as an alternative to the term 'regulatory regime' which has been used

for formal regulatory activity as a more rationally designed and systematic process.

Rhodes developed the idea of 'policy networks' for explaining variations in power distribution and dominant interests in networks (Rhodes 1997). According to this perspective, policy networks are important tools in public policy analysis as they give insight into the manner in which powerful individuals, located in the maze of public and private organisations that govern a policy domain, connect with each other (John 1999). Key features of policy networks are that they limit participation in the policy process, define the role of actors, decide which issues are included and excluded from the policy agenda, determine behaviour of actors by defining the rules of the game, privilege certain interests and substitute private government for public accountability (Rhodes 1997: 9-10). Simply put, policy networks reflect who rules, how, and in whose interest. This is a useful notion to depict the complex configurations of R&D and policy actors involved in domains of risk and regulation in tissue engineering, as also touched upon earlier in this section.

My understanding of notions of risk and regulation is thus informed by several concepts that define the boundaries of these domains, while also acknowledging the importance of different interest groups and their negotiated interactions over what counts as risk, and what shapes the context of regulation - although I prefer a less static and systematic approach to these concepts as found by many authors in this field. Mere 'politics' (or, as it happens, mandated bureaucracy) is not sufficient to engage with these themes though, and earlier in this chapter I have given insight into my understanding of the social dynamics in approaches to risk.

The next section contains my final empirical limitation, which concerns the notion of tissue engineering.

3.2.4 Definitions in the construction of a technology

In order to define what is subject to control, a clear picture is needed of the scope of the domain under regulation. For tissue engineering this is problematic, as there are many different definitions and terms to refer to the technology, and the various technological aspects of tissue engineering show overlap with other existing treatments and therapies. Because of the fast developments in the field, with tissue engineering as such still emerging, definitions of the technology tend to be flexible and open to debate. Many more definitions of the technology exist than there are tissue engineered products currently on the market.

As previously described, boundary-work is one way of demarcating a professional domain. Early efforts in boundary-work become visible if we make an inventory of the range of definitions of the technology that have been coined since the early development of the field (see for more detail: Geesink 1998).[18] Some of these focus on the techno-scientific possibilities of regenerating human bodily functions (DG SANCO: SCMPMD 2001), while others point out the therapeutic promises and interdisciplinary character of the emerging sector (European Commission (EC) 2004).

For regulatory purposes the need has been expressed to produce a 'scientifically valid and legally sustainable definition' of tissue engineering, because this provides the basis for demarcation between tissue engineered products on the one hand and adjacent categories such as medical devices, pharmaceutical products and cell therapy on the other (DG SANCO: SCMPMD 2001: 2). Thus the lack of stable definitions of tissue engineering is relevant in the light of controlling the technology, as it draws the boundaries between

[18] Tissue engineering as a technology was born long before it had a name. According to several reviewers, the debut of the term 'tissue engineering' can be traced back to a set of meetings organised by the US National Science Foundation (NSF) during the Spring of 1987, where tissue engineering was identified as emerging technology and funding priority. In a subsequent meeting on the topic, held 26-29 February 1988 in Lake Tahoe, California, the following definition was developed: "Tissue engineering is the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve tissue functions." (Skalak and Fox, 1988). For a more elaborate account on the social-historical development of tissue engineering as a research field in the United States, including the early origins of the technology, see Viola et al (2003).

techno-scientific domains. Determining the scope of tissue engineering is then of key importance in terms of the inclusion and exclusion of different facets of the technology in the regulatory domain, based on different or similar risks that can be associated with a particular application.

It has been argued that the absence of agreed terminology within the policy arena indicates both the discursive construction of these objects and their 'instability' (Bijker et al. 1987; in Kent et al. 2006). The stabilisation of technological artefacts, according to this approach, is bound up with their adoption by relevant social groups as an acceptable solution to their problems (Pinch and Bijker 1987). Coming from a similar tradition of social construction of technology (see also MacKenzie and Wajcman 1999), an interesting account is provided by Adam Hedgecoe in his exploration of the way in which social explanations and commercial interest underpin the names of particular disciplines, in this case pharmacogenomics (2003). Hedgecoe argues how pharmacogenomics, as opposed to the term pharmacogenetics used previously, not just represents a research area, but can also be seen 'as a rhetorical device used to gain support among policy makers and funders for particular research topics and technologies' (Hedgecoe 2003: 513-14). In this way a future view or vision is created which leads to the production of new technologies, and to other developments such as regulatory changes and social attitudes (2003: 530-531). This analysis resembles efforts in the tissue engineering field to present the technology as 'new and exciting' enough to attract funding and special enough from adjacent technological domains to warrant specific regulatory controls, while at the same time demarcations take place where tissue engineering is singled out from more controversial applications in embryonic stem cell therapy. The details of these dynamics are discussed elsewhere in this thesis. The next paragraph contains a note on usage of my understanding of tissue engineering is this study.

Terminology

With this context in mind, for the purposes of this research I follow the European Commission in its definition of the term 'tissue engineering' as a field and 'tissue engineered products' for the (commercial) results of its scientific

activities. With due notion of ongoing debate in this area (DG Enterprise 2004a), tissue engineering means for now:

> Any autologous or allogeneic product which: contains, consists of, or results in engineered human cells or tissues; and has properties for, or is presented as having properties for, the regeneration, repair or replacement of a human tissue or human cells, where the new tissue or the new cells, in whole or in part, are structurally and functionally analogous to the tissue or the cells that are being regenerated, repaired or replaced (DG Enterprise 2004b).

An important notion for regulatory purposes is the degree of manipulation of the tissues or cells, i.e. to determine whether tissue engineering applications are categorised as 'basic' cells or tissues or whether their degree of manipulation requires specific tissue engineering regulation. For this reason a definition is required of what 'engineered' means in this context:

> *Engineering* 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 (DG Enterprise 2004b).

Finally of major relevance for regulatory control of tissue engineered products is the origin of the cells or tissues used. The following two definitions are adopted for the purposes of this thesis (DG Enterprise 2004b):

> An *autologous product* is a product derived from cells and tissues removed from one person and used in or on the same person. An autograft is a tissue or an organ transplanted into a new position within or on the same individual.
>
> An *allogeneic product* is a product derived from cells or tissues removed from one person and used in or on another person. An allograft or homograft is a tissue or an organ transplant between individuals of the same species, but genetically non-identical.

This distinction in cell sources is key to understanding risk and regulation regimes in tissue engineering. Interestingly in this respect is that *xenogeneic products* (of animal origin) are not explicitly defined by the European Commission in relation to tissue engineering. Initially the Commission considered these still in 'the infant phase of development' and because of the complex safety and ethical issues difficult to regulate in this early stage. Gradually this perception changed, as this research demonstrates.

Summary

The first section of this chapter has focused on notions of risk and presented a classification of risk domains that structure and inform my analysis. In this section the second main theme of my research, regulation, was further explored. While chapter 2 has explained the policy context in order to understand the current regulatory efforts in tissue engineering regulation, this section has set the empirical focus and boundaries of my research. The relevant actors of my research were introduced, the time limits and geographical scope of my engagement with EU regulatory policy development, my understanding of the shaping of a regulatory regime for tissue engineering in this context, and finally my adoption of a definition of tissue engineering technology for this research. Discussed next are the methods used to inform my analysis.

3.3 Methodological discussion

The previous sections focused on my understanding of risk and regulation as key themes in my research. In this section I demonstrate my methodological engagement with these themes, and review and reflect upon the research process and specific methods used to capture these data.

3.3.1 On projects and PhDs

My interest in tissue engineering dates back from early 1997, when I read an article in a Dutch opinion magazine about this new medical technology that promised to restore all kind of bodily functions and provide spare body parts 'off the shelf'. The culture-your-own approach was fascinating, especially to a sociologist looking for a suitable subject for her Master's thesis in Science Studies. So tissue engineering it was. As part of my degree I interviewed scientists and clinicians to get an idea of their impression of this new developing field and about the interaction between lab and clinic. I spent some time at IsoTis, a tissue engineering company based in the Netherlands, which gave a useful insight into what was actually happening in these clean rooms, and how to present the technology to investors and 'the public'.

A couple of years later, on 24 May 2002 to be more precise, I came across a vacancy for a position at Cardiff University to study regulation of tissue engineering products in the UK and EU. It all looked very interesting, especially to a sociologist looking for a suitable subject for her PhD thesis.

In the summer of 2002 I moved to Cardiff, to conduct research on a project called Tissue Engineering Regulation and Governance (TERG). This project was funded under the ESRC/MRC programme on Innovative Health Technologies (IHT), running from June 2002 till October 2004. I worked as a Research Associate on this project for two years, between September 2002 and the end of August 2004.

When I took on this role, it was agreed I could study for a PhD degree alongside the project, based on data gathered during the project. This gave the obvious advantage of being able to collect the majority of the data for my PhD during project time and on project resources. Because of the empirical overlap between the ESRC project and PhD, it is important to make a distinction between the work carried out by the project team, including myself, and the work more exclusively dedicated to my PhD thesis. In this chapter I present and clarify these differences, and explain how, when and where the empirical data in this thesis rely on those collected for the ESRC project, while maintaining an 'original contribution' for the doctoral.

Before getting to the specific methodology used, the next section provides a reflexive account of the research process and my position as researcher in the field.

3.3.2 A note on the research process: the sociologist in science

Below I give a reflection on the research process, driven by considerations that qualitative research raises more than purely technical issues about data collection (Atkinson et al. 2003). Issues discussed include engagement with complex data and power and inequality relations in conducting interviews - which constitutes the heart of my fieldwork.

One issue that was prominent during the entire research process concerns the technical nature of the topic and data. Although earlier research had made me familiar with the 'science' behind tissue engineering, the amount and complexity of techno-scientific and clinical data was at times daunting. Even, or perhaps exactly in order to provide a socio-political analysis of tissue engineering, I had to know the basics. This meant updating my technical knowledge by consulting tissue engineering handbooks, scientific articles and online resources explaining the ins and outs of the technology. Especially during my interactions with scientists, but also with manufacturers and clinicians, I informed the respondent of my technical naivety. None of the interviewees seemed reluctant to meet my request for more explanation or elaboration.

This position does have repercussions though for the 'authority of the researcher' and affects the kind of data and possibly their validity in a given context. As documented in several methodological studies about conducting fieldwork, the researcher is engaged in practical activities that are not neutral, nor result in 'an unmediated representation of an independently truthful representation of the social world' (Atkinson et al. 2003: 13).

Another aspect that affected the relationship and interactions with my 'research subjects' concerns my position as non-UK junior female researcher in a social science discipline. Most interviewees were senior professionals and male, and experts in their respective fields. In political terms this had the advantage there was no 'competition' or tension as generated from a power relation. This could lead to the conclusion that the interviewee is 'in control' of the situation, simply based on this unequal distribution of power from the outset (Gilbert 1993). Indeed, some respondents were not always or necessarily directly guided by the interviewer. Several interviewees, especially those familiar with communicating information outside their own field of expertise, had a story ready to be told, being less inclined to follow the order of topics suggested by the researcher (or, in rare occasions, the topics brought up at all). I like to think this is more a matter of dealing with experienced communicators than reflecting lack of control of the situation on behalf of the researcher. Also, even 'losing control' over my topic list has generally brought up interesting additional insights. Furthermore, it has been suggested that for 'the perfect match' between interviewer and interviewee it is not always meaningful to think in terms of similarity, and that 'it may be easier to confide in a stranger, that female interviewers may be less threatening to both female and male respondents and that deference may encourage rather than inhibit response' (Fielding 1993: 145).

But there were also other forces at play. For example the fact that English is not my mother tongue, while interviews were conducted in this language, meant on the positive note that I could use my language inability, sometimes as an excuse, to prompt the respondent to further clarification. Secondly the fact that a number of interviewees at EU level or on the continent did not speak

English as their first language either was an advantage in terms of (in)equality; my impression is that these interviewees felt probably more at ease knowing that there was more than one person in the equation trying to express themselves in a foreign language. Which is not to suggest that language barriers were overall non-existent or not problematic. Especially with the phone interviews, where it is obviously harder to communicate non-verbal language, I felt I had to more strictly stick to the literal questions written out in the interview guide. Overall my impression is that the face-to-face interactions provided more rich material than telephone (or, for that matter, email) conversations.

These issues all more or less relate to general communication (strategies) during the interviews. It has been argued that two principles should inform interviews: the questioning should be as open-ended as possible to gain spontaneous information, and the questioning techniques should encourage the informant to communicate underlying attitudes and belief rather than trying to get away with easy answers. The idea, then, is to have an as frankly discussion as possible. But reality bites, and for centuries researchers have been warned for the effects the interviewer has on the respondent's statements. It is acknowledged widely that respondents may attempt to rationalise their behaviour by trying to give logical answers rather than emotional reasons which may gain more insight. Also lack of awareness and lack of information have been reported. Over-politeness towards the interviewer is another issue which can hamper frank discussion, for example when respondents give answer they anticipate the interviewer wants to hear. Several suggestions have been made to alleviate these communication problems, many of which come down to putting the respondent at ease, and being experienced in the interviewing technique and familiar with your interview guides (Fielding 1993). These suggestions were only in so far helpful for my research, in that the most crucial and high-level interviews, for example those at the European Commission, were saved till last to benefit from the insights and experience gathered during earlier data collection and to feel more at ease with both the interviewing guides and overall process. This on the pragmatic level. As a more conceptual issue it is interesting to notice how much of the literature on 'how to conduct a proper interview' has a very technical understanding of what the interview procedure should look like. Much of the

guidance is about controlling the process to maximise the flow of valid and reliable information. The simple assumption is that if the interviewer asks questions properly, the respondent will come up with the desired information. Without wanting to address a more philosophical discussion here of positivist versus constructivist realities in interviewing,[19] or even general quests for the truth out there, this does connect to a related issue, namely validity and reliability of data.

The next section discusses my methods for data collection, followed by a section on data management and analysis.

3.3.3 Research methods: data collection

A preferred line in the social sciences is the use of triangulation: the application and combination of several research methodologies in the study of the same phenomenon. By combining multiple observers, theories, methods, and empirical materials, researchers attempt to overcome the weakness or intrinsic biases and the problems that come from single method, single-observer, single-theory studies. Stemming from work by Denzin (1970, 1978) and further described by many researchers (this account comes from Macdonald and Tipton (1993: 199)) there are four basic types of triangulation:

- Data triangulation, involving time, space, and persons. This means that data should be collected at different times, in changing locations and from a range of persons.
- Investigator triangulation, which consist of the use of multiple, rather than single observers in studying the same object
- Theory triangulation, which consists of using more than one theoretical scheme in the interpretation of the phenomenon to generate categories of analysis
- Methodological triangulation, which involves using more than one method and may consist of within-method or the more important between-method strategies.

Then there is this thing called 'multiple triangulation', when the researcher combines in one investigation multiple observers, theoretical perspectives, sources of data, and methodologies. My research is a modest attempt in this

[19] A rather comprehensive account on this is provided by Miller and Glassner (in Atkinson, 2003: chapter 5).

direction. In terms of data collection the research for this thesis can broadly be characterised as a combination of documentary study and analysis, a small-scale postal survey, participation in field conferences and expert meetings, and extensive semi-structured interviews. What follows in the next few paragraphs is a more detailed account of the data collection methods, with a focus on the interviews as most dominant source of information.

3.3.3.1 Documents and databases

Out of the toolbox available to the qualitative researcher,[20] interviewing was chosen as most appropriate technique to the specific research subject. This choice was mainly driven by the lack of sources available on social-scientific aspects of tissue engineering technology. The plus side of this observation is that my research adds to knowledge development in a domain not previously explored in any detail by social scientists. The drawback of my specific concern with issues of risk and regulation as guiding themes informing my analysis is the limited amount of documentary data in the public domain.[21] For example risk assessment studies are scarce, and overall of a narrow techno-scientific nature. While the clinical and scientific literature on tissue engineering is abundant and growing,[22] these sources only functioned to inform the research design and sampling before the interviews took place, and for further refinement and comparative analysis during and after this process of data collection. I kept record of all documents in an EndNote database, which also served as bibliographical tool for other literature.

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[20] This thesis mostly draws on accounts by Atkinson et al. (2003a); Coffey and Atkinson (1996); Crabtree and Miller (1992); Flick (1998); Gilbert (1993); and Silverman (1997).

[21] The following documentary sources have been included: Clinical evaluation and technology assessment literature; Trade journals dealing with regulatory affairs (RAPS) and commercial magazines covering medical and biotechnology in Europe (MDT); Labelling information and protocols for existing products; Information about EU regulatory activity; Information about national regulatory activity across Europe and, to a lesser extent, in the US; Official publications of the Commission and EU legislation and policy documents; Limited media reports and comments in EU countries, on regulatory issues and new products; National and EU-level working papers and some risk assessment reports; Selected national government policy documents; and manufacturers' annual reports and product advertising material.

[22] For example a Medline search on 'tissue engineering' conducted in May 2006 brings up 6720 records (of which 1400 reviews). In comparison, the same search terms for publications up till May 2000 results in 587 hits (including 194 reviews). To inform my research more specific searches were conducted. These included combinations of search terms: tissue, engineering, regeneration, repair, bio-organ, artificial organ; and/or combinations with specific clinical application areas such as skin, cartilage, bone, ACI, vascular; and/or combinations with specific product names.

Documentary sources on regulatory policy in tissue engineering were equally limited (with the exception of online legislative databases as discussed below), reflecting the developing character of this endeavour. A small-scale postal survey was undertaken early on during the research, addressed at regulatory authorities in Europe, to get an impression of the variation in national regulatory policies and stances (TERG 2003). The results of this survey were fed into the interviews conducted subsequently.[23]

While my data chapters on risk are mainly based on interview material (as also discussed later), my analysis of regulatory policy was aided by a number of online sources. Websites starting with 'europa.eu.int' in the URL listed general background information on EU policy processes and structures, such as glossaries of key terms, bulletins and fact sheets, while specific unit websites (such as those of DG SANCO and DG Enterprise) provided keynote speeches, press releases and official legislative documents. Of most relevance was the OEIL Legislative Observatory of the European Parliament.[24] This web tool allows one to track the legislative cycle of Directives and Regulations after the initial proposal by the European Commission has been adopted (which is at the same time its limitation, as only the 'democratic' part of the legislation is covered). EUR-Lex[25] is a free-access service by the European Commission for legislative information, but only includes official full-text versions of legislative documents such as EU Treaties, proposed and adopted legislation and publications in the Official Journal of the European Community. Pre-Lex,[26] also from the European Commission, is a good alternative for tracing progress in legislative initiatives. It is presented as tool for monitoring of the decision-making process between institutions (European Commission, Council, Parliament) but again only contains official or final versions and mostly refers to other databases such as EUR-Lex. In addition to these legislative sources,

[23] Altogether 38 questionnaires were distributed between November 2002 and March 2003 to regulatory authorities and experts in 17 countries: all EU Member States (pre-enlargement), plus Norway and Switzerland. 12 countries responded. The questionnaire consisted of 28 questions; a combination of structured items, with little leeway in answering, and open-ended items. Most questions gave an opportunity for the respondents to make comments, which was useful for further exploration via other methods (documentary analysis, interviews etc). The most relevant results for my research included the information on national legislation and variation, products currently on the market and under clinical trial, future plans for regulation and possible involvement in EU regulatory activity.

[24] See http://www.europarl.europa.eu/oeil/index.jsp

[25] See http://europa.eu.int/eur-lex/lex/

[26] See http://prelex.europa.eu

online press releases from EurActiv[27] ('EU news & policy positions') were particularly interesting for the way in which the EU presents the 'summary points' of policy discussions to the public.

These sources can be considered 'raw data' informing my socio-political analysis of regulatory policy. In all their limitations (only official and final documents, purely legislative, often tedious and time-consuming to find your way through the databases) at least these sources were freely available with an online connection. Furthermore the European Documentation Centre, one of the Cardiff University libraries, has an extensive collection of publications on European policy, plus a password to an online database called 'European Sources Online'. This added amongst others access to media coverage on European policy topics. For reasons of time-restraints and sanity I decided to not include any of these media sources, and focus on the material available from the interviews. These are discussed next.

3.3.3.2 Interviewing experts

Interviews constitute the core of my fieldwork, and my engagement with themes of risk and regulation draws heavily on these data. A total of 69 semi-structured interviews was conducted, 63 of which took place as part of the data collection for the ESRC project. These included expert interviews (see: Flick 1998: 91-92) with stakeholders and key informants involved in scientific, clinical, regulatory and commercial activity in tissue engineering.

The aim of the interviews was to find out the views and experiences of a diverse group of stakeholders in the tissue engineering field, mostly in Europe and at EU level, and to a lesser extent specifically focused on the UK. Initially six primary constituencies were identified: regulators, manufacturers, clinicians, scientists, consumers/patient groups, and EU advisory groups. Furthermore this sample aimed to reflect product types representing 'adopted' (skin systems and knee cartilage processes), 'emerging' (bone) or 'experimental' (e.g. vascular prostheses) positions. Also a good balance was sought in the different implications of 'autologous' and 'allogeneic' products or processes, which

[27] See http://www.euractiv.com/en/

seemed to be emerging as important in regulatory policy statements and in the identification of different levels of risk.

Topic lists and interview guides were developed, based on initial understanding of what was problematic and interesting about tissue engineering regulation, that were adjusted during the piloting phase of interviewing (one interview in each category). Most interviews took place face-to-face in the work environment of the interviewee, and some over the phone. The vast majority of these interviews was conducted between December 2002 and March 2004 for the first phase of data collection, while follow-up interviews and email exchanges were undertaken in 2005 specifically for the PhD research (see later under phase 2).

The tables below demonstrate the number of interviews (63) conducted under the ESCR project at UK and EU level per stakeholder category (table 1), the distribution over telephone and face-to-face contacts (table 2), and the geographical distribution (table 3).

TABLE 1:
Overview UK and EU and total number of interviews, per category

Category	UK	EU	TOTAL
Regulators	3	6	**9**
Manufacturers	3	11	**14**
Clinicians	6	6	**12**
Scientists	8	2	**10**
Consumers	5	0	**5**
EU advisory	0	9	**9**
Other	4	0	**4**
TOTAL	**29**	**34**	**63**

TABLE 2:
Distribution telephone interviews and face-to-face discussions:

Category	UK face to face	UK telephone	EU face to face	EU telephone	TOTAL
Regulators	3	0	5	1	**9**
Manufacturers	3	0	6	5	**14**
Clinicians	5	1	4	2	**12**
Scientists	8	0	0	2	**10**
Consumers	4	1	0	0	**5**
EU advisory	0	0	7	2	**9**
Other	4	0	0	0	**4**
TOTAL	**27**	**2**	**22**	**12**	**63**

TABLE 3:
Distribution per country for UK and EU interviews

	Regulat.	Manufact.	Clinic.	Scient.	Consu.	EU Advis.	Other	TOTAL
Austria								**0**
Belgium	1	2	1			1		**5**
Denmark	1							**1**
France	1	1				2		**4**
Germany		4	1					**5**
Italy		1		1				**2**
Luxembourg						1		**1**
Netherlands	1	2	2					**5**
Spain	1							**1**
Sweden			2	1				**3**
Switzerland	1							**1**
UK (EU)		1				5		**6**
TOTAL	**6**	**11**	**6**	**2**	**0**	**9**	**0**	**34**
UK (UK)	3	3	6	8	5	0	4	**29**
TOTAL	**9**	**14**	**12**	**10**	**7**	**9**	**4**	**63**

Response rates

Overall the response rate was high, although precise figures are difficult to estimate. A 'long-list' of names was created of potential interviewees per category, with some key figures but also many 'reserves'. Names were added along the interview process, based on recommendations by interviewees and from documentary sources. Invitation letters were sent out to some 80 people. About 30 of these did not participate personally (out of time restraints, unwillingness, unavailability during data collection period of the project, illness and leave etc) but most people did pass the interview request on to colleagues in the organisation or other professionals in the field. In this way the response rate was only marginally affected, although in some cases it can be argued that the specific expertise or status of the respondent was not equalled. Especially EU officials and patient organisations were difficult to get involved, for different reasons. Also a large proportion of manufacturers did not respond to the request for interview, or found more or less valid excuses not to participate. Given this category was over-represented in the research sample, the absolute number of commercial providers participating was high.

Accountability and additional interviews

The interviews as described in this section were all conducted within the framework of the ESRC project. I was responsible for arranging most of the fieldwork (making appointments and organise travel), but the interviews were carried out by different team members, and some interviews (especially the pilot and EU level ones) were carried out by two members of the team. Below is an overview of the interviews that I conducted myself or together with another member of the team. Out of a total of 63 interviews, 34 were (co-)conducted by myself (IG).

Category	UK IG	UK other	EU IG	EU other	TOTAL IG	TOTAL other	TOTAL all
Regulators	1	2	3	3	4	5	**9**
Manufacturers	2	1	6	5	8	6	**14**
Clinicians	2	4	6	0	8	4	**12**
Scientists	5	3	1	1	6	4	**10**
Consumers	2	3	0	0	2	3	**5**
EU advisory	0	0	5	4	5	4	**9**
Other	1	3	0	0	1	3	**4**
TOTAL	**13**	**16**	**21**	**13**	**34**	**29**	**63**

Beyond the scope and timeframe of the ESRC project, additional interviews took place. This included a round of follow-up telephone conversations with two key informants at EU level, taking place over the course of 2005, mainly to get an update on regulatory developments in the field and more specific guidance on EU procedures. Also three commercial informants in the field were contacted again to keep abreast with regulatory developments, and one new one. The richest source of additional data collection took place during a stakeholders meeting in Brussels organised by trade association EuropaBio, as also discussed later (under phase 2).

Characteristics of interviewees

While it was helpful to make an initial classification of different stakeholder groups, it should be noted that this interview sample is affected by the observation that many respondents occupy different roles. The tissue engineering field is very interdisciplinary, and professionals move between different settings with different hats on. For example, scientists work in academic labs, in clinical settings and in industry, and regulatory affairs professionals in industry are often trained in the life sciences and/or have had previous careers in government agencies (or vice versa). Clinicians in this sample are based in hospitals and academic labs, but do not always practise as physician. Furthermore, many scientists have close links with industrial partners, if they are not heading university spin-offs themselves. The revolving door between academia, industry and government is a fast moving one.
This does have repercussions for the representation of these stakeholder groups, and makes a typology based on just professional background or affiliation problematic.
I have organised my interview quotes in a manner to reflect the professional background of respondents as accurate as possible and meaningful for the given context. The appendix gives a full list of descriptions and codes of my interviewees.

In terms of boundary objects, the interviewees in this sample have multiple memberships of many social worlds simultaneously. Interviewees occupy a number of roles and positions, associated with a variety of institutional and organisational settings in academia, science, government, and industry.

Because of these hybrid careers and identities (Geesink 1998) these actors are able to translate and exchange their work and ambitions across different settings. In other words, these actors can be seen as 'boundary people' between the different social worlds of tissue engineering.

Unstructured interviews and participant observation

In addition to these semi-structured and previously arranged interviews, some unstructured interviewing took place as part of participant observation exercises and my attendance at expert meetings and fieldwork conferences. These included a regulatory affairs workshop during an industry-sponsored scientific conference,[28] engagement in the local tissue engineering community via several meetings and annual conferences of the Cardiff Institute for Tissue Engineering and Repair (CITER), and attendance of an industrial stakeholders meeting in Brussels where the Commission presented the final proposal for a Regulation on tissue engineering products.[29] In addition I had access to fieldwork data collected by my fellow-researchers of the ESRC project.[30]

Extensive field notes were produced based on observation and participation in these meetings and conferences, and documents collected in the form of speakers' presentations, papers and associated materials. This generated a large and complex amount of data in relation to tissue engineering science, industry activities, regulatory issues, and ethical debates in the development of regulatory policy. In this way I had access to information that was not otherwise available; some of this was commercial or scientific information not in the public

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[28] Tissue Engineering Regulatory Affairs Workshop. Organiser Smith & Nephew, at Georgia Tech, Atlanta, USA, October 2002.

[29] EuropaBio Industry Hearing: Tissue engineering and advanced therapies. Radisson SAS Brussels, 9 November 2005. In order to get access to this meeting without having to pay a substantial fee I agreed with the organisers to produce a written report of the meeting. I audio recorded and fully transcribed the presentations and discussions of this meeting, and provided a summary report which is published on the website of trade organisation EuropaBio: www.europabio.org/events/IndustryHearing/ REPORT%20of%20Hearing-051206.doc

[30] European level sources included a Public Hearing on Quality and Safety of Human Tissues and Cells (European Parliament, January 2003, Brussels) and a multi-stakeholder meeting at the European Commission DG Enterprise to discuss proposed new Tissue Engineering Products/Approval Directive (Brussels, 16 April 2004). A national level source included: UK Medical Devices Agency Annual Stakeholders Meeting (October 2002, London). Conferences included: 'Discussion Forum: Development and Regulation of Cell-based and related Therapies,' organised by Regulatory Affairs Professional Society (March 2003, London); and 'The Commercialisation of Tissue Engineering and Regenerative Medicine,' organised by Marcus Evans Conferences, supported by the International Society for Cellular Therapy (April 2003, London).

domain yet, but quite often these meetings were excellent opportunities for an analysis of stakeholders' networks (who knows who), and for extending my own contacts database. Thus the more 'hidden' processes and relationships between actors in regulatory decision making were revealed by observation of the context in which they engage as part of their professional roles. This also informed the analysis of interviews and key documents, as discussed next.

3.3.4 Data management and analysis

All but two interviews were audio-recorded and verbatim transcribed. Because of the possibly sensitive issues coming up during the discussions, and to demonstrate awareness of ethical and legal implications of the research carried out, informed consent was sought from all participants.[31] The transcripts were anonymised by replacing full names by abbreviations and date by a code (in the format of for example: S1-SMI 120303, for a scientist called Smith being interviewed on 12 March 2003). In this thesis only the prefix code and year of interview are used (S1, 2003) with a short description of the respondents background and affiliation.

The data analysis for this research is a combination of basic and ethnographic content analysis (Miller and Crabtree 1992: 17-23). A codebook was developed based on dominant pre-structured themes which were organised in different categories (including 'families' of codes). A specific analysis took place with an exclusive focus on themes for the PhD research, following a more intuitive and interpretative approach to the data. The coding frame developed for the ESRC project was refined and revised during the process of data collection, which enabled me to engage with 'upcoming' themes, also informed by theoretical perspectives and other data sources. For example one dominant theme emerging from the data concerned different perceptions of interviewees on risk, where I developed several 'subcategories' to capture this variety. On the other

[31] In line with the ethical guidelines issued by the British Sociological Association (BSA, 2002) the consent form stated that interviewees: have received a copy of the information leaflet about the aims of the project; are willing to be interviewed for this research and for the interview to be tape recorded; understand that the interview is confidential and the data are anonymised; and finally that they understand that taking part in the research is voluntary and that they may withdraw at any time. Each interviewee is given assurances of anonymity and confidentiality, and they were told that the tapes are kept secure and would be destroyed after the project.

hand not all project material was useful for my specific focus. For example I limited my data presentation of risk perceptions to R&D actors, thereby excluding such groups as consumer organisations, regulators and advisory groups (although their perceptions did inform my analysis).

Thus a specific code-book was designed to cover themes for the PhD research.[32] These codes followed on the one hand a more 'grounded' approach, with a fair degree of 'intuitive crystallisation' as some would call it (Coffey and Atkinson 1996), and in an almost editing style of engaging with the text, while on the other hand a selection of pre-existing codes specifically targeted at my PhD research were part of this additional coding frame. In this way meaningful parts of the text could be identified that relate to the purpose of my study, but also ones with a 'stand alone' value that could be organised into categories and additional codes.

The coding procedure simplified and reduced the data and enabled segments ('chunks') of data to be easily retrieved, which helped my analysis and interpretation of the data for drawing conclusions. This data analysis mainly concerns the interview material, most notably the transcripts, and the field notes from observations and less structured interviews. Also the documents were analysed with a particular coding frame in mind, but in much less detail (for example there was no codebook for the documentary analysis) and without the aid of a computer programme for coding.

The interview transcripts where stored in an electronic database set up for the analysis. I used the software package Atlas-ti, which is designed to assist with management and analysis of qualitative data. Initial coding of the data was carried out in 2004, and more detailed coding and analysis took place over 2005 and early 2006 to cover additional data collection and interpretation for the PhD. During the writing up of the research these codes, in electronic

[32] Additional codes were developed for a more specific analysis for certain parts of the PhD. These focused on expertise and EU advise structures, comitology, more specific sub-codes for 'risk' (scientific/technical, commercial, clinical risk; risk assessment; precaution, risk versus safety; etc), and codes that cover the more detailed analysis of EU regulatory procedures. To elicit the tensions between market and safety, also a subset of codes was created covering issues such as commercialisation, business climate, commodification, globalisation, and more extensive combinations of codes for interactions between specific key players, such as DG Enterprise and DG SANCO.

format, proved useful as a first selection tool in analysis. As it turned out that many (combinations of) codes retrieved too much data - which reflects both the overall amount of data and the fact that codes were still too general - I performed a 'sub coding' exercise on paper aided by highlighters and ballpoint.

3.3.5 Phase 2: follow-up data collection and analysis

This section summarises the distinction between ESRC and PhD focus. The majority of the empirical data on which this thesis draws are collected as part of my involvement in the ESRC project. Additional data collection consists of documentary research (amongst others in the European Documentation Centre and of several online legislation tracking tools) and 6 follow-up phone interviews with key informants. Also informal email exchanges gained additional insights and updates. Finally a significant source of fieldwork information was collected during my attendance at an industrial stakeholders meeting in Brussels, where the Commission presented the final proposal for the Enterprise Regulation on tissue engineering products. This meeting took place in November 2005, and marked my final data collection.
I audio recorded and fully transcribed the formal presentations and discussions during this meeting, and turned these into a report for the organising trade body, which published it on their website and disseminated to speakers (Geesink 2005). In addition I gained access to an expert meeting of industry representatives which took place before the formal presentations. This gave the opportunity to listen to the discussion of strategies, and to ask some questions. Most valuably it provided me with contacts that I followed up after the meeting over email and phone for clarification and updates.

This phase 2 research is based on a 'grounded' approach, where emerging themes from the existing data are further explored and linked to additional fieldwork. These additional empirical data and the analysis focus on issues of risk, regulation and expertise in policymaking on tissue engineering, which are interpreted from a conceptual concern with boundary drawing around these respective domains.

In terms of 'original contribution' then, the chapters 4, 5 and 6 of this thesis on risk perceptions by R&D actors in tissue engineering are based on data collected during the ESRC project. This includes interviews with scientists, clinicians and manufactures involved in tissue engineering technology. Part of the analysis on risk perceptions of these actors is currently under review for publication in a social scientific journal. The last chapter of this risk part (7), where I analyse these data in terms of risk hierarchy and risk balance, is an additional contribution exclusively part of the PhD research.

The following chapters on regulatory policy development reflect more recent data collection and analysis, beyond the project. This part is a combination of interview data, partly collected during the ESRC project and followed up after my involvement in this project had finished, and of analysis of policy documents. Given the timeframe of data collection under the ESRC project, with most interviews conducted in 2003, the PhD research phase was a good opportunity for updating regulatory developments and adding new insights. Chapters 8, 9, 10 and 11 of this thesis reflect this additional data input.

In terms of conceptual framework and inspiration the research presented in this thesis follows an alternative route. My concern with boundary work and regulatory science is an exclusive focus of the PhD research. The PhD research goes beyond project work in that it links risk perceptions with regulatory discourses, where one of the main questions addressed is the extent to which risk frames translate into EU regulatory policy.

What is next

This chapter has explained my conceptual understanding of risk, the empirical focus of my study in relation to risk and regulation, and the methods used for my research. Discussed next are three main empirical chapters (4-6) on risk perceptions by interviewees, where I follow the structure of the risk classification outlined earlier. Chapter 7 draws these different risk domains together by analysing cross-cutting themes and reflecting on these risk perceptions. Key markers in this chapter lead into a discussion of the next part of this thesis, focusing on risk regulation (chapter 8 onwards).

4 Technological risk

The last chapter outlined a tripartite model for the classification of risk perceptions by R&D actors in tissue engineering. This chapter discusses the first tier of this model: technological risk. This includes risk perceptions related to the creation of tissue engineered applications in the lab or manufacturing unit. The main boundary objects in this domain are biological materials that form the basis for processed tissue engineered products. R&D actors perform particular ways of boundary drawing around these materials, where notions of risk and safety are attached to particular cell sources and defined in terms of 'zero' to low to high risk. These boundaries are not fixed, and remain open for negotiating and reconstruction. As demonstrated in later chapters, biological materials have a different function as boundary objects outside the techno-scientific domain.

4.1 A dominant frame of technological risk

One of the key issues of concern and controversy in tissue engineering relates to the quality and safety of products containing human tissue or cells. Asked about the risks associated with this technology in general, the first and foremost set of issues brought up in this sample of interviewees concerns risks related to the donation, processing and manufacturing of human tissues and cells. This refers to processes such as the sourcing of tissues and cells, their handling during production of a tissue engineered product, including the culturing in the laboratory, the preservation and storage of products and the logistical process on the way to final (re-) implantation into the patient. This category covers a broad and diverse range of concerns – from transmitting infectious diseases to contamination and toxicity - which are here discussed under the heading of technological risk. The main concern here is with safety, and most risks as described in this category affect the patient, although some reference is made to exposure to risk of staff working in tissue engineering labs or in the clinic.

What follows below is a selection of interview data with scientists, clinicians and manufacturers in tissue engineering R&D that demonstrate their view and perception on what I have labelled technological risk. The perceptions of risk as discussed in this section are organised under two general subheadings. In short, the first category looks at where the cells come from and what this implies for their further use, while the second one is about the engineering and processing of these cells, and what safety concerns are related to this process.

The first main heading concerns risks related to cell sourcing and handling, including disease transmission, contamination and infection. Disease transmission refers to the transmission of (infectious) diseases between humans (such as HIV and hepatitis), but also potential transgenic transfer and the introduction of novel human and animal viruses (zoonoses) into the human population. Contamination and infection of the tissues and cells can take place during the production and manufacturing process, and can include contamination of the source material.

A broad second category of concerns is related to the cell behaviour during the processing and manufacturing of tissue engineered constructs, and after implantation in the human body. This includes (immune) rejection by the body, but also problems with controlling the cell growth (unwanted cells, cell modification, uncontrolled cell proliferation and differentiation) to prevent tumour formation or other unwanted effects such as the 'travelling' of cells through the body to places where they can cause harm. Also the interplay between cells and their supporting materials, so-called cell-scaffold interactions, and bio-incompatibility are issues addressed under this heading. Furthermore there are concerns with the limited shelf-life of many of these products and both the quality and quantity of cells needed to be effective, so to produce a sufficient amount of quality living cells for transplantation into the patient (cell viability). Other factors include toxicity of processing materials, such as growth factors and antibiotics added during the culturing process and to support the cells during transport, and problems with the sterility and final testing of the product.

For analytical purposes it is useful to discriminate between concerns related to cell sourcing and cell behaviour, and the data presented in this chapter are initially grouped around these subcategories. It is important to note though that interviewees have used an alternative set of criteria that cut through these categories, based on the starting material or types of cells and tissues used in the manufacturing of tissue engineered constructs, to express what they consider 'higher' and 'lower' risk. Thus risks are perceived different depending on the source material used. The distinction between autologous and allogeneic material is considered key in the eyes of these interviewees. The use of animal derived material is a category much more boxed out, with particular boundary negotiations taking place over the level or degree of risk.

4.2 Constructions of technological risk and safety

> There are a huge number of issues. In terms of cells – if you have a product with cells within them, there are issues about infection transfer, so you're talking about donation and proof of that. Depending on the source of cells, for instance if it's a xenograft type cell that you're generating this cross species... There's concern about tumour generation if you're using stem or a cell that is highly proliferative. Concerns about migration of cells away from the site where they were due to act, so a cell that could be very good, if it was implanted into the brain could be damaging if it went to another part of the brain or it went to another part of the [body]... Rejection and immune responses to the cells... It would impose a course of immunosuppressive drugs on the patient for a long period of time... that's about actually what does a cell do when it's in the body, but then there's a whole range of manufacture issues about how do you quality assure with a product based on living tissue. (Academic research scientist in tissue engineering lab S7, 2003)

4.2.1 On donors and diseases

Disease transmission is the most commonly perceived risk by interviewees in this sample. Most of them explain this in the first place as the transfer of infectious diseases between human donors, which applies to allogeneic tissue engineering applications. As the extract from a clinical scientist below demonstrates, these risks are considered similar to those of organ and blood-donors, while at the same time there is a strong suggestion that in the case of tissue engineering these risks can be 'for life' due to the permanent character of the implantation of cells into the body:

> Obviously if we're going down donor cells then you have to think about infection risks from the donor, immuno-rejection and those sorts of issues. (...) I think we have to err on the side of caution and assume that an adult donor cell from another person has to be at least well matched in terms of HLA status, in terms of the sort of cell matching that goes on with blood donor and so on and I'm not sure that's a risk we should be taking for chronic implantation. I mean we're talking about people who may have these cells for years implanted in their bodies. (Academic research scientist in clinical care S4, 2003)

Thus many interviewees stress the need for donor screening and testing in order to control the transfer of infectious disease from donor to recipient and to prevent microbiological contamination associated with the sourcing of the tissue. In this way a particular subworld of technological risk is created, which makes these issues 'controllable' (see also later). The donation of tissue covers a broad area of safety concerns including the suitability of donors, the screening of donated substances, and the traceability from donor to patient and vice versa. At the moment, donors are usually screened on infectious diseases such as HIV, hepatitis B and C, and syphilis. One example of such extensive screening is the skin product Apligraf. Because this product is made from human neonatal foreskin tissue, the foreskin donor's mother needs to be tested for human viruses that can cause infectious diseases.[33]

However, this controllable domain is troubled by uncertain risk. Here the main concern is not just with the transfer of serious health-threatening but known and 'testable' diseases, but also with introducing and spreading as yet unidentified diseases:

> The problem which comes when you think about donor cells, is that you have to find the donors and then you must be sure that the donor, you know, is in good health and this is the big problem because we are always afraid, that maybe the donor can have something that we still do not know. You remember that when the AIDS virus, you know, come out, the HIV virus, you know, because it, nobody knew that this virus was present in some patients and maybe this is another, the problem to use donor cells. (Academic research scientist S-EU1, 2003)

[33] Currently these tests include antibodies to human immunodeficiency virus type 1 and 2 (HIV-1 and HIV-2), human T-lymphotropic virus type 1 (HTLV-1, which is associated with leukaemia cancer), hepatitis C virus (HCV), hepatitis B surface antigen (HbsAg), and syphilis.

Available tests are not always satisfactory, and new disease threats continue to appear – with severe acute respiratory syndrome (SARS) being a specific example in place (Bronson 2003).

As also illustrated by this quote, tissue engineering is surrounded by uncertainty about both specific risks to take into consideration, and how to manage those risks. This relates to issues of disease transfer and donor screening, but also to for example cell behaviour after implantation of the cells:

> With the allogeneic [donor] cell source there could be, and I guess the cells have to be screened, but there could always be risks of viral transfer, whether the cells will differentiate, de-differentiate back to something else, I don't think we know. So I think there are risks and I don't know whether the potential of those risks is being evaluated because of the time scale involved.
> (Academic research scientist in UK tissue engineering lab S1, 2003)

This remark covers concerns with cell sourcing and cell behaviour during the processing of tissue engineered constructs, and after implantation in the human body. Differentiation of the cells refers to a process where cells, in their natural environment, develop into certain structures (for example cartilage cells or neurons). All cells other than stem cells are differentiated and have specific specialised functions in the body. During the culturing process the cells age, and often lose their specific characteristics (dedifferentiation), which makes it hard to maintain the differentiated phenotype. As another scientist explains, one of the main techno-scientific concerns is making sure that the cultured cells keep their specific beneficial functions:

> Maintaining the specialised functions, called differentiation, after the cells have been cultured, is a formidable requirement for tissue engineering constructs. That the cells in culture tend almost universally to lose some of the characteristics of the in vivo environment because they do not have all of the cells signalling the environment around them and they don't have the same nutrient environment that the living cells, the in vivo cells, do. Because the patient own cells that have a certain characteristic inside the patient, lose those characteristics outside the patient. That is one of the reasons that there are very few successful tissue engineering products available now.
> (Academic research scientist in UK S6, 2003)

Thus this remark is about controlling the cell growth and cell behaviour in order to prevent the creation of unwanted cells and cell modification, or uncontrolled

cell proliferation and differentiation that can lead to tumour formation or other unwanted effects such as the 'travelling' of cells through the body to places where they do not belong. At the same time, this narrow scientific frame refers to the possibility to produce a sufficient amount of quality living cells for transplantation into the patient (cell viability) to be effective. Sometimes the quality and quantity of living cells is so poor, that they do not have any therapeutic effect at all (discussed more fully in the next chapter).

4.2.2 Quality and safety controls

Many interviewees have stressed the need for donor screening and testing in order to control the transfer of infectious disease from donor to recipient, which could affect the individual patient or the population at large. Although uncertainty exists about specific safety factors in relation to donation, screening and testing, especially amongst manufacturers an optimistic scenario exists about the ability to control these risks:

> Well the risk is just, well if you're doing tissue engineering and cellular work you have to make sure like in terms of infection, that kind of thing, so you're not transferring to patients, or other cellular work not getting mixed up, maybe putting the patient wrong. You control those matters.
> (Academic research scientist in UK hospital S8, 2003)

> This is quite simple, the risk I can just tell you from our products. The risk with our products is really minimal because due to the qualitatively high production standards there is nearly no risk of any infection, any cross-contamination. There is no risk because there is nothing that is infected, unclean, whatever is used on our production site. No risk here.
> (European manufacturer M-EU3, 2003)

As also hinted at by the last respondent, disease transfer or infection is not always caused by the source material used (in this case the donor of the tissues or cells) and safety checks are also critical during the process of production and storage of the cells:

> Well tissues should be screened for HIV and Hepatitis and should obviously be stored well, bagged up and away from any material that might be put into patients.
> (Academic research scientist in UK tissue engineering lab S1, 2003)

Donor cells and tissues that are used to produce tissue engineered products are usually stored in tissue banks or master cell banks. These banks have to be screened as well for human and animal viruses, retroviruses, bacteria, fungi et cetera to make sure no contamination takes place during the production process. This is needed from a patient safety point of view, but also to protect personnel working in the laboratory handling and processing the cells. Thus these respondents rely on a frame constituting a controlled environment with standard operating procedures and quality systems as an important measure to prevent process-related contamination and to help ensure product safety and quality.

Thus a second technological risk frame is related to cell and product behaviour during the processing and manufacturing phase. This can include so called cell-scaffold interactions and issues of bio-incompatibility, but also for example making sure that processing materials (such as growth factors and antibiotics) used during the culturing process are not toxic. Tissue engineering products can consist of a combination of living cells, natural or synthetic materials and biomolecules. Because of the combination of different components, the identification of hazards is considered to be more complex for these products. Here not only the final product should be taken into account, but also the different components - cells, materials, molecules - of it, and their interaction (Tienhoven et al. 2001).

The following clinician sums up the issues as follows:

> I don't suppose you can maintain sterility with a living product, but as clean as is possible from the point of view of having any [contamination] within them... something which will not be damaging to the tissue itself... you have to be sure that you are not just supplying dead tissue. ... to be able to prove that a certain quantity of the tissue will have survived... it's usually a freeze process and a de-frost process to give you some viable tissue there so that they are going to be efficacious. ... obviously the production things sort of maintaining the purity of the cell culture and, you know, being sure that you're not introducing cells that are themselves abnormal. And then proving that you will get a quantity of living cells from that and that you're not producing, providing something that has been contaminated on the way from the manufacturer to the clinician.
> (UK clinician in wound healing Co2, 2003)

One specific concern for these products, as also described in more detail by the scientist below, is the sterilisation of tissue engineered products. Whereas for some other implant materials sterilisation is maintained during the whole manufacturing process, for living biological constructs such as tissue engineered products this is problematic, because the sterilisation processes will kill the human cells:

> Another problem... is the need to obtain and maintain sterilisation throughout the whole pathway or at some point. The process that is typically used to sterilise implant materials will kill the cells that are present in the scaffold... Almost a restriction imposed right from the very beginning that the scaffolds going into a tissue engineering production must go into the cell stage as sterile products; then sterility maintains throughout all of the subsequent handling, seeding, growth, proliferation, differentiation, storage, transport, handling and implantation. So that's a sequence of probably ten different steps. It is not known at the present time how to make all the steps in sterile conditions at low cost. (Academic research scientist in UK centre tissue engineering S6, 2003)

So far the technological risks associated with tissue engineering products, according to these interviewees, range from infectious disease transfer and infection to biocompatibility issues such as immuno-rejection, toxicity, uncontrolled cell proliferation and differentiation, while also quality and safety concerns during the manufacturing and final product testing stage have been expressed. Some of these risks are almost exclusively related to the use of donor material in tissue engineered constructs, with the potential to affect the larger population. This also has implications for testing and risk management strategies:

> If allogeneic cells are enormously expanded in number and if it is the intention that the cells are used in many recipients, then the microbiological testing should reflect the increased size of the population at risk. Whilst cells are in culture, there is the opportunity for microbiological contamination and also for expansion of microbiological agents. When cells are cultured in vitro, the relevant processes must be monitored. This should include the demonstration of lack of malignant transformation and that the relevant biological properties of the cells are maintained. In the case of tissue engineering, these principles also apply including in any commercial environment. (Warwick and Kearney 2002: 381-2)

Allogeneic and autologous cell sources, and the distinction between the two, serve as important boundary objects for the ways in which interviewees attach

value and weight to particular risks. Furthermore, another main technological and social concern that features largely in these accounts relates to the effects of including animal-derived material in tissue engineered products. In terms of disease transfer, this concerns risk of transmission between human donors, but also between human and non-human populations (transgenic) and potentially over generations. As part of what is later referred to as the 'risk hierarchy', interviewees construct and reconstruct the level of risk in terms of cell source.

4.3 Reconstructing risk depending on cell source

As discussed so far, specific but also not always 'known' risks are connected to the sourcing of cells and tissues, their handling during production of tissue engineered products, the preservation or storage of the product, and the implantation process – issues which are framed in techno-scientific terms by these interviewees. This section demonstrates how interviewees make a distinction and ranking between different cell sources in their constructions of risk, where the perceived level of risk also dictates their acceptability.

4.3.1 Autologous versus allogeneic applications

The distinction between the use of autologous and allogeneic cells is important in interviewees' perceptions of risk. In relation to autologous material, there are two interesting and interrelated risk frames: one of them is based on the assumption that the technology of culturing patient-own cells is simple and straightforward, or 'not rocket science' as one interviewee put it (M-EU9, 2003). As such the technology is considered uncontroversial, and moreover there are *no risks* involved. The other frame compares autologous treatments to those based on allogeneic cell sources, arguing how the former are *less risky*. The fragments below illustrate this.

One clinician calls upon a broader framework by making a comparison with more controversial but also much more complex biotechnologies:

> I don't think it's like using genetic manipulation on the food we eat or whatever, you're just taking the patient's own cells.

(UK clinician working in orthopaedics CI2, 2003)

A clinical scientist working on the culturing of autologous skin cells for diabetic ulcers explains the simple and routine nature of the technology as follows:

> All we are doing is poking at the cells in the lab and then pulling them back on the wound bed - week in, week out.
> (Academic research scientist in clinical setting S5, 2003)

As also the following research scientist explains, this is pretty straightforward in comparison to donor cells:

> The only thing you're doing is taking patients' cells out, growing a few more and putting them back in. I think that's very different from a patient coming along and being given a product which has got somebody else's cells in it or another source of cells.
> (Academic research scientist in UK tissue engineering lab S1, 2003)

This interviewee continues to argue that this also implies the 'less likely' risks associated with autologous treatments, because of the level of risk involved (individual versus a collective/public health risk frame):

> I think we have to be careful that we divide this into the use of a patient's own cells that get put back into the patient's own body, as opposed to the use of some kind of third party, universal [stem cell] that could be used to treat a huge population of patients. Now my own feeling is that we're going to see advances in tissue engineering for patients by using the autologous cell routes, using a patients' own cell treating somewhere, putting them back into their body and there, I think, the risks probably are less likely than with the other [allogeneic] route because we just don't, because we just don't know.
> (Academic research scientist in UK tissue engineering lab S1, 2003)

The following manufacturer has a similar understanding of the 'inherently safer' nature of autologous applications:

> I think it would generally be seen that autologous tissue would be inherently safer because it's come from the patients themselves and the patient is getting their own tissue back. So there's not the potential risk of introducing something from a source of tissue elsewhere.
> (Scientific manager corporate product safety assurance for multinational company M2, 2003)

The following scientist, at an academic tissue engineering lab, goes further and speaks of 'no risk', even in the case of infectious diseases being present in the tissues or cells:

> I would say that our strategy was the use of the cells of the same patients, so we do not have risks... so even in some case we are also using the cells of the people who have infected diseases like, you know, hepatitis. By using the same cells of the patients you are, you know, in the best situation because you have to return to the patient, his own cells, so without any problems.
> (Academic research scientist in connective tissue research S-EU1, 2003)

Possibly the most extreme perception comes from this scientist who speaks of 'zero risk' in relation to possible contamination in the case of autologous treatment, but a 'very difficult' issue when it concerns donor cells:

> Now we're talking about cell sourcing and the cells which is something else, which is much more important. If you take cells from a patient and you're talking about cell therapy, it's easy to implant back and the risk of viral contamination is zero, at least. The patient has no infection from the beginning. If you start taking cells from one patient to another, then it's a completely different story. This is difficult, very difficult.
> (Academic research scientist S-EU2, 2004)

Thus there is a strong understanding amongst interviewees that autologous cells do not pose any risks, or that the risks are marginal compared to allogeneic applications - when it comes to transferring infection and disease, but also for example in terms of immune rejection by the body. As such autologous sources are part of a 'safety frame' which is presented as unproblematic. But as underlined by the following scientist, also autologous cells undergo an often complex trajectory of processing and handling, from the moment the cells are sampled from the patient to the culturing and multiplication in the lab to transport and logistics on the way back to the clinician for final re-implantation in the patient. According to the scientist below, the extensive handling of cells is 'always a risk' irrespective of the cell source:

> You might say the least risk might be in almost like autologous taking cells and minimally handling them and putting them back in... So, you might envisage that being the least risk. And probably not without risk as things are handled and that's maybe always a risk.
> (Academic research scientist in UK tissue engineering centre S3, 2003)

Also autologous tissues and cells require careful handling to minimise risk of infection (also to lab personnel) or contamination. Furthermore, a specific risk in the case of handling autologous applications, where cells from one patient

have to be returned to that same patient, is the 'mixing up' of cell samples and re-implantation in the wrong patient.

> Well this is one of the reasons why we decided to work with autologous tissues only, so basically there is no risk. No risk in terms of disease transmission, HIV, hepatitis, and so on so on. So from this point of view there is no risk and we never had a case. There is maybe one risk, if for example, if we would exchange the cells in our production and send the wrong cells to the wrong patient for example, you understand?
> (European manufacturer of autologous applications M-EU10, 2003)

As this extract demonstrates, the 'choice' for a particular engineering route – again with the understanding of autologous being safer - also has commercial implications, with the underlying liability issues that could be associated with 'a case' where products pose safety threats. At the same time emphasis is placed on working under controlled conditions in the labs and manufacturing units to avoid mixing up cells and to ensure general quality and safety of the products before implantation. Thus quality control and standards such as Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) are important tools in protecting public and occupational health. As this scientist demonstrates, safety measures are strict:

> When we culture cells from the patient to go back on the [same] patient, we deliberately do not test whether they are HIV positive or negative. We have thought this through. We treat every sample that we get from the patient as though it was HIV infected. So from the operating point of view we assume the worst.
> (Academic research scientist in clinical setting S5, 2003)

But as this scientist continues to argue, the current production of tissue engineered constructs takes place on a small scale, where cells of only a limited number of patients are being cultured at a time. This would mean that for example the chances of mixing up human cells would be 'almost negligible':

> Part of it is logistics. We are not culturing for many patients at one time. So we have not got vast numbers. The other is we segregate as far as we are able in terms of space. Now I know the standard to which I would like to be working, and I know the standard that we are currently working at. I would like to be able to say that we only ever handle one lot of cells in the hood at one time. I would love to have more space and more hoods and to be able to segregate things further than we do. But we make sure that we only have one operator handling one set of cells, from one patient, at one time. And then it's a case really of maintaining a trail of labelling that goes all the way through.

(Academic research scientist in clinical setting S5, 2003)

As the manufacturer below explains, the small production scale of many providers, where the handling of tissues and cells is limited in location and time, also has implications for what can be produced within the safety margins. In this case precaution is pushed to the point where patients may be denied treatment in case of an infection:

> If we get the cells into our laboratory we go first through the quality control, which means there are several tests first before we start manufacturing or culturing these tissues. So one of the tests for example is a test on the hepatitis or HIV and so on so on; so if the test is positive then we do not produce. We could produce but we would have to set up an extra laboratory to be a hundred percent sure that there is no risk of transmission because right now these cultures are made in the same laboratory. So this is the only risk, but we limit it because we say: if there is HIV or hepatitis or other transmission diseases we do not produce. We inform the patient, we inform the doctor and so we do not even start. (Director of European company producing autologous tissue engineering applications M-EU10, 2003)

Here the initial processing and manipulation process in the lab is not seen as overly problematic for autologous applications. More weight is attached to proper manufacturing processes and quality systems to control the facilities and to make sure there is some tracking or labelling system in place which prevents cells and patients getting mixed up. Furthermore, as has been demonstrated throughout this section, there is an important technological risk discourse based on the level of risk and safety. Autologous applications, because of their individual and customised nature, are considered to affect 'just' the respective patient receiving the treatment, and quality control systems have a main function in protecting staff in laboratories and manufacturing units dealing with these tissues and cells. This brings us back to the distinction outlined at the beginning of this section, about the relative safety of autologous applications over allogeneic products. It has been argued that these different engineering routes should be covered by different risk assessment strategies. With disease transfer being the main concern, the interviewee below explains how the risks of allogeneic products would have a larger health impact – transcending the level of the individual patient and potentially posing public health threats:

> One of the most important points is a clear evaluation of the different risks involved in autologous versus allogeneic. They cannot be considered products with the same class of risks... Allogeneic products must be controlled very carefully because you are able to infect many, many people.
> (Quality controller in multinational tissue engineering company M-EU3, 2004)

So risk frames include a certain level of risk, where risk has been individualised for autologous tissue engineering applications, and a comparative risk factor, where autologous tissue is thought to be less risky than allogeneic products. With donor products being considered problematic in terms of their potential for virus transfer, infection and rejection of the cells – which their autologous counterparts are thought to stay clear off – the safety impacts take place on a much larger scale. But as also demonstrated in this section, the extensive handling of these cells can produce hazards for individual patients (e.g. implantation in the wrong patient) and staff alike (e.g. biohazards; contamination and infection during handling). However, when looking closer at the actual culturing and engineering process of autologous cells, a much more problematic scenario arises.

4.3.2 The inclusion of animal derived material

The preceding section has focused on the relatively unproblematic nature of autologous applications, in the eyes of most interviewees. The demarcation between different cell sources is driven by perceptions of differing degrees of risk. This section questions these boundaries by analysing the more complex process of culturing cells for constructing tissue engineered products of both autologous and allogeneic origin.

After a cell sample is taken from the patient (via biopsy), the cells are manipulated as part of the culturing process in the laboratory, before implantation back into the same patient. One concern refers to the culture media used to grow and differentiate the cells (so called in vitro cell proliferation). Several substances are added to the culture medium, including growth factors to stimulate cell growth, antibiotics against infection, and foetal calf serum to support cell growth. It has been documented how residues from these components or contaminations, like endotoxins, could remain associated

with cells and 'could induce an unwanted immunogenic or toxic response after implantation' (Tienhoven et al. 2001: 14).

A product example can demonstrate the underlying safety issues and implications for patients. Epicel is a tissue engineered skin product which was developed by Genzyme Tissue Repair (USA) and first introduced in the market in 1987 as a permanent skin replacement for patients with severe burns. Epicel is a so-called cultured epidermal autograft: grown from a patient's own skin cells. The cells are harvested via a biopsy of healthy skin and in a good two weeks enough skin is cultured to cover a patient's entire body surface. The sheets of tissue are attached to a dressing material for easier use by the burns surgeon. Over 700 patients have been treated with Epicel, and the product is marketed in the US, France and Greece and has been used in other European countries, Japan, and Canada (Genzyme 2002).

But the product comes with a safety warning:

> **Important Safety Information**
>
> Epicel is contraindicated in patients with known hypersensitivity to agents used in the manufacture of Epicel. Epicel should not be used in patients with a known history of anaphylaxis to vancomycin or amikacin. Epicel is cultured in media containing vancomycin and amikacin. Trace quantities of these antibiotics may adhere to the Epicel autograft.
>
> Epicel should not be used in patients with known sensitivities to materials of bovine origin. The cell culture medium used in the culture of Epicel contains bovine serum. The medium used to package and transport Epicel does not contain serum; however, trace quantities of bovine derived proteins may be present. This tissue is intended for autologous use and has not been tested for biohazards. Health care providers should handle this product as if infectious agents are present.
>
> During the Epicel manufacturing, patient's cells are co-cultured with mouse cells. Although the mouse cells have been tested and found to be free of bacteria, fungi and virus, an infection can not be excluded. As a safety measure, the Epicel treated patients are precluded from donation of blood or blood parts, tissue, breast milk, egg, sperm, or other body parts for use in humans.
>
> Source: Genzyme Epical website (2006)

The cell culture medium used in the culture of Epicel contains bovine serum, while during manufacturing patients' cells are co-cultured with mouse cells (murine 3T3 cell feeder layer) to support the growth. The company's safety information leaflet issues contraindications for patients who are allergic to

material of bovine origin, and also those with sensitivities to the antibiotics used in the culture. Although the mouse cells have been tested, an infection can not be excluded, and patients are precluded from donation.

Several other tissue engineered products make use of bovine serum for their cell culture or production process, or of other xenogeneic materials. These materials can be classified in different categories: those that include components that are extracted from xenogeneic tissues, animal serum to use as cell growth supplement and animal cells (Warwick and Kearney 2002). An example of an animal extract is bovine collagen that is used in a variety of tissue engineered products including several skin replacements for burns and plastic surgery. Also porcine (pig) dermal collagen is used. For example TransCyte, developed by US company Advanced Tissue Sciences (ATS) for burn patients is produced from dermal cells isolated from newborn foreskins that are seeded in a polymer scaffold, which is coated with porcine dermal collagen and cultured with the use of bovine serum. Because of the use of animal material during the manufacturing process, the product comes with the following precaution:

> TransCyte is contraindicated in those patients with known hypersensitivity to porcine dermal collagen or bovine serum albumin. TransCyte may contain trace amounts of animal proteins due to exposure in the manufacturing process and the pre-coating of the nylon mesh with porcine dermal collagen (Smith&Nephew 2005).

In terms of animal serum, foetal calf serum is the most commonly used supplement that is added to the culture medium, although also normal calf serum and serum from other animals such as horses is used. In tissue engineering this serum has been used for several decades by laboratories and commercial developers, and for a wide variety of applications, including the cell culturing for skin supplements for burns and diabetic ulcers (e.g. Apligraf, Dermagraft, TransCyte) and for autologous cartilage repair applications (e.g. Carticel). For some time, before foetal calf serum came in widespread use in the 1980s, so called bovine pituitary extract was added to cell cultures (typically for skin cells) as an alternative growth supplement. This extract can be sourced from the bovine pituitary gland, which is based in the lower part of the brain and which produces (growth) hormones. In an attempt to remove the xenogeneic

elements from the cell culture, many laboratories culture their skin grafts in a medium without serum towards the end of the processing stage, 'but the efficacy of this step is not clear' (Warwick and Kearney 2002: 387). Several developers of tissue engineered products that include bovine serum in their culture media have issued claims that traces of the serum can stay behind in the final product. As one commercial developer of autologous cartilage cells explains:

> Now although those bovine materials are washed from the manufacturing process before shipping there is always a minute potential that you could end up with trace amounts of bovine material or bovine serum out of that material in your final product.
> (Regulatory affairs professional in multinational industry M-EU9, 2003)

A safety warning that comes with these products is related to the exclusive autologous use. One manufacturer points out that because of this customised treatment, patients are 'not routinely tested for transmissible infectious diseases', which poses potential risks to the healthcare provider handling the cells and product (Genzyme 2004)

Finally, animal cells can be part of the cell culturing process for tissue engineered products, most notably with human skin cells (keratinocytes) such as discussed above with Epicel. These are typically needed to form a layer of feeder cells, and the most commonly used source are so called mouse 3T3 fibroblasts. Before implantation in the human body, these cells undergo a process of irradiation or they are treated with antibiotic agents (such as Mitomycin C) to prevent tumour formation due to uncontrolled cell proliferation – although, again, there is no guarantee that this is successful.

Although debatable in how far xeno-constructs are part of the definition of tissue engineering technology (we return to this discussion later), based on their material composition some of these products can be classified as xenotransplants (Brown et al. 2006).

Thus several safety concerns are associated with the inclusion of animal derived material in tissue engineering applications, irrespective of the cell sources used as starting material. Many autologous skin and cartilage products

consist of some xenogeneic element. So far these applications have been considered in terms of individualised risk (for the patient), and many developers of these products have pointed out the potential risk of hypersensitivity and allergy to bovine components (or of the antibiotics used during cell culturing). But as the product examples demonstrate, in addition to potential rejection and other immune responses or side effects that affect the patient, there is a broader concern with biohazards, infection and disease transmission, with the potential introduction of novel viruses (zoonoses) in the human population – one of the reasons for excluding these patients from the donation pool. This concern transcends the level of the individual patient. Furthermore, and interestingly, many of these concerns are framed in narrow scientific terms, where close boundaries are maintained around the techno-scientific domain. But one of the major drawbacks of using animal-derived material lies in the potential of introducing (unknown) infectious agents such as viruses and mycoplasma in the human population. These developments are set in a context of growing public concern and controversy, with the BSE crisis being one example that has affected both the scientific and commercial development of tissue engineering technology.

As the following interviewee from a UK tissue engineering lab explains:

> So safety issues are that bovine material might pass on bovine spongiform encephalopathy (BSE). Depending where you get your material from, so some people culture in media that contains bovine pituitary extract which I find totally and utterly unacceptable. We use it experimentally but never clinically. All of us culture using foetal calf serum which is bovine which we currently source usually from New Zealand. The culture groups, we all feel OK-ish about that. We don't feel totally confident about that because we are aware of the sleight of hand that can happen with paperwork. Commercially we pay about four to five times the price if we buy a bottle of serum from New Zealand than if we get whatever's cheapest from the UK or whatever. What we are actually paying for is the piece of paper saying that it came from New Zealand from a herd that is never known to have had BSE.
> (Academic research scientist in clinical setting for wound healing S5, 2003)

Since the BSE outbreak limitations are set on the purchase of bovine serum to 'BSE free' places such as Canada, New Zealand, Australia and, originally, also the USA. As this scientist continues, both scientists and regulators are

concerned about the use of these animal derived materials in the cell culturing process, but not to the same degree:

> Another driver for innovation is the regulatory issues concerning use of mouse fibroblasts in the culture of cells and the safety issue with the respect of using bovine products in tissue engineering. Now I guess, I guess the bovine products has been an issue... for a while. It is something that we are very concerned about and we are very keen to develop a methodology that doesn't use any bovine materials... Personally I'm more concerned about using bovine products than about using mouse fibroblast as a feeder layer. But the regulatory authority are more concerned about - this is where things get more crazy - the [UK] Xenotransplantation Authority are very concerned with our groups using mouse fibroblasts, but when I ask them 'aren't you concerned about bovine material?', they say that's not part of our remit because the cells are not alive. At which point you put your head in your hands and cry. (Academic research scientist in clinical setting for wound healing S5, 2003)

Several cell culturing groups in universities and the commercial sector are working on alternatives to the use of bovine extracts and serum. One option being explored is using 'serum free' culture media, to take patient own cells (skin cells such as fibroblasts) as a substitute for the serum. The performance and clinical effectiveness of this medium is not yet up to standard though, as the quality and stability varies. Furthermore there are logistical and social issues connected to using patient own cells for the serum; one is that a deeper biopsy has to be taken, implying more discomfort for the patient, and two that the culturing process takes longer than usual and is more unpredictable. This complicates the logistical process of these living cells, which after culturing have to be shipped or otherwise transported to the clinician for the scheduled re-implantation into the patient (M-EU9).

Thus scientific attempts have been undertaken to develop a less controversial version of the bovine serum for cell culture, steering the field towards more acceptable applications in both technological and social terms. But the fear for disease transfer or other unwanted side effects from animal based material in tissue engineering applications is not shared by all R&D actors in this field. Thus also in technological terms, different constructions of risk are called upon.

One scientist points out the reluctance by patients to have animal derived components (such as scaffold that are used to support the living cells) implanted into their bodies:

> In terms of producing scaffolds, only the origin of the scaffold when there are animal derived or human derived materials, I think there is always going to be concern. And this is going to be a hurdle for introduction... Because it's always a reluctance and the risk that there will be some viral contamination.
> (Academic research scientist in biomaterials and tissue engineering S-EU2, 2004)

In contrast, a scientist with experience in a clinical setting for wound healing, points out how usually patients are not too bothered about these constructs:

> We find that if we are culturing autologous keratinocytes [patient own skin cells] to heal a patients' ulcer, the patients are very happy with that. It's their cells being used to heal their problem... So the patients don't have any concern with that. We can tell them about the bovine serum and the mouse fibroblasts, but they are not actually that interested to be frank. They're not. No. Will this heal my ulcer? That's what they want to know.
> (Academic research scientist in wound healing and clinical management S5, 2003)

While patients might perceive these risks, according to this scientist, as 'acceptable' in the light of overall treatment benefits, there is also the issue of full information about longer term effects. Although this interview excerpt suggests informed consent about the inclusion of animal-derived material in the tissue engineered construct, a recent study conducted upon medical professionals delivering skin treatments, concluded that many clinicians are not aware of the exact composition of tissue engineered products they offer to their patients (Enoch et al. 2005). A survey on healthcare professionals demonstrated that only a small percentage of respondents was aware that some of these products contain human donor or animal derived material (including bovine contents). This would suggest that knowledge about the material composition of tissue engineered products should precede full informed consent.

Also other constructions of downplaying these risks are put forward. The following scientist feels that tissue engineering technology in the future will not

rely too much on 'non-human cells', most notably in the context of the promise of stem cell therapies, while furthermore arguing that most risks take place on individual rather than collective level:

> The one [risk] that springs to mind that could have a big effect would be use of non-human cells and risk of introducing new viruses into the human population. But the way the field is moving it seems that it's less and less likely that there'll be a lot of products based on non-human cells. Our sources of human cells are improving, we're finding new stem cells so there's probably less of a reason for it. Apart from that I think most of the risks are borne by the patients themselves.
> (Academic research scientist in UK tissue engineering lab S7, 2003)

And even if animal derived materials are part of tissue engineered constructs, the potential harmful effects to the patient would be minimal, according to the following scientist:

> If you compare it in general terms it's like either you die or you take it. And there is not many people that take it that's going to die from it, from viral infection. So the risk is very small when you talk about these scaffolds that are animal derived, that are carefully handled.
> (Academic research scientist in biomaterials and tissue engineering S-EU2, 2004)

Finally, there is a techno-scientific discourse acknowledging the potential risk of in particular bovine serum, but as these interviewees demonstrate, this needs to be considered in the context of an overall therapeutic balance of risks and benefits and gradation of risk - thus creating acceptability to some degree.

> I think that people have been overshooting a little bit. The whole BSE story and so on... you just eat a piece of cake and you take more potential BSE material in your body than growing a cell in foetal bovine serum, you know... all the gelatine we have in our cakes are all coming from bovine you know. So what I am saying is obviously you take all precautions in order to make sure that things are brought to the lowest level of toxicity one can anticipate. But again, every treatment has the efficacy toxicity ratio issue. You always have to look at what I call the therapeutic index.
> (European clinician involved in start-up company CL-EU5, 2003)

While this interviewee responds to public concerns about BSE, thus including socio-political factors in the risk equation, at the same time this concern is marginalised by pointing out the low degree of risk attached to bovine serum. The following interviewee uses a similar frame by referring to a risk ranking that makes bovine serum, in the big scheme of things, not such an unacceptable

solution after all – while at the same time referring to the commercial potential of a more social acceptable solution:

> Now, bovine serum, if you look at the WHO classifications for health risks, bovine serum [is] one of the lowest risk bovine products. You have a spinal cord and eyes and all that sort of stuff as being particularly high risk of TSE transmission whereas serum is pretty low down on the list. So although there is a minute chance that you could have that some people are known to be allergic to those materials so again, it's a liability risk that you have to put in. (...)
> You can only apply sound scientific principles to the way that you manufacture the product. You can do the best you can to eliminate those materials. You can make sure that the materials that you use if they are of that source come from credible documentary sources and that you include those particular statements within your risk assessments. Unfortunately at this moment in time there's no real alternative for adding things like bovine serum to growth media because your cells won't grow otherwise. And the first company who develops a serum free media will be a very rich company.
> (Regulatory affairs professional in multinational industry M-EU9, 2003)

4.4 Drawing boundaries of technological risk

In this chapter I discussed the differentiated views of scientists, clinicians and manufacturers on technological dimensions of tissue engineering risk. Asked about their views on risks of tissue engineering applications, interviewees make an implicit but sometimes inconsistent ranking of risk as related to the particular cell source of the application. Especially the distinction between autologous and allogeneic material is considered key in the eyes of these interviewees, where these biological materials serve as boundary objects in defining the 'riskyness' of the product. The main concerns mentioned are disease transmission and infection, especially, and initially, in relation to the use of donor material. Autologous applications, on the other hand, are seen as relatively safe and 'risk-free' and as such unproblematic from both a technological and patient perspective. But closer inspection of the cell culturing process reveals how autologous cell sources also inhibit a problematic frame.

Thus risks are perceived different depending on the source material used. The use of animal derived material, for example during the culturing process or as part of the transport and logistical system to deliver the cells to the patient, is a demarcated category generally singled out of the equation in these accounts. Furthermore particular boundary negotiations take place over the level or degree of risk: interviewees have downplayed the issue of animal-derived material, especially with reference to the use of bovine serum, pointing out how this is 'relatively safe' and low down on the list of potential risk of transferring TSE, thus stressing the comparative unproblematic character in technologic terms - even in the face of public concern after health scares such as BSE.

Interviewees have constructed and reconstructed risks in particular frames, with specific perceptions and differentiated values attached to different applications, based on cell source, while also taking into account the level of risk (individual versus collective) and the degree of risk (high to low), plus an overall balance of risks versus benefits in what is perceived as acceptable risk.

Generally speaking, and so far, these different frames are of a techno-scientific nature, and there is a strong belief that these risks can be controlled in the right (e.g. quality controlled) environment. Furthermore, many technological risks have implications for clinical development and market performance of tissue engineered products and services. The following chapters describe the next steps in the innovation cycle of respectively therapeutic effectiveness and commercial potential, demonstrating how the different risk perceptions are interlinked both between categories of the risk trilogy (technological – clinical – commercial) and with respect to the level and degree of risk - later in this study referred to as the risk hierarchy and the risk balance.

5 Clinical risk

A particular framing of perceptions of risk of tissue engineered applications relates to the long-term clinical effects of these products in the patient. I have labelled this category 'clinical risk'. The main issues under this heading are the question of efficacy of tissue engineered applications (if they actually 'work'), what clinical evidence is available and how to interpret this, and what tools are needed to evaluate the efficacy and safety of the technology on the long-term.

Clinical risk is the intermediate step between concerns related to the development and manufacturing of tissue engineering constructs (discussed under technological risk) and the introduction of these products in the marketplace (commercial risk, to be discussed next). Whereas technological risk is mainly concerned with safety of tissue engineered products, clinical risk considers safety as part of a more complex and elaborate trajectory of performance testing, taking into account the efficacy of these products over a longer period of time.

Demonstrated in this chapter is how participants in the clinical domain create very mechanical and narrowly defined boundaries around what is perceived as 'proper' clinical evidence, while subsequently arguing how the unique status of (particular) tissue engineered applications warrants exclusion from this frame. Demarcation, then, takes place by referring to 'traditional' clinical models for evaluating medical technology. The notion of efficacy of tissue engineering technology is furthermore related to another dominant framework, where the worlds of clinic and market meet.

5.1 Framing clinical risk

The starting point of this chapter is the perceived lack of evidence of efficacy for tissue engineered products. The efficacy of a treatment is usually defined as the ability to produce a result, or in other words the question whether the

therapy works for the particular treatment for which it is tested.[34] This efficacy is being questioned by many interviewees. As one scientist expresses his concern:

> I think perhaps the biggest risk is, whether they [tissue engineering products] actually work or not, as opposed to whether there's any risk to the patient. (Academic research scientist in UK lab S1, 2003)

A commercial producer of a variety of tissue engineered products explains:

> The risks to my mind are in efficacy. They run the risk of not doing anything. (Manufacturer in tissue engineering M1, 2003)

And as a clinician admits in a similar vein:

> So sometimes, yes, it doesn't work. The cells just... don't do any better job than the normal healing. (Clinician in academic hospital Cl2, 2003)

Thus in addition to safety concerns, there is a risk of lacking efficacy of tissue engineered applications. This expression of clinical risk relates in the first place to an anxiety that the treatment or product does not work, in that the therapeutic effects are minimal or absent. While the clinician of the last quote compares the performance of the product to the normal healing process, this concern has led to a broader discussion about the best ways of finding out if a particular treatment has any effect or not, and compared to what potential alternative treatments.

This discussion has focused on two of the most advanced tissue engineering applications that have been available on the market for some years, namely skin systems and autologous cartilage repair constructs. Tissue engineered skin products have mainly provoked questions about efficacy in relation to cost of applications, as part of a broader debate on the cost-benefit ratio of these products – which also links into the commercial risk category as discussed

[34] There is some discussion about terminology here in relation to the terms efficacy and effectiveness. Effectiveness usually describes how well an approved treatment (or drug) works during regular use and in a regular clinical setting, while efficacy is used to describe how well a treatment works under optimum conditions, such as during a closely monitored clinical trial. Efficacy is measured by evaluating the clinical and statistical results of clinical tests. Thus efficacy and effectiveness are not the same, and a treatment is effective if it works in 'real life' under non-ideal circumstances. Effectiveness cannot be measured in controlled trials, because of the inclusion criteria that reflect a distortion of usual practice. For my research I use the term 'efficacy' in relation to clinical testing, as the ability of a treatment to bring about its intended effect under ideal (controlled) circumstances.

later. The cartilage case is interesting because it flags up methodological questions that are specific for autologous applications, and that could potentially conflict with existing models of clinical evaluation.

A main transition phase in the research and development process of tissue engineering, and biomedical innovation more general, is translating findings from basic research into clinical practice and, finally, marketable products. In clinical trials new therapies are tested on humans to determine safety and efficacy, usually following the pre-clinical stage where the therapy is tested in the lab (in-vitro) and on animal models. This model is used for many different medical therapies, but has mostly been applied to testing of novel pharmaceuticals (Medical Research Council (MRC) 2001, 2005). Here the so-called randomised controlled trial (RCT) - in which participants are randomly assigned to one of two or more treatment arms of a clinical trial - is considered the 'golden standard' and the safest, fastest and most scientific way of gathering evidence that a particular treatment or drug is safe and effective.

For tissue engineering this model proves more problematic though, as the 'usual' ways of collecting data on safety and efficacy, both in animal studies and in clinical trials, are not considered the most appropriate in this particular domain. As summed up by a commercial developer:

> Many of these [tissue engineered] products cannot undergo a traditional double-blinded, placebo-controlled clinical study, and animal models have not been shown to reliably predict the human outcomes. Few animal disease models truly mimic the human condition, and long-term follow-up studies may be required, both in the preclinical and clinical setting, before regulatory approval is granted. (Naughton 2002: 382).

In this chapter data are presented that demonstrate how the relevance and methodology of these classical models of clinical evaluation and testing are debated and found controversial for the assessment of efficacy in tissue engineered products. By using a case study of one particular tissue engineering application, cartilage repair (ACI), I discuss the underlying issues in demonstrating clinical efficacy and safety in this domain. I then place these issues in the broader context of the search for clinical evidence, to analyse in how far this particular application is exemplar for tissue engineering technology more general. This will lead to the concluding remarks, in which I emphasise

how clinical risks have implications for the way tissue engineered products are controlled and regulated, and that there is a direct link between the question of efficacy of these products and their marketability.

5.2 Pre-clinical testing

The need for clinical efficacy is to be considered as an intermediate phase and intrinsic part of the broader innovation process. Efficacy is relevant in the final stages, in getting marketing approval or reimbursement for products, but also earlier in the trajectory. Assessment of tissue engineered products is problematic already in the pre-clinical stage, where new therapies are tested in the laboratory and in animal studies to determine their safety (and toxicology) before entering human trials. Especially the relevance of animal models has been questioned, because of the dependence of tissue engineering technology on the performance of cells and tissues in the human body.

In order to interpreted clinical risk in tissue engineering, we need to look at this earlier step in the innovation process, where uncertainty exists about the value of pre-clinical data. Several interviewees have expressed concerns with finding appropriate animal models for tissue engineered applications to test efficacy measures before the step to testing in human populations can be made. As one scientist, heading one of the UK national tissue engineering centres answers, when asked about his view on the sorts of evidence that are needed to evaluate these technologies:

> I don't think we know as yet. It's obviously something I've thought of an awful lot. I don't know how effective pre-clinical data, i.e. animal testing, is going to be in terms of predicting how things will happen in humans and I think that's a big problem. (Academic scientist and policy advisor A-EU6, 2003)

A manufacturer of a diverse range of tissue engineered applications in development and on the market, expresses a similar concern:

> It's difficult with cell products, they could get infected, how do you guarantee that there is no safety concerns, and how do you make it effective so that it works for a human being? And that's what you see, a lot of companies are struggling with... the theoretical part is nice, but

> then proving it in humans or proving it in animals is already being difficult. Because a human cell, you can't just put that in an animal. (...) I mean what does a goat say, when you put in goat cells, if the product that you have is human cells? It probably doesn't say as much. (...) So how do you test that, and what are appropriate test models? So you see companies struggle with that.
> (QA and regulatory affairs manager in multinational tissue engineering company M-EU4, 2003)

A scientist working in a technology assessment unit explains that, indeed, pre-clinical testing is not applicable, as 'you get into problems if you want to test human tissue in an animal' (R-EU3, 2003). This concern has been mentioned in relation to different application areas, including cartilage repair and wound healing, but also more experimental work in for example vascular applications. A scientist working on tissue engineered blood vessels explains the limited use of animal models in this particular area, because animal cells behave differently from human cells:

> It has only been possible to do some animal testing before, and since we are working with human cells, so we are producing vessels with human cells, there we have a problem: how shall we test those in animals? (...) I mean the real test is done in the clinical study and the ethical dilemma is to find a suitable model in human studies.
> (Academic clinician in vascular surgery CL-EU2, 2003)

In addition to appropriate animal models, this scientist also expresses concern with finding an appropriate model in human testing. For high-risk and potentially life-saving treatments in cardiovascular surgery, high levels of safety and efficacy have to be established before the transition to clinical trials can be made; the application simply 'has to work' as failure could be lethal for patients. This puts particular pressure on selecting the first human volunteers entering clinical trials, also posing ethical difficulties in terms of risks and benefits to patients taking part in this trial, against a background of uncertainty that only a certain level of efficacy can be tested in the pre-clinical stage.
Efficacy standards differ per clinical application area in tissue engineering, with 'irreversible' and life-saving treatments in the cardiovascular area reflecting one extreme, while more 'low-risk' applications in for example wound healing and cartilage repair, for which alternative treatment exists and which do not pose direct safety risks to the patient in case of failure, towards the other end of the spectrum.

To sum up, respondents frame pre-clinical studies of diverse tissue engineering applications, most notably the testing of cells in animal models, as particularly problematic in estimating the levels of efficacy and safety needed to proceed into clinical studies in humans. This might put extra pressure on producing valid data from clinical evaluation and testing, with 'the big test' taking place in clinical studies in humans.

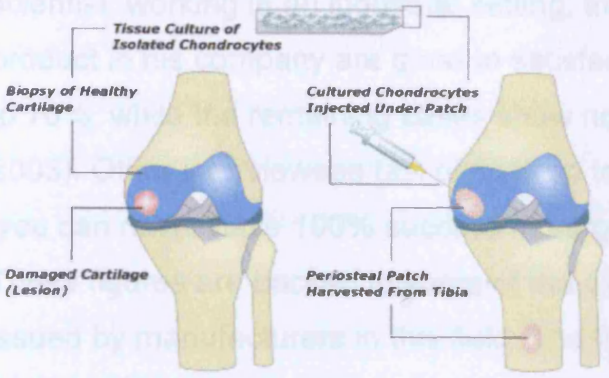
In the next section one particular tissue engineering application in cartilage repair, known as ACI, serves as example to demonstrate underlying issues in clinical testing, and why also in this phase of the innovation process efficacy as gathered in a clinical setting is controversial and debated. Also for this cartilage application concerns have been expressed regarding pre-clinical testing. As the extract below from a commercial provider of ACI confirms:

> [W]e had a little bit of pre-clinical data but not a lot of pre-clinical data because to be honest it was autologous tissue, there's not a lot of safety you can develop around that, maybe more on the risk analysis side as to whether or not tissue will bind in with surrounding tissue of and re-model. But you can only really assess that by looking at the human experience because if you do that in a dog or a rat or whatever then they all behave differently and stresses on the joints are very different so therefore you can really only test it in the human experience. (Regulatory affairs manager of multinational company producing autologous cartilage product M-EU9, 2003)

5.3 A search for clinical efficacy - the case of ACI

In addressing the question of clinical evidence, most interviewees refer to autologous chondrocyte implantation (ACI) as an example of a tissue engineered application that has provoked debate on efficacy and safety testing. This technique, also known as Autologous Chondrocyte Transplantation, involves a procedure whereby the surgeon takes a small amount of healthy cartilage cells (a biopsy) from the patient's damaged knee, 'about the size of two pencil erasers' (Genzyme 2005), which are then manipulated and multiplied in cell culture. After a few weeks the cells are implanted back into the same patient in a second surgical procedure. After this intervention, a recovery

time of between two and six months is needed for full regeneration of the cartilage (Harrison et al. 2000).[35] The ACI process can be pictured as follows:



Source: A. Biggs from Oscell (Hospital 2005)

The technique was developed in the 1980s in Sweden and more widespread clinical experience has been gained over the last decade in Europe and the US (Brittberg et al. 1994). Currently a handful of commercial cartilage products are available on the European market, while local hospitals also offer this service to patients in need of articular cartilage repair, usually for (sports) injuries in the knee. The prices of the ACI services differ per provider, and also depend on local arrangements, with commercial agencies charging from £3200 (Verigen) up to £5000 (Genzyme) per procedure, while a UK hospital based service working under the NHS Trust estimates cost of its in-house cell culture service at about £2000 per patient (NICE 2005). The use of ACI requires special training of hospital staff, which is provided by the commercial developers of cartilage repair products.

The next sections go into the underlying issues in gathering the evidence needed of safety and efficacy in ACI, which has been subject to extensive debate and has stirred some controversy in the field. Main issues relate to the concept of clinical efficacy, including its relevance for ACI, and to the best tools of gaining insight into efficacy for this procedure.

[35] The procedure of ACI and its results are well documented, see for example key reviews by Harrison (2000);Hardingham (2002); Sittinger (1999);Temenoff (2000); Bentley (2000); Brittberg (2001, 2003); Lindahl (2003); and Peterson (1996, 2002a, 2002b)

5.3.1 Defining efficacy

Wide variation exists in estimations of how effective particular tissue engineering applications are, ACI not being an exception. According to one scientist, working in an industrial setting, the clinical results for the cartilage product in his company are good to satisfactory, with success ranges from 60 to 70%, while the remaining cases show no benefit to the patient at all (S-EU1, 2003). Other interviewees talk of 60% up to 80% success (CI2) adding how 'you can never have 100% success in surgery, so 80% is very good' (CI5). These figures are backed in some of the clinical literature and in annual reports issued by manufacturers in this field. The International Cartilage Repair Society, a professional body that keeps a record of several European studies on ACI treatment, reports that most studies have shown up to 80% clinical success rate. But both these success scores and the measurements of evidence are contested. An academic clinician involved in health services research on arthritis and joint replacement is critical of the current ACI treatment:

> I think the problem is that what we're looking at here is a procedure [ACI] for which there is no good evidence of efficacy or effectiveness. Now no good evidence doesn't mean that it doesn't work, it means there's no good evidence that it works. (UK academic clinician C1, 2003)

Precise success rates are difficult to estimate, and uncertainty and disagreement exists about what precise outcome counts as successful, and how to evaluate the efficacy on the long term. A scientist involved in basic and clinical research in cartilage repair phrases this concern as follows:

> I'm not that concerned about safety regulations, they have to be as high as you can make them within reason and I don't have any problems with that. I have real problems over the current lack of efficacy outcome data and real problems with whether a realistic view will be taken on how to acquire that data, and how to measure it. (UK academic research scientist in clinical care and cartilage repair S4, 2003)

5.3.2 Finding the right tools

There are different means of acquiring data on performance and longer-term efficacy of medical interventions, for example based on experience of medical professionals using the particular technique, or on patient satisfaction and

perception. In ACI both these data sources are available, with an emphasis on 'sharing experiences' between academic centres working on this procedure.

When asked about their views on evidence available for ACI, many interviewees refer to scientific and medical experience with this procedure, also labelled as 'experiential evidence' (May 2005). Most clinical experience exists in a specialised centre for cartilage repair in Gothenburg, Sweden, where the ACI procedure was originally developed in the 1980s, with the first clinical results reported in 1994 (CI-EU3, 2003). Many scientists, clinicians and manufacturers involved in cartilage repair mention 'the Swedish study' when asked about the clinical evidence on which their cartilage services and products are based.

As part of this experiential evidence, also systems have been developed for following patients after treatment to monitor long-term effects of the procedure. A clinician in a specialised centre for ACI in a UK hospital, which has developed its own in-house methods for chondrocyte culture, describes how their treatment is modelled on the Swedish procedure, and how a lot of exchange of data of the technique and its evaluation takes place between the academic centres ('they came and taught us how to do the operation, how to grow the cells' CI2, 2003). In this UK hospital a patient monitoring system was developed ('a database for life') for which patients fill out self assessment questionnaires before and at set times after the surgical intervention, in addition to the biopsy samples that are used to gain longer term insight into the performance of ACI (CI2, 2003). Similar means of evaluation and patient follow-up take place in other academic centres across Europe, for example via a collaboration of specialist orthopaedic centres working on ACI called EURO-CELL.

5.3.3 More robust evidence: running trials

But experiential evidence and patient follow-up are not sufficient, and it has been argued that large scale clinical trials are needed to gain more 'valid' and robust evidence of experimental clinical efficacy. A model used for many medical therapies, though mostly applied in the testing of experimental drugs,

is that of the randomised controlled trial which is considered the 'golden standard' and most scientific way of gathering evidence that a particular treatment or drug is safe and effective.

At the time of fieldwork for this research[36] interviewees put great emphasis on the need for more (randomised) controlled trials that compare ACI in large numbers of patients, potentially from different settings (multi-centre), with alternative treatments to assess safety and efficacy. The main problem with clinical studies has been the lack of numbers (patients) involved in the experimental design, and the localised nature of many of these studies:

> People are doing small case series still.... so I mean, they're not even comparative studies, they're just a few cases. 'I did these half dozen people and they got better. Isn't it wonderful?' (...) I think almost inadmissible evidence, let alone poor evidence. (UK academic clinician in health service research on arthritis and joint replacement C1, 2003)

According to this clinician the design of current clinical studies does not provide the data needed for long-term evaluation of safety and efficacy of ACI. A similar view was expressed by the UK National Institute for Clinical Excellence (NICE), an organisation that provides guidance on the use of new and existing treatments within the NHS in England and Wales. The NICE appraisal Committee did a review on ACI in the year 2000, and concluded that its use is not recommended for 'routine primary treatment of articular cartilage defects on the knee joint in the NHS' (NICE 2000), which is the main application area.[37] Another review and re-appraisal of the procedure[38] was conducted in 2005, which more strongly underlined the experimental status of ACI:

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[36] In ACI several clinical studies have been set up over the last few years but only more recently results have been published from five randomised or quasi-randomised controlled trials (see for more details on these studies NICE 2005). The results of these studies where not yet known during the time of interviewing.

[37] In Germany a similar decision was made by the Bundesausschuss der Arzte und Krankenkassen (Hüsing et al. 2003). The Blue Cross Technology Evaluation Centre in the US did a product review of ACI product Carticel in 2003, and concluded that it did not meet the criteria, mainly due to lack of (public) data on clinical effectiveness (TEC, 2003). Manufacturer Genzyme warded off this critique by pointing out the ethical problems of doing a placebo-controlled study, which was one of the requirements of the Evaluation Center, due to the customised nature of the surgery (Genzyme, 2005).

[38] For its appraisal NICE looked at the results of five randomised controlled trials, published over the two most recent years, the largest of which included 100 patients. In its summary the appraisal committee stated that 'these trials provide inconsistent evidence of the clinical effectiveness of ACI' and that 'the studies were heterogeneous in terms of the patients recruited, the ACI technique used and the measures used to assess outcome.' (NICE 2005 13).

> Autologous chondrocyte implantation (ACI) is not recommended for the treatment of articular cartilage defects of the knee joint except in the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up. Patients should be fully informed of the uncertainties about the long-term effectiveness and the potential adverse effects of this procedure (NICE 2005).

The recommendation means that ACI is only available as part of a clinical trial in the UK. In addition to the earlier guidance, the need was articulated for explicitly informing patients about possible adverse effects of the procedure (such as 'joint locking' and infections) and of the fact that due to lack of long-term outcome data, not a lot is known about effects over time.

The clinical literature reporting on the results and efficacy of ACI is growing (Brittberg et al. 2003; Lindahl et al. 2001, 2003), but it has been stressed that more detailed studies are needed in support of this particular technique (Peterson 2002; Peterson et al. 2003). Only most recently a number of multi-centre randomised controlled trials have been set up in Europe, including in Germany and the UK. One of these studies compares ACI with non-ACI surgical treatment as part of regulatory requirements by the US authorities FDA, which also asked the commercial provider involved, Genzyme, to collect post-marketing data (phase IV clinical trials).

But setting up large scale clinical trials has proven problematic in this field. For example, clinicians have reported problems in securing funding from national research councils (such as the MRC in the UK) and from European funding agencies (for example under the EC framework programmes) to organise multi-centre randomised trials of ACI (CI2, 2003).

> It's a bit of a chicken and egg particularly with surgical techniques. How do you prove your technique is beneficial if you can't invest in treating large enough numbers of patients over a long enough period of time, but no one's willing to pay for that many patients over that long a time to do the work when its not been proven, so how do you get there? There are ways around that to do with companies funding trials and multi centre trials and so on but it's going to take time.
> (UK academic research scientist in cartilage repair S4, 2003)

In contrast, commercial providers of tissue engineered products are relatively small, and do not have the financial means to fund large trials or personnel to

organise them. Also, as explained by a clinical scientist with a commercial background, some companies are reluctant to take part in clinical trials, because in most countries products are not reimbursed by national health or insurance systems as long as they are offered in an experimental setting, which means no profit can be made over these products.

> Whenever you're talking cells you really need long term studies to show safety, real safety, because these are unpredictable, are you going to get something growing from those cells that you didn't anticipate? And that's going to be long term clinical studies. And companies can't afford and don't like long term studies, because the way companies work is that you've got to get your product onto the market to get revenue. And if you're a start-up company and somebody says do a 15 year study, yeh.... So for a lot of technologies evidence of safety is accumulated along with use. So products are launched before people have got all the information they'd really like but that has to be.
> (Clinical scientist in multinational industrial setting M-EU1, 2003)

Furthermore it has been argued that clinicians lack the expertise and means, and sometimes the willingness, to become involved in these experimental treatments. One clinician involved in ACI work stresses the need for specialised knowledge to set-up large scale trials, and the lack of such expertise in most clinical settings (CI5, 2003). Another clinician is pessimistic about the feasibility of these trials because of different 'mindsets' of most orthopaedic surgeons, who are the ones usually performing the ACI procedure. He reports on a workshop organised to discuss the need for clinical trials in ACI, where...

> ... It became completely clear that they [orthopaedic surgeons] don't understand trials, don't believe in them and never heard of issues like equipoise and just think it's a lot of nonsense. 'Let's get on and cure the customers,' was the kind of feedback we were getting. So with all the proponents being of that mind set, difficulties in designing the trials, of ethics of the trials and in deciding what the appropriate outcomes and the length of time of the study, I think it probably won't happen. It's all very depressing, isn't it?
> (UK academic clinician in health service research on arthritis and joint replacement C1, 2003)

In addition to problems in setting up and running clinical trials, ACI highlights more fundamental concerns with the particular design and methodology of these experimental studies. As touched upon before, there are particular models and standards for clinical evaluation which are used for a range of medical interventions, and controversy exists over the question in how far ACI

fits into these. With customised treatments such as ACI, where cells from one patient have to be re-implanted into the same patient, the often used standard of single or double blinded clinical trial (where it is not known which patient is receiving experimental treatment) is not applicable. Also placebo-controlled studies that are often used for pharmaceuticals - in which an inactive substance (the placebo) which mimics the effect is given to one group of participants, while the experimental treatment is being tested in another group - is not considered an option in ACI, or in any tissue engineered application irrespective of whether it is autologous or allogeneic. Several manufacturers have reported issues with the trial format and which experimental format to follow. Most current trials are based on a model that is used for pharmaceuticals or medical devices.

> I mean the product, yes of course: it's cells and they're modified whatever way they modify it and then you have the product. It sounds simple. I think everyone who's been to a manufacturing plant of cell therapy products realises there are lots of clinical trials. It's very different from medical devices and pharma. And so they are very specific both in clinical trials and in producing them, manufacturing them. (...) First of all, to give an example, let's say you're doing a double blind study for example. How are you going to do that when you inject cells in a person? So forget about them. I think the double blind was one of the main [issues], and finding a large patient population or a patients centre. Repeating a trial, how are you going to do that? So it's a very specific field that demands very specific knowledge.
> (Corporate affairs manager in multinational company M-EU5, 2003)

Another manufacturer described in a similar way how the company was struggling with the trial format for their ACI product, trying to fit in their clinical studies into the more accepted standard of pharmaceutical trials:

> It was at that point I think that we realised that trying to match for example pharmaceutical clinical trials around orthopaedic studies is nigh on impossible. First of all you have numbers of patients. You can't do a thousand patients in a medical device type trial. You can't really blind the study which means you can't necessarily randomise it.
> (Regulatory affairs manager of multinational company producing autologous cartilage product, M-EU9, 2003)

As one scientist in a national government agency simply put it:

> You cannot do a double-blinded trial because you don't want to implant cells just for fun into a healthy person (R-EU5, 2003).

Another underlying issue in the design of randomised clinical trials is the need for a control group that receives alternative treatment. For one clinician this is a reason to not take part in this format of clinical research:

> I cannot persuade my patients into doing a randomised study here. It's impossible. Because they come to me because they want to have Autologous Chondrocyte Transplantation, you understand? So that has to be done by others, universities in England, or Sweden, or... (Orthopaedic surgeon and director of specialist medical centre for ACI, CI-EU3, 2003)

Furthermore, controlled clinical trials are often based on measuring effects of an experimental therapy compared to a standard therapy. In the case of ACI it is difficult to find a comparative treatment for cartilage repair that is based on a similar technique, namely cell culture. In the few studies that have been published, cell culturing techniques have been compared to surgical techniques including microfracture and mosaicplasty.[39] One study compared different sorts of ACI. There has been some debate in the ACI field as to what counts as proper comparative treatment. Most clinicians and scientists in this study feel that a cell culturing technique such as ACI is considerably different from more conventional surgical procedures. At the same time it has been stressed that for many (other) clinical applications in the field outcome data are lacking altogether:

> I think you should have of course evidence based studies, and randomised control studies to compare the effect, or the efficiency, of this treatment to other treatments. But I think they [the NICE appraisal committee] made a great mistake because there is no other treatment that has been proven in the way they want Autologous Chondrocyte Transplantation [ACI] to be proved. (...) What treatment is proven for cartilage repair? Is there any treatment? (...)
> If you look into orthopaedics then you see very few treatments have been established on a five year follow up, on randomised control studies. Very few. But I think that if you get too scientific you may stop the development of new treatments. So you have to give some treatments a period of time... (...) If an independent clinic, or university, can repeat the results, I think that is a confirmation of that this is working. And data is coming off now... that it's not a disaster in any way. It's better than what we have in most studies.
> (Orthopaedic surgeon and director of specialist medical centre for ACI, CI-EU3, 2003)

[39] Respectively the shaving and drilling of bone to promote growth and the grafting of healthy cartilage from within the joint also known as osteochondral transplantation.

So far, clinicians, scientists and manufacturers in this sample have adopted different frames about the use of evidence based studies to produce data on efficacy, but also on the means of gathering these data, where the need for randomised controlled trials is contrasted with long-term clinical experience. But two more underlying issues have arisen here that are specific to ACI therapy; one relating to an 'uncontrollable' factor determining clinical outcome, namely professional skills of the person performing the procedure, and the other related to clinical effects and patient safety when the ACI product or service does not 'work'.

5.3.4 Clinical expertise and demarcating safety

A specific issue determining clinical outcome in ACI is that the procedure requires special training. Most commercial providers in Europe offer training courses to physicians in surgical techniques and in how to select the appropriate patient population (while in the US this training is part of the FDA requirements to get marketing approval for ACI products). So in addition to the quality of the product and the efficacy of the cartilage cells that constitute it, the specific skills of the surgeon conducting the procedure determine the efficacy of the final product. As a representative of a multinational company offering ACI products explains:

> Tied in with that of course is that as a surgical technique it is quite complicated, so clinical efficacy can sometimes be combined with surgical training and the abilities of the surgeon. So you could have exactly the same product, exactly the same patient. For example if he has lesions in the left knee and then another one in the right knee he can go and have exactly the same technique applied to him but with one surgeon and then go to another surgeon and have the same procedure, and the effectiveness will be different simply because of the abilities of the surgeon.
> (Regulatory affairs manager of multinational company producing autologous cartilage product M-EU9, 2003)

This poses questions about the specialist expertise needed to conduct the procedure, and about larger availability and marketability of products, as the 'average' surgeon is not able to perform the complicated re-implantation of the ACI construct – or even allowed to diverge from the protocol and detailed

guidance that comes with these products, as another commercial provider explains:

> So the last risk which remains, is that these pieces of cartilage or bone would from the operating point of view, come off or not stay in place. That is why we have been using a teaching centre to allow the doctors using one technique, which we tested in a clinical trial and of which we are a hundred percent sure that it works. So if a doctor uses another technique for example, he doesn't want to fix it as we suggest, it is his problem but we do not allow it. This is written in the conditions when we distribute this product.
> (Director of multinational company for ACI, M-EU10, 2003)

The second factor relating to clinical efficacy is the issue of adverse effects and patient safety. In contrast to concerns about the role of the clinical professional carrying out the surgical procedure of ACI, which affects clinical outcome, the effects of an 'ineffective' and as such failing treatment on the patient are defined as minimal. Several interviewees stress that lack of efficacy does not necessarily mean that the patient is in a worse clinical condition than before the intervention. With ACI the lack of 'working cells' to heal the defect does not pose safety threats to the patient:

> Well the other problem is, of course, some patients don't get better; about twenty per cent who don't get better. I think it's fair to say we've never really made anyone worse. (UK academic clinician in ACI CI5, 2003)

An industrial scientist working in a multinational company offering cartilage repair services, explains in a similar way how the wound site is not affected 'so if you have failure of the treatment, you can do something else, (...) you do not ruin the site' (S-EU1, 2003).

It has to be noted that this argument of 'no gain, no pain' might apply to ACI as a particular exponent of tissue engineering technology, but may not translate to other clinical application areas. Cartilage repair has a range of alternative treatment options beyond cell culture - and this also goes for relatively simple applications for non-life threatening conditions such as skin constructs for diabetic ulcers. More irreversible treatments such as heart valve replacement pose more severe safety concerns, and the demands for efficacy for these therapies are considered higher.

Thus ACI is illustrative of some of the issues underlying the clinical risks associated with tissue engineering technology more general, such as a concern with clinical efficacy, what counts as evidence and how one should go about collecting and interpreting this evidence of efficacy and safety.
Many 'classical' ways of gathering efficacy and safety data, most notably the golden standard of the RCT, have been singled out of the domain, while respondents also refer to practical considerations in demarcating what the appropriate objects are for inclusion. The lack of possibilities for randomisation, placebo-controlled or blinded studies in ACI is intrinsically linked with the customised nature of the treatment, which, it can be argued, applies to other autologous cell therapies as well. For example, there can not be a control group of healthy volunteers to compare cell implants with, as it is not possible to implant cells into healthy people. Single or double blinded studies[40] are no solution in a therapy which efficacy and safety for most part relies on implanting the same cells back into the same patient. Also the comparative nature of randomisation, where an experimental treatment is compared with (usually) standard therapies available poses dilemmas in the case of ACI, where selecting an appropriate 'alternative treatment' with a shown track record of clinical efficacy has proven contentious. Finally the skills of the surgeon performing the ACI procedure are a determining factor in establishing clinical efficacy of the final product after implantation, which is a variable that is hard to control in an experimental setting.

5.4 Extending boundaries: From clinical efficacy to cost-effectiveness

In terms of the broader framework of clinical risk of tissue engineering, ACI is one example which clearly demonstrates concerns about clinical outcome and the search for clinical efficacy. But what about other clinical application areas and why is clinical efficacy so important? The purpose of this section is twofold. First, it discusses ACI in the light of other tissue engineered applications, most notably in wound healing, to point out that ACI is not a unique or isolated case.

[40] Where neither the participating individuals nor the study-staff knows which participants are receiving the experimental treatment and which are receiving a placebo or another therapy.

Second, it demonstrates the broader relevance of the need for clinical efficacy, arguing how this not only relates to patient safety, but also provides a mechanism for controlling commercial risk.

First, ACI should be compared to other tissue engineered applications in order to assess the broader meaning of the search for clinical efficacy. As demonstrated in this section, many of the clinical risks and concerns regarding efficacy of ACI are echoed in wound healing as another example of a more advanced tissue engineered therapy. Here too practical concerns in setting up clinical trials have been mentioned as a heavy burden by scientists, clinicians and manufacturers alike. As the following extract illustrates from a clinician with both an academic and commercial background:

> Well the well known methods, like clinical research, multi centre research, experimental research... Nowadays everything has to be evidence based but evidence based is... that's not difficult but it needs so much effort that in my position if I want to make all my experiments in animals evidence based that's impossible because I lack time, I lack money, I lack personnel.... And it's the same in the clinical situation because in the clinical situation people are too busy to set something up in such a way... At least in [this country] with the burn centres, they can never manage those things evidence based. If you want to use the skin substitute and you want evidence based controlled studies of the skin substitute, to prove that the quality of the healed skin is superior to the method that exists, that will cost at least five years and I think ten years or more is more reasonable to say that the product is working. But what's going on in those ten years with other engineered tissues which are coming? So you can only make one selection and that selection is not based on evidence but on emotion.
> (European clinician in wound care CL-EU4, 2003)

In addition to these rather pragmatic concerns, the assessment of efficacy in a clinical trial setting for wound healing products comes with a range of 'uncontrollable' factors that are borne with the individuals taking part in the study, and which makes comparison across settings (for example in multiple centre trials) problematic. The interview fragments below by a clinician and a manufacturer involved in clinical trials for tissue engineered skin products demonstrate the difficulty of assessing the clinical efficacy in these experimental settings:

> Any trial of a wound healing product is very difficult to assess because there are so many factors that you can't control for: the patients'

> systemic health, patients' level of activity, the size of the wound, you know, the infection of the wound, the duration of the wound. It's hugely difficult to actually see a weighing up, you know, risk against benefit. (Clinician and professional member of consumer organisation in wound healing Co2, 2003)

> Normally you're taking what's seen as either the best conventional practice or the most typical type of treatment and looking for a statistically significant benefit in some aspect, wound healing for instance, to demonstrate that. (...) It's probably more complicated than in treating some of the more medicinal product type of treatments, partly because of the nature of the technology involved and the design of trials. I guess that's developing all the time. And identifying the right number of patients. 'Cos obviously if you're targeting things like hard to heal wounds or chronic wound areas, you're often dealing with patients who are significantly compromised and they have a lot of other ailments associated with them as well. It'd just be the fact that they've got an ulcer that's not healing. (...) You might find that general health issues, yeah, can have other effects, kidney damage all kinds of aspects. And so it would greatly complicate I guess the analysis of some of the studies in trying to, having enough patients controlled in a certain way that you would get the best statistical analysis. And I think that's something that a lot of companies are still struggling with.
> (Scientific manager corporate product safety assurance for UK based multinational company M2, 2003)

Thus some of the clinical risks as expressed in relation to ACI are comparable. Here too people talk of lacking resources, time and expertise, difficulties in running large scale clinical trials and the selection of appropriate patient populations to gather evidence based data. In contrast though with ACI treatment, the area of wound healing highlights another important issue which places clinical efficacy in a broader framework, namely the cost-efficacy of these therapies.

Interestingly, the issue of cost-efficacy of ACI in relation to clinical efficacy has only been marginally addressed by interviewees in this sample. As the clinician below stresses, ACI is an expensive technology (of up to several thousands pounds per procedure), and from an cost-economic perspective this puts pressure on the long-term performance of the procedure as compared to other treatments that are potentially cheaper, safer or less experimental.

> If it's cheap it's accepted. If it's expensive, it's not accepted. Then you have to have randomised studies. (...) I think because it's expensive it's been a nightmare for most of the payers (...). So I understand that, but after sixteen years of clinical experience and twenty thousand patients

> treated and no real serious side effects shown, and repeated results from other independent clinics, I think it's more proven with this technique than in any other cartilage repair technique.
> (Orthopaedic surgeon and director of specialist medical centre for ACI, CI-EU3, 2003)

Thus cost-efficacy is an important factor in the broader discussion on efficacy of ACI treatment, and of other tissue engineered applications that have entered the market place in recent years. This is also what NICE took into account in their appraisal of ACI, where in addition to clinical efficacy also the cost effectiveness of ACI was studied – based on factors of the cost of the cell culture and treatment costs including those of surgery, days as an in-patient, and follow-up physiotherapy. With the need for effective use of NHS resources in mind, ACI was compared with two other surgical procedures for cartilage repair and a model was developed to assess cost effectiveness and quality of life improvement in different stages.[41]

Whereas a concern with cost of ACI is relatively underplayed by interviewees in this sample, this is of key concern in the wound healing market. In the case of ACI only a limited number of alternative treatments are available, which are all surgical procedures of some kind, and with some more established therapies than others (for example microfracture and the still relatively experimental mosaicplasty technique). This is not the case in wound healing, where a range of dressings and other therapies with varying wound healing capacities enter and exit the clinic over shorter or longer periods of time (one interviewee spoke of 'the current fashion' in this respect; Co2, 2003). In other words tissue engineered applications in wound care, for example for the treatment of diabetic ulcers or burns, have to compete with a variety of clinical alternatives, some of which have an established safety profile, and most of which are generally cheaper or easier in use. This does not mean these alternatives are more effective in healing wounds, but cost-efficacy plays a more prominent role in the evaluation of this particular technology. The extract below is from a clinical professional with experience in the use of many different therapies for healing ulcers:

[41] Based on short-term data it was argued that a slightly higher success rate of ACI compared to alternative treatments would not justify additional cost, but because of lack of (consistent) data over a longer period of time the relative effectiveness of ACI compared to other treatments could not be assessed, nor the quality of life gain from treating with ACI (NICE 2005: 15).

> I think money is a big limiting factor and I think it is getting enough evidence of efficacy. There is not enough hard evidence of efficacy. And at some stage you've got to go with the faith and think: well, I don't think I'm going to do any harm using this product so I'm going to monitor it very, very carefully and see if it is beneficial. That's definitely the big restriction. If this was brought out and was costing 50p an application, it would be used universally up and down the country. But I think definitely the cost is a big, big, factor.
> (Clinician and professional member of consumer organisation in wound healing Co2, 2003)

Thus cost is an 'added' factor in not just the introduction of these products into the clinic and marketplace, but also in gaining long-term experience and gathering outcome data on the clinical efficacy. As such, the example of wound healing illustrates a strong correlation between clinical efficacy and cost-effectiveness, which turns the discussion on clinical risk to questions about the need for clinical efficacy as related to both safety and commercialisation of the technology.

To conclude, this chapter has focused on clinical risk, defined in terms of evidence of efficacy of tissue engineered applications. The starting point for this search for clinical efficacy is the perceived inadequacy of animal models for the pre-clinical testing of tissue engineered applications, where experimental studies in humans are seen as 'the big test' for assessing safety and efficacy of these products. The need for clinical efficacy is driven by the limitations of other means of assessing efficacy, in the light of uncertainty of predictability in pre-clinical research, i.e. in finding an appropriate animal model for initial testing on safety and efficacy, before entering in the human trial population. But the case study example of ACI has shown how particular boundaries are articulated, where the 'classical' ways of collecting data on safety and efficacy, most notably via randomised controlled trials, are not considered the most appropriate ways of gaining the desired information. Thus one of the concerns as expressed by scientists and clinicians in this study, and with a more commercial agenda in mind brought up by the manufacturers in this sample, relates to the kind of evidence that is needed to gain insight into efficacy and safety of (particular) tissue engineering applications, the methods to collect this evidence and the tools to evaluate the technology more general.

The second reason why clinical efficacy is important relates to the trajectory after the clinical study phase, more specifically the need of efficacy data for cost-benefit studies, for regulatory approval of tissue engineered applications, and for reimbursement of these products by national insurance and healthcare providers. The medical profession needs to get convinced of clinical efficacy and safety to make the transition from lab to clinic, whereas regulators need evidence of efficacy and safety for the smooth transition to the market and to wider applications in search for commercial success. How clinical risk is linked with commercial risk is described in more detail in the next chapter.

6 Commercial risk

This chapter starts by demonstrating how clinical risk is linked with commercial risk, which is the last tier of the risk classification as outlined before. Commercial risk covers the economic implications and hurdles for introducing novel therapies and products in the market place. This is first discussed in relation to cost and cost effectiveness for tissue engineered products. These issues are referred to as the 'fourth hurdle', representing the increasing need for manufacturers to demonstrate the economic value of their product before they are able to obtain marketing approval and reimbursement. But commercial risk also has a broader connotation. These developments are set in an unstable commercial environment of start-up biotech companies that do not have the means or expertise to successfully commercialise and launch products in a climate of fading investors' confidence and lack of unified regulatory controls, taking place against a socio-political background of diminishing public confidence in biotechnology more general after health scares such as BSE and public controversies such as those over genetically modified organisms (GMOs). The second part of this chapter considers the commercial climate and setting in which tissue engineered applications are developed, which poses additional barriers to product marketing.

In this domain new social worlds are created and alternative boundaries drawn. The risks of biological starting materials, identified as strong boundary objects in technological risk, are in this context reconstructed: where autologous sources were considered 'safe' in the initial R&D phases, these become part of a considerably more risky frame when entering the commercial cycle. Furthermore, the value of clinical risk changes when efficacy does not just affect the patient but also the taxpayer. These considerations lead to a more dynamic model to get to grips with categorising interviewees' risk perceptions, which is discussed in the subsequent chapter.

6.1 The fourth hurdle

A dominant issue impacting on the commercial development and marketing success of tissue engineered applications concerns the cost effectiveness and reimbursement of the treatment. Demonstration of efficacy is needed in some countries to get marketing approval for tissue engineered applications, depending on the regulatory framework. But marketing authorisation is not enough:

> Because it's not only regulation, that's point one, if you get the regulation at least the reimbursement agency will recognise it, like okay it's a medical product, but then we're still not there and we still need to solve how do we get the reimbursement? The problem with small companies is of course that... everybody knows these products are expensive, more expensive than maybe other products out there, but we know they bring much more value to the patients. But when do you prove that with hard data? If you have 5 -6-7 years follow-up data... you cannot wait for that amount of data. So that's the difficulty. That's the difficulty and that's why you see all the small companies, they just cannot afford to be in this business anymore because you are not getting paid for these products. (Regulatory affairs specialist in European tissue engineering company M-EU4, 2003)

Many products are not reimbursed by national health services and insurance systems in absence of long-term data to show the superiority of these products in terms of clinical efficacy and cost-effectiveness. Thus therapeutic effectiveness is also relevant in lifting experimental therapies from the clinic to the market place. However, as pointed out by the European Commission:

> Many of the tissue-engineered products are still in early stages of development. The small biotech companies involved do not have the resources for large, long-term clinical trials to provide information on the cost-effectiveness of the treatment compared to conventional alternatives. Lack of cost-effectiveness data is the main reason for which insurance companies are reluctant to reimburse treatment with tissue-engineered products. (European Commission (EC) 2004).

Until recently, the usual procedure for reimbursement and market access for many innovative health technologies included ensuring the safety, efficacy and quality of the manufacturing process of the product – also known as the three regulatory hurdles. With the increased availability of novel medical technologies, rising patient expectations and changing demographics in recent

years, healthcare systems have come under extensive pressure to work towards more efficient ways of providing care. Thus in addition to safety, efficacy and quality, the clinical cost and cost-effectiveness of medical interventions are increasingly taken into consideration for purposes of regulation and reimbursement (Kanavos et al. 2000).[42]

Critics have argued how this development is part of a broader trend which has driven policy reform in the healthcare sector. Globalisation, the crisis of the welfare state and the neoliberal narrative in health policy have called for increasing standardisation with more significant pressure for free market solutions, alongside an acceleration of techno-scientific innovation in medicine (Gottweis 2005). The more efficient organisation and provision of healthcare is exemplar for the rise of the healthcare market (Moran 1998, 1999), where healthcare systems have recognised how a technical or medical frame of reference is no longer sufficient (Drummond 1980).

Against this background economic evaluation has become more central. Several countries have now made economic evaluation part of the formal authorisation procedure as part of their national reimbursement strategies, particularly in Europe, while in some other countries the submission of economic evidence is voluntary. National agencies have been set up to conduct health technology assessments (HTA) to review new and existing healthcare interventions and to provide recommendations to funding and

[42] A note should be added here about the use of terminology and meaning. Cost-effectiveness in the economic sense of the word is a comparison of the relative expenditure (costs) and outcomes (effects). In health care a variety of models has been developed to assess the comparative impacts of expenditures on different health interventions, which have provoked extensive debate on both the appropriate methodology and the role of these studies in decision-making about medical treatments and therapies. Some of these models use monetary units to measure outcomes or benefits (cost-benefit analysis) while others express benefit in quality adjusted life years (cost-utility analysis). Cost-benefit analysis usually compares different health interventions by using a ratio where the denominator is the gain in health (such as adverse reactions avoided) and the numerator is the incremental cost of obtaining benefits. The denominator may be expressed in years of lives saved or undesirable outcomes averted. One of the criticisms of this cost effectiveness approach is that it does not take into account other benefit factors of a clinical intervention such as quality of life, satisfaction, different preferences and values et cetera.
The purpose of this chapter is not to provide a cost-effectiveness analysis of tissue engineered products, nor to revisit the debate on the use of these different economic evaluation models. Cost-effectiveness is part of a broader consideration of commercial factors and risks that affect the marketing of tissue engineered products as expressed by interviewees in my research sample. This chapter provides an analysis and some explanation of the increasing need for cost-effectiveness studies in gaining regulatory approval and reimbursement, rather than attempting to provide such a study.

reimbursement bodies (see for an overview Paul and Trueman (2001) and Drummond (2003)).[43] Critical sociologists have described the use of rhetorical discourse in the construction of a 'need' for health technology assessment, arguing how the cost-containment justification for HTA has been used as rhetorical device in boundary setting (Faulkner 1997). Concern of expenditure might have been an original cause, but assessment of healthcare technologies is also - and arguably increasingly - driven by other concerns, such as health benefits and risks of technology and its social implications.

The introduction of this fourth hurdle affects the development and commercialisation of innovative health technologies. Although it has now become a familiar concept in the licensing process for pharmaceuticals and to a lesser extent medical devices and biotech products, the fourth hurdle has also gained ground in tissue engineering. As the clinician below explains, with an expensive technology such as tissue engineering the collection of economic outcome data in this field is becoming inevitable:

> We need science behind that [tissue engineering technology] and we need proper prospective studies because after all it's going to be more expensive, so we will have to validate this not only for efficacy but then also the second wave, the cost effectiveness of what we are doing here. (...) Like any other treatment, we will have to make sure that we can get the proper treatment to the proper patient. And for that you will need reimbursement. And the reimbursement will only be obtained if you have reasonable efficacy studies and prospective randomised trials, if you follow the evidence based medicine and the rules and the regulations and if you can come up with some cost effectiveness studies. (Clinician involved in European start-up company CL-EU5, 2003)

Thus beyond the need for clinical efficacy, as discussed in the last chapter, also in tissue engineering an arguably upcoming trend can be witnessed of including cost effectiveness parameters in assessing the comparative health gains of a treatment or product. A manufacturer of autologous cartilage applications described this fourth hurdle procedure in a European country as follows:

[43] The work of the technology appraisal committees under the UK National Institute for Clinical Excellence (NICE) is a well-documented example, while other countries with similar arrangements include the Netherlands, Belgium, Finland, Portugal, Norway, Sweden and more recently Hungary. Australia has been reported to be the first healthcare system to make these requirements part of the formal authorisation procedure in 1993. See for national examples Taylor et al (2004).

> If you want to be reimbursed you have to submit a dossier. (...) This authority basically needs to know two things, first of all: what is the clinical efficacy of your product, which you have to prove providing them with clinical data. Describe what type of studies, good clinical practices, how many patients, the statistics etc and this is with precision. And so the clinical efficacy, that is what they ask for first, and secondly they ask for the commercial efficiency, which means: is it cheaper, is it a cheaper treatment compared to the other treatments, existing treatments or is it more expensive? Because before they say that they will reimburse it they have to know what impact it will have on the insurance companies. (...) You understand this problem, if you have a new product which is fantastic clinically but costs too much, they can not put it on the list because they will say that this is good for the patients but who is going to pay for this?
> (Director of multinational company in Europe producing autologous tissue engineering applications including cartilage M-EU10, 2003)

This section starts with a focus on these economic aspects of the marketing process, including a concern with both cost and cost effectiveness of the technology, while the second part provides more detail about reimbursement policies in Europe.

6.1.1 Cost and cost effectiveness

Tissue engineered products are expensive, which is a potential limitation in bringing these products to the (public) market and gain profit. The costs of individual applications in tissue engineering are high compared to older, more established treatments. As one scientist explains, over the last years many products have benefited from modern biotechnological developments in which much has been invested, 'so as you are growing in sophistication you are also growing in cost' (A-EU8, 2003).

Interviewees have given several reasons for the high cost of tissue engineered applications. The most important factor relates to the production process of cell culturing, which is a very labour intense activity that takes time (CL-EU3, 2003; CI6, 2003). Special facilities are needed, such as clean rooms, to control the culturing process and to guarantee a sufficient amount of quality cells that are viable and effective. Cell culturing of this kind also requires high-skilled and specialised staff working in the laboratories and manufacturing units. In addition, some products undergo a complicated logistic process, where cells

are transported under monitored and controlled conditions over different sites, often operating in short time windows. This is of particular importance for autologous products, which are extra vulnerable because the timing of use is more difficult to manage compared to donor products that are ready from stock on ordering by the clinician.

Cost is an especially pressing issue in woundcare management, which is one of the most developed areas of tissue engineering technology with several products already on the US and European markets. As such these have the longest 'track record'. Major differences in application area exist, some more acute than others, and alternative treatments are available. Most skin equivalents currently approved are based on human donor material, which means they are available 'off the shelf'; less time is lost in planning of the culturing process while transport and delivery is more flexible compared to autologous applications. Thus most woundcare products are available on a mass-produced basis rather than as customised treatment. From a commercial perspective tissue engineered applications for woundcare are the most advanced applications of its kind. But they are also more expensive, difficult to attach to a specific target market, their therapeutic effectiveness is debated and none of these products are in widespread or routine clinical use, as illustrated below.

The price of human skin equivalents ranges between under a few hundred US dollars to over a thousand dollars per unit, which can on average cover a square foot of skin. Depending on the wound more than one application is needed. Apligraf costs about US$1000 per unit, which comes in a circular disk of 75 mm, while similar products for treating venous leg ulcers and diabetic foot ulcers are available for around the same unit cost (Hanft et al. 2003; Thuesen 2001). In comparison, cadaver skin costs only a little over $2 per square inch (and usually comes in much larger sheets). Also simple dressings are relatively cheap, from a few cents to usually not exceeding the $5. Especially with the limited shelf life of many tissue engineered products, there is an inherent risk of having to discard the product after the expiry date has gone. Also practitioners' unfamiliarity with these relatively novel products in routine practice can lead to misuse and waste.

With increasing importance of cost-effectiveness of innovative therapies, these tissue engineered applications have to compete with usually cheaper and often more 'proven' effective therapeutic alternatives. This means that, to justify the cost, the product needs to compensate in other areas, such as efficacy or ease of use. As a research scientist put it, a small improvement over current therapeutic possibilities is not enough to convince clinicians: 'So the major limit is that what we do is going to have to be fantastically better than what is already out there on the market' (S7, 2003). But as another scientist explains, the treatment regime for many tissue engineered products is long and complicated, adding to cost and hesitation by clinicians and insurance companies alike:

> And then there's the cost implication which has been identified, that some of these tissue engineering products are so expensive or they are so fiddly to apply that they're not as easy as giving, you know, a little old lady a pill to pop once a day. You know, these are people who might need to go into clinics a couple of times a week to have aftercare, and that's expensive... unless there's a real reason to, for the extra expense and tissue engineering product, then there's not going to be approval by... the insurance companies. And so the markets for some of these products are a lot, lot more smaller than people originally thought.
> (Academic research scientist in UK tissue engineering lab S1, 2003)

Issues to do with ease of use in the clinic and familiarity with how the product performs are thus, in combination with high cost, one limitation. Although the *potential* market for woundcare products has been estimated to be large and growing, it has been argued that the *precise* market size and the specific target population of patients who would potentially benefit from this technology are as yet unknown:

> The current population of patients that require repair of chronic wounds... there are many hundred thousand patients; one fraction of those could be helped with a minimally invasive type of treatment? We don't know.
> (Academic research scientist in UK S6, 2003)

This uncertainty around actual market size is further complicated by the effect that many clinicians do not consider tissue engineering to be a 'first line treatment' or preference out of a range of possible therapeutic interventions:

> I guess recognising that the high cost and high tech aspect of tissue engineering at the present time... you won't use it as first line treatment for all the patients, that... is to say, well let's use simple things for the patients first but if the simple things don't work then ah, select the appropriate tissue engineered or other biologically based therapy, that might correct the abnormality as stage two.
> (Clinician in wound healing in UK university hospital CI3, 2003)

The adagio to 'keep things simple' is pervasive in many medical specialisations, as also illustrated by another clinician who argues that there is a tradition to 'find simple solutions, and even if it takes longer for the patient to get back to work or even if it's not as good, it's acceptable on the basis that it's cheaper.' (CI2, 2003).

Thus commercial risk is framed in terms of high initial cost of high-tech individual applications, that are furthermore targeted at only a specific but as yet unknown sub-population of patients that could potentially benefit from the intervention, and for which long-term evidence of therapeutic effectiveness is in most cases limited or absent. Especially in wound management an overall scepticism exists towards tissue engineered skin products, as there are alternative treatment options that are cheaper and with a stronger medical-scientific basis (CI4, 2003).

> The difficulties that, I think, the commercial things have, is that they see the total picture of that wound problem and say: that's the business which we should be chasing. And the business is huge if they see the whole and total number of patients there with wounds. But my view would be, be more realistic and carve a sub group of that total population and make sure your products are being used efficiently and effectively and then you're going to have an even bigger argument that you are actually using it appropriately. Because the other problem we have is this concept that wounds equals dressing equals fifty p a go and even if that fifty p a go goes on for months or years it doesn't matter because a unit cost the dressing is fifty p. If you suddenly come in now and say: I want to put a five hundred pound piece of something on there, they see that as a huge increase... we're talking about a huge differential in cost and even if the five hundred pound was expensive as a unit cost, if I could heal more patients within a shorter period of time, that should be much better.
> (Clinician in wound healing in UK university hospital CI3, 2003)

But as this quote illustrates there is also an underlying alternative scenario of explaining economic cost in a more differential manner, which is especially dominant amongst manufacturers and some clinicians. While the initial high

product cost is being recognised and criticised, the economic add-up should also include overall treatment costs as part of a broader cost-benefit analysis. As several clinicians underline, the 'true cost' of treatment in woundcare is determined by staffing and hospitalisation at least as much as the unit cost for individual products. Measuring these costs is complicated in some countries, such as the UK, due to separate budget management strategies in hospitals. Thus reductions in for example the costs of nursing staff are not visible in the supply department, and different budgets are not linked or matched. This is also the experience of another healthcare professional in woundcare management:

> As with any specialist wound dressing off-loading treatment method, if it doesn't involve the patient becoming an in-patient, it is a different budget. So it's cheaper to have them in bed, in the hospital ward for one budget, for our budget, than for us to actually be treating them as out-patients, keeping them out of hospital where they are healthier, happier and probably cheaper to treat unless they become an in-patient with the added risks of that and then coming off someone else's budget. This is the problem; it's a budget situation definitely.
> (UK clinician in wound healing Co2, 2003)

Many interviewees stress how the current way of assessing cost and benefit is a difficult model to apply to tissue engineering, mainly pointing out the longer term benefits for both economy and patients. Furthermore, and this is an interesting shift compared to promises in the early days of tissue engineering, they argue that tissue engineering has an added value in improving quality of life rather than providing life saving treatments, and as such cannot compete on a direct cost basis:

> Let me take say skin used for diabetic wound healing. This may be more expensive treatment but the results and prognosis for the patient is much better and the result is much quicker. Now this is going to make some interesting questions about comparing that more expensive initial treatment against something that seems to be cheaper but in fact requires a revision and constant returns to the hospital, and this is where health care technology assessment is going to be very difficult I think for some of these products.
> (Representative European industry association M-EU2, 2003)

And as a consultant for a multinational agrees, 'it requires almost a reappraisal of how the costs are managed within health systems... health evaluation in a bigger picture sort of way' (M2, 2003). Healthcare assessment models should

take into account longer term benefits to patients and healthcare budgets as well as more broad definitions of cost.

Interviewees frame this in terms of a tension between short term costs of purchasing individual applications and longer term cost-benefit solutions in terms of hospitalisation. But also less narrow economic parameters such as quality of life for patients, improved health outcomes, and less side effects are mentioned as important factors in the overall balance. As an official in supply and purchase explains, the element of cost has diverse dimensions:

> When you're looking at wound care products, you're not just looking at cost factors, you're also looking at cost in use of the product, as for how long, if it's a dressing, how long does it stay in place for that patient – is it five days, is it seven days? You're looking at total cost. You're also looking at how it conforms to the individual patients in that, maybe the adhesive can be aggressive on your skin (...) What I'm saying is more than one type, you can't just look at cost in that respect.
> (Policy advisor in purchase and supply office of national healthcare provider O1, 2003)

Thus cost-cost comparisons have only limited value, and are part of a bigger frame in which to assess the costs and benefits of these treatments. In a similar vein, the following clinician in woundcare feels there are different outcome measures for improved health, beyond the question whether a wound is healed or not:

> If I could measure an improvement in quality of life or... reduction of hospital in-patient days or reduction of district nurse visits, that is another way of measuring success... When we're looking at healing as the only measure but, as I say, if I can reduce the pain, if I can reduce the frequency of visits and I can get the patient back out and about going to the shops, that for a patient may be just as important as healing them.
> (Clinician in wound healing in UK university hospital CI3, 2003)

According to these interviewees cost is not just a narrow economic factor which is a simple add-up of initial product cost and linked to an exclusive desired clinical outcome. Furthermore, commercial risk is to a certain extent acceptable, also depending on the specific application area. As has been discussed before in relation to quality and safety aspects, also in framing commercial risk interviewees make a distinction between potentially life-saving treatments and those interventions aimed at improvement of quality of life. In woundcare management this differentiation is most visible in treatment

strategies for clinical interventions of burns and (diabetic) ulcers – the most common treatment areas where tissue engineered products have been used so far. It has been argued that product cost is less of a barrier for introduction and use in the clinic when the condition to be treated is more expensive and 'serious':

> The difference between burns and a chronic leg ulcer is if somebody comes in with a burn, if I don't give them what they need, they're going to die. Somebody like an old lady with a leg ulcer, she ain't going to die from a leg ulcer but she will just become socially more and more isolated and smelly and, you know, more and more dependent on others. The other thing within the cost of treating somebody with a severe burn, the cost of my tissue engineered product is minuscule compared to the cost of the overall treatment of that patient, in terms of intensive care time and drugs, surgical interventions, the repeated trips back to the theatre. So all of those things would say that burns are expensive conditions to treat, therefore an expensive piece of tissue engineered product is, the nap of the backside of the total treatment cost of that. Whereas, because the vast majority of these chronic wounds go on for months or years and a vast majority of those costs are actually borne in the community by district nurses who quite fairly and understandably at the moment, can go and see a patient every day for months or years with no measure of success. You know, how many minutes, how many hours, how much travelling time, how much petrol allowance, how much of all of those other things will actually add to the total treatment cost of that patient in their own home. (...) I think that at this moment in time nobody conceptualises the contribution of staff costs to total treatment costs of chronic wounds.
> (Clinician in wound healing in UK university hospital CI3, 2003)

But costly development of a technology shows only one side of the coin. More problematic, as underlined by commercial developers in this field, is the current scarcity and fragmentation of reimbursement policies for these products in Europe. Clinicians have some autonomy in deciding which products are used in individual treatment plans for patients, but these decisions have to be cleared by health authorities for reimbursement. This is especially pressing when more expensive therapies are used, whereby limited budgets prohibit large-scale use. The interviewee below has experience in a national purchase and supply agency, explaining how only a small selection of patients can benefit from tissue engineered technology under a national health scheme:

> It would be down to the clinicians actually to using it, to actually decide all that, how cost effective it would be at the end. Because they've got their budgets, to be honest, and these [tissue engineered] products, you

> know, you'd be struggling to actually maybe get one person per year actually on these products because of their tight budget.
> (Policy advisor in purchase and supply office of national healthcare provider O1, 2003)

6.1.2 Reimbursement

Reimbursement of tissue engineering technologies is problematic in Europe as long as many products are still in early development stages, with the current commercial set-up of mainly small start-up companies and the scarcity of long-term clinical data, and limited cost-effectiveness of the treatment compared to conventional alternatives. Currently no public health system or private health insurance in any of the EU Member States offers general coverage for tissue engineering treatments.

Many interviewees construct a direct link between the current absence of a pan-European system for marketing approval of tissue engineered products and the lack of reimbursement of these treatments. A spokesperson of an influential European trade association explains:

> The other thing that is a little bit of a disincentive at the moment is the absence of a unified regulatory system. People are becoming wary about investing a lot of money in research and development and without let's say the stability that a regulatory system will give - and not just that; without a regulatory system there is likely to be an absence of reimbursement system and if you're going to invest a lot of money into developing products you reasonably want to be reimbursed for them. But without a regulatory system there is no real ground rules for that either.
> (Representative of European industry association for medical devices M-EU2, 2003)

The current confusion around the proper regulatory pathways for tissue engineering is reflected in reimbursement strategies. A regulatory affairs consultant for a multinational company argues how a fragmented regulatory system can have short term benefits for companies wanting to target unregulated markets - until the reimbursement issue comes in:

> Basically they [tissue engineered products] are unregulated. That might be seen initially as an advantage in some countries until you realise that the reimbursement system through health services etc require some kind of regulatory approval. So you may be able to sell but much of your reimbursement, a lot of your market. will disappear. (...)

> So that's why industry has really been in the unusual position of really pushing very much for a pan-European regulatory structure.
> (Scientific manager corporate product safety assurance for multinational company M2, 2003)

Although regulatory measures as such do not have a direct impact on reimbursement policies in individual countries, the negotiation position of companies might improve once regulatory controls are in place to cover these products in Europe (Bock et al. 2005).

While regulatory initiatives can be set and negotiated at European level, the health insurance system in Europe is not standardised. Individual EU Member States have separate national arrangements for their respective health care systems, whether public or private, leading to a wide array of care and reimbursement options:

> I think it's up to companies to make the case for people to use their products, and healthcare providers to decide whether that case is convincing, that's the market. I mean healthcare is a sort of controlled market and you get national bodies like NICE [the UK National Institute for Health and Clinical Excellence] making recommendations. I mean it's up to society to determine how monolithic it wants that choice to be. Do you have national reimbursement, local reimbursement, whatever. That's a major societal choice, a health-care funding choice. (...) Funding of healthcare is one area where you can't say there is a European approach.
> (Clinical scientist in multinational industrial setting M-EU1, 2003)

Reimbursement is generally left to the (sub)national level, creating wide variety and fragmentation in healthcare funding and reimbursement policies. Reimbursement issues are discussed as part of a broader concern with regulation and marketing approval for tissue engineered products in Europe, but is left outside the scope of any European legislation, based on Treaty agreements that place healthcare arrangements under autonomy of Member States. In these circumstances manufacturers have an interest in some standard or 'high level principles', as a representative of a multinational company put it during an industrial stakeholders meeting:

> First of all, it's not whether you have a good product or a bad product which decides if you will have success on the market; if you don't have the right regulatory framework, there is no chance. But it's not only the regulatory framework as such.... There needs to be some level of harmonisation for reimbursement. This is one of the very sticky points. It

> is unconceivable that there are ways out of this dilemma by agreeing on some high level principles without dictating every Member State what to do with it. At least they can agree on those principles, which will be used to evaluate what a product is worth and being reimbursed by the payer or not. (Niese 2005)

In Europe large national differences exist in the openness of both clinicians and regulatory or financing bodies towards novel therapies. In the US approval of an innovative treatment by the FDA is generally followed by a quick diffusion and reimbursement. Although this system provides clarity, it has major drawbacks for manufacturers in terms of high-cost, long lead-times and a strict approach. Commercial providers are pressing for possible reimbursement of the manufacturing costs of products while in the clinical trials stage, which would especially benefit the many small companies that lack the means and resources for long-term investment.

But larger companies in the field, familiar with a longer term 'pharmaceutical' type of investment and return model, are also affected by the current gap in regulation and reimbursement strategies. Lack of general reimbursement was one of the main reasons for the exit from the European market by the biggest commercial provider of tissue engineered cartilage repair treatment (ACI), Genzyme. Some national health systems only reimburse part of the treatment, or have a case by case procedure, while under other schemes the treatment is only available on the private market.[44]

Developers have become creative in finding solutions to market their products. Some products are made available as part of a clinical trial, and as such 'on the market'. The treatments as part of clinical research are usually small and of

[44] For example, the clinic in Sweden, where ACI was originally developed, has agreements with the Swedish and Norwegian state, so that patients with a referral from a Head of a Department of Orthopaedics can get the treatment under the national social welfare systems. According to one clinician in this clinic "probably fifty percent of the patients have a referral for cartilage. And then we have foreigners... We have a lot of patients from different countries but of course they have to pay themselves" (CL-EU3, 2003). Some national health systems only reimburse part of the treatment, or have a case by case procedure. For example in Germany most public and private insurance systems do provide coverage for the surgical procedure for ACI and aftercare such as physiotherapy, but not for the laboratory work needed to culture the cartilage cells, which is where profit is made for companies. As a manufacturer of ACI explains, this means that: "Either the patient is paying himself or he has to ask the insurance company for every single treatment if they are going to pay for it or not. So every single patient means that the doctor needs to write a letter to the insurance, the insurance answers five weeks later: no." (M-EU10, 2003).

limited duration and are not or only partially funded via national healthcare systems (S4, 2003). Also, applications in an experimental setting are generally not being reimbursed. Thus 'one could perform clinical trials indefinitely, but you are not reimbursed for the material used in the clinical trials, so we need to have a situation where we know how we can access the market with these products' (M-EU8, 2003).

6.2 Effects of the fourth hurdle on innovation and public health

This section demonstrates how fourth hurdle strategies affect manufacturers in their search for profit and innovation, while high cost and lack of reimbursement have the potential for creating or widening health inequalities by limiting the availability of this technology to patients.

6.2.1 Effects on commercial development and innovation

Also in tissue engineering the fourth hurdle is 'real' and getting closer. Many interviewees express concerns with an increasingly demanding climate of cost, in combination with clinical evaluation of new medical interventions. They frame this as representing a form of commercial risk that in the first instance affects manufacturers. In tissue engineering cost-effectiveness is becoming a significant barrier to market to sit alongside safety, efficacy and quality. The rationale behind fourth hurdle strategies relates to the distribution of scarce resources to obtain maximum health gain - for a certain price:

> This requirement [to demonstrate economic efficiency] challenges the wealth creation ethic of industry (money) with the population health ethic of public health and health economics (your life). Despite practical and methodological obstacles to the use of economic evidence in decisions, the logic of this development is evident: in order to maximise improvements in population health, scarce resources must be targeted towards developing and applying technologies that deliver the greatest health gains per unit cost. The impact of this policy change on industry practice and profits will be considerable, and companies that fail to demonstrate the economic efficiency of their products will stumble at the fourth hurdle (Maynard and Cookson 2001).

Some speculation exists about effects of the fourth hurdle on reimbursement policies, but also on the price of interventions or products. In the pharmaceuticals market for example it has been reported that fourth hurdle policies have contributed to more cost-effective use of drugs (Taylor et al. 2004). Because of the less stabilised and more marginal position of tissue engineered products in the European market, it is difficult to extrapolate these suggestions and predict the beneficial effects of cost-effectiveness requirements. Currently most interviewees underline their awareness of the need for economic evaluation – although there is discussion about the specific models and data requirements that would apply to tissue engineering. The dominant discourse then relates to the negative impact of cost-effectiveness requirements on the innovation process, where (especially small) manufacturers are unable to recoup cost and make profit. As such, this would in the first place affect the position of commercial developers.

Another layer in the construction of commercial risk puts strong emphasis on the link between regulation and reimbursement, where it is argued that the current lack of pan-European controls for tissue engineering undermines the grounds for consideration of reimbursement by health authorities and insurance companies. An added difficulty is the localised and fragmented nature of reimbursement policies in Europe. Whereas regulatory controls can and currently are being negotiated at European level, decisions about reimbursement are left to national or local authorities within Member States. This is especially problematic in the face of a growing need for cost-effectiveness data that are measurable, comparable and transferable across countries and local healthcare situations (Pang 2002: 76).[45] Although pan-European regulation of tissue engineered products does not guarantee general reimbursement by national systems, currently there is wide variety in both regulatory and reimbursement policies within and between different countries in

[45] As has been pointed out by several authors (e.g. Pang, 2002), there is a growing need for cost-effectiveness data globally. For pharmaceuticals it is increasingly common for economic evaluations to be conducted on an international or at least pan-European scale, for example as part of randomised controlled trials. In tissue engineering though the set-up is much smaller (and often the means are lacking to collect these data, as discussed in the chapter on clinical risk). Thus while often the collection of economic data is being piggy-backed on to phase III randomised controlled clinical trials, where the effectiveness of the treatment is tested in a large population and compared to other available treatments, this format is problematic in tissue engineering.

Europe. Also the weight attached to economic evaluations, either as part of or as separate track in marketing approval and reimbursement strategies, differs per country.

On the one hand industry pleads for European guidance on general principles for reimbursement of tissue engineering technologies, while on the other hand debate exists on the specific economic evaluation models to be used and how these often narrowly defined cost-effectiveness data are to be interpreted for decision making purposes. This is part of a larger discussion on the use of economic models in healthcare evaluations. Here the need for including cost containment measures has not been questioned. However, the methodology of evaluation and the exclusive focus on cost-effectiveness of medical interventions in health-care decisions is seen as problematic, especially in its use for determining reimbursement policy decisions (Drummond 2003).

6.2.2 Implications for patient access

Issues of cost and reimbursement are, according to the interviewees in this sample, first and foremost problematic for commercial developers of tissue engineering technology. But while it seems like manufacturers are the most affected by fourth hurdle policies, implications for patients are limited availability of potentially beneficial technology. Patient access to tissue engineering technology thus depends on more than just product availability, with reimbursement policies being of particular significance (Bock et al. 2005: 10). But reimbursement relates to use in public markets. Some private insurance companies cover (part of) the treatment with tissue engineered products. Current diversity in reimbursement strategies highlights issues of accessibility and affordability to the population at large. This touches upon the relation between cost and patient access, as also demonstrated by the scientist below:

> The big difficulty all health care systems are facing, with these new technologies, that you can do so much. And who's the patient that you want to save? It's sort of a fundamental question. And we don't have enough money to save everyone but ethically we should save everyone. If you're a medical doctor you should save the patient that you have, but someone has to pay for it.
> (Academic scientist based in clinical setting S-EU2, 2003)

As argued throughout this section, high cost has been framed as problematic for commercial developers of tissue engineered products, especially in the face of an unknown market. But cost also has socio-political implications in terms of availability of novel therapies to the public and access of patients to technology, and as such affects end-users as well as developers. As the interviewees below explain, the high cost of tissue engineered technology limits the availability of products to the patient in a healthcare system based on public markets:

> The risks, the risk are perhaps more commercial, that it's going to take a lot of money to get some of these products. So one of the risks could be that tissue engineering products may only be available to those who can afford them.
> (Academic research scientist in UK tissue engineering lab S1, 2003)

> There's issues relating to cost because I suspect the NHS will never be able to afford the people to be able to have tissue engineering procedures done on them. We're already seeing this with drug treatment from the point of view that you get this postcode lottery on certain expensive drugs. I think it will be very difficult to imagine a situation whereby the NHS pays for a lot of the treatments.
> (Academic research scientist in UK tissue engineering lab S7, 2003)

> This [technology] is expensive. It's just possible that a significant number of Americans might be able to afford it and a few Europeans, but basically you're inventing a technology which is not going to be available to most of the world.
> (Clinical scientist in academic centre for health services research CI1, 2003)

Lack of reimbursement is an economic risk for commercial developers, but the limited uptake by national health service systems has broader implications in the potential for social and health inequalities. Furthermore, cost and cost-effectiveness criteria pose one barrier in the successful transition to the market. The next section places these issues in the context of the broader economic climate. Here commercial risk is not just about expensive technologies only available to the lucky few. Several other factors have an impact on the commercial performance of tissue engineered products, some of them inherent to the industrial setting and configuration of the innovation process, with many small companies entering and exiting the competitive arena of tissue engineering R&D. The next section provides the socio-economic background of product development in this highly dynamic field.

6.3 Commercialisation and the industrial setting

Commercial risks in terms of the high cost of the technology, lack of data on cost-effectiveness and problems with getting products reimbursed by national healthcare systems must be considered in a broader framework of commercialisation of tissue engineering and the economic climate in which current innovation takes place. This section focuses in more detail on the commercial environment in tissue engineering R&D, to gain insight into some of the hurdles en route to getting marketing approval for products and successfully launch products in the market.

6.3.1 Promises and bubbles

> I suppose perhaps my naïve view is that there's been too much pressure on getting products to market, to recover the investments that have been made by venture capital, without perhaps doing the underpinning science properly. I think there's a really good analogy here with the biotechnology industry. When the bio-technology started and then genetic engineering... everyone said this is the future for mankind, you know, we can cure all the world's ills. And investments by venture capital companies were stupendous. I mean there's so many biotech firms but now, twenty or thirty years later, there's only really a few or a handful that have actually made it. And tissue engineering is at that stage now; that the hype at the beginning of tissue engineering was, that we're going to, you know, new livers, new brain, we're going to solve the problem. And in reality, first of all, it's much more complex than that scientifically, and as you are identifying the regulatory hurdles, are completely new, sort of... products that are falling between regulatory stools. And then there's the cost implication...
> (Academic research scientist in UK tissue engineering lab S1, 2003)

Attention for tissue engineering reached its height in the mid 1990s, with popular media describing the immense potential of the technology, venture capitalists queuing to invest and start-up companies mushrooming. Tissue engineering was placed at similar height as genetics to be labelled the 'greatest scientific achievements of the twentieth century'. A career in this field was seen as one of the '10 hottest jobs of the future', and tissue engineering was well on its way to become an estimated $100 billion industry (Lysaght and Hazlehurst 2004).

As such, tissue engineering can be considered as a typical example of a technology surrounded by 'potentiality' (Ganchoff 2004). This potentiality is translated into hopes for an imagined therapeutic intervention on behalf of patients and developers, but also refers to a commercial hype generated by those with investments in the technology.

But this picture only partially reflected the R&D status at the time, with a limited amount of products on the market or awaiting approval, and many technological and regulatory problems to tackle. More recently tissue engineering is referred to in terms of 'disappointing product launches' in an economic unstable climate, with limited regulatory approval and issues of cost and reimbursement - and with some products under clinical trial, but none to be considered commercially successful. Notwithstanding optimistic future scenarios by market analysts, it has been argued that tissue engineering is having difficulty transitioning from a development stage industry to one with a successful product portfolio (Lysaght and Hazlehurst 2004). As the experience of this commercial developer reflects:

> You don't see any of these products taking up well. There is not any tissue engineering technology that shows some success today in the market. And it will come, for sure it will come, but nobody foresees it. The technology is complex, the costs are high, convincing people high, people are scared or reluctant to give you approvals and then reimbursement agencies don't want to wait five years before they see an effect in money. So today you have not seen any tissue engineering product...
> (Regulatory affairs specialist in company M-EU4, 2003)

The commercial environment for tissue engineering R&D is unstable and surrounded by uncertainty. The current tissue engineering activity takes place on a very small and developmental scale, with many biotech companies formed as university spin-offs, and markets that are nowhere near the order of magnitude as those for pharmaceutical products. To date, only a small number of tissue engineered products has entered the market, but none are considered commercially successful. According to interviewees in the inner circle of tissue engineering R&D, it is exactly the step from early innovation to commercial development that has proven problematic. The next section discusses the views and experiences of these respondents in more detail.

6.3.2 From early innovation to commercialisation

> If you looked at it in purely commercial terms, you could say maybe the tissue engineering commercial development bubble has already burst. But if you stand back from it and look at it in terms of research and product development, ignore the financial side, then I think more things are going on. (Academic scientist S5, 2003)

6.3.2.1 Limited markets and major funding streams

Disappointment has been expressed over the limited number of tissue engineered products currently on the market, and the poor market acceptance of products that have been introduced so far. The fate of the first firms offering tissue engineered products has been discouraging, with bankruptcies, discontinuation of operations or considerable downsizing, sometimes after mergers and take-overs.[46] It has been pointed out how the initial sales of these new products did not live up to expectations, because they generally did not attract large enough numbers of customers or because the improvements over existing therapies were limited to small subsets of patients.

The first generation of tissue engineering products actually entering the market included skin products and cartilage applications. These products were the most technically feasible ones, and by many developers considered as a stepping stone to more lucrative areas, such as orthopaedic and cardiovascular applications - and hopefully, one day, whole organs to replace heart valves, blood vessels, kidney, liver and pancreas etc. Here the real market potential was envisaged, with vast markets that lack effective alternatives and where shortage is most acute. But these applications are still in the category of early scientific exploration and far away from entering the clinic (Petit-Zeman 2001). As also pointed out by the European Commission:

> The current commercialised products focus on comparatively simple tissues such as skin, cartilage and bone. Researchers have not yet developed tissue-engineered products with unique life saving functions or outstanding comparative advantages regarding effectiveness or

[46] During the poor economic climate of the past few years, many tissue engineering companies had to downsize or restructure their businesses. Two prominent tissue engineering firms in the US, Organogenesis and Advanced Tissue Sciences, went bankrupt before the turn of the century (Bouchie 2002). The financial difficulties of pioneering companies adversely affects follow on companies.

> treatment costs. Alternative conventional treatments exist, which are firmly rooted in the market. (European Commission (EC) 2004)

Furthermore, the current R&D efforts are said to be imbalanced. For example many companies have focused on developing skin replacement products, thus 'overserving' the wound care market. Consolidation would be needed to reduce the number of low-profit 'me-too' products, especially in the face of uncertainty around precise market size and target population for these products.

The global tissue engineering market to date is modest and smaller than originally envisaged, although great variability exists in estimations. Latest figures on the global market for tissue engineered products are estimated at up to 400 billion euro per year, but this is an estimation only found in industrial reports (EUCOMED 2006). Worldwide the US represents the largest and most advanced market.[47] The European Union market has been estimated in the region of 50 to 100 million euros (Schutte 2003) although also more modest estimates have been mentioned, in the order of only several million a year (Hüsing et al. 2003: 84). A study carried out by the Commission's research centre IPTS speaks of current sales not exceeding 60 million euros per year worldwide, which is a modest figure, but estimates a substantial future market growth with a global potential of roughly 100 billion euros (DG Enterprise 2005d).

Until recently there was only a very rough idea of the actual size of the market and sales revenues of individual products. One much quoted study identified 89 firms active in tissue engineering R&D over the year 2002, spread over 15 countries and employing some 2611 FTEs, while global annual spending for that year was estimated at US$ 487 million (Lysaght and Hazlehurst 2004:

[47] Commercialisation of tissue engineering started earlier in the States than in Europe, arguably because of the more favourable general climate of start-up companies and the availability of more venture capital. But this advantage over the rest of the world is changing. In 2001 'an interesting recent trend' was observed with the emergence of significant activity in tissue engineering outside the United States, with at least 15 European companies being active in the field (2003). As later confirmed by Lysaght (2004), in the year 2000 about 80% of employees in tissue engineering were located in the US, while two years later this was only 54%, as opposed to 46% workforce in the rest of the world. These percentages relate to stationing of employees rather than location of firms. Possible explanations for this shift include that the two main tissue engineering companies that went bankrupt, Organogenesis and Advanced Tissue Sciences, counted exclusively towards the US situation. Also the US policy on the use of stem cells and therapeutic cloning has possibly affected companies' strategies for locating their business within or rather outside US borders.

311). In the US markets have been identified and described since the mid 1990s (see reports in: Lysaght 1995; Lysaght and Hazlehurst 2004; Lysaght et al. 1998; Lysaght and Reyes 2001). In contrast, data on markets, business developments and product output in Europe are patchy. A survey of regulatory authorities of European member states found that most were unable to list products currently available in their countries, highlighting the lack of information available here on the commercial aspects of the technology (TERG 2003). Thus the availability of tissue engineered products in the EU is difficult to assess, and surrounded by uncertainty. A study for the European Commission identified about 35 products on the European market, mainly skin replacements, cartilage repair and some bone products. The European market is very fragmented and localised, with most products available on the home markets of companies, but no product available in all EU Member States (Bock et al. 2005).

Interviewees have expressed various rationales on the current poor market performance and availability of tissue engineering technologies. Most notably, as the following spokesperson of a European trade organisation demonstrates, there is an underlying framework where the innovation and funding model for biotechnologies such as tissue engineering is being questioned, if not blamed.

> Well, what do we want? We want patients to have access to that innovation. Research has to continue. But the problem is: how much do you invest into research if you don't know how to put the product on the market? It's the chicken and egg syndrome... If the product doesn't come on the market, you stop the research... In big companies the product disappears; in small companies the company disappears. And that is dramatic. We have to be aware that young innovative companies live on borrowed money. They live on money from venture capitalists... they want to have a return. And that return, we fail to explain to them, will take ten years to come (Vanhemelrijck 2005).

An overall characteristic is that the investment in R&D and market development cannot be covered by the current product sales: product revenues do not cover operating costs such as the high costs for production, maintenance and shipping of products, the high investments in R&D and budgets needed for marketing development (Hüsing et al. 2003: 83).

The economic circumstances of tissue engineering companies are thought to be similar to those affecting the biotechnology industry as a whole (see Alper (2002) on bioentrepreneurship). The tissue engineering sector has relied heavily on investment capital rather than sales as a source of funds, and although perceived to be comparable to other high-tech sectors such as biotech and dot.com, it is exactly in these areas that the investors' appetite has declined. Especially amongst scientists and manufacturers there is a strong discourse of pointing the finger to the investors' climate and discussing the current poor uptake of these products in economical terms – rather than for example safety or efficacy concerns, according to this scientist:

> If you look at it in commercial terms, I think it looks pretty hiccuppy because a lot of the good products that have been developed on a commercial basis belong to companies that have gone bankrupt recently. Now these are good folk and they are doing good things, so research-wise and clinically it is not that their products are rubbish, far from it; they haven't got fast enough revenue stream to keep them afloat on a commercial basis.
> (Academic research scientist S5, 2003)

Despite the economic instability of the technology, tissue engineering R&D has been a major area for investment from both public and private sources (Lysaght and Reyes 2001).[48] So far, tissue engineering is primarily funded by the private sector in the US, while federal funding has traditionally been more predominant in Europe (McIntire et al. 2002: ii). These different funding strategies are reflected in the R&D of the technology, where academic research groups tend to benefit from government funding for their basic research, while industry is more focussed on technology-based product development. Especially in Europe a large number of companies was formed in the late 1990s, partly with government and university funding, while industrial support was sought during later stages of development. But this trend is shifting towards more public investment, where the US government follows initiatives in Europe and Japan in initiating major programmes of government-sponsored support for new research.[49] Recent European Framework Programmes have reserved

[48] In a little over a decade, more than US$3.5 billion has been invested in worldwide research and development in tissue engineering. Over 90% of this financial investment has been from the private sector (Lysaght and Reyes 2001)

[49] For example US federal institutes such as the National Institutes of Health (NIH), National Science Foundation (NSF) and the Food and Drug Administration (FDA) have all taken steps to support the field by rewarding research grants (NIH) and establishing regulatory structures for

considerable research funds for tissue engineering applications and for specific support of SMEs in this field (Hogan 2005). As an interesting aside, there is also another reason for the more recent change in US funding priorities, as one interviewee explains:

> It has changed in the US too. It has changed and strangely due to the Iraq war. The army said: we want now that the whole research be organised, we want to have skin replacement on the battlefields. And they are pushing. And they said to the Pittsburgh group [the main research centre]: you co-ordinate all the effort inside the United Sates for making that we get what we want where we want. So the military in the United States have decided to take the leadership in these things... So they are trying to bring altogether the research all over the place because it's evident that - you know the two biggest companies doing tissue engineering went bankrupt... it could be a dangerous business. (EC official in DG Enterprise A-EU3, 2003)[50]

Another effect of the financial difficulties of many pioneering tissue engineering companies is visible in the increasing number of mergers and partnerships over the last few years. Many companies are small start ups that lack financial backing to further develop their research and product portfolio, which has led some companies to merge in response to market pressures. But as one possible explanation for limited market impact of tissue engineering to date, critics point at the lack of collaborations between the relative small biotech companies in tissue engineering and the much larger and more profitable pharmaceutical industry. Instead of partnering up with the pharmaceutical industry, and follow the 'big pharma' path of commercialisation, many tissue engineering companies looked for connections with the much smaller and more specialised medical device sector, for example in the orthopaedics field.

The current commercial set-up of the tissue engineering sector has been mentioned as potential stumbling block towards commercialisation and is discussed next.

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the specific control over combination products being developed via tissue engineering approaches (FDA).

[50] This military involvement is not entirely new though. For example the multinational company Advanced Tissue Sciences got funding by the US Army Institute of Chemical Defence for a clinical trial for their human skin equivalent Dermagraft, to test it for the treatment of chemical burns (Persidis 1999: 508).

6.3.2.2 Sector dynamics: small companies and high stakes

The European tissue engineering sector is characterised as 'young, small, research-based and technology-oriented' (DG Enterprise European Commission (EC) 2004: see also IPTS study 2003). The main players in this domain include commercial companies, followed by academic laboratories and specialist research hospitals. Tissue banks and clinics are active in the field as well, although these tend to operate on a very local level (Bock et al. 2005).

Main geographical centres of innovation and commercialisation include the United States, Europe and Japan. The commercial tissue engineering sector in Europe is currently concentrated in the old (EU-15) Member States, with Germany and the UK in leading positions.

Typically the core tissue engineering companies are small and medium-sized enterprises (SMEs), with in most cases less than 50 FTEs (Bock et al. 2003; Hüsing et al. 2003). Some medical device companies participate in tissue engineering R&D activities, and to a lesser extent the usually larger and multinational pharmaceutical companies, but most of these companies are university spin-offs with a background in biotechnology. These companies have a strong scientific basis rather than a commercial eye for manufacturing products at low cost:

> But you see they are all small [companies], all spin offs of universities and this is where the danger is. They have learnt something in the university, they have found something in the university and they say: now we will do a company. They don't think they have to sell. To have a product is not the only thing, you have to sell!
> (EC official DG Enterprise A-EU3, 2003)

The tissue engineering sector is clustered into small companies, many of which are focusing exclusively on for example cell culturing, biomaterial development or stem cells, which also means that intellectual property is scattered around and fragmented. While most start-up companies have a narrow techno-scientific focus on just one part of the technology, they lack know-how or access to wider aspects of the clinical and production process, such as expertise on quality control, marketing and regulatory affairs. Thus while most have a strong scientific and pre-clinical knowledge base, the next steps to make the transition from scientific exploration to adapt clinical research into

marketable products is often problematic. Furthermore the tissue engineering sector is a very interdisciplinary one, requiring specific expertise on both research and development aspects in different areas. Whereas specialised start-up companies might be too small or inexperienced, also established industry moving into this new field is 'at risk':

> If you're realistic, when companies move into new areas there's an inherent risk. If a device company whose core R&D skills are engineering, moves into an area where you need more knowledge on pharmaceuticals or biological materials, yes there's more potential for misunderstandings and accidents. Everybody who invents or develops something is convinced it's safe and great, that's human nature. So companies developing new technologies are always to some extent a risk. (Clinical scientist in industrial setting M-EU1, 2003).

A lack of specific expertise and experience is not just playing up during the early R&D stages. An important factor brought up by many interviewees is the marketing process and regulatory approval phase. Several smaller companies have marketing agreements with larger commercial providers in medical devices or the pharmaceuticals sector, but it has been argued that marketing strategies need to be more tailored to cover the specific characteristics of tissue engineered products (Hüsing et al. 2003: 87-89).

Manufacturers and regulatory bodies alike have been juggling with the particular approval route for tissue engineered products, where dominant models for pharmaceuticals or medical devices did not or only partially apply to these combination products, with large variety in approach between countries. Also the fact that many tissue engineering firms do not have clear reimbursement strategies for their products has created uncertainty over for example the potential willingness of patients to pay for the treatments themselves. Furthermore, as also stressed by the interviewee below, the marketing trajectory is long and expensive – often beyond initial expectations.

> So the regulatory process... it basically imposes certain standards to things like clinical trials. And as we know from the pharmaceutical industry, the amount of money that you have to spend on regulation in clinical trials is much greater often than the amount of money you spend on research and development of the initial drug molecule. It's okay for the pharmaceutical industry, the pharmaceutical industry can deal with that because it has close on 100 years worth of profit and shareholder returns, and people will accept the fact that it has to spend 100 million

> pounds getting its new drug through clinical trials and through the regulatory process. In tissue engineering there is no product on the market that has made anything like that amount of money, so therefore people aren't willing to risk their investments on the clinical trials. And worse still, when a drug company goes for regulatory approval it quite often has a simple drug molecule, so you can tell the regulatory authorities everything they want to know about it. Whereas tissue engineering products are based on cells which by their very nature are very heterogeneous... The products tend to be very, very complex. (Academic research scientist in UK tissue engineering lab S7, 2003)

Overall most companies have not been prepared for the long and costly process of regulatory approval, [51] slowing down returns on their product investment (Lysaght and Hazlehurst 2004). Thus a tension exists between short term biotech type high investment and long term returns on these products, and several interviewees have argued that the lead times for regulatory approval, and then reimbursement, resemble pharmaceutical type of products, 'so you've got to be in it for the long term' (M2, 2003).

Some have argued that instead of following scientific curiosity, tissue engineering companies have to put more effort into communicating with the clinical community to gain insight in the needs and practical aspects of product application, and that customer needs have to be addressed more seriously as part of a broader market orientation (Hüsing et al. 2003). As analysed in the next section, tissue engineering technology is not just a risk capital category in the books of investors.

6.3.2.3 Public concerns over controversial therapies

The current fading investors' confidence can be placed in a social-political climate where the public domain has had to deal with 'similar' high-tech novel products, such as genetically modified foods that have stirred controversy, and recent public health scares that have called for stricter controls over biotechnology products more general. Public concern over for example BSE has been a major influence on governance and regulation of new products

[51] Furthermore, this overall long trajectory of commercialisation also has implications for intellectual property. With a long and costly R&D process that can take up several years including regulation and reimbursement clearance, "by the time it's ready to market your product you are left with a few years before the patent expires. And it doesn't make good business sense for a lot of people to have, say, if it takes such a long time and then you have a few years left to have market exclusivity for your patent right." (Legal professional in regulation of biotechnology O2, 2003)

entering the European market. The interviewee below explains the commercial effects of that as follows:

> But as things have developed and obviously within the scenario BSE and TSEs, the concerns maybe over using biological material at all, the demand for more regulation has increased. And I think then that the cost element involved in meeting all these additional requirements are such that a lot of industries, or a lot of companies, haven't been able to meet that. And basically they've run into a cash flow situation. So a lot of these capital venture based companies, they went through a lot of money, they would hope to have their products on the market, they looked at it pretty optimistically. And then as more and more demands are made on them in terms of extra testing or requirements then you know, unless they're associated with a partner like [a large multinational] who have been willing to keep funding these unanticipated extra costs... (Scientific manager corporate product safety assurance for multinational company M2, 2003)

Safety concerns or technological risks are associated with a public climate in which (potentially) controversial therapies are subject to increased regulatory controls, which affects the commercial status and performance of products. It is also in this context that commercial risk is related to a particular safety issue in tissue engineering, namely the inclusion of animal derived material. In commercial terms, this implies liability issues on behalf of companies trying to market these products:

> If there are alternatives where there is no risk for a company, if you have a synthetic product, they're not liable for bio contaminations so the market is wide open if you come with something that is safe. (...) So as soon as you go away from the animal derived products and you come with something that has similar performance, that's the way for success. (Academic research scientist S-EU2, 2003)

To sum up, several factors have been brought forward by interviewees to explain the current lack of commercial success of tissue engineered applications - ranging from small inexperienced start-ups with business models that are too dependant on venture capital and short term returns to stricter controls in an increasingly risk-aware social-political climate. Some see the initial poor sales of some of these early products as part of a common process for medical products, reflecting the 'incubation period' they have to go through before clinical use and commercial success (Lysaght and Hazlehurst 2004: 313-314).

But another dominant model in explaining marketing struggles, especially for the European situation, concerns the production system of different tissue engineering applications. As discussed under technological risk, particular perceptions of risk are attached to either the autologous route of engineering or the use of donor material. As demonstrated in the next section, these technological risks also have implications for the commercialisation process and the types of organisations competing in tissue engineering R&D.

6.3.2.4 Production systems and scaling up issues

Two basic models of tissue engineering technology have been developed: autologous applications and allogeneic products. As discussed earlier, this distinction plays an important role in the construction and perception of safety issues of particular tissue engineering applications. Here it is argued that this distinction is also closely tied into the processing and manufacturing process, with implications for the timing and general availability of products, and for their market potential.

Autologous applications necessarily need time for the cells to be removed, cultured and implanted back into the patient, while the donor cells may be stored in a tissue bank or as a cultured cell line, thus providing a basis for off the shelf availability. The preservation and storage of live engineered tissues is considered a major obstacle for commercialisation. One of the key issues for tissue engineered applications is maintaining product viability: to keep the cells alive following transportation and storage. Most tissue engineered products have a limited shelf life. More important in terms of commercialisation, this means impractical scheduling restraints for both the manufacturer and the clinician (and ultimately the patient) of these tissue engineered products, and added costs that come with overproduction, changed demand, unplanned losses and the management of patient scheduling (Naughton 2002).

Thus the production mode dictates availability of these products within a certain time window and over geographical space. For example for acute medical conditions time is too short to culture patient-own material and indulge in complicated and expensive logistic processes. Equally important from a

commercial perspective is the fact that the autologous engineering route offers an individualised and customised treatment; an inherent system of production which is more problematic in terms of 'scaling up' for purposes of commercialisation (McIntire et al. 2002: X). As explained by one of the pioneers in the field:

> The challenge of imitating nature does not stop with the design and engineering of a specific tissuelike construct or substitute. This is because the patient need that exists cannot be met by making one construct at a time on a bench top in some research laboratory. Accepting the challenge of imitating nature must include the development of cost-effective manufacturing processes. These must allow for a scale-up from making one at a time to a production quantity of 100 or 1000 constructs per week. Anything significantly less would not be cost-effective, and if a product cannot be manufactured in large quantities and cost-effectively, then it will not be widely available for routine use. (Nerem 2000: 13)

Scale-up for clinical use, where not just one but hundreds or thousands of tissues must be grown and cryopreserved under sterile conditions, is a critical factor in tissue engineering (Griffith and Naughton 2002). Tissue culture is a labour-intensive and time consuming process, and because of their laboratory environment many tissue engineering processes use manual procedures which do not always provide optimal quality control. The product quality is important for the scale-up process of tissue engineering, which in turn is needed for commercialisation of the technology. Various processes have been developed to support the manufacture of a uniform, reproducible tissue, for example with the use of closed systems such as bioreactors.

We also witness an interesting shift of boundaries here. The scientist below feels that the autologous route might be preferable from a health and safety perspective, but in commercial terms it is problematic:

> Using autologous cells strips away a lot of the potential risks of the technique as long as getting those cells doesn't damage the patient. You eliminate most of the risks but unfortunately it's very difficult to think of how you're going to do autologous treatments for many therapies. There's a commercial issue and there's a clinical issue. Autologous processes can't be scaled up. So in the case of the cartilage procedure, it's autologous, the patient has to go in, have cells removed, those cells personally have to be expanded in culture and they have to go back into that patient – it's massively labour intensive. If you have a lab that can

> do 100 of those a year, the only way to double that capacity is to employ twice as many people and have twice the size of lab. So the only way we're going to get the scale up is the use of allogeneic made tissue and then you have the problems of immune rejection of the tissue. (Academic research scientist in UK tissue engineering lab S7, 2003)

The individualised therapy requires extensive manual handling, which is a costly approach that requires specialised skills and training. Furthermore the system of production poses limitations on logistics and transport. In the US both engineering routes are explored, but the donor-based products, most notably for woundcare applications, have attracted most attention of commercial developers. As also stressed by the scientist below, the divide between a customised service model versus an 'off the shelf' available product has implications for the particular type of developing organisation that is involved:

> All of the academic groups I know are doing autologous. All of the commercial groups I know are doing allogeneic. (Academic research scientist S5, 2003)

In Europe (and Japan for that matter) the R&D effort focuses primarily upon autologous, patient-customised applications, which is more likely to lead to a service industry relying on more local and regional cell banking. Thus whereas the allogeneic manufacturing process usually serves a more globalised market with higher commercial potential, autologous services are more localised and – according to the interviewee below – more controlled in time and space:

> That's for allogeneic products. Obviously it can be taken in one country, developed as a worldwide product could be, [with] the storage techniques now developed here it can be stored for six months or a year possibly, distributed all over the place. Yeah, there are theoretical greater risks with that in terms of what's happened to the materials, where it's going to. Whereas with autologous you tend to be looking at it in say a single hospital situation. (...) It's going to be more local probably. I mean, it's not, you only look at the theoretical risk involved. There could be contamination depending what the laboratory procedures were like, for instance. But inherently it would be controlled more in time and location than obviously allogeneic tissue engineered products. The big benefit with the allogeneic side is that you have a reproducible high quality product effectively available off the shelf to be replenished when they need it. So in terms of meeting a great demand out there, autologous treatment is not going to do it. It's going to be good for the particular individual involved but hospitals won't be set up to do that on a huge scale, whereas all of the allogeneic products will be able to meet that need in a much better way.

(Scientific manager corporate product safety assurance for multinational company M2, 2003)

Especially in Europe this configuration of commercial providers alongside local, often not-for-profit organisations has redefined the competitive climate of tissue engineering technology.[52] As a representative of a large multinational company for autologous cartilage applications explains, there is steep competition from local hospitals, tissue banks and smaller companies that provide similar services for a lower price – which was one of the reasons for this company's withdrawal from the European market.

> From a commercial perspective, it makes things a lot easier for these very small companies. And if you think of autologous tissue, if you were to be perfectly honest and frank, it's not rocket science... it's all pretty much standard techniques, techniques which can be engineered within a hospital tissue bank for example. So [in this country] a number of local groups have emerged within hospitals which do these sorts of products for surgeons, just covering their expenses and covering the holidays to Barbados with the tissue bankers. Oh God I shouldn't have said that 'cos it's on tape. But you know what I mean. They sort of work on a very local basis, they may cover three or four hospitals in a local district... but it makes it difficult for a multinational company to get involved in that system. (...) why should a hospital pay a premium price... for a product which they can manufacture using their own little tissue bank? Absolutely no reason whatsoever. So it kicks the bottom out of your commercial market from a multinational perspective.
> (Regulatory affairs manager of multinational company producing autologous cartilage product M-EU9, 2003)

While competition from less profit-seeking providers of autologous services poses commercial risks for larger companies, for their local counterparts scaling up of technology is an essential prerequisite for commercialisation. Especially with respect to these smaller companies, and also local providers of these services that do not have routine experience, the ability to work up to certain quality standards, such as GLP and GMP, is sometimes questioned (M-EU9, 2003). A problematic part of this process, it has been added, is the

[52] The European Commission has taken into consideration the different models for production and commercialisation, including mechanisms for the regulation of European trade and exchange of these products within the internal market. It is argued that while 'small business operators, hospitals and tissue banks often produce autologous products for local or "in-house" use... This does not mean that autologous products are produced exclusively for the local market or for internal use: tissues may be treated outside the donor's country and should therefore be able to circulate within the Community... Allogeneic products are more likely to be produced in batch and marketed in different Member States, but single applications remain possible.' (DG Enterprise 2004b)

current lack of automation of the quality control process by many small providers. Controlling the production process – 'to have these batteries of tissue engineering all controlled by computer permanently' (A-EU3, 2003) – would lead to cost reduction of a procedure which is currently still labour-intense and subject to human error because of the extensive handling. Economies of large-scale production are important from a commercial perspective, while standardisation of manufacturing and quality control standards is also important in obtaining marketing approval for products. Some European providers are now working on so-called 'mass-customisation technologies' to offer individualised treatment on a mass-produced scale that can be standardised and that is hoped to provide the reproducible quality desired by many regulatory authorities (Bader 2005).

6.4 Reconstructing boundaries for commercial risk

Representing the last tier in the risk classification as outlined before, commercial risk has been used in this chapter as a term to describe the issues that commercial providers face in bringing tissue engineered products to the market. Whereas technological risk is mainly concerned with quality and safety, and clinical risk with therapeutic effectiveness, commercial risk relates to the final stages of the innovation cycle including commercialisation of the technology.

As demonstrated so far, commercial risk is interrelated with clinical risk, most notably with the increasing need to obtain long-term data on both clinical performance and cost effectiveness of treatments in order to obtain regulatory approval and to get product reimbursement. With tissue engineering entering the fourth hurdle domain, companies are struggling to market their products in Europe due to high cost, low risk-benefit ratio, and lack of reimbursement in public markets. As also described in this chapter, these developments need to be placed in the context of an unstable commercial environment of predominantly small start-up biotech companies that do not have the means or expertise to successfully commercialise and launch products in a climate of

fading investors' confidence and lack of regulatory controls. This is especially pressing in the case of autologous applications, the main focus of R&D efforts by European developers, where issues around scaling up and a complicated competitive environment have led to disappointment over commercial potential and market performance. Furthermore these developments are taking place against a socio-political background of diminishing public confidence in biotech more general. Especially in Europe concerns over controversial technologies such as GMOs and health scares such as BSE have led to a risk-aware (if not risk-averse) climate with increasing safety controls, for example over the use of animal-derived material, thus also pointing out the ways in which technological risk is tied in with commercial risk. In this way interviewees redefine the level of risk of products based on different cell sources, by drawing boundaries around the safety of these biological materials in lab and clinic, but by reconstructing and revising these boundaries when it concerns commercialisation. We return to these notions in the next chapter.

Finally it has been argued that while commercial risk is in the first place problematic for commercial developers of tissue engineering technology in their search for profitable markets, including effects on innovation in this dynamic field, also patients are affected by limited access to and diminishing availability of potentially beneficial treatments. Thus commercial risk affects both production and consumption.

7 Ranking and balancing risk

The literature on risks related to tissue engineering is scarce and often incomplete. One study identified 'the risk of transmitting infectious diseases from donor to recipient, the risk of inducing bioincompatibility and the risk of lack of clinical efficacy' as the most serious concerns for these products. However, at the same time it is acknowledged that 'given the novelty of these products, their hazards and associated potential harm have not yet been clearly identified' (Tienhoven et al. 2001: 8). Furthermore, the few studies available have focused exclusively on narrow technological definitions of risk (Wassenaar et al. 2001).

In the previous three chapters I discussed the differentiated views on tissue engineering risk including and beyond these limited technological understandings. The main conceptual assumption is that risks in tissue engineering technology are socially constructed and framed by professional actors involved in the frond-end of tissue engineering R&D, namely scientists, clinicians and manufacturers. I use a tripartite typology of risk as analytical tool to throw light on risk perceptions. The next part of this thesis discusses how these risk frames translate into (debates on) regulatory policy in tissue engineering.

My typology is based on three general categories of risk: technological risk, clinical risk and commercial risk. Technological risk to covers concerns related to the processing and manufacturing of human tissue and cells, and reflects an overall concern with safety. Clinical risk is about perceptions of risk related to clinical evidence available for these products, with therapeutic effectiveness as key word. Commercial risk concerns the market and business climate for tissue engineering, and includes factors such as cost-efficacy, reimbursement and general marketability of tissue engineered products. Thus this typology is a reflection of the innovation process from lab to clinic to market. It covers the different phases in the R&D process with a focus on primary scientific work and basic research in the lab (technological risk), to the clinical phase in which the constructs are translated into initial clinical testing in humans (clinical risk), as a

first transition into the market place, where the products enter the commercial cycle (commercial risk).

As argued throughout, these frames are (re)defined by interviewees in terms of quality and safety, therapeutic effectiveness and cost efficacy and in terms of marketability of products. As demonstrated in the preceding chapters, there are two general engineering routes on the basis of which interviewees define the level of risk: autologous versus allogeneic tissue constructs. These pathways are associated with particular but often debated values or levels of risk that cut across the three domains of the risk classification. Thus risks have different meanings per risk domain, and the value attached to each differs and changes. As discussed in more detail in this section, the 'risk hierarchy' represents a ranking and revaluation of risk based on the particular source material used for tissue engineered construct.

Furthermore, professional R&D groups in tissue engineering show wide variability in their perceptions of the (un)acceptability of risk, the level of risk (in terms of individual versus collective) and over short term versus long-term effects. Thus the levels of aggregation and the time-scale involved are critical. I use the concept of a 'risk balance' to demonstrate different perceptions of (levels of) acceptable risk in a given context at one point in time and for particular groups affected. Thus the risk balance determines the level of risk and benefits for particular receivers, but also takes into account acceptability over time. As a wider perspective on these particular constructions it is argued how tissue engineering as a new medical technology is situated in a complex society troubled by uncertainty about outcomes and consequences, and as such constituting uncertain risks. Before turning to these issues, some general observations can be made of the risk typology as related to professional R&D groups.

7.1 Risk frames compared

Risk domains are interrelated and connected in several ways, and the values attached to each component differ per professional and – to an extent – per

profession. An analysis based on absolute segregation per professional group does not hold, not the least because of the multidisciplinary background and hybrid careers of most interviewees, and the relationships they maintain across settings. As discussed in the methodological section (chapter 3), the revolving door is very active in tissue engineering, and strategic links between scientists, industrial partners and clinical collaborators are commonplace. Thus while the respective domains of this typology are not exclusively related to particular professional actors or interest groups, some general observations can be made.

First and foremost, although interviewees have drawn upon risk frames broadly across the three-way classification, technological risks represent a dominant discourse. But more specific frames are also called upon. Perhaps not surprisingly most scientists bring up issues related to safety and quality – which are labelled technological risk in this study. These issues are expressed as technological rather than social or public concerns, for example by elaborating on the scientific stumbling blocks that have to be overcome in terms of producing high quantities of high quality living cells, preventing uncontrolled cell growth or by finding ways to sterilise final products. Whereas scientists tend to interpret these as 'lab problems', thereby demarcating the professional domain, manufacturers have a stronger focus on maintaining cell and product quality during the full product cycle, for example also during transport. Furthermore, especially amongst manufacturers a strong belief exists in controlling these risks by putting in place quality assurance systems such as Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP). Working in a controlled environment would minimise technological risks such as contamination and infection or the mixing up of cells. In this way these actors create particular 'safe heavens' which make risks controllable and overseeable.

Clinical risk then, the lack of long term clinical evidence of effectiveness, is mostly addressed by clinicians and other health professionals, but largely overlooked by scientists. Most scientists frame this issue in techno-scientific terms of cell behaviour and cell viability, arguing how a large enough amount of quality cells is needed to 'make it work', rather than looking at the performance of the complete intervention in the clinic. Clinicians in their turn have more

elaborate views on the need for clinical effectiveness, and what the safety concerns are for the final recipient of a tissue engineered construct: the patient. Furthermore clinicians in this sample have more defined perceptions of comparative treatment options, what specific kind of clinical evidence is needed, and of course in the end: is the tissue engineered product not only safe but also a better treatment alternative for the patient?

While for clinicians patient safety is the main driver of concerns in this area, manufacturers share an interest in clinical risk for the implied economic effects. Manufacturers tend to address this issue in relation to commercialisation of technology: lack of data on long-term effectiveness of an expensive technology such as tissue engineering, also generated by the high cost of setting up multi-centre controlled clinical trials to get these data, means that eventually regulatory bodies will not be satisfied. Not being able to get marketing approval for products has implications for reimbursement by health insurance companies and adoption into national health systems. Thus for manufacturers clinical risk means commercial risk.

Commercial risk, then, is addressed to some extent by all interviewees. But while scientists express this predominantly in terms of high product cost that comes with highly innovative technology, and clinicians frame this as a low cost-benefit ratio in relation to therapeutic effectiveness, manufacturers make a direct connection between high cost, limited availability of clinical data and lack of reimbursement. Thus for manufacturers commercial risk is a combination of technological and clinical risk.

In this way respondents have defined what is problematic in the respective risk domains, but also framed the ways in which issues have a different value and meaning across settings. As also discussed next, boundary objects are fluent and hybrid entities that can move between different social worlds (here: risk domains) without necessarily threatening the borders of these domains.
We also need to take note here of 'boundary people' as particular exponents in this process. A comparison of risk frames per professional group reveals only part of the story: interviewees have shown a remarkable capacity to move and

switch between categories, while at the same time recognising the connection between these domains.

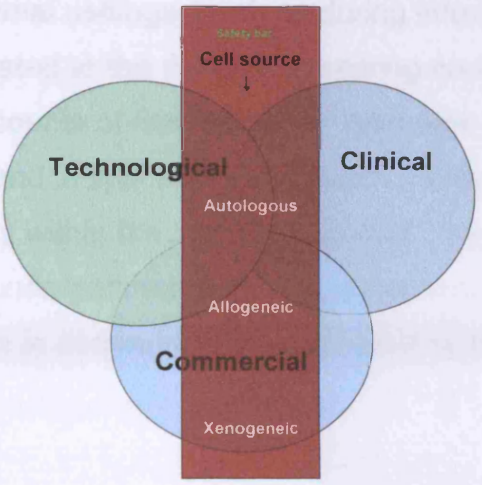
Moreover, two specific dynamics have arisen in relation to risk perceptions by interviewees in this sample. One of these dimensions I have labelled the 'risk hierarchy', which is a reclassification of risk in terms of the particular source material used for tissue engineered constructs. It is here that biological materials as most important boundary objects travel between different risk domains. For the second dimension I have used the concept of the 'risk balance' to illustrate the different levels of acceptable risk as considered by these interviewees. Finally these perceptions of risk should be understood in a climate of huge technological uncertainty and complexity, which has implications for risk management and control strategies in tissue engineering.

7.2 The risk hierarchy

As argued throughout, different risk frames are defined and redefined by interviewees in terms of quality and safety, therapeutic effectiveness and in relation to cost efficacy and marketability of products. But risks have different meanings per tier of the risk classification, and the value attached to each differs and changes. The 'risk hierarchy' refers to the reclassification and revaluation of risk based on the particular source material used for a tissue engineered construct. As discussed for technological risk, autologous applications are generally considered 'less risky' than products based on allogeneic material. But the hierarchy of risk does not just apply to safety concerns in technological terms, as the use of a particular cell source determines not only scientific endeavours but also drives clinical concerns and commercial strategies. This reveals a slightly different dynamic. For example, while the use of autologous cells is considered 'less risky' from a scientific point of view, and arguably from a clinical perspective, it poses substantial risks to manufacturers in the commercialisation cycle, as these products are usually locally produced and require extensive handling and complicated logistics, adding to cost and labour-intensity. Most notably, because of the customised nature of autologous applications scaling up is problematic – while this is

considered a major condition for market success. Vice versa, allogeneic applications are considered more desirable from a commercial perspective, because of their 'off the shelf' availability, while safety concerns are placed on a higher level by interviewees in this sample.

As such, it was observed that particular risk vectors and perceptions of safety can be translated from the science-based domain to areas of health and economy. Furthermore it is argued here that cell source is a determinant for perception of risk level along a low to high continuum – as also demonstrated in the taxonomy below:



As also discussed though, this picture is troubled by the inclusion of animal derived (bovine, mice) material in the processing of tissue engineering constructs via both the autologous and allogeneic engineering routes. Thus the perception of autologous material being safer from a scientific perspective clashes with the dominant discourse of technological but also, most notably, commercial risks associated with animal derived material. Although many manufacturers and scientists have expressed a certain acceptability and 'unavoidableness' of xenogeneic sources, the use of this material is controversial in a socio-political context, thus affecting risk control strategies and general (current and future) availability of these products on the market. In other words risks have a different meaning and value per domain, underlining the social constructive character of risk perceptions. Furthermore the hierarchy of risk depicts a differentiated and arguably inconsistent

discourse of risk ranking, given that xenogeneic materials are integral part of tissue engineered constructs.

Two observations can be made in this respect, both of a methodological nature. First of all it can be argued that interviewees use different rhetoric repertoires in framing and communicating risk. This possibility has been discussed in STS literature, most notably by Gilbert and Mulkay in their studies of the social world of biochemists (Gilbert and Mulkay 1984). They demonstrate how scientists use two different interpretative repertoires in giving accounts for their activities. In formal contexts (academic articles, conferences) they described their work different than in informal settings (such as during interviews with the researchers). Translated to the tissue engineering context, this could point towards different accounts of risk 'on paper' (although formal accounts are scarce in this area) and in interview interactions. However, this would not explain any variability within the interview context. The use of rhetorics in this context is not to be underestimated though, especially amongst respondents with large experience in communicating their work outside their field of expertise.

The second observation, arguably more valid, refers to weaknesses in the model that I developed to capture these perceptions of risk. As such, the hierarchy of risk (represented in the vertical safety bar in this model) is based on perceptions of technological risk, *as presented by interviewees*. The role of the social scientist would ideally be to unravel the complex data dimensions and interpretations. After analysis of interviewees' accounts, then, a more dynamic model can be developed. This would take into account the level of risk from a 'zero' or low to high continuum, based on interviewees' perceptions, but in a less static way.

A matrix version of this model could have the following values:

Risk domain → ↓ Cell source	Technological	Clinical	Commercial
autologous	Z	L	H
allogeneic	H	H	L
xenogeneic	?	H	H

Z = 'zero risk'

L = low risk

H = high risk

In this way the 'consensus' values of risk levels as associated with cell sources can be depicted, although it does not allow for any conflicting views or nuance. For example the use of xenogeneic material is described by some interviewees as highly problematic, while others marginalise the potential harmful effects in the science domain. Thus any ranking is an exercise in reductionism, but also problematic in the face of another dominant, though less explicit discourse in tissue engineering, which links risk with uncertainty and complexity. This is discussed later. In the section below it is argued that the level of risk and the balance between risks and benefits is of key concern in deciding on the acceptability of risks.

7.3 The risk balance

In addition to a hierarchy of risk, which covers the ranking of risks on a low to high continuum, another dimension of risk is described in what I have called the 'risk balance'. The risk balance is about acceptability of risk and for whom, where perceived risks of tissue engineering are differentiated into levels and degrees of risk for particular applications, subsets of populations, and the envisaged effects over time. The risk balance thus takes into account the specific therapeutic purpose of the tissue engineering application, across stages of the innovation process (e.g. lab, clinic and market), and is concerned with both risks and benefits of the technology and the trade-off between the two in determining acceptability of risk. The content of the balance of risk and the

hierarchy of risk provide the context for risk management approaches, which is the concern of later chapters.

7.3.1 The risk balance: it is different if you are going to die

> It's all about risk, isn't it? (...) If you're going to have a treatment which is not - either cosmetic or it's not life threatening, you might be more concerned about the origins of the material than if you knew you had to have it because you knew you were going to die.
> So, I think, what I'm really getting at, I think, there are so, so many variants of tissue engineering here, I think, you've almost got to, not look at them individual because that wouldn't be very helpful but when we start to classify them to a stage where that either the treatment or the aspect of the patient who is having the treatment has to be taken into account and will vary from somebody with a different experience. (Academic research scientist in UK tissue engineering lab S1, 2003).

This interview fragment highlights two important issues. First, there is talk of 'the patient', recognising the diversity in meanings and experiences of the final receivers of tissue engineered products. Second, a particular dominant discourse in assessing the risk-benefit ratio (e.g. the risk to individual patients in relation to the potential benefits of the technology) concerns the condition being treated. Many interviewees have argued how both the desired therapeutic effect and condition at which the tissue engineering product is targeted are part of a wide spectrum ranging from seriously life-threatening disease to mere elective interventions:

> If for, particularly for a TE application, it's not a life threatening condition, so the risk benefit is not, a different balance and if the benefit is going to improve the quality of life but not save the life it's very different weighting compared with something that's going to save a life. So the equation is rather different. (Academic research scientist in UK tissue engineering centre S3, 2003)

> If I have a spinal cord injury and I'm going to face the rest of my life paralysed, the benefit of injecting a stem cell into my spinal cord, and getting repair is massive. At the moment I think the risk is also quite high that that cell will cause a bad effect. But that risk-benefit probably works for most people. Most people would probably want to give that a try. If you're talking for example about cartilage degeneration from someone aged 70, when it has worn out cartilage in their knee, the risk-benefit is totally different. The benefit is good but probably not good enough to justify taking any sort of risk with transfer of infection or major rejections. (Academic research scientist in UK tissue engineering lab S7, 2003)

> I wouldn't do it, I mean if I was a patient I would not accept donor cells from another patient at this stage. (...) When you're dealing with a non terminal disease you want to be more cautious than you would if you had cancer or something. (Academic research scientist in clinical care S4, 2003)

Thus the risk-benefit ratio may differ depending on the condition being treated. Furthermore, as underlined by respondent S7, also the health condition and age of the patient are important factors in determining whether it is 'worth taking the risk'. Also other interviewees have expressed the importance of age of the recipient, especially in the absence of longer term evidence on the performance of tissue engineered applications in the patient in combination with the intended permanent character of implantation, while at the same time it is pointed out that many medical implant technologies do not last for a lifetime in most cases.

In addition, as also pointed out by interviewee S4, who would be reluctant to use allogeneic tissue engineered products on himself with the current risk profile attached to it, there is the notion of 'developing technology'. The interviewee below, working in industry, would be confident in using tissue engineering technologies as a patient, but also talks of a 'moving target' in relation to risks and benefits: with scientific advances and developing insights in the technology over time, the ratio might change.

> Personally I suppose I'm a little bit biased having worked with tissue engineering products for as long as I have and seeing the evidence of effectiveness I would have no qualms about using tissue engineering myself as a patient. How I personally perceive that risk-benefit? It is of course a moving target because your risk-benefit can only be as accurate as the current state of the art. So you can for example characterise a product now but in three, four years' time if you've been a recipient of a tissue engineered product and a new test comes out which is more accurate, more sensitive to the material or contaminants that could be in that product or introduced into that product then the risk-benefit changes as you go along. (Regulatory affairs professional in multinational industry M-EU9, 2003)

Thus the perceived risk-benefit ratio is dependant on factors such as therapeutic indication, health condition and age of the patient, and status of the technology, stressing the developing character of the innovation. Although these factors cannot be considered exclusive for tissue engineering technology – or in other words are rather typical for innovative medical technologies –

these are important considerations in determining acceptability of risks but also of uncertainties surrounding this particular domain. Furthermore and of major relevance, this diversity has implications for the regulatory reach of these products (Welsh 2000).

7.3.2 From risk assessment to management

The assessment of risk informs the management of these risks, where a main concern is how to incorporate diverging and different risk perceptions into regulatory policy. As such, tissue engineering is typically treated as a generic technology for regulatory purposes. But many interviewees have argued how a specific and alternative type of risk assessment is needed for new technological applications such as tissue engineered products, to take into account both the developing character of the technology and the associated (unknown) risks, with its diverse current and future applications. One such argument is provided by a prominent scientist of a UK tissue engineering lab:

> Tissue engineering, xenotransplantation, gene and cell therapy and other emerging products and processes are altering the way in which risks can be assessed and are bringing new challenges to product demarcation (Williams 2001: 12).

Tissue engineering is perceived as one of a range of novel technologies that could change the way in which risks are assessed and managed. This is also reflected in interviewees' accounts. Many argue how tissue engineering cannot be considered as a one-dimensional technology creating generic risks, and as such regulatory activities should focus on the different dimensions and classifications of risk. Risk assessment procedures should include such notions as cell source, functionality, type of application and therapeutic goal of products.

> And then also you get the risk profile of these products, because not all of these products have the same risks. Based on the risk you should be able to sort of maybe have a different barrier and different assessment. (Regulatory affairs professional in industry M-EU3, 2003)

Furthermore, and in line with the risk hierarchy as discussed, several interviewees have argued that based on a differentiation of cell sources,

accordingly less stringent controls should be attached to autologous applications. The interview fragment below is from a scientist, who explains the need for differentiating between allogeneic and autologous cell sources in risk analysis:

> I think one needs a regulatory framework for a tissue engineering product which says how risky it is, and part of that assessment should be infection risk from donor cells, or risk of immune rejection. (...) it could be incorporated into one's general risk assessment and then for autologous cells it's simply a tick in the box saying "no risk because". (Academic research scientist S4, 2003)

In the fragment below, from a regulatory affairs professional in a large commercial firm, beyond the risk divide of autologous and allogeneic applications also a risk-based approach applies to specific products within the range:

> As with all products... risks must be balanced by benefits, and this should be reflected in the applicable regulations. In this context, it would seem that a range of tissue products does not warrant a blanket `high-risk' label. For example, autologous tissue-based products have far different risks and requirements from those originating from allogeneic tissue. Also, application of certain allogeneic tissue (such as cartilage or bone) will pose significantly less risk than tissue derived from the central nervous system (Brown et al. 2001: 296)

Thus one of the main arguments of interviewees is in favour of a product-based risk assessment, where control measures could be specified for particular product subgroups that are stratified according to increasing risk. In this respect also other criteria are mentioned as relevant. According to the following interviewee, these criteria could include the route of administration, the tissue type and the degree of processing of tissue engineered products:

> One has to look at the hierarchy of risks and also depending on how you're going to administer or implant the products. The route of administration will be a determining factor. It's very difficult for me to generalise it because I think that is not the approach of risk assessment. You have to look at various factors. Factors like route administration, the type of tissues will be relevant, and how the tissues are processed will be relevant. (Legal professional in regulation of biotechnology O2, 2003)

An underlying motivation for a product-based risk approach is the large standard deviation in the range of current and experimental applications in tissue engineering. The interview fragment below illustrates this variety:

> There's quite an extreme. When you think of the technologies involved you go from anything from irradiated bone which is used for packing materials in orthopaedic surgery or dental surgery or whatever right up to incredibly sophisticated cells that have been manipulated and grown into very specific shapes and are on scaffolds, they may be three dimensional tissues that have different structures within them and so on and so on. You can have... each product is quite unique and has to be evaluated in that way.
> (Regulatory affairs manager of multinational company M-EU9, 2003)

Many interviewees have commented on the need for accounting for variety in risk assessment in order to cover this very broad set of current and potential applications of the technology, with corresponding different levels of risk.

> I think in a lot of the new technology products you have to do that, you have to look at each particular product on its own merit. It's not a case of one size fits all.
> (Product safety assurance manager in multinational company M2, 2003)

Thus one of the criteria for risk analysis in this domain is the assessment of individual products. Indeed, this is backed by one of the few risk management documents that have been published, in which it was stated that 'different TEMPs [tissue engineered medical products] will certainly carry various combinations of risks, each varying in character and magnitude. Classification of products into risk groups can help in designing efficient control measures' (Wassenaar et al. 2001: 33). An influential expert opinion on risk factors in tissue engineering makes a similar distinction between high risk applications that address important clinical conditions (heart valves) and low risk ones aimed at non-life threatening conditions for which alternatives exist (cosmetic surgery). With varying degrees of risk and benefit, it was argued that regulatory procedures for tissue engineering may not have to be uniformly applied:

> In consideration of the wide range of risks inherent in tissue engineering, tissue engineered products and processes should be classified according to the level of risk to the patient. The process of categorisation needs to be developed but in the first instance this should be confined to levels of low risk and high risk (DG SANCO: SCMPMD 2001: 9).

A risk-based approach in tissue engineering is problematic though for policy purposes, pointing towards large heterogeneity of tissue engineered applications currently on the market and in experimental stages of

development. Regulatory policy has to balance between covering the current product portfolio, of applications 'out there' at this moment in time, and of envisaged products potentially entering the market in the near future. This is a complicated task given the current developing status of the technology, where relatively simple applications such as skin and cartilage have been available for some years, but with more complex and arguably much more risky outputs of current R&D efforts in the pipeline. Risk assessments require looking at the range of future options, and the potential benefits and risks of each. Regulation has to be able to incorporate the diverse and innovative nature of products, and be flexible enough to adapt to technological progress to prevent itself from running out of date. As a developing innovation, tissue engineering is an interesting case for the conflict between the level of certainty that industry needs in terms of consistent rules and predictable evaluation, while at the same time flexibility is needed in the evaluation of safety and efficacy of these products, given their complexity and broad range of applications (Bartlett Foote 2002). Therefore one particular concern in the development of a regulatory framework is the difficulty of foreseeing the consequences of a technology during early stages of development, and designing control mechanisms for when the potential harmful consequences of the technological innovation become visible for society. This is furthermore complicated by the fact that significant risks might develop that have not been seen in healthcare before. Thus notions of uncertainty and complexity pose difficulties to regulators trying to cover future outcomes of innovative therapies.

Before discussing this in more detail, the next sections give an impression of how to differentiate between the levels of risk in the risk balance.

7.3.3 Residual risks and the zero risk society

As discussed in the last section, the acceptability of risk depends on several factors. For most interviewees this is based on the general assumption that there will always be some level of risk involved:

> At the end of the day you may have a certain level of residual risk left with any product. It may be a lower risk or it may be a higher risk but you have to balance that then against the benefit to the patient. Now if the

> patient is in a very serious state, you may be willing to accept a slightly higher risk product. If the patient is going for elective surgery for cosmetic reasons or something like that, there may be no grounds whatsoever to accept a high risk at all.
> (European trade body representative M-EU2, 2003)

Thus some degree of risk is 'part of the game'. Especially manufacturers have stressed how demands for a 'zero risk society' are idle and simply impossible in the light of uncertainties surrounding medical technologies. Furthermore one should not outweigh the potential benefits to patients:

> All life is a risk and you cannot guarantee or make any product 100% safe. I think sometimes there is a tendency to think that the product should be 100% safe and I know it must be very difficult for those users and patients who perhaps do not enjoy the benefit of the product, but say the vast majority of people will. You have two options: you either produce a product which has got profound benefits but with certain risks or if you want a zero risk society, well you don't have the product and lot of people will suffer. So these are profound debates, aren't they?
> (Industry consultant and representative national healthcare industry body M3, 2003)

As these fragments demonstrate, a strong rhetoric exists in stressing benefits of the technology rather than focusing on 'just the risks'. But in addition to perceived risks that would affect the population at large, specific nuances and hesitations are expressed when it concerns specific groups in society. Thus the definition of the population at risk is another important factor in framing the acceptability of risk and making up the risk balance:

> I think some level of risk is justified but if you have someone say has superficial burns injury and it's not that very extensive, what's the risk of using donor skin from skin banks or mouse cells or foetal calf serum. Most of the surgeons, especially where [it involves] children, they look at that and say: no I'd rather not. We are going to be able to manage fine. We don't have to go near tissue engineering products with whatever risks. So we live with these equations all the time.
> (Academic research scientist in wound healing and clinical management S5, 2003)

With the example of clinicians being reluctant to apply tissue engineered applications to children as a particular vulnerable group, the question arises of who is actually affected by particular risks and how to define the at-risk-population. While the benefits to individual patients can be considered clear and visible at one point in time for a given application, the same can not be said

of the distribution of risk. The section below discusses this issue in terms of individual versus collective risk.

7.3.4 Collective versus individual risk

This section focuses on another dimension of risk, namely the distributive character of risk in relation to the acceptability of tissue engineered applications. Determining the level of risk is important for a number of reasons, one of them concerning the question of who bears responsibility for controlling these risks. This relates in particular to the role of the state vis-à-vis other actors involved in regulatory decision making and control. Thus the definition of the level of risk dictates the responsibility of particular actors to manage these risks, but also implies judgements about the acceptability of risk. Furthermore, tissue engineering is an interesting case because it is presented as a medical technology. Technologies in the healthcare domain are usually considered as applicable to individual patients – unlike environmental risks which are seen as impacting on a societal level via public health. Thus whereas public health risks can be considered as collective risks, most medical applications are typically perceived as a form of individual risk (see also: Welsh and Evans 1999). Initially this is also the response of many interviewees in this sample, asked about whether the perceived risks of tissue engineering would be potential threats to public health:

> I think most of the risks are borne by the patients themselves. If there's rejection of inflammation. If you have a new piece of cartilage in and it causes a big inflammation you're going to be in a lot of pain and you're going to have that removed but it doesn't actually affect anyone else... yeah public health isn't affected.
> (Academic research scientist in UK tissue engineering lab S7, 2003)

Obviously the level of risk is related to the perception of what is considered a risk and the value attached to that. This scientist talks about individual risk in terms of side effects referring to autologous applications. Other examples of this patient-centred individual form of (technological) risk are allergies, tumour formation, or ineffective treatment. But as discussed earlier, the transfer of infectious disease is a prominent safety concern and mentioned as the main technological risk. Asked about the use of donor cells in tissue engineered

applications, and the effects for the population at large, the following scientist responds:

> So if you mean is there a risk to the general public? I don't think that is a major risk. You would have to have people take the laboratory side of things. (Academic research scientist S5, 2003)

What follows is a description of the lab safety procedures and how all possible quality control measures are taken to prevent tissues and cells from being infected or contaminated. In other words there is, again, a strong belief in 'controlling' technological risk. Another scientist explains how even with human donor cells the impacts of 'anything going wrong' are limited to a small pool of individuals rather than affecting the collective:

> If they were xenogeneic then there are huge public health issues, but not with allogeneic. These are largely risks which are almost customised to the individual. I think it's actually, it's an important issue because generally speaking the risks, it depends who the donor is. Generally speaking the risks are going to be confined really to a very, very small number of people. If you had a donor source and the issues here are: is the donor carrying any disease, is it detectable and is there any possibility of infectivity arising from some, let's say infected or contaminated donor? The chance of that getting to a large number of recipients is very small. It's not like having a medical device or drug where there has been, as we've seen several times, there has been a problem with production where tens of thousands devices come out and suddenly you find ten thousand people have your device and it's going to go wrong. In tissue engineering that's not, that wouldn't happen I don't think. Although having said that some of the existing products such as Dermagraft [a tissue engineering skin product] and so on that, they are manufactured from one, largely from one cell source but I think that is now so well characterised that there's not going to be an infectivity from the source. There could be contamination in the way, and that's a secondary issue I think, process contamination.
> (Scientists, head of UK tissue engineering centre, expert advisor in EU policy A-EU6, 2003)

But, most importantly, this quote also mentions the use of xenogeneic cells, and it is here where the potential lies for earlier expressed concerns about introducing novel diseases (zoonoses) into the human population. While the incorporation of living tissues or cells from human donors into tissue engineered constructs might, at least according to the interviewee above, only affect a small number of individuals at risk, the use of viable or non-viable animal derived material could open the door to large scale disease transmission. Thus the issue of including animal (cell) sources, although

downplayed by many interviewees as being 'safe enough' for current purposes, would potentially extend the level of risk over time and generation, thus creating a form of inter-generational risk. Potentially, because not a lot is known about the risks and effects.

7.4 Uncertain risks and complexity

> ...How are we going to know because we don't know how cells react at that level - we don't know, and that would be the risks...
> (Industrial scientist at consultancy agency M-EU8, 2003)

An underlying perspective in the evaluation of perceptions of risk in tissue engineering concerns the unknown character of many of these risks. While it has been demonstrated that many interviewees express views about the ability of controlling risk, for example via the implementation of quality control systems and safety standards in labs and manufacturing units, tissue engineering is an example par excellence of a technology with many 'unknown unknowns'.
It has been argued in the literature how risk and uncertainty are intermingled, and how risks cannot any longer be seen as controllable or calculable entities. Uncertainty and risk cannot be easily distinguished and mutually constitute each other (Asselt and Vos XX). With progressing innovation and change in Western society, new forms of uncertainty are created, and with them uncertain risks (Nowotny et al. 2001). Thus uncertain risks spring from the inherent unpredictability due to complexity.
Tissue engineering can be considered a good example of the introduction of an innovative technology where uncertainties exist about the complex relation between cause and effect, and other underlying processes that make it hard to predict what will happen in the long run. Both risk and uncertainty are central notions in the complex risk management strategies for this technology.

In tissue engineering two domains have been identified where particular forms of uncertainty persist, which are interrelated. One of these concerns the potential for disease transfer, and the fear that new viruses pop up that can not be tested for with the current means and state-of-the-art in science and technology:

> I mean there's always a potential risk. The thing is you can't ever protect yourself against something you don't know about. So if you went back to the time before HIV, before it happened no one could have predicted it or tested for it. So people won't ever be able to stop from some virus getting into the process. But I think if you tend to grow the cells from donors now, I mean we're talking about nearly ten years time now that a virus comes on the scene, if we were using cell banks that were made today, it would have been produced, I mean the serum would never have been produced like it is. I mean you can never safeguard against those kinds of things happening in the future, but once you know what to test for it becomes pretty safe.
> (UK manufacturer in tissue engineering M1, 2003)

A related concern is expressed by the scientist below, who identifies several areas of uncertainty but feels the risk of disease transfer is the most pressing:

> How we going to know, how are we going to ensure that those cells do not transmit... and the concern is that transmittable disease really. How do we know that they're not going attract some nasty virus? Viruses are coming out of everywhere. How do we know that we're not going to give them some kind of carcinogenic element? (...)
> Nevertheless how do we know? And those are the kinds of questions that could keep you awake at night. It really is the transmitted disease, I think, because if you put a cell into somebody it's either going to die, it's not really going to kill them, is it? Do you know what I mean? You can give somebody an overdose of morphine and it will kill them. The chances of killing somebody with an overdose of cells, is slightly, this is a completely different parameter. (...) The ultimate thing is to keep records on donors and any possible risk that they might have particular viruses or you know, CJD exposure and things like that. I think ultimately you can test the blood all you want but it's very difficult to know about the viruses we don't know about, so...
> (Industrial scientist at multinational consultancy company M-EU8, 2003)

As also illustrated in the above quote, many of these uncertain risks are of a technological nature, where it is uncertain what effects and potential harm can be expected from, in this case, the use of donor cells. This is related to a second and underlying main area of uncertainty in tissue engineering, namely the starting components used; the behaviour of living cells in the body and of biological materials in general are difficult to estimate:

> Dealing with biological materials is always much more complicated and unpredictable than dealing with the types of materials that engineers deal with. Controlling biological materials is difficult. Batch control is difficult so anything you do with biological materials is more unpredictable. An engineer would probably kill me for saying this but I guess there's a limited quantity of knowledge on steel or plastic: you can get to know all there is to know about steel. But it'll be a long, long time

> before you get to know everything about even fairly purified biological materials. So I think there's an inherent – a definite – increased unpredictability which is a potential risk.
> (Clinical scientist in multinational industrial setting M-EU1, 2003)

And as the interviewee below explains, this has implications for the risk management process, where uncertainty has to be translated in ways of at least predicting 'reasonable foreseeable risks':

> In this kind of area with a biological system you are always dealing to a certain extent with the unknown as well, and one of the things one does in risk management is also to try and identify reasonably foreseeable risks which I think is quite an important principle. So you look beyond the obvious into even slightly beyond that into what could be some of the other things [that] could conceivably go wrong and you try and predict this as far as possible
> (European trade body representative M-EU2, 2003)

Thus uncertain risks are not or only partially calculable and controllable, because the probability of occurrence or the potential damage and harmful effects are difficult to estimate. In policy circles an often heard argument is that uncertainty is a matter of limited knowledge (so called epistemic uncertainty), or the result of variability in natural systems behaviour, human behaviour, socio-economic and cultural dynamics or technological surprises (variability uncertainty). But as argued by Van Asselt and Vos, uncertainty is not simply caused by lack of knowledge:

> Experts and scientists often have quite informed ideas on which uncertainties may be important and why, what are underlying sources of uncertainty, whether and how uncertainties may be reduced or at least better understood, which interpretations of uncertainty seem valid and which contradict the established state-of-the-art. This whole of answers and insights can be referred to as 'uncertainty information'. Experts can provide such uncertainty information, but they cannot provide certainty about uncertain risks (Asselt and Vos XX: 5).

As discussed in this section, interviewees in tissue engineering have adopted certain frames of what the areas of uncertainty are, such as viral transfer and controlling biological material, and why they matter. Furthermore strong suggestions have been expressed on how to reduce these uncertainties, for example via screening of donors and testing of products:

> I think there is a great deal of awareness of a whole range of routes of possible risk that those developing are trying to be aware of possible risk

> and trying to understand how you can minimise them, how you would try and test for them... I'm not sure that there is... nothing can be entirely safe, but all the perceived risks - to keep them to a minimum, to try and ensure that...Many straightforward applications may not be difficult to try and ensure there are reasonable levels of low risk. (Academic research scientist in UK tissue engineering centre S3, 2003)

Thus the uncertainty information is to some extent available, but this does not change the suggestion one has to deal with certain uncertain risks. Thus uncertainty functions as underlying framework and backdrop for analysing risks of tissue engineering technology. We will come back to this issue in discussing ways and means into how to manage risk in a situation of uncertainty.

7.5 Transgressing boundaries: deconstructing and reframing risk

The purpose of this part of my thesis has been to analyse the socially constructed or framed nature of risk in tissue engineering. The main research question addressed concerns how and to which extent expert definitions of risk are articulated in tissue engineering R&D and in which ways they are framed and differentiated. My research has sought to unravel the dimensions of different types of risk as perceived by professional actors involved in the early research and development stages of tissue engineering, thus representing a model of the early innovation process or front-end stage where products emerge from lab to clinic into the commercial cycle. Furthermore, attention was focussed on the framing of these issues according to different categories and levels of risk and uncertainty as defined by these actors. Insight into these issues is needed to analyse how different discourses on risk translate into regulatory policy making in this area, and what the implications are for the shaping of a regulatory regime in tissue engineering, which is the broader concern of my research and the subject of the next part of this thesis.

7.5.1 Revisiting risk

To analytically approach different risk frames I have developed a tripartite classification to discriminate between risks in the different phases of the innovation process from lab to clinic to market. It has been demonstrated how different risk frames are defined and redefined by professional R&D groups in this domain in terms of quality and safety, therapeutic effectiveness and in relation to cost efficacy and marketability of products. Whereas variability in the framing of risk has been described in the literature, my study is a confirmation of how the debate on risk reveals broad variability in perception and assessment of risk within and, to a certain extent, between different professional groups involved in R&D in this technological domain. But risks have different meanings per tier of the risk classification, and the value attached to each differs and changes, thus underlining the social constructive character of risk.

Furthermore I have outlined cross cutting dimensions of risk, which I have labelled the risk hierarchy and the risk balance. The 'risk hierarchy' contains a reclassification and revaluation of risk on a low to high continuum based on the particular source material used for tissue engineered construct. This model was based on initial presentations of risk by interviewees, but appeared too static to explain the differentiated and inconsistent discourse of risk ranking, surrounded by uncertainty. Risks related to particular cell sources have led to different regulatory scenarios, where initially a distinction was made between autologous and allogeneic cell sources in regulatory controls, while subsequently this distinction was abandoned. In order words the ambiguity in this particular risk frame resounds in the regulatory debate and policy shaping around tissue engineering.

But in addition to risk variability per domain, interviewees take into account the population affected and the short term versus long-term effects in both perceived risks and benefits of these applications, underlining the importance of the levels of aggregation and the time-scale involved. A second dimension of risk is described in what I have called the 'risk balance'. The risk balance is about acceptability of risk, where perceived risks of tissue engineering are differentiated into levels and degrees of risk for particular applications, subsets of populations, and the envisaged effects over time. The risk balance thus takes into account the specific therapeutic purpose of the tissue engineering application (over a spectrum from life saving till merely cosmetic) across stages of the innovation process, and is concerned with both risks and benefits of the technology and the trade-off between the two in determining acceptability of risk. It has been argued how tissue engineering technology will always imply a certain level of 'residual risk' as demands for a zero risk society are considered unrealistic. But this residual risk is not a generic category, as the risk balance also looks at the population at risk and the final risk-receiver, where acceptability is dependant on whether potentially harmful effects are limited to individuals or the society as a whole (e.g. individual versus collective risk) and in how far these risk are extended over time (inter-generational risk). Thus also the risk balance is a socially constructed notion.

The content of the risk hierarchy and the risk balance provide the context for risk management approaches, which are troubled by large heterogeneity in product categories and associated risks of current and future applications. As also discussed, these perceptions of risks need to be understood against a background of large technological uncertainty and complexity in this domain, where outcomes or possibly harmful effects are difficult to estimate and predict, effectively creating uncertain risks.

Thus these different frameworks are important because they dictate which issues are seen as problematic and which 'solutions' are constructed in the policy process, e.g. which risk management strategies are considered valuable and feasible, and what information is needed and useful in reaching a decision. It also has implications for the legitimacy of different viewpoints in the policy process. The construction of risk discourses is tied in with the expression of a technological, political or social acceptable solution. Thus the definition of risk is at the same time the definition of a solution.

By making the transition form risk assessment to risk management, one could argue that some consensus is needed on the definition of risk, as this dictates policy solutions to risk-based problems. In other words, some negotiated common framework is to be articulated, in which interested individuals and institutions adopt a similar or at least compatible conceptualisation of the risk issue in question. The next part of this thesis departs from a potentially problematic understanding of divergent perceptions and constructions of risk, and the question how this diversity can be incorporated into the policy domain.

In other words, claims can be made about the policy implications of different risk discourses. As pointed out by Vaughan & Seifert, 'variability in the framing of risk issues can exacerbate conflict, leading to differences in which perspectives are judged legitimate or valid, what solutions are seen as reasonable, and what type of information is seen as useful or relevant' (Vaughan and Seifert 1992: 119). Understanding how different actors structure or frame complex risk issues can thus provide insight into the basis of policy disagreement. This is a two-way system, where the framing of a risk issue – the conceptualisation of a problem – amplifies certain values and beliefs, but also

where these values play a role in how individuals frame the decision elements to be considered in a risk situation (Dietz et al. 1989).

The remaining part of this thesis will analyse these professional risk frames in the light of regulatory policy making and in particular take into account the different subsets and constructions of risk as put forward by a category of experts and professionals further down in the innovation chain, namely regulators, scientific experts and policy advisors involved in regulatory activity. Here alternative risk frames are called upon for the purpose of risk management and control, where risks have to manageable and 'regulatable' in order to enter the policy domain. In this process particular risk frames and definitions are adopted for inclusion in policy and practice, while others are neglected or downplayed as not being suitable for control and management.

Before analysing this process in more detail, it is important to consider the frames that are left out or marginalised in accounts of interviewees. One of the main contrasts between R&D risks and regulatory risks is the different values attached to social and ethical considerations by different sets of actors in these domains. The next part of this thesis analyses how arguments of a less narrowly defined techno-scientific frame are intertwined with discussions on the scope of regulatory policy, and how boundaries are drawn around the social acceptability of tissue engineering technology. To put this regulatory debate in perspective, insight is needed into the ways in which R&D actors deal with social and ethical concerns.

7.5.2 Moral considerations in different risk domains

The focus so far has been on R&D expert definitions of risk which have been framed in a rather crude three-way of scientific, clinical and commercial discourses. An important notion largely underdeveloped so far concerns the inclusion and implications of dealing with socio-political and ethical concerns related to tissue engineering technology. These concerns have been largely deprived of in current accounts of interviewees in this sample. This is not to imply that these issues are absent:

> Tissue engineering involves more than scientific or medical issues. Many people voice concerns about the ethical issues raised by experimenting on animals or humans, cloning, using fetal tissues in research and treatments, and creating cutting-edge treatments that might only be available to people of certain economic classes (Hypertech Online, 2001).

The discussion of moral dilemmas and 'ethical aspects' of tissue engineering has entered authoritative writing about the technology, arguing how other than purely techno-scientific issues need to be addressed in order to create a societal beneficiary solution. The issues referred to differ. While the quote above considers tissue engineering on a similar level as potentially more controversial technologies such as cloning, some of the early pioneers in the field touch upon issues of funding, regulation, clinical testing and proprietary implications, and how these issues affect the institutional structure:

> If tissue engineering is to play an important role in human therapy, in addition to scientific issues, fundamental issues that are economic, social and ethical in nature will arise. Something as simple as a new vocabulary will need to be developed and uniformly applied. A universal problem is funding. Can philanthropic dollars be accessed for the purposes of potential new human therapies? Will industry recognize the potential for commercialization and invest heavily? If this occurs, will the focus be changed from that of a purely academic endeavour? What role will governmental agencies play as the field develops? How will the field be regulated to ensure its safety and efficacy prior to human application? Is the new tissue to be considered transplanted tissue and, therefore, not subject to regulation, or is it a pharmaceutical that must be subjected to the closest scrutiny by regulatory agencies? If lifesaving, should the track be accelerated toward human trials? There are legal ramifications of this emerging technology as new knowledge is gained. What becomes proprietary through patents? Who owns the cells that will be sourced to provide the living part of tissue fabrication? (Vacanti and Vacanti 2000: 6-7).

Interestingly, these issues are phrased in terms of the need for advancement of the field, considered from a developers' or insiders' perspective, where ethical concerns are translated as problems belonging to the domains of science or commerce. Furthermore, what these fragments have in common is an understanding that ethical concerns are a problem of 'other people', e.g. the public or 'society' that needs to be convinced or even educated about the therapeutic benefits, which would subsequently lead to smooth adoption of the technology. This demarcation is also visible when asking interviewees involved in tissue engineering R&D activities about potential ethical concerns. It is

generally argued that tissue engineering is uncontroversial, given the current state of technology, or at least external to the technology itself. Thus while handbooks and overview articles on the technology do not linger on expressing various ethical concerns, or at least referring to various concerns under this heading, these do not play a dominant role in interviewees' accounts.

But risk can be considered integral part of this reflection. Or more specific, the balance of risk or the weighting of risks against benefits poses questions of a moral and political nature. The general understanding is that a certain amount of risk is acceptable when it is balanced by a specific amount of benefit. But the question is whose risks are weighed against whose benefits. As described earlier, risks can be defined by different criteria, and different actors attach different values to particular risks, which also has implications for risk assessment strategies, as these can not be restricted to narrow techno-scientific or medical frames. Similarly, the assessment of benefits is troubled by different definitions and whether the benefits are to be gained on individual or collective level; for example for the patient or for public health, for the individual scientist or the research community, for commercial developers of these products or national economies. Thus the very notion of risk perception and acceptability is fraught with moral implications about the receivers of risks and benefits and the distribution of the risk balance. More specific, concepts of both risk and safety have become matters of moral concern by raising questions about responsibility, accountability and justifiability (Reiss and Straughan 1996) and the assessment of risk includes ethical considerations, thus underlining the interrelatedness of risk and ethics in modern technology.

This section discusses emerging ethical and social concerns which can be brought back to specific phases in the innovation cycle and the corresponding broad typology of technological, clinical and commercial risk. These issues range from general safety concerns and risks of ineffectiveness to implications of commercialisation and ownership of innovations. Partly drawing on documentary sources, also the limited interviewees' accounts of specific ethical dilemmas are presented in relation to tissue engineering technology, investigating in how far we can consider these discourses as external or

internalised accounts, and with which implications for regulatory policymaking in this domain.

Of conceptual relevance in this respect is that ethical concerns can be considered as transgressing boundaries of risk domains, while also shaping the regulatory domain. Moral issues are not fixed but fluent and hybrid, not static but permeable; they remain open for negotiation and reconsideration, and as such for continuous boundary drawing. As discussed later it is particularly difficult to achieve closure in this process, and ethical arguments are powerful boundary objects in regulatory policy shaping, where organised interests are gathered around specific ethical objections and legal possibilities.

7.5.2.1 Technological concerns

Technological concerns relate to the early stages of sourcing, donating and processing human tissues and cells to create tissue engineered products. Some of these issues are considered to apply more generally to donor and organ donation and tissue banking activities, for example in relation to gaining informed consent, the nature of donation, traceability of donors and overall safety concerns. Others can be regarded more specific for tissue engineering technology, such as debates on the meaning of 'engineered' and 'manipulated' human material and concerns around specific cell sources used in the construction of these products.

To produce tissue engineered products, tissues and cells can be sourced from living or deceased donors, cell lines, (aborted) foetuses and human embryos. Each of these cell sources is associated with quite different ranges of ethical questions, also depending on the conditions of use – most notably for research versus therapeutic purposes and in terms of whether the intended use is medical or cosmetic. In this respect the risk balance as discussed earlier reflects these concerns. For example, some have expressed concerns that tissue engineered products might be developed that are not just aimed at restoring human tissue but also improving bodily functions, creating the potential for enhancing performance of human beings (Bock et al. 2005).

First of all, a whole set of concerns relates to the donation of human tissues and cells. Especially in Europe a strong tradition exists of altruistic donation (as opposed to commercialisation of human tissue, as also discussed later) where the procurement of human tissues requires prior informed and free consent of the person concerned. Comparable to organ donation, donating tissues or cells is seen as a voluntary act of solidarity. Connected to this free donation frame are ideas about ensuring bodily integrity when procuring tissue or cells from both living and dead donors, and with taking into account certain health safety measures to control and test, as far as possible, the potential of disease transmission. This includes checking the donors' personal and medical history to detect transmissible diseases, but also making sure a system is in place for surveillance and traceability of both donors and recipients. But part of the informed consent agreement, at least ideally, covers the extent of anonymity of the donor, conditions of database registration and protection of private life and medical confidentiality. The sourcing and donation stage, but also subsequent handling and use of human tissues and cells requires the acquisition of personal data by companies or biobanks and storage of these data for prolonged periods of time in order to trace back the tissues for safeguarding patient safety. Especially these traceability requirements for tissue engineered products and patients could potentially clash with issues of privacy, data protection, confidentiality and anonymity of patients. We will return to these issues in the discussion on developing regulatory policy, where especially the Tissue and Cells Directive by DG SANCO takes into account these concerns.

Other social and ethical concerns around tissue engineering relate to the use of other cell sources, where most notably the use of human embryos for derivation of embryonic stem cells has stirred controversy. Ethical issues underlying debates about the generation and use of human embryonic stem cells are well documented (Cogle et al. 2003; Colman and Burley 2001; Denker 1999; Dresser 2001; Gottweis 2002; Henon 2003; Holm 2002, 2003a, 2003b, 2004; Romeo-Casabona 2002; Stock 2003; Sutherland and Mayer 2003; Sylvester and Longaker 2004; Zwanziger 2003). While proponents point at the growing evidence that embryonic stem cell research will enable the cure and treatment of a wide range of diseases and conditions, for some of which no current treatment exists, opponents worry about the use of early embryos for

utilitarian purposes. As embryonic stem cells are often derived from excess IVF embryos and terminated pregnancies (abortion), questions are raised regarding the moral status of this embryonic material and its human dignity. Interestingly though, as also discussed in the next section, tissue engineering is often described as 'a less conflicting alternative for the future of regenerative medicine' given its current focus on adult stem cells rather than embryonic ones (Henon 2003: 27).

Related concerns about cell source include the use of animal-derived material in tissue engineering, reviving issues from the xenotransplantation debate such as the breeding of animals solely for human benefit and animal welfare issues more generally (Frey 2002). The use of xenogeneic material also illuminates critical concerns such as pathogens posing safety risks for the treated individual but also for the public in general. The risk of potential retroviral contagion thus calls for a need for balancing individual treatment benefits versus collective risks (Bach et al. 2002; Welsh and Evans 1999). Furthermore, the use of animal (derived) material raises issues of identity and personality on behalf of the recipient of these tissues or cells, and on the relationship between humans and animals, not to mention possible religious concerns regarding the material composition of these products. The ways in which interviewees regard these issues in relation to drafting regulation are discussed in chapters to come.

7.5.2.2 Clinical concerns

Also in the phase of therapeutic application, in an experimental setting or as part of more routine clinical use, diverse ethical concerns have been raised. As discussed under the heading of clinical risk, lack of clinical evidence and debated therapeutic effectiveness also have a socio-political component in that it is considered unethical to offer treatments against high cost for which no or insufficient long-term evidence exists of therapeutic benefit. Two issues are dominant here, one relating to the set-up of clinical trials and the other to patient access to potentially beneficial technology.

In the absence of unified standards and regulation, it has been argued that clinical trials are the best alternative currently available to test the general

safety and efficacy of products. As with many medical interventions and research involving human subjects more generally, these clinical studies pose restrictions on design and conduct, in particular in relation to concerns about the protection of health of participants, the overall balance between risks and benefits, issues of data protecting, traceability and privacy and the notion of obtaining proper free and informed consent of participants. Fundamental ethical principles include respecting the moral agency of subjects (including protection for those with diminished autonomy), fostering the best interests of subjects while avoiding unnecessary harm, and promoting principles of justice and equity between those who benefit from and those who bear the burdens of research. With respect to informed consent clear and sufficient information should be provided about risks and benefits, and making sure people enrolled in the trial are competent to participate and do so without coercion (Brannigan 2001). This can be problematic though when vulnerable groups are involved such as children (see for example trials for tissue engineered heart muscle) or mentally less able patients (e.g. trials for Alzheimer). Most notably it has been argued that true informed consent is debatable in the case of tissue engineering, where many risks are uncertain and long-term consequences unknown in terms of effectiveness and sustainability. In addition, it has been demonstrated how many health professionals are not aware of the precise material composition of tissue engineered skin products and dressings, thus being unable to provide full information to patients about the treatment and unaware of possible cultural or religious sensitivities around the use of these products (Enoch et al. 2005).

In addition to the ethical conduct of clinical trials, issues have been raised about the provision of equal access to tissue engineering treatments in the context of limited resources of health care systems (Bock et al. 2005). As discussed earlier under clinical and commercial risk, many tissue engineered products are not currently reimbursed by national healthcare systems in Europe, also due to high cost of these applications, thus creating a potential for social and health inequalities. The principle of distributive justice requires equity, so that all potential patients have reasonable access to treatments, but this principle can be seriously challenged when only the more affluent patients can benefit (Brannigan 2001). Especially given the substantial amount of public

funds into this area of research, one could question the legitimacy of a structure where only privileged parties can benefit from tissue engineered applications.

7.5.2.3 Commercial concerns

An extensive set of moral dilemmas with human tissues and cells relates to the commercialisation aspects of the technology and use. One concern addresses the motivation of people involved in tissue engineering research and development, more specifically when working under pressure of expectations for commercial success and profit. Especially given the close ties between science and business in this field, conflicts of interest could trouble the view of patient and public health, where one could question the priority strategies for developing treatments that might be more profitable than medically urgent. Related to this is the issue of patenting of tissues and cells that have potential commercial value, and whether or not the donors of these cells have patent rights when their tissues and cells reap financial gain for (commercial) product developers.

Commercialisation of human tissue furthermore links in with discussions about the nature of donation, where in Europe strong belief exists in voluntary and unpaid donation as an act of solidarity. While commercial use of biotechnology products is often considered ethically legitimate on the condition of full informed consent of the donor, and as such the tissues and cells become company's property, commercial benefit for donors is to be avoided on the basis that it could stimulate commercial exploitation of the human body, foster notions of the human being as an object or harvesting source of organs and tissues, and undermine solidarity. Altruistic unpaid donation is also favoured to avoid exploitation of the most vulnerable social economic groups to donate primarily for financial reasons. But a strong tension exists between the non-commercial nature of donation and the commercial use of the resultant products - including the profit aims of its developers (Furness 2004). As discussed later in the analysis of the SANCO Directive, the nature of donation was one of the most debated issues.

Most notably in this respect, the commodification of body parts in novel therapeutic applications has been discussed (Dickenson 2002; Lock 2001;

Rajan 2003; Sharp 2000; Wilkinson 2000). When human tissues and cells are processed and manufactured some amount of value is added that translates them into tradable entities or commodities for exchange on the market place. Acknowledging the growing capital value of biological fragments, some have argued how a margin of 'biovalue' is being created by engineering tissues and cells (Waldby 2002).

As also discussed under regulatory efforts in this field, debate exists about the degree of manipulation of tissues and cells, thus drawing boundaries between more traditional tissue banking activities and commercial endeavours to create these products. This institutional divide also highlights different value systems and cultural connotations between for profit and not-for-profit models of providing these services and products to patients. Furthermore, the tension between unpaid donation and commodification of tissues and cells has refuelled the discussion about the basic act and nature of donation.

So far, documented ethical dimensions have been discussed over different risk domains. Within the different risk domains it can be argued that the origin of cells is the most dominant issue of technological risk, while proper clinical trials design and consent are most pressing in the category of clinical risk. Commercially related issues such as commodification are reflected in commercial risk. Added to this three-way classification could be conflicting ideas about identity and personhood, of what it means to be human in the context of implanting tissues and cells from different sources, and in how far the body can be seen as both object and subject (Kent 2005). The conception of oneself and of being human might change if the body consists of replacement parts and is considered 'renewable' (Bock et al. 2003: Satava, 2002).

The notion of risk is intrinsically connected to moral concerns of tissue engineering technology, as it incorporates diverging views about acceptability and the distribution of risk over different levels, and raises questions about accountability and responsibility and about what is justifiable. Especially in the face of uncertainty about implications and long term risks and safety, ethical considerations around tissue engineering technology are paramount.

Interestingly though, only a small but narrowly defined selection of issues features in interviewees' accounts. When asked about potential ethical concerns around use or implications of tissue engineering technology, the majority of core R&D constituencies expresses how in their view tissue engineering largely stays clear from ethical or moral dilemmas. Some interviewees, mostly clinicians, have expressed the problematic nature of clinical trial design and gaining proper informed consent. Others have referred to possible religious concerns, but this was phrased in relation to xenotransplants rather than the inclusion of animal derived material in tissue engineered applications. There is one large domain though over which interviewees do worry: the potential use of embryonic stem cells in (future) tissue engineered applications. Although scientifically largely uncontroversial, according to these interviewees, the impact of embryonic stem cells therapies in the public eyes is fore grounded as shared concern. It is to these perceptions that we will turn next, because these provide the backdrop for interpreting the shaping of EU regulatory policymaking, where the value of these particular concerns has followed different tracks.

7.5.3 Interviewees' accounts: moral concerns in tissue engineering

> I don't see perhaps to such a great extent the ethics around tissue engineering... I see that string of people in the clinic in the morning, you know, waiting for this answer that [they] think medicine can give them. (Clinician in wound healing Co2, 2003)

Overall it can be argued that ethical issues have been largely overlooked by interviewees in this sample, with minor exceptions.[53] For example some respondents have pointed out the problematic design of clinical trials. The interviewee below (M-EU1) is based in a commercial setting, and explains the main dilemmas:

[53] I appreciate the extensive discussion on definitions of 'morality' and 'ethics'. Here I will treat this as a largely linguistic issue, thus ignoring philosophical traditions and bypassing political thinking about precise meanings and connotations. Worse still, I use 'moral' and 'ethical' concerns as interchangeable terms - and for those interested refer to Reiss and Straughan (1996) or even Habermas (2003).

> Well, any medical product, there's always medical issues. I mean the clinical trial is an exercise in ethics. We spend a lot of time worrying about that. (...) any clinical trial is an experiment on people. So how much evidence do you have before you start, how many people do you involve, what stage do you go to the market, what clinical trials do you do after you're on the market, what claims do you do in clinical trials and how do you develop those? Because obviously within a new technology the first patients would probably be the ones – the aim is to use it in the patients without other choices, if the risks are to some extent unknown. Yes any new technology, there are huge ethical questions in medicine. (Clinical scientist in multinational industrial setting M-EU1, 2003)

In other words tissue engineering poses similar ethical concerns as any other innovative medical technology which enters the experimental clinical phase. Thus there is a strong discourse of 'in-exclusiveness' in considering this particular technology, arguing how ethical considerations are not connected uniquely to tissue engineering but part of the common medical innovation cycle with all its usual considerations and limitations. Furthermore the proper design of clinical trials is conceived here as mainly a scientific or commercial issue, without any reference to social or political implications or potential different views of patients. In a similar vein, concepts of a more moral nature remain unquestioned by most interviewees, and views are dominant that controversy is absent as long as the usual procedure of good practice is taken into account – for example in relation to informed consent as part of proper trial design:

> If it's done properly... if there's consent between people, I don't see a problem with using cells from another individual. (UK academic clinician Cl5, 2003)

The interview fragment below addresses the issue of providing the patient with full information, which is an especially strong principle amongst clinicians, while also pointing out how it would be unethical to not provide patients with access to new technology – in this case according to a reversed burden of proof of clinical effectiveness:

> You have to be upfront and say: this is what the product is. This is how it was produced. Do you want it used on you? But I think it's wrong not to make them available unless we have got absolutely no proof that they work at all and then, you know, that would be wrong.
> (UK clinician in wound healing Co2, 2003)

This view is backed by many other R&D actors, especially those in clinical practice, stating how the use of different cell sources is unproblematic as long

as the patient gives full informed consent – so in other words is aware of the procedure and the risks involved. But as the following scientist explains, patients or 'the lay public' have different perceptions of risk compared to (medical) professionals. In addition, true informed consent is problematic in the absence of certainty of both short and long-term outcomes of tissue engineering therapies:

> Communicating the uncertainties to the lay public is one of the major problems, because an individual that is in pain or immobile doesn't want to make a decision based upon statistics or probabilities. They want to make it based upon: Am I going to be better or not? And so the short term decision is often driven by the magnitude of suffering. The longer term consequences can be easily overlooked and informed consent requires both the decision to be made on both those standpoints, both short term and long term. The medical community often does not have the information available to present this information of long term consequences completely enough to for the decision to be based on truly informed consent.
> (UK academic research scientist S6, 2003)

Thus, again, the perception of unknown risks is important. As has been argued extensively in the literature, perceptions of the public about risk are different from expert views. Thus one issue is that risk can mean very different things to different constituencies, the other is uncertainty. In this case uncertainty exists over the risk of, amongst others, transmission of infection from donors to recipients, so no accurate assessment of the level of such risks can be made.

In addition to issues around experimental design of studies, a small number of interviewees have expressed how religious or cultural concerns can 'interfere' with the use of donor material, especially when xenogeneic sources are involved. For example, one scientist based at a UK university explains his work on engineered vascular grafts, and the experimental use of porcine arteries, adding how he was told after a lecture on this subject that 'this would be no good for a Muslim patient because of use of porcine tissue' (S1, 2003). Similarly, one clinician talks about his confusion regarding the exclusion of porcine material in wound healing applications in certain cultures, questioning why pig skin is not allowed in Israel (Cl-EU4, 2003).

These are considered 'typical tissue banking' issues though, echoing classical discussions about cultural and religious sensitivities in relation to cell sources

and donation. At the same time there is a strong awareness of what is considered a more controversial technology: xenotransplantation. The implantation of animal tissues or cells into humans is used as an extreme example of what tissue engineering is not about. In other words, R&D actors go a long way in explaining how clear boundaries need to be drawn between the 'separate technologies' of xenotransplantation and tissue engineering. Remarkably, these actors do not see significant ethical issues around the use of bovine or other animal-derived material, an integral part of the processing of most tissue engineered constructs.

A similar if not stronger discourse is found in relation to embryonic stem cells (ESCs). The main argument put forward by interviewees is that tissue engineering is relatively uncontroversial as long as it does not involve or is not associated with embryonic stem cell research. An interesting way of bracketing out is evident in this domain, where a sharp distinction is made between the scientific potential of ESCs and the public perception of these cells. Furthermore both within and outside the scientific community two opposing discourses are presented: one that stresses the potentiality of this cell source, and another which tempers the excitement by pointing out the risks of the technology and need for further research before clinical applications are in sight. The following interview extracts demonstrate this tension.
The first two quotes refer to the need for precaution and warn against too high expectations on the short term. The third one (S1) speaks of a near future scenario where ESCs will at some point enter the clinic. The last quotes (S4 and A-EU6) represents the view that tissue engineering will involve embryonic sources at some point, and that these will be controversial in the public eye, but that continued research efforts are legitimate:

> If we were going to introduce embryonic stem cells for example, that would be much more complicated. I mean that technology is not that advanced yet to be used.
> (Academic clinician in vascular surgery Cl-EU2, 2003)

> Well embryonic stem cell research, at this moment everybody's scared of it. And not without reason you know. We have injected these cells and tumour formation is part of the game you know. So embryonic stem cells you have to do quite some science.
> (European clinician involved in start-up company CL-EU5, 2003)

> I mean, I guess, the whole thing about embryonic stem cells, growing embryonic stem cells and cloning will cause both social and ethical reasons but the kind of tissue engineering products I'm thinking of, the ones that are most likely to succeed are not those - those are going to be, sort of, second and third, fourth generation products, in my view.
> (Academic research scientist in UK tissue engineering lab S1, 2003)

> I think understanding how to use stem cells is critical. Fortunately or unfortunately, depending on your perspective, I think that inevitably moves us towards the question of embryonic stem cells and whether in the future the tissue engineering world should go down the route of embryonic stem cells to repair all sorts of tissues which gets us into all sorts of ethical nightmares... Embryonic stem cells has all the obvious ethical issues but I think we shouldn't duck those, we should tackle them... if collectively on the whole we feel it's appropriate that we should explore embryonic stem cells then I think we should go ahead and do that and if they reach clinical use in some years' time then those who are ethically opposed should simply not allow those therapies to be used for themselves.
> (Academic research scientist in clinical care S4, 2003)

> There is no doubt that embryonic stem cells probably, leaving ethical issues apart, probably represent the best source of stem cells for tissue engineering and regenerative medicine. And there's an awful lot known now about the use [of] stem cells but they can't be used yet.
> (Scientist and European expert advisor A-EU6, 2003)

The discussion on ESCs in relation to tissue engineering is double-edged. On the one hand tissue engineering is portrayed as a technology that is much less controversial, because currently the science and technology behind engineering human tissues and cells largely draws upon the less contested adult cell sources. As such tissue engineering does not involve embryonic or foetal sources, which would make it a socially acceptable solution. On the other hand within the scientific community large debate takes place over the potential usefulness of ESCs and whether tissue engineering 'should go down that path'. According to many scientists this is an inevitable next step in the innovation process, but at the same time great awareness exists of the risk and safety concerns but most notably the contested nature of these cells in the public opinion. Thus an interesting form of boundary drawing takes place here, where tissue engineering is presented as a separate technology, not to be misunderstood as or confused with ESC research, while at the same time it holds the scientific promise of more and better therapeutic applications which should be pursued. From a regulatory perspective this ambiguity is problematic though, because legislative efforts focus on current application areas of the

technology while also necessarily have to provide flexibility in order to keep up with technological innovation and to avoid a regulatory lag.

As a last observation, it can be argued that the hierarchy of risk as discussed earlier in relation to the different cell sources also applies to ethical dimensions. Many interviewees link the degree of (potential or perceived) moral controversy with the particular cell source used, where autologous sources represent the least contested category and embryonic ones the highest. Thus a parallel can be dawn between risk and safety concerns according to interviewees and the 'ethical nightmare' grade attached to these sources. Put simply: safer cells sources are also less controversial. Or as the following interviewee explains:

> Scientifically, especially from the immunological point of view, autologous is better. And from the ethical point of view autologous is far, far better I think.
> (Scientist and European expert advisor A-EU6, 2003)

There is one exception in this respect, which concerns the question whether embryonic stem cells are rated as more controversial, and higher in the ethical risk hierarchy, than xenogeneic cells. This notion is also relevant in relation to the regulatory debates around tissue engineering. Interviewees in the R&D part of the innovation cycle have expressed concerns over xenotransplants, but they do not include animal-derived material in this definition. For these respondents embryonic sources rate top in the moral controversy ladder. As discussed in the next part of this thesis, concerns over including most notably ESCs (and cloning techniques to derive these cells) in the scope of the SANCO Directive on human tissues and cells have influenced the direction but also timeframe of this regulation. The main reason for the delay of this Directive relates to the long and controversial discussions over in- or excluding ESCs under its scope. But also the use of xenogeneic cells has stirred debate within EU regulatory bodies and beyond, again affecting the course of legislative events. Discussion over these cell sources became more prominent in the tissue engineering product regulation by DG Enterprise. This illustrates the dynamic relationship between risks of technology and ethical considerations surrounding its potential use.

The remaining part of this thesis analyses risk regulation in tissue engineering, where also issues of a moral order are foregrounded. In contrast to the limited awareness of R&D actors, during the policy shaping process many concerns have been expressed over the ethical and health implications of the use of human tissues and cells, and of its manufactured offspring. These concerns are part of a broader risk assessment and risk management frame, with organised interests around including or excluding particular items and selective agenda-setting, thus entering the politicised domain of risk regulation of tissue engineering in Europe and of drawing boundaries around the social and political acceptability of the technology.

8 Constructing regulatory boundaries

This chapter marks the transition from risk to regulation. It presents my conceptual concern with notions of 'regulatable risk' and uncertainty in a regulatory society. I describe the implications of this 'shift' from risk to regulation in analytical terms, while the second part of this chapter contains a short empirical introduction to the specific legislations that I cover in this research. The last section gives an overview of what to expect next and how I conceptually approach these themes.

8.1 From risk to regulation: conceptual concerns

In the last few chapters attention was focussed on the framing of risk issues by core R&D actors in the early innovation process of tissue engineering, and how boundaries are drawn and reconstructed within and across risk domains. The dynamic nature of risk is reproduced and frames are redefined yet again when risk becomes the subject of regulatory controls. The purpose of this part of the thesis is to analyse how different discourses on risk translate into regulatory policy making, and what the implications are for the shaping of a regulatory regime in tissue engineering. Therefore this chapter makes the transition from perceptions of risk by core R&D constituencies to regulatory policy shaping and making at EU level. This shift of attention has several implications, which are discussed below.

8.1.1 Regulatable risk

First of all, moving from perceptions of risk to risk regulation implies a different concept and scope, and involving a different set of actors. Risks are redefined and attributed a different value when entering the policy domain. Typically, risks are characterised in terms of probability, as the possibility of unwanted or adverse effects occurring. As such, risk includes three elements: an undesirable outcome, probability of occurrence and the state of reality (Renn

1992). Deeply rooted in this concept of risk is the understanding of a causal relationship between action and effect, and the need and indeed ability to avoid or modify undesirable outcomes, which discriminates risk from danger (Vos 1999). Risk is thus both a descriptive and normative concept. Furthermore, risks can not be separated from the contexts in which they occur. Thus rather than treating it as an almost 'stand alone' or independent concept, the meaning of risk takes a different form and shape in a regulatory context, where perceptions of risk have to be translated into systematic means of risk assessment for regulatory purposes. Most notably, when risk forms the basis of regulation the notion of acceptable risk is becoming increasingly important. This is also where a new set of actors comes in, as regulatory risk is the domain of regulators, policy advisors and experts. These actors are faced with particular difficulties in interpreting risk and determining the level of acceptable risk – not the least because of ambiguity about the definition of acceptable risk.

Defining the very meaning of risk is furthermore complicated by the particular context in which regulators find themselves, where some consensus or common understanding is needed on the definition of risk, as this dictates policy solutions to risk-based problems. In other words, some negotiated common framework is to be articulated, in which interested individuals and institutions adopt a similar or at least compatible conceptualisation of the risk issue at stake. Given the diversity of risk frames as expressed in the last part, and the added complication of finding a single definition of risk for policy purposes, the question how this diversity can be incorporated into the policy domain is a difficult one.

Analysed here are professional risk frames in the light of regulatory policy making and in particular taking into account the different subsets and constructions of risk as put forward by a category of experts and professionals further down in the innovation chain, namely regulators, scientific experts and policy advisors involved in regulatory activity. Data are presented on how these professional groups have partly overlapping, but mostly alternative risk frames for the purpose of risk management and control. It is argued how for regulators and policymakers risks have to manageable and 'regulatable' in order to enter the policy domain. I demonstrate how particular risk frames and definitions are

adopted for inclusion in policy and practice, while others are neglected or downplayed as not being suitable for control and management. In this way the transition - and often taken for granted fluent cause or linear logic - from risk assessment to risk management is redefined. I consider this in terms of boundary drawing and the articulation of particular powerful or dominant risk discourses, where certain arguments are fore grounded and others 'boxed out' in favour of what is perceived to be belonging to the regulatable domain – and more generally how in this process translation the risk boundaries that are formalised are different from those acted upon in the shaping of regulatory policy.

Thus an important shift is that from 'isolated' risk to 'acceptable' risk for policy purposes. In the regulatory process scientific data are gathered, and systems and procedures designed to assess and manage risk. Built into this is the understanding that risk is not an abstract notion of probability of harm anymore, but related to specific processes and products that are considered 'safe' when its associated risks are judged to be acceptable. The regulation of risk, especially in the health and safety domain, encompasses estimations of both a scientific and social value, both of which are subject to ongoing change and adaptation. Furthermore, as also outlined earlier, risk assessment is complicated by factors of uncertainty and controversy, where outcomes or possibly harmful effects are difficult to estimate and predict, effectively creating uncertain risks. The implications of controlling risk in times of uncertainty and complexity are also subject of investigation in this part.

8.1.2 Uncertainties in the regulatory society

With the proclaimed 'risk society' (Beck 1992) new kinds of risks, created by modern industrial society, came under the attention of sociologists: risks that are catastrophic in effect, unknowable in advance and collective in their incidence. These risks are more difficult to control on individual level, and perceptions of increasing risk have called for more elaborate regulation to maximise safety and protect consumers and citizens against potentially risky substances.

In the risk society risks have become more global. Rather than representing some simple reality, risks have become a type of 'virtuality' which leaves society to deal with probabilities and potentialities (see also Ganchoff (2004) in this respect) of risks that might become disasters at some point in the future. Furthermore these risks are no objective and quantifiable entities, but risk calculations entail values. Another feature of the globalised risk society is that rational attempts to control risk are overshadowed by a broadening range of uncertainties. Finally the globalised character of these uncertain risks means that nation states are no longer perceived to be the best risk managers (Irwin and Michael 2003).

Thus the risk society has created a regulatory society, where regulatory action involves the assessment of risks associated with specific substances or products and based on this are regulatory decisions on how to manage these risks. While adopting a framework of risk as the basis for regulatory action has remained largely unquestioned, the type of risk to take into account for these provisions has stirred debate (Newell 2002a, 2002b). Risk is not a generic category, and some have argued how the selection of particular risk issues reflects the willingness of the state to accept responsibility for certain problems (Levidow et al. 1996). The level of acceptable risk forms a typical basis for regulatory action, but it also constitutes a very difficult notion to translate into policy because of the social constructive and dynamic character of what is perceived as acceptable risk at one point in time and space. Thus acceptable risk is both a political and regulatory tool, both a scientific concept and a policy objective, belonging to the domains of both risk assessment and risk management. The acceptability of risk then becomes a regulatory instrument in determining which risks society can take on, and which as such implicitly harbours a ranking of norms and values (Vos 1999). In this way, risks cannot be isolated from social and political questions about acceptable levels of risk and uncertainty.

Central to regulatory frameworks are standardised approaches to assessing potential risks to human health (and the environment). The development of simple and standardised procedures in order to create uniform and harmonised regulatory policy can be considered part of a narrow form of technically based

risk assessment (Scoones 2001). For regulators standardised regulatory approaches are handy tools, as they save time and trouble in avoiding duplication across countries, where regulatory officials can rely on mutually agreed best practices and consensus over data. Standardisation is also supposed to reduce opportunities for arbitrary regulatory discretion. For industry, as also outlined later, harmonisation provides clarity and access to a single market for their tissue engineered products. The promotion of global trade is one strong imperative for standardisation approaches, and especially the WTO has been influential in lobbying the case for universally agreed regulatory policies. Finally, and this has also been used as rhetoric device in tissue engineering, investment in technology might be encouraged when standardised regulatory procedures are in place, as these limit ambiguity and uncertainty. As pointed out in this respect, 'with uncertainty surrounding regulatory policy making, investors may shy away from the necessary up-front investments in technologies if there is a chance of no payback following regulatory approval.' (Scoones 2001: 26).

Different risk assessment approaches have been called upon for regulatory purposes. Whereas risk assessment, as a way to identify and measure the actual extent of risk, is usually seen as an endeavour in the science domain, risk management is considered a tool for policy makers in the process of deciding on measures to reduce risk. Regulatory policy includes both, though the distinction and boundaries between risk assessment and management are often blurred. Most notably, the exact means and tools for both the assessment and management of risk are under constant debate, which the case of tissue engineering regulation clearly demonstrates.

One observation also highlighted in accounts on the risk society, is that technological risks have become more difficult to assess. From a technical risk assessment point of view risks are defined as the probabilities of physical harm due to given technological or other processes. But risk is more than merely probability times the magnitude of the hazard (Krimsky and Golding 1992). Risk has many dimensions, including immediacy, severity, reversibility and spatial and temporal distribution (Stirling et al. 1999). This makes a single measurement of risk problematic, especially where it concerns modern

technologies (Scoones 2001). Modern technology has created risks that are more complicated and uncertain, more far reaching and invisible, more intense and uncontrollable. Furthermore, risks can not always be articulated (Krimsky 1991: 212). Risk as related to modern technologies needs to take into account the complexity, uncertainty and ambiguity inherent in the interaction of modern technology, society and the environment. Risk analysis of these technologies, it is argued, should not just aim to quantify undesirable consequences of technologies, as done in standard risk assessments, but also evaluate unintended impacts. In a similar vein, risk management strategies should not be limited to applying a set of universal rules and principles but encompass contextual or situational aspects in order to take account of degrees of uncertainty and ambiguity.

Yet many conventional risk assessment strategies are ill-equipped to take into account these diverse criteria in the face of uncertainty and indeterminacy, as they are usually based on the assessment of a limited number of criteria where technical assessments are seen to be sufficient (Krimsky and Golding 1992). In other words, more complex types of risk assessment are required (Krimsky 2000). In this context also the need has been expressed for an extension of technocratic risk assessment to encompass the broader societal concerns raised by the far-reaching effects of technological risk and uncertainty (Scoones 2001). Society requires a 'broader' socio-political and economic assessment of the risk of its technologies.

But in the regulatory reality of limited time, budget and expertise to develop policy, a narrowing of scope is considered inevitable to get things done; "The consequence, of course, is that more complex criteria are left out of the equation, uncertainties are 'black boxed', and areas of ignorance avoided ' (Sahl and Bernstein 1995 in: Scoones 2001: 18-19).

This is also where the relationship with broader questions of norms, ethics and values come into play. An important notion concerns the inclusion and implications of dealing with socio-political and ethical concerns related to tissue engineering technology. As we have seen, these concerns have been largely deprived of in accounts of R&D actors. But social and ethical dimensions are

paramount and form an intrinsic part of not just the construction of technological, clinical and commercial risk frames but also of managing uncertainty and complexity in this domain. These socio-political and ethical issues are relevant in the face of policy shaping, where the main concern is with delivering implementable solutions to narrowly defined science-based problems (judicial default mode). As demonstrated in the next chapters, also in tissue engineering a technical rather than ethical framework is called upon in attempts to reduce uncertainty and complexity in this domain, although large variability exists in the ways in which 'ethics induced' ambiguity is managed institutionally across the different regulatory initiatives. Most notably attempts are undertaken to exclude ethical concerns from 'science-based' regulation. But as also illustrated, these debates represent a complex mix of arguments where technical and ethical considerations of risk and safety are intimately connected. This research departs from the assumption that ethical considerations cannot be segregated from techno-scientific assessments for regulatory purposes, thus questioning the current institutional set-up of tissue engineering regulation in the EU.

This is not a straightforward assumption though. As has also been demonstrated for other innovative technologies (see for example: Levidow and Carr 1997; Salter and Jones 2002b), the regulatory process of tissue engineering swings between technical and social concerns. This development is also echoed in the institutional management of risk, where technical risk assessment is treated as a separate task from socio-economic or ethical analyses. In order to institutionally manage complexity and uncertainty in technological risk assessment, responsibilities for policy and regulatory choices are often divided up, 'with environmental and health appraisal seen as the domain of scientific assessment, while ethical and moral considerations are allocated to other areas of professional expertise and social and economic issues are deemed best dealt with by consumer choice and market response' (Scoones 2001:19). By separating technical assessment from socio-political and ethical dimensions, the role of the independent and objective expert advice becomes more prominent.

8.1.3 Translating risk into regulation

To sum up, this part of the thesis has three conceptual concerns. First of all, I am interested in the ways in which the transition is made from perceptions of risk to the regulation of risk. How do risk discourses translate into regulatory policy making in tissue engineering? In what ways is a 'fit' created to make risks 'regulatable' and manageable? Which boundaries are drawn around the regulatory domain? And what are the implications of these boundaries for incorporating risk concerns?

Thus from perceptions of risk we move to the assessment and management of risk for regulatory purposes. This introduces a new set of actors; a shift from core R&D actors to those individuals and groups in charge of agenda setting and policy shaping for regulatory decision making. This includes regulatory professionals and advisors, plus other actors actively involved in this part of the innovation cycle, such as scientific experts, manufacturers and tissue banks. With these new players, also new interests are represented and new agendas introduced, and with them different values about what risks should be regulated and the very meaning of the aim of regulation.

My second conceptual concern encompasses a political analysis of who is involved in regulatory decision making, and what this means for representation of interests, and also refers to broader concerns that enter the debate on tissue engineering regulation. Most notably this relates to the role of socio-political and ethical arguments vis-à-vis technical concerns in regulatory policymaking. This is placed in the perspective of the translation of technological, clinical and commercial risks as described in the last part. Focusing on actors in regulatory decision-making means analysing a process where different subjects are being prioritised in terms of risk and safety, where underlying value systems are made explicit and where diverse institutional tensions exist between these different actors and what they represent. Discussions about acceptable levels of risk and uncertainty, and of the trade-off between risk and benefit, positions regulation in the heart of a domain where technical issues are intertwined with socio-political and ethical dimensions. This is about entering the politicised domain of risk regulation of tissue engineering in Europe, with organised interests around including or excluding particular items and selective agenda-

setting, and of drawing boundaries around the social and political acceptability of the technology.

To unravel these dimensions I analyse the two key regulatory initiatives at EU level: the SANCO Directive on quality and safety of human tissues and cells, and the Tissue Engineering Regulation by DG Enterprise. In other words I am interested in the 'politicalisation' of risk for regulatory purposes, and in the tensions that arise between different agendas and views on how to go about regulating risks of tissue engineering technology. This is based in the context of a need for broader risk assessment and management strategies in attempts to deal with risk and uncertainty of tissue engineering technology in a policy context.

This leads to my final and more encompassing concern, which is that with regulatory science as a way to look at science and policy as separate but intertwined domains and with the role of expertise in regulatory decision making. The EU system is mainly based on scientific and technical advice, and tissue engineering is a prime example of where scientists are called upon to provide advice or an expert opinion in all kind of committees or commissions. But also the influence of ethical advisory groups, such as the European Group on Ethics (EGE), on European governance of health technologies is significant. Some speak of bioethicists as the new regulatory 'experts' in this respect (Salter and Jones 2002b: 325). My analysis includes an account of this alternative format of expert knowledge.

8.2 In short: the SANCO Directive and Enterprise Regulation

In this context, the next chapters discuss the two EU initiatives that lie at the heart of the making of a regulatory regime for tissue engineering. The first one concerns European regulation on quality and safety of human tissues (SANCO Directive), while the second is a product based approach for the marketing of tissue engineered products in the EU (Enterprise Regulation). These legislations cannot be seen as independent of the broader regulatory framework and debate on innovative biotechnology. The introduction has

focused on the dual role of the European Commission in both promoting and regulating European biotech, while chapter 2 illustrated the tensions between health protection and fostering competitiveness and trade in regulatory policy. These developments provide the context for 'the making of' of the respective regulatory initiatives.

These legislations are not described in chronological detail, which is why the next section gives a brief outline of timelines and main steps in the respective legislative cycles. A more detailed account of this is provided in appendix 2. The SANCO Directive and the Enterprise Regulation are in different stages of the legislative procedure, which has implications for the data coverage and for the scope of discussion in this thesis.

8.2.1 The SANCO Directive 2002-2004

The first main legislation is "Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells", also known as the 'Tissues and Cells Directive' or TCD (DG SANCO 2004). In this research I refer to this as the SANCO Directive, by its initiator DG SANCO, the Health and Consumer Protection Directorate General of the European Commission. The Directive covers all tissues and cells of human origin intended for application in the human body, and introduces quality and safety standards across the European Union.

The initial proposal for this Directive was published in June 2002. This document was forwarded to the European Parliament (EP), which had two readings over the proposal. Early 2003 two public hearings took place, led by Peter Liese, who was appointed rapporteur. The first discussion of the final report took place during a plenary session of the Parliament in April 2003, after which the Commission had to modify the proposal over a number of amendments. In July that year the Council formulated its common position, to which the Commission responded in a Communication. On 16 December 2003 the second reading in the European Parliament took place, in which again a number of amendments were made before the proposal was adopted. The

European Council adopted the proposal on 3 March 2004, with all the revised amendments proposed by the European Parliament in second reading, while also the Commission accepted the amended version. The final act was tabled on 31 March 2004, with publication in the Official Journal of the European Union on the 7th of April 2004. From this date Member States have two years time to implement the Directive in national policy and legislation. Thus on 7 April 2006 the Directive is to be operational in all 25 Member States. There is one exception to this implementation date, as the Directive contains a provision that allows Member States to not apply the Directive until April 2007 if they already have national regulations in place (with the UK being an example in place).

While the SANCO Directive has completed its legislative cycle, regulatory activity continues over the details. In addition to this general framework of principles, the Commission provides further technical requirements during the comitology procedure, for which consultation rounds are organised. This concerns two Commission Directives, the so called Technical Annexes, which outline detailed standards that organisations working in the field need to take into account and that apply to quality and safety aspects of all human tissues and cells. The first Technical Annex was adopted in February 2006 and covers technical requirements for the first phase of the donation and procurement process. A proposal for the second set of technical requirements is expected to be adopted around the summer of 2006, and will cover the second phase, including storage, processing and preservation criteria for tissues and cells.

In this research I focus mainly on the later stages of legislative development, taking the proposed Commission Directive of June 2002 as starting point and analysing the debates in the European Parliament and Council running until April 2004. I furthermore briefly consider the comitology procedure that followed upon adoption of the Directive, in which experts define the technical details of the main legislative framework. Given that implementation of this Directive is a future exercise, my research is necessary limited to an analysis of the policymaking process.

8.2.2 The DG Enterprise Regulation 2002-2006

The SANCO Directive covers everything to do with the process of getting the tissues and cells that then become starting materials for tissue engineered products. The second significant initiative concerns the placing on the market of tissue engineered products in EU Member States. In June 2002, simultaneously with the initial SANCO proposal, DG Enterprise, with its aim to promote completion of the single market and competitiveness in the EU, issued a public web consultation document which discussed the means and scope of legislation covering tissue engineering products. A summary of responses was published in January 2003. A good year later a second consultation round followed, requesting input on a specific future regulatory framework for human tissue engineered products, which closed in April 2004. The outcome of this consultation exercise led to a first draft regulatory framework, which was presented on 6 April 2004 in Brussels: a Regulation rather than a Directive (as was anticipated) or any other legal instrument. In July 2004 the summary of responses was published, and then it went quiet for a while.
Another year later, on 4 May 2005, DG Enterprise published a third consultation document, a 'proposal for a community regulatory framework on advanced therapies', together with the details of the full proposal for a Regulation, outlining the regulatory strategy. Following the regulatory regime already in place for pharmaceuticals, tissue engineered products were now part of a group of technologies called 'advanced therapies', which also include gene therapy and somatic cell therapy. Until 20 June 2005 the public was invited to comment on this draft proposal, and in the meantime several stakeholder meetings were organised with representatives from industry, Member States and national experts. Also a general stakeholders meeting was held in Brussels on June 7 that year.

In addition to these three consultation rounds an impact assessment study was conducted, and two supporting studies from the Joint Research Centre of the European Commission were carried out to assess the potential impact of the proposal on the tissue engineering market. The diverse initiatives led to the presentation of the final 'Proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004' (DG Enterprise

2005f). This proposal was adopted on 16 November 2005. In this study I refer to this as the Enterprise Regulation, although the proposal has not reached the end of the legislative cycle yet.

Currently, the proposal goes through the so called 'co-decision' procedure, where it is delivered to the European Parliament and to the Council. It will also be transmitted to the European Economic and Social Committee and to the Committee of the Regions, for consultation. Although hopes are expressed that this process will be finalised by the end of 2006, it is unclear when the Regulation is adopted to become law.

In the meantime some preparatory work is done, most notably in relation to a new expert Committee to be installed to evaluate tissue engineered products and other advanced therapies (the CAT) and to advice on marketing authorisation. The first meeting of this Committee is currently scheduled for July 2006. Also already in December 2005 a rapporteur was appointed to prepare a report for discussion in the European Parliament, the Slovakian Mikolášik Miroslav from the Christian Democrats (PPE-DE), while the co-rapporteur is Locatelli Pia Elda (PSE). A public hearing in Parliament was organised in May, while the forecast is that the first debate in the Council takes place in June 2006. The report for adoption in the standing committee in the Parliament is scheduled for 13 September, with a session for first reading on the 24th of October 2006.

In terms of data capture I am mainly concerned with the earlier phase of policy shaping, looking at the different consultation exercises and draft proposals. My main concern here is with the definition and scope of tissue engineering technology. The point of exit is the final Proposal for a Regulation that the Commission issued in November 2005, and which currently goes through co-decision in the European Parliament and Council.

8.3 Overview

This chapter serves as background for subsequent chapters (9-11) where I turn to two specific legislative initiatives that shape the EU regulatory domain of tissue engineering: the SANCO Directive and the Enterprise Regulation. I analyse how particular forms of boundary drawing take place over the scope of these legislations, focusing on how interested parties negotiate the conditions of their interactions. This reveals several tensions: amongst institutional players and professional stakeholders, between technical and ethical values they represent, in commercial and public health objectives, and last but not least between risk perceptions and what is considered to be belonging to the regulatable domain. Thus these chapters are concerned with the main participants in regulatory science and their conflicting views on how to shape regulation. Here boundaries are drawn between different value and belief systems (such as public health and commercial concerns – tissue banking and industry) as represented by these interest groups. It becomes clear how interested parties draw boundaries around the regulatory world itself, thereby excluding certain risks, while also within the regulatory domain boundary demarcation takes place in negotiating the scope of the legislation. In the SANCO Directive this is witnessed in attempts to establish fixed boundaries around the legal remits of the EU in regulating tissues and cells, thereby ruling out ethical concerns. In the Enterprise Regulation an opposite trend is visible. Here the scope of the legislation is not narrowed down to purely 'technical' matters (versus socio-political and ethical stances) but are technical definitions of the technology extended in order to accommodate more recent innovation, including tissue engineered products based on animal cells. Thereby the legislative scope is widened to allow potentially controversial cell sources entering the European market.

Thus my analysis of these two EU legislative initiatives focuses on two particular forms of boundary drawing: one over the role of ethical arguments in shaping this legislation, and the other over the definitions and scope of the Directive. The next chapter (9) discusses ethical concerns, and how participants in the policy shaping stage of the SANCO Directive have

systematically renegotiated the legal and practical boundaries of the legislation over ethical considerations. This chapter also demonstrates a change in focus of the Directive, under influence of industrial interest groups, thereby connecting the SANCO initiative with the product Regulation by DG Enterprise. Chapter 10 takes up ethical considerations again, this time by focusing on contested cell sources under the Enterprise Regulation, analysing how these are dealt with differently from SANCO. The last and brief chapter (11) reflects on these developments and discusses implications for the future regulation of tissue engineering in Europe.

9 The SANCO Directive: Regulating ethics

> It's really a question of whether you want to bring ethics into it or not (S4, 2003).

Analysis of the legislative cycle of the SANCO Directive has brought to the fore two key concerns that have dominated the debate: the scope of the Directive and the role of ethical principles. These dominate the drafting of legislation and rules for implementation. This chapter first discusses ethical concerns, and how participants in the policy shaping stage of the Directive have systematically renegotiated the legal and practical boundaries of the legislation over ethical considerations. The last section looks at interest representation in relation to the changing scope of the SANCO Directive, while in the next chapter I return to these issues in discussing the Enterprise Regulation.

9.1 The subsidiarity excuse

An important starting point for a discussion on 'regulating ethics' is the initial phrasing, in the proposal for a Directive that the Commission adopted in June 2002, of the remit and responsibilities of the EU in regulating human tissues and cells at Community level. The proposal explicitly refers to the legislative basis of this Directive, Treaty article 152 for public health, where the role of the Commission vis-à-vis national Member States is clarified: the principles of subsidiarity and proportionality are maintained, which means that for health related matters the responsibility of Member States is fully respected. Because of the trans-national dimension of the use of human tissue and cells within the Community, a common approach was developed. This does not prevent Member States from maintaining or introducing more stringent protective measures (DG SANCO 2002). This is an important principle as it gives Member States a possibility to diverge from the Directive, based on public health and safety considerations. However, as analysed below, resort to the subsidiarity

principle was part of an attempt by national governments to ban contested cell sources from entering their territories.

In the scope of the proposed Directive it is defined that, apart from some exclusions as also discussed later (see under scope), 'all other types of tissues and cells are covered.' This means that the provisions of the Directive apply to all cell types, including germ cells, foetal tissues and cells and embryonic stem cells. The Commission is also explicit in its view that some of these cells pose ethical concerns in Member States. A memorandum attached to the proposal states how 'to date, there is no consensus among Member States upon which basic harmonized decisions at EU level can be taken with regards to their use or prohibition' (DG SANCO 2002: 5). In other words the Commission does not prescribe any rules for the use or non-use of controversial human cell types, other than that they would be subject to the Directive when Member States choose to authorise these applications. This section demonstrates the implications of this provision.

9.1.1 Ethics on stage

The first time ethical concerns were openly expressed was during a set of public hearings that the European Parliament organised early 2003. Here the Commission's proposal was discussed with representatives from the European institutions, industry associations, NGOs and the scientific community, as well as the audience (EurActiv 2003c). Especially government officials flagged up issues around informed consent and donation, which the Commission proposed to be voluntary and unpaid. Extensive discussion took place over financial compensation of donors: whether donation should be considered an act of altruism (Christian Action Research and Education) or if donors should receive a payment (trade body EuropaBio). During a subsequent hearing patient representatives questioned the basis of some of the ethical considerations underlying the Directive. One speaker brought up whether technical aspects can be completely held separate from associated ethical issues, strongly disagreeing with 'the idea of leaving them simply untouched only because no consensus can be reached easily'. This patient representative continued to argue how harmonising technical requirements while localising

ethical problems would 'eventually jeopardise the validity of the basic right of physical integrity in all European societies' (Kruip 2003). This is an interesting notion, and a fierce critique towards the Commission, that has only focused on provisions to harmonise technical aspects of human tissues and cells, without addressing any ethical problems associated with these materials.

These ethical concerns dominated debate during the first reading of the Commission proposal in Parliament, in March 2003. The responsible standing Committee – the Committee on the Environment, Public Health and Consumer Policy – tabled 159 amendments on the proposal, mostly concerning the scope, nature of donations, traceability and anonymity, donor consent and ethical issues (EurActiv 2003b).

During this passage through Parliament ethical issues caused most discontent. The key phrase 'respect for fundamental ethical principles' was a recurring addition to many of the original articles in the proposed Directive. A broad set of amendments was accompanied by a call on Member States to prohibit research on human reproductive cloning and on research designed to create human embryos solely for research purposes or to supply stem cells, including by means of the transfer of somatic cell nuclei. Moreover MEPs stated that no tissues or cells derived from human embryos should be used for transplantation: cloned human embryos, and human/animal hybrid embryos produced by cloning, including cells and tissues derived from them, should be excluded as sources of material for transplant. These statements are repeated in different forms and filter through in several amendments.
Other articles give Member States the right to prohibit use of 'cells of a certain origin' and to ban the import of cells or products derived from them, based on the subsidiarity principle. Amendment 30, on prohibiting research on human reproductive cloning and on the creation of embryos as stem cell suppliers, gives the following justification, which illustrates the underlying rationale of many others:

> The European Union like the Member States should regulate and focus research efforts on techniques that do not undermine respect for life and human dignity and should prohibit any technique involving the use of human beings as a material, even at the embryo stage.
> (European Parliament (EP) 2003c: 23)

In other words the MEPs designed a long list of amendments that addressed ethically sensitive cell sources and techniques. Arguable the role of the rapporteur, the German MEP Peter Liese from the Christian Democrats (EPP-ED), was decisive in foregrounding these ethical issues. In an explanatory statement that was attached to the report for discussion in Parliament, rapporteur Liese made a strong plea for incorporating these principles in the Directive by referring to the legal possibilities to do so based on other Community legislation ('case law'):

> The view is expressed that it is not appropriate to regulate ethical issues such as informed consent or voluntary unpaid donations under a European directive. Your rapporteur firmly rejects this view. Discussion at European level, e.g. within the context of the Biopatent Directive, show that it is not possible to take a decision on regulating genetic and biotechnology without duly taking account of the ethical aspects. It is argued that this is not possible on legal grounds. However, the Directive on blood products, the Directive on clinical testing and the Biopatent Directive are unequivocal evidence that matters which are generally regarded as ethical issues can be regulated by the European Union on the basis of various articles of the Treaty. In addition, in the case of the present proposal, blood safety and quality of cells and tissues cannot be considered irrespective of the ethical issues, such as voluntary unpaid donations and informed consent, as it is obvious that the manner in which cells and tissue are obtained have an effect on quality and safety. (European Parliament (EP) 2003c: 55)

This statement reveals the problematic nature of regulating ethics, given the legal limitations in incorporating these diverse concerns in Community law. Here this issue is only addressed in relation to the nature of donation (voluntary unpaid) and the conditions for informed consent. It was only later in the explanatory statement that the use of human embryonic stem cells (ESCs) and cloning of embryos were discussed. The rapporteur reminded his fellow MEPs of the majority vote in Parliament against producing embryos for research purposes, while recognising how more disagreement exists over the use of ESCs in labs.

During the plenary discussion and Parliament vote in April 2003 some consensus was reached over excluding human reproductive cloning from the Directive, but strongly opposing views were expressed over the use of ESCs. Below are two extracts from MEPs illustrating these positions:

> While the European Union has no competence to ban the therapeutic use of embryos or embryonic stem cells, it certainly has no obligation to okay this kind of use by establishing safety and quality standards for embryonic stem cells. (European Parliament (EP) 2003a: 27)

> I cannot entirely support all the amendments tabled by some of my colleagues. Those amendments seeking, for example, to ban or restrict the use of embryonic stem cells totally are doing the European public no favours. They are not protecting human health, nor are they protecting the vulnerable (EP news 2003).

Furthermore, large discussion took place over whether it was possible to make these ethical statements at all in this particular legal way. During the Parliament debate MEP John Purvis of the Scottish Conservative and Unionist Party delivered a speech arguing how the amendments and report are lacking the legal basis to cover ethical considerations:

> There are technical difficulties concerned with consent by donors and anonymity of donors. There are highly questionable forays into areas of ethics which are irrelevant to the purpose and legal basis of this directive. Even the Legal Affairs Committee has seen fit to insert the legally undefinable term "fundamental ethical principles" into what purports to be a legal legislative text. Very importantly there are attempts to impose European prohibitions on ethical aspects of research and therapy which are clearly the subject of the subsidiarity principle and must remain the right of Member States to decide (Purvis 2003).

This legal basis was indeed problematic. In May 2003 the Commission presented the revised text of the proposal for a Directive, after consideration of the various changes and EP amendments suggested (COM (2003) 0340). Here it was stated how:

> The Commission can accept provisions related to the anonymity of donors and/or non-profit procurement. Other provisions, however, cannot be accepted as they fall outside the scope of Article 152 of the Treaty, which provides for public health protection and not for the implementation of ethical objectives (DG SANCO 2003).

Thus a substantial number of EP amendments were ruled out, most notably those which contained the phrase 'fundamental ethical principles'. Later that year, in July 2003, the Council came to the same verdict in its common position on the proposed Directive (Council of the European Union 2003: (EC) No 50/2003). The Council rejected the majority of the EP's amendments dealing with ethics, arguing that the legal basis for these in article 152 was lacking (EurActiv 2003a).

Legal principles were thus used to box out many of the EP amendments, including calls on the prohibition of certain types of tissues and cells or of processes to create these cells (i.e. embryo cloning) and ethical issues such as voluntary or unpaid donation, non-profit procurement, and consent. This provoked a strong reaction from several Member States; during a Council meeting two countries in particular, Germany and Italy, declared to reserve the right to lay down more stringent protection measures when the Directive is transposed into national law, under the subsidiarity approach and as provided for in the Directive. In other words unanimity was reached in formulating a common position in the Council, but several national delegations expressed their intention to find other legislative ways to prohibit use of specific cell sources.

9.2 Inside and outside views

The strong focus on ESCs and cloning during this part of the legislative cycle was viewed by 'outsiders' with a mix of surprise and awkwardness. An industrial developer explains how this turn of events was not entirely anticipated:

> With the SANCO Directive for example we thought that we had a pretty good view on how the vote was going to in Parliament... And the whole discussion, the whole vote was overwhelmed by a discussion on inclusion or not of R&D cells - which came out of, all the rest didn't seem important anymore, it was just that discussion, one point... And cells, when you speak about cells and tissues the debate was very easily into stem cells, very easily. And stem cells are of course embryonic stem cells, nobody seems to be knowing of different kinds of stem cells. (Corporate affairs manager in multinational company M-EU5, 2003)

In the meantime, behind Commission doors an ongoing discussion had taken place over the legal basis of certain cell sources, and in what ways the concern of several Member States could be accommodated. An EC official explains the problematic nature of dealing with ethics at EU level:

> Of course one of the issues, the ongoing discussion now between Parliament and Council, and the Commission, is the ethical issues... The

> idea is that Article 152 gives to the commission and to the European Union the power to make legislation on quality and safety. But we cannot impose member states ethical imperatives as such. So the directive covers a number of ethical principles that we consider that are the same by all the member states. Of course principles of ethics who are linked in a way with the quality and safety. But there are some ethical principles who the directive cannot go further because we have no legal basis to do that. The European Union cannot impose voluntary and unpaid donation unless we can prove with evidence that the voluntary and unpaid donation have a related link with the quality and safety. And there are a number of more principles like this. For example, consent. We can go in the consent until a certain limit and what is related with the protection of the donor. For example, use or not use of different types of tissues and cells. The classic example of embryonic stem cells. We cannot impose the prohibition or authorisation of the use of tissues and cells; that is in the hands of the member states. And of course Parliament sometimes has or would like to impose other use in the Directive but we are trying to explain what are the limits of the Treaty and what we can do or not.
> (Official at DG SANCO A-EU5, 2003)

Therefore the discussion on ethical principles was legally bound by Treaty objectives and the subsidiarity principle, which dictates that Member States have a final say in prohibiting or authorising certain cell sources on their national markets, if based on public health and safety concerns, while the EU has no mandate to interfere with these decisions (unless they pose trade barriers and disrupt the single market). This also applies to other ethical principles, implying that the Commission and Council, even if they had wished to adopt the amendments based on ethical positions, did not have a possibility to do so. Not the validity but legality of principles was at play.

But also the need for consensus and harmonisation on this controversial topic was problematic, as was hinted at in the Commission's reply to the Council's adoption. In August 2003 the Commission responded to the Council with a 'communication on the common position' (COD/2002/0128). In relation to therapeutic cloning, one of the key amendments rejected by both Commission and Council, the Commission stated that it *aimed* to prohibit the use of cells derived from cloned embryos for transplantation purposes, but because of the controversy around these applications it would be impossible to get a consistent opinion in Member States (European Commission (EC) 2003a).

While the Commission was largely entranced with the common position, industry was less so. The industry response to the Council common position, communicated via its trade associations EuropaBio and EUCOMED, was welcoming on some aspects but critical of many others. In relation to the use of ESCs industry was in favour of the subsidiarity approach, but 'in the case where Member States decide to prohibit the use of specific cell(s), industry calls for transparency and requires that the reasons for prohibition are made public' (EuropaBio 2003: 1). One of the European trade associations was very explicit in its position towards ESCs:

> [We are] of course very, very aware of the ethical issues... From EUCOMED's point of view what we have proposed is to exclude things like embryonic cells and embryos from the scope of the Directive because there is no need, indeed no need at this time to go into these ethically contentious issues. You can get perfectly good stem cells from adult sources - this is the general consensus of most researchers at the moment. So there is no need to enter into this ethically contentious area which should simplify the process of getting legislation we hope. (Representative of European industry association for medical devices M-EU2, 2003)

And as a manufacturer expresses the considerations of industry in a similar vein:

> There is clearly an ethical debate which has [to] be had because I guess tissue engineering in the future will include all manner of things. It will include stem cell research ... and there has to be an ethical debate to it. However it would be not necessarily, in my view, a good idea to include ethics within a regulatory classification come approval process because you will always have different views on ethics whereas you can only have one real way of proving your product's safety and efficacy. Ethics is a very personal thing whereas science is very defined in many ways. (Regulatory affairs manager of multinational company M-EU9, 2003)

From these fragments it is clear that also commercial providers draw strict boundaries around the scope of the Directive, but from an alternative frame with different underlying values. Not ethical concerns as such are problematic, but their role in complicating and slowing down a much needed legislation.

9.3 Trading ethics for consensus

The legislative procedure continued, and in November 2003 the amended proposal came back to the European Parliament for second reading. The course of events in Parliament was anticipated with some excitement, because it could make or break the Directive to some extent.

Rapporteur Liese produced a new report for this second Parliament reading and in preparation for the vote on the Commission proposal for a Directive, to take place in December 2003 (European Parliament (EP) 2003d). This report reflected a remarkable change: it still referred to aspects of donation (where it was argued that Member States should 'ensure', rather than merely 'encourage' voluntary and unpaid donations), but the original amendments on ethical aspects were absent. The only amendment that survived the previous version of the report was that cloned human embryos should be excluded as sources of material for transplantation.

Finally, and this is important for the later stages of the Directive, there was discussion over which topics were to be referred to comitology. As also discussed later in more detail, comitology is the EU committee system where experts fill in the technical and detailed requirements of the Directive. The comitology committee is made up of civil servants representing the Member States, and is often used as a shortcut procedure to adapt technical requirements (which are laid down in the technical annex to the Directive and not the main text) to accommodate fast changing technological developments and new scientific insights. In other words it creates flexibility to keep the technical requirements up to date. But this also means that the long legislative procedure under co-decision is avoided, because the Parliament and Council are not involved in comitology. It is for this reason that MEPs were opposed to the comitology procedure being used to decide on the conditions for donor selection, evaluation and procurement in the case of cells used for reproduction purposes. They argued that Parliament should be able to scrutinise any rules proposed in this very sensitive area. We will come back to this comitology procedure later.

During the second reading in Parliament the amendments relating to the ethical aspects were largely withdrawn or rejected, in line with the Council's common position and the Commission's assessment of this common position. In other words the MEPs dropped the most sensitive ethical aspects from their position on the SANCO Directive (EurActiv 2003d).

This was a pragmatic solution though. In the meantime a turn of events had taken place, which prevented the Directive from a legalistic impasse. With the support of other political groups, the rapporteur had started negotiations with the Council. In his address to the Parliament, rapporteur Liese explained how over the last week an agreement was reached with the Italian Presidency of the Council on a whole range of amendments, most notably around donation. This meant that the MEPs are voting over a 'package of compromises' to which the Council had already agreed with the permanent representatives. Most importantly this would imply that a conciliation procedure could be avoided if the Parliament adopts the deal.[54]

During the debate Liese made his final plea for what had become the last hiccup in ethical terms, namely to prevent the commercialisation of tissue and cell donation. Under the fresh agreement with the Council clearer rules were set over the prohibition of any direct payment for donation, and the permission of compensation of costs incurred by a donor. Under this agreement donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation, while leaving it to Member States to define the conditions under which compensation may be paid. As Liese argued in his speech to Parliament:

> It was at this point that great controversy erupted, with the Council and the Commission initially contending that Parliament's demands lacked any basis in law. We were, however, able to persuade them both that a

[54] If no agreement is reached in this stage, a so called conciliation procedure starts in order to formulate a compromise between the Council and Parliament. To this effect a conciliation committee is convened, which is composed of members of the Council or their representatives and an equal number of representatives from the European Parliament, which has to reach an agreement on a compromise text within the very short time-span of six weeks. The Commission is also represented in the conciliation committee where its role is circumscribed, however, as it can no longer withdraw its proposals and prevent an agreement between EP and Council (EIPA 2000).

> non-commercial approach was called for not only in terms of considerations of ethics, but also of health protection. (European Parliament (EP) 2003b: rapporteur address)

The health element is that medical risks could be concealed when money is being paid for donation, which could pose safety threats to both donor and recipient. Thus a ban on commercialisation is necessary to avoid trade in human tissues and cells, but to accommodate industry there is no objection to trading medical products manufactured from them.

The rapporteur also addressed that other main concern of Parliament during first reading, a call for a comprehensive ban on the cloning of human beings. As Liese explained, consequently...

> ...in the negotiations, I no longer insisted on it in order to avoid the need for a conciliation procedure. This does not, however, mean that Parliament has changed its opinion about this. I believe this to be another area in which safety considerations demand that we be very careful, and we will continue to keep a watchful eye on this in the future. (European Parliament (EP) 2003b: rapporteur address)

The agreement with the Council encompassed that existing legislation in the Member States should remain into force regarding cloned human embryos. The Directive does not interfere with their decisions to prohibit or authorise any specific type of human cells, including germ cells and embryonic stem cells, as long as such use is in line with all the provisions in the Directive 'necessary to protect public health, given the specific risks of these cells based on the scientific knowledge and their particular nature, and guarantee respect for fundamental rights' (European Parliament (EP) 2003d).

Thus in order to prevent the Directive from stalling, in the package of compromises with the Council the cloning ban was traded for the non-commercialisation provision around donation. But not entirely on Parliament's terms, as also the Commission had a say in this case. David Byrne, commissioner of DG SANCO, expressed the need 'to make it clear that this compromise solution goes to the very limit of what the Commission believes to be legally acceptable, given the restrictions of the Treaty.' (European Parliament (EP) 2003b: Commission reply)

While the Rapporteur and his Committee had come to agreement with the Council, and also the Commission expressed its willingness in reaching a solution, not all MEPs were impressed with the political pressure imposed on them to reach consensus. The debate in Parliament continued. The first extract below is from an MEP of the Christian Democrats, arguing how ethical considerations are part and parcel of Community values, while the second response is from a socialist MEP who feels the maximum has been reached already in this respect:

> It would be a big mistake to exclude ethical issues from EU decision-making, especially when we talk about a Community which likes to call itself a community of values. Besides, ethical issues rarely arise in isolation in some moral vacuum. They are ethical for the very reason that they have an effect on people's health, for example, as in this case (European Parliament (EP) 2003b: reply Korhola, PPE-DE).

> New technologies, such as embryo stem cell research, cannot be ruled out as sources of future therapies for either medical or ethical reasons. We have gone as far as we can to satisfy those people with specific ethical concerns on those issues and with regard to other new technologies. We must recognise that our primary duty here today is to ensure the quality and safety of tissues and cells that are going to be used for the relief of human suffering, as they move around the single market to various destinations (European Parliament (EP) 2003b: reply Bowe, PSE).

Therefore the rapporteur and his Committee had reached agreement behind closed doors in a get-together with the Council, but opposing views were persistent amongst individual MEPs. Notwithstanding opposition, in the end the Parliament adopted the proposed Directive in a majority vote just before the Christmas break (European Parliament (EP) 2003d).

The legislative final act, as the Directive was now officially coined, appeared on 31 March 2004. It was published in the Official Journal of the European Communities on 7 April 2004 as 'Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells' (DG SANCO 2004). This is the official date of entry into force of the Directive, while the date of transposition is 7 April 2006. Thus Member States have two years to implement the provisions of the Directive into national law.

A quick word search learns that the term 'embryonic stem cells' appears in two places: once under article 7, which lists all the particular cell sources which are covered under the scope of the Directive; and on another occasion in article 12, which states how the Directive should not interfere with decisions made by Member States concerning the use or non-use of any specific type of human cells, including germ cells and embryonic stem cells (DG SANCO 2004). The word 'cloning' is nowhere to be found in the text, nor is the term 'ethical'.

9.4 Inclusive and exclusive ethics

In the course of the policy cycle 'ethics' has become a 'political toy' that was tossed from one corner to the other. The EU trading zone for ethical considerations was enlarged in an attempt to unite (national represented) moral concerns with socio-political considerations and pragmatic policymaking, resembling tensions between cultural biopolitics and the moral bio-economy. The main ethical concerns were over the use of ESCs and of therapeutic cloning techniques in order to retrieve these cells, while during the comitology procedure also reproductive cells stirred debate. It can be argued that one reason for the delay of this Directive was exactly over these cells sources, as the Parliament tried to use the Directive as a tool to prohibit embryonic stem cell research and therapeutic cloning (Liddell and Wallace 2005). When these provisions were discarded, because the Commission felt it was not competent to legislate upon ethical matters, the focus of MEP attention shifted towards at least making sure that the Directive would include principles of voluntary unpaid donation. This was another ethically fuelled issue, where again matters of safety had to prevail over ethical considerations. This time the Parliament 'won', as the final Directive stipulates how donors should not be paid (although some room was left to Member States to decide upon 'compensation' for donation), but this victory was part of a package deal between Parliament and Council in order to move the much needed Directive forward, rather than stalling the legislation and playing it high up by going into a conciliation procedure. As one interviewee commented:

> It wasn't made by the people who prepared the first draft of the DG SANCO Directive. It was made maybe at political level.
> (Quality controller multinational tissue engineering company M-EU3, 2004)

Thus the main ethical pot hangers during the SANCO debate were over the inclusion or exclusion of specific cell sources, and over the nature of donation. Interestingly, one of the areas not discussed into any length concerns the role of xenogeneic material as another potentially contested cell source. Early on during the legislative cycle, in the first proposal on the SANCO Directive, reference was made to xenotransplantation, where it was argued how 'organs, tissues, and cells of animal origin for human therapy are still in the research phase, but nevertheless pose different regulatory problems that will need to be addressed in due course.' (DG SANCO 2002: 5). No reference was made to so called non-viable animal sources, such as the bovine serum used during cell culturing. Nor were these animal-derived substances put on the agenda at any point during the debate. A similar silence was witnessed over genetically modified tissues or cells, where the Commission felt it was too early to consider this material, or the techniques used to engineer particular cell sources, as a realistic clinical option that had to be addressed at this stage. In other words, while ESCs and therapeutic cloning, and to some extent reproductive cells, were at centre stage during the debate, other potentially controversial cell sources and techniques did not enter the discussion at all. That is, so far. In the proposal building stages of the Enterprise Regulation, analysed in later chapters, the focus of attention changes slightly, where in addition to embryonic material also xenogeneic and other cell sources enter the debate.

Thus so far the discussion on ethical considerations has been very narrowly focused. Especially given the safety considerations of different cell sources, it is remarkable to note the limited discussion over whether for example autologous and allogeneic cells should be regulated differently. As discussed in the part on risk perceptions by R&D actors, many of these interviewees make a distinction between these cells sources, which rank differently in terms of safety, and arguably also in terms of potential moral controversy. In the SANCO debate this distinction played a minor part. Only during the early stages this issue was addressed, where the initial proposal envisaged excluding 'tissues and cells

used as an autologous graft within the same surgical procedure' from the first steps of use and stating how 'autologous cells used for medicinal products are not covered by this Directive' (DG SANCO 2002: 4). While the Commission in its early wisdom felt that a different regulatory approach was needed for products based on autologous cells, especially industrial developers opposed to this provision. Also the advisory Committee EESC argued for clearer definitions to lessen confusion between allogeneic and autologous cell sources. During the Parliament reading the exclusion of autologous cells used for the manufacturing of medicinal products in the proposal was deleted (amendment 21), and also the Council wanted to extent the scope of the Directive to include these cells. In the end the Commission surrendered on this point. The reason why this provision was abandoned was not directly based on considerations of different safety though, but to reduce complexity and provide coherence. An EC official stated that 'they [Council and Parliament] couldn't find enough reasons why we should exclude autologous cells from the procurement and testing if we are including all of the rest of the cells in the Directive. So at the end the commission agreed that it really was a more coherent approach to have all tissues and cells covered in the first few steps in our Directive' (A-EU5, 2003). With respect to the next steps in the process, such as processing and distribution, these cells were excluded though.

So while R&D actors applied a hierarchy of risk in which autologous cells were considered safer than their allogeneic counterparts, this perception was in the end not translated into regulatory policy. Furthermore, no different safety labels were attached to these respective cell sources, and more so, no debate existed over different ethical stances towards them. This is interesting from more than one angle, as discussed below.

According to one manufacturer with advisory involvement in regulatory policy, the limited focus on the distinction between autologous and allogeneic cells is that the former do not pose any moral dilemmas, and that the provisions in the SANCO Directive would be mostly relevant to allogeneic cells of different origin. Furthermore the debate did not focus on different cell sources used within tissue engineering, but on a comparison with other technologies of cell manipulation:

> There was a big ethical debate at the beginning of this whole saga and there was clearly a demarcation between what you saw as tissues and cells which you would use for the benefit of patients, which were more of an altruistic type donation, to those and the ethics that are involved for example that you find now with stem cell research, genetics and all those sorts of things. There's a clear difference. When you're working with tissue engineering, with autologous products, there's no real ethical debate as far as I'm concerned because all you're doing is consenting as a patient to have your own cells taken away from you and given back... ultimately there's no real ethical debate, it's just whether you consent to have the operation or not.
>
> With allogeneic tissue, yes there are ethics of donation; there are ethics of consent from that perspective. There's also ethics as well and debates have been taking place about donation of tissue and whether or not you should be donating tissue for nothing or whether you should be [paid] and that's why tissue banks work on a non-profit basis. But then if as a company you're taking cells and applying the manufacturing process... surely as an industrial company it would be unethical for you not to be able to charge money for them. Why would you develop such a process if you are not going to make any financial gain from it? Then you would stop any piece of research. You wouldn't get anything at all and that would be probably detrimental to the public.
> (Regulatory affairs manager of multinational company M-EU9, 2003)

This interviewee also refers to 'the ethics' around commercial use of tissues and cells, which is discussed later. The following fragment is from a scientist with large involvement in developing the SANCO Directive as expert advisor, sharing the belief in the uncontroversial nature of autologous cell use, but pointing out some other ethical considerations:

> I think the ethical issues are immensely important here. And I used the phrase that autologous tissue engineering is an ethics free zone. There is an ethical issue there if you are taking the patient's own cells and using those cells to generate the patient's own tissue - the only time ethics would really come in is if you're using gene transfer in that process. But even then I don't think that's a big issue. If you're using allogeneic sources, you have to, obviously there are scientific issues and then you have to ask the question then where are the cells coming from, who's intellectual property is it, who's cells are they? Did the donor know that they were actually donating those cells? And the answer is in most cases, no they had no idea. And I think that those are issues which have to be very, very carefully answered. There are a whole lot of issues down that path. (European expert advisor and scientist A-EU6, 2003)

This interviewee makes a sharp distinction between autologous cells, which are 'an ethics free zone', and refers to gene transfer as one technique which would

make this particular tissue engineering route controversial. In contrast, the use of allogeneic or donor cells raises questions of ownership and property right, and of informed consent around donation. If we translate these concerns to what the SANCO Directive covers, and what was brought up during the shaping of this legislation, only the issue of informed consent has been taken up. While an original first amendment from the European Parliament addressed ownership of bodily material - stating how the human body is in inviolable and inalienable and cannot be the subject of property rights - this provision was discarded in later versions. And with that the agenda was set. Thus with the exclusive focus during especially the Parliament debate on ESCs, and later on donation, other potential controversial issues with an ethical undertone were left out of the equation.

For industry this focus on ESCs is problematic in wishing to present tissue engineering as a less contested technology, and some have argued how still a lot of education needs to be done in order to convince 'the public' of the beneficial rather than controversial outputs envisaged. In order to secure a future for other tissue and cell based technologies, distancing is needed from the contested embryonic sources:

> It is important to highlight when speaking about this kind of technologies that there is a huge variety things which enter into the definition of tissue engineering. The problem we face and I think we will face for a long time is that on the regulatory scenario, is that when ever we speak about human tissue engineering, immediately the lay person, politician, the - some groups of religious convincement immediately think to work made on foetus or embryos or these sorts of things which puts the entire, the entire sector under a different light.
> (Representative of European industry association for medical devices M-EU2, 2003)

An EC official involved in drafting the SANCO Directive recalls how stem cells were at the heart of the debate from early on, while at the same time expressing how in his view this topic was not actual yet. Furthermore he refers to an important issue by implying how the boundary drawing around tissue engineering has extended the scope to embryonic material:

> I suppose the first time that we were going to present our [SANCO] Directive that is focusing on other things and then the people are only interested in stem cells though, who is future anyway... and even more

> they are talking about the cloning, trying to find the use of cells that you get from cloning for transplantation. This is a possibility so remote I think it's...For me, I have a clear range of things that I consider are tissue engineering... But again there are some boundaries who are not easy to define.
> (Official at European Commission DG SANCO A-EU5, 2003)

According to this interviewee the rather exclusive focus on ESCs in Parliament could also be explained by the echo of another influential policy development: the discussion that took place around the same time on funding research in this domain under the 6th Framework Programme.[55] Thus against the background of the SANCO debate, Member States were also confronted with the question of future research efforts into human ESCs, again creating agitation and diverging views.

Finally the debate on ethical considerations has always centred on article 152 of the Amsterdam Treaty, which not only outlines the need for regulation but also refers to the subsidiarity principle. As discussed, it was this principle that led the Commission and Council to conclude that the decision on prohibition or authorisation of specific cell sources was left to the national level, with the option to impose stricter safety rules. But there is also another provision in this Treaty, article 30, which gives Member States the right to prohibit or bind the use of certain source materials from abroad for ethical reasons. The exact applicability of this principle is as yet unknown though (A-EU5, 2003). At no point during the debate the possibility of retreat to this article was made.

9.5 'Representative ethics': the role of EGE

So far the discussion on ethical principles has focused on the role of the European Commission, Council and Parliament as representatives of the main legislative bodies in the EU. Not discussed in too much detail yet is the position of ethical advisory bodies in this debate. The most important of these is the European Group on Ethics in Science and New Technologies (EGE), an

[55] A moratorium to fund embryonic stem cell derivation for research was in place till the end of 2003, but in July that year the Commission submitted a proposal to the Council and Parliament for establishing detailed guidelines for EU funding of research involving human embryos and human embryonic stem cells, to be implemented by the end of 2003.

influential specialist advisory body reporting directly to the President of the European Commission.[56]

The group has issued several opinions with relevance to tissue engineering. Most notably, the EGE gave the creation of tissue engineering regulation a significant push by stating in their 1998 expert opinion that there was an 'urgent need to regulate the conditions under which human tissues circulate within the European Market' (EGE 1998). In its Opinion on ethical aspects of tissue banking the EGE addressed a range of ethical considerations, including commercialisation and the need to keep the tissue domain under control of public health institutions and non profit-making organisations. This Opinion was influential in steering the policy debate.[57] However, the EGE's principle on the non-profit character of tissue establishments was controversial, and the Commission diverged from this advice in the SANCO Directive. As discussed later, the extension of tissue banking activities to those of tissue establishments was highly debated, given this opened up the market for commercial providers operating in the field.

But the most specific Opinion from the EGE came after the final SANCO Directive was published. In April 2004 the President of the Commission requested the EGE to prepare a report on the ethical aspects of human tissue engineering. The Opinion on this topic was published in June 2004 (EGE 2004).

[56] The EGE was created by the Commission in 1997 as 'a neutral, independent, pluralist and multidisciplinary body which advises the European Commission on ethical aspects of science and new technologies in connection with the preparation and implementation of Community legislation or policies' (EGE 2006). On request by the Commission or on its own initiative the group writes reports and publishes so called Opinions. The EGE was the successor of the Group of Advisers on the Ethical Implications of Biotechnology (GAEIB 1991-1997), initially set up by Jacques Delores.

[57] Some of its ethical principles are quoted in the explanatory memorandum prefacing the SANCO Directive. These include the ethical imperative to protect human health, including testing standards for prevention of disease transmission; ensuring the integrity of the human body in procurement of living and dead donors; prior, informed and free consent of donors; and the protection of identity, including anonymity of both donor and recipient to prevent possible discrimination (DG SANCO 2002). Furthermore the SANCO Directive refers to the EGE Opinion in its discussion of role and responsibilities of tissue banks (and their profit or non-profit character); equitable access to the therapeutic opportunities afforded by the use of human tissues; and the need for tissue imports from third countries to be subject to at least equivalent ethical and health requirements (2002: 3).

The advice takes the SANCO Directive as starting point, but points out the limitations of this legislation by only setting quality and safety standards. This means a high and same level of protection of human health throughout the EU is ensured. Not covered by this Directive though are the products resulting of substantial modification or manipulations of tissues and cells. Against the background of a rapidly developing tissue engineering sector, the EGE notes the lack of European legislation on specifically controlling the marketing authorisation for products. Thus the Opinion is mainly concerned with the ethical aspects around production and marketing of products, and fits in with the efforts by DG Enterprise in preparing specific regulation to this effect.[58] While the details of this regulation are discussed later, here the main issues brought up in the EGE Opinion are critically reviewed.

The tissue engineering Opinion is a rather peculiar document consisting of a long list of references to previous Opinions of the group on related issues, such as tissue banking (EGE 1998), stem cell research and use (EGE 2000), and patenting of stem cells (EGE 2002). While the scope of the Opinion is rather limited, and is mostly interesting for what it leaves out, the document does point out some itchy ethical considerations which also put the SANCO Directive in a different light.

The document first addresses general ethical questions related to tissues and cells, and continues to describe three areas of specific concern for tissue engineered products. Under the first heading ethical concerns are listed around information and consent, donation, privacy and data protection, traceability, safety, priorities of access, and finally research and clinical trials. While many of these issues have been discussed already in relation to the SANCO Directive, EGE made some interesting observations about their (in)applicability to tissue engineering. For example the group notes how donor consent can be problematic in some cases, notably when tissues have been stored for a long time, where the donor was not informed of potential future use of the donated tissue for producing tissue engineered products. Traceability of these tissues

[58] So far, the influence of EGE opinions on the Enterprise Regulation has not been clearly visible, but based on the experience with the SANCO Directive this may change with the passage of the proposed Regulation through co-decision (which falls beyond the scope of this research).

can be complicated, especially if stored anonymously. Furthermore the informed consent notion of so called 'foreseeable use' of the tissues, where the ethical principle dictates that the donor may withdraw his or her consent at any time, needs clarification by providing an exit point of where withdrawing consent is not possible anymore (plus the option to refuse specific future use). The main underlying question here is in how far the donor has control over future use of his or her donated material, and as such addresses ownership issues, which is currently subject to different standards and values in countries worldwide. A final note on informing the donor reads that consent is necessary in any context of procurement, also when it concerns the collection of surgical waste. This refers to a critical notion, although not addressed in the Opinion, where some manufacturers have claimed that donor consent is not needed, or indeed impossible, when the products are based on discarded clinical waste, such as the circumcised foreskins which form the basis of several tissue engineered skin products currently commercially available.

Finally, and only briefly, the Opinion turns to what the EGE considers 'specific ethical questions' in relation to tissue engineering. Summed up here are the distinction between medical and cosmetic use, the use of embryonic stem cells and patenting. The first one is a remarkable issue to point out, also because it was not previously debated during any point in the legislative cycle of the SANCO Directive.[59] The EGE comments that the distinction between therapeutic uses and cosmetics uses may sometimes be difficult to state, referring to cases when the definition of health is not only related to pathological features but also to quality of life. Ethical issues around ESCs are not properly addressed (only mentioned here is that some EGE members have strong ethical reservations regarding their use), while patenting is discussed in relation to concerns with profit obtained with an invention resulting of the use of donated tissues (EGE 2004). Of all the ethical concerns brought to the fore, it is interesting to note that the SANCO Directive does not address patentability of tissues and cells.

[59] Article 10 of this Directive states that: This Directive covers tissues and cells intended for human applications, including human tissues and cells used for the preparation of cosmetic products. However, in view of the risk of transmission of communicable diseases, the use of human cells, tissues and products in cosmetic products is prohibited by the Cosmetic Products Directive' (DG SANCO 2004: 2).

While the EGE Opinion highlighted some relevant ethical considerations in relation to the SANCO Directive and the product side of tissue engineering, it was summary in scope. In none of the Opinions reference is made to xenogeneic cells or animal-derived material. Also potential concern around therapeutic effectiveness and how to go about collecting clinical evidence in this field is not addressed, nor the issue of equal access to an expensive technology for which generally no reimbursement exists. While these can be considered general concerns in innovative medicine, the small selection of arguments that EGE developed as specifically relating to tissue engineering is in a sense exotic and – apart obviously from the ESC case - not reflected in any of the debates so far.

As conceptual reflection, it becomes clear in this context how the boundaries around specific ethical concerns are expressed differently by an institutionalised expert body such as EGE.

9.6 From bio-society to bio-economy

The foregrounding of ethical issues and social impact of tissue engineering technology, as witnessed in this chapter, could indicate a silent move towards notions of the bio-society. The debate in Parliament over ethical concerns reflects varying democratic positions in Member States, which is problematic at European level given the lack of consensus. This points towards an underlying notion; the inability of the EU to deal with the impact of contested technologies. Regulating ethics at this level has proved difficult and is bound by legal constraints as formulated in Treaties. As such, the European regulatory state (Majone 1994) is not a state of European values. This threatens the bio-society, where different stances towards the desirability and impact of tissue engineering result in boxing out these concerns altogether. This chapter has demonstrated this point by analysing the debate on ESCs and the incorporation of 'less controversial' ethical concerns around donation into the final version of the SANCO Directive. As such, this episode of the regulatory cycle resembles biotechnological developments that have been described in terms of 'cultural biopolitics' in parallel to 'moral economies' (Salter 2006). Dynamic discourses

of cultural values about the desirability of techno-scientific innovations (in this case a role played by embryonic stem cells) are accompanied by a moral economy in which these values can be traded and exchanged. As such, the trading of values facilitates negotiation and facilitates achieving a political compromise.

The bio-society also becomes problematic under the influence of a second main development during the policy shaping process of the SANCO Directive, namely a shift in stakeholder participation. The next section demonstrates how gradually during this process the role and influence of commercial developers increased. This created friction over the scope of the Directive. Here, conflicting views between the tissue banking community and industrial players became visible. These different groups, both operating in the tissue and cell domain, represent different value systems. Tissue banks have been involved in procurement, storage and distribution of tissue and cells for a long time. Typically they work on a not-for-profit basis (although exceptions exist). This resounds in debates on, most notably, the nature of donation, where Europe has a long tradition of unpaid and voluntary donation of bodily material based on free and informed consent. With the growing international trade in human tissues and cells and the increased activity of (multinational) commercial providers in this field, discussion arose over the nature of donation and the commodification of bodily material. The main question was not only if donors should be paid for donation, but also whether it was kosher for companies to make profit over freely donated tissues and cells that form the basis of tissue engineered products. These issues have been touched upon in this chapter in the analysis of the Parliament debate. The next section discusses this configuration of players in more detail, speculating on the implications of a possible extension of boundaries from bio-society type of actors (tissue banks) to bio-economic players (industry). As such, the concerns with ethical considerations can be placed in a larger context of EU policy and trends. Discussions over the scope further support this statement.

9.7 Opening up the Directive

A second major strain in the analysis of the SANCO Directive, in addition to ethical considerations, is the gradual broadening of the scope. Two interrelated trends are visible here; one from regulating traditional tissue banking activities to also include manufactured products based on human tissues and cells, while the other focuses on the relation between the SANCO Directive on quality and safety and the new Regulation that was being developed around the same time by DG Enterprise, and which covers the marketing of these products. These trends imply a shift in the involvement of different stakeholder groups in the policy shaping process. This had a direct influence on 'opening up' a Directive that was originally developed to just accommodate traditional tissues and cells. Conflicts of interests become visible between actors in traditional tissue banking culture, which has typically been associated with local and hospital based practices on a national level, versus commercial developers in an increasingly multinational tissue engineering sector. This can be considered in the light of a growing regulatory reach (Welsh and Evans 1999) and stronger move towards Europeanisation of tissue and cell regulation, where the SANCO Directive represents the shift from local production to commercialisation on trans-national scale. Also it underlines the tensions between public health and competitiveness agendas. This is furthermore complicated by internal politics and bureaucratic competition within the Commission, which has also shaped the scope and means of the SANCO Directive.

The original aim of the SANCO Directive was to regulate non-manipulated or traditional tissues and cells and to safeguard the use of tissues preserved in tissue banks by requiring binding measures on quality and safety (Elmalem 2002). It focused on activities of procurement and processing in the tissue banking sector. This was evident from the first proposals for a Directive and from the expertise drawn upon to advise the Commission, which included specialists from transplantation medicine and tissue banks in Europe. Involvement of industrial players was limited during these early stages. During the transition of the proposal through Parliament and Council, when also other stakeholders where invited to present their positions, the reach of the Directive

was broadened. Industry expressed concern that the proposal for the Directive only covered tissue banks, and not commercial providers (Schutte 2003). They lobbied for a 'level playing field' with the then dominant tissue banking sector (Luyten 2003), which allowed companies to have direct involvement in the procurement of tissues and cells, rather than having to access their starting materials via tissue banks. According to a commercial provider the SANCO proposal was for a long time unclear in how to deal with both not-for-profit and commercial providers:

> You end up with two different rules for the different players in the market. I think what industry is saying is that there should be the same rules for everyone whether they're tissue banks, whether they're a commercial company or whoever. The same rules, whether you're going sourcing or whether you're going into processing and modifying into a product. And that was not clear from the SANCO directive. And apparently now they've changed tissue banking to tissue establishment, meaning anybody that is working. But it was still very unclear... That's why someone used the word 'mess' because it's just so unclear of where we are going.
> (Corporate affairs manager in multinational company M-EU5, 2003)

The influence of commercial providers is witnessed in the amended version of the proposed Directive, which the Commission presented in May 2003 (DG SANCO 2003). While the original proposal promoted not-for-profit procurement institutions[60] (basically public sector tissue banks, though this was not phrased like this), the revised proposal coined the new concept of 'tissue establishment'. This change of definition had far-reaching consequences, because it meant that the original scope of transplantation, and as such of traditional tissue banks as institutional actors, was broadened to include all establishments where activities take place related to the application of human tissues and cells. Therefore companies could also get involved in the procurement of tissue, and were subject to similar rules as tissue banks for the later steps of processing and distribution.

Thus while the original SANCO proposal was very tissue bank oriented, this changed into incorporating more and more provisions that reflect the increased

[60] In addition to procurement activities, the original article 6 of the Directive stated that "Member States shall ensure that all activities relating to the processing, preservation, storage, and distribution of human tissues and cells for human transplantation are undertaken only by tissue banks that have been accredited by a competent authority for that purpose" (DG SANCO 2002: article 6).

activity of tissue engineering companies in the sector. But the meaning and context of this change of focus was also coloured by the fact that the Enterprise product legislation was still in preparation. This regulation would focus specifically on marketing of tissue engineered products but it was as yet unclear in what way, and most notably how long it would take to be effective. This caused confusion in the field, where many companies were afraid they would be subject to different sets of regulations that were not compatible, or with clashing provisions of different sets of Community legislation.

> It's knowing where the boundaries are, so I guess ideally would say: right OK the DG SANCO Directive is useful particularly for tissue banks and the sourcing of materials and that's fine. But really we'd want to be controlled under the DG Enterprise Directive that specifically covers all the issues of producing these high technology products and actually placing products on the market.
> (Product safety manager for multinational company M2, 2003)

In the absence of further product legislation, it also becomes clearer why there was another remarkable change in the wording and intention of the SANCO Directive: from only including traditional tissues to covering all tissue and cell based products for which no other Community legislation exists. This had important implications for the way tissue engineering was treated, and in how far it would be covered by the provisions of the SANCO Directive. A SANCO official explains:

> In the first version of the Directive we cover full transplantation. Now we cover everything which is not covered by other Community Directives. This is a slight change... that we will not cover tissue engineering products when the Directive of tissue engineering products, the new directive, the new proposal will be in place. But in the meantime when there is nothing in place for these... It's a drastic change in scope, I mean now we cover... tissue engineering has to comply also with the basic requirements of our Directive, also for their steps. Everything of this taken into account that the Commission is really under the idea that we need a specific regulation or specific framework for tissue engineering products. And this is entering a period... waiting for these further regulations.
> (Official at European Commission DG SANCO A-EU5, 2003)

In other words the SANCO Directive became an 'in between solution' for tissue engineered products, until the DG Enterprise Regulation, which was under preparation but delayed, would be effective.

The lack of clarity between the two legislations also pointed towards another development, namely one of competition between the different Directorates in question: DG SANCO and DG Enterprise. Interviewees have described their astonishment with 'the sudden pop up' of the SANCO Directive (M-EU4, 2003), which was developed 'almost in isolation to Enterprise' (M-EU9, 2003). They describe how the SANCO proposal, while already in advanced stages of preparation, came not only as a surprise to industry, but also to DG Enterprise, which was just about to launch its first consultation round to inquire about the need for a specific legislative framework for tissue engineering. Asked about the internal politics behind this state of affairs, one interviewee's view is as follows:

> I think it's a mixture of both [politics between and within DGs] in that if you see the way the DG SANCO Directive was produced, it was almost - obviously a lot of work had been happening quietly in the background. I think when they produced it was: hang on, here's suddenly a fifty page document which they felt was then ready for public scrutiny. I think DG Enterprise were taken aback but I got the impression there hasn't been a great deal of communication between the different DGs on that. So it's almost as though DG SANCO were like whoa, they've got their house in order and suddenly whoa there's a document and DG Enterprise was left trailing is this getting into what their strategy was as they were developing one. But I think there's a lot of politics too within DG Enterprise 'cos obviously you've got the medical device groups and medicinal product groups within DG Enterprise and so there's concerns there, certainly the feeling that medicinal products group would certainly like to control all this if they could.
> (Product safety manager for multinational company M2, 2003)

Therefore tensions arose not only between DG SANCO and the industry sector, but also between Directorates. And within the different divisions of the Enterprise DG, which is responsible for both medical device and pharmaceutical regulation.

The change of focus in the SANCO Directive was perceived differently by traditional tissue banking communities and commercial providers, where arguably tensions between the different approaches were at their sharpest. One manufacturer recalls a meeting with some experts involved in preparing a draft proposal, stating how DG SANCO only wanted to cover the donation and procurement side, but not the application of products based on tissues and cells, nor any tissues or cells with extensive manipulation:

> I think that the last version was far from what they wanted to happen... It was different. They wanted to regulate classical tissues, and that's all. Donor skin, corneas, bone, bone chips... And what is currently provided by tissue banks in Europe. They didn't want to have inside tissue engineering products. But at the end, someone decided that since there was no regulation for them, they started asking for a regulation for tissue engineering products. DG Enterprise didn't react very quickly, so DG SANCO became one of the pieces of the regulation.
> (Scientist quality controller in multinational tissue engineering company M-EU3, 2004)

The statement that the SANCO Directive would only temporarily cover tissue engineered products until a specific legislation is issued, did not make it to the final text though (Elmalem 2002). In the revised version of the SANCO proposal, article 2 on the scope was altered in the following way:

> The provisions of this Directive shall apply to the donation, procurement, testing ~~of human tissues and cells for application to the human body. The provisions of this Directive shall also apply to the~~ processing, preservation, storage and distribution of human tissues and cells ~~when they are to be used for human transplantation~~ intended for human application and of manufactured products intended for human application derived from human tissues and cells.
>
> Where the processing, preservation, storage and distribution of those ~~In the case of such~~ ~~industrially~~ manufactured products is regulated ~~covered~~ by other Community legislation ~~provisions derived from tissues and cells~~, this Directive shall apply ~~applies~~ only to donation, procurement and testing. (DG SANCO 2003: article 2)

This was the text that made it to the final Directive of 2004 (DG SANCO 2004). This provided some clarity as to which extent tissue engineered products were covered, namely only for the quality and safety aspects around donation, procurement and testing of the human tissues and cells that are used as starting materials for these products. The subsequent steps of processing, preservation, storage and distribution are covered by other Community legislation. We will discuss the specifics of this 'other Community legislation' in the next chapter.

Recap

This section has described how industrial representatives successfully lobbied for a 'level playing field' with other parties in the tissue domain, thereby widening the scope of the Directive from traditional tissue banking activities to also allow other institutions in procurement activities. This was important for companies in order to directly access their starting materials for product manufacturing. With this the tissue banking monopoly was broken down. The industry involvement also had other implications, as it opened up discussion about 'tissue banking values' over the nature of donation, which had always been linked to arguments of non-profit. This also explains the discussions in Parliament over ethical considerations, as these were mostly based on perspectives of public-health protection and patient safety – the very aim and legal basis of the SANCO Directive. These traditional values were called into question by the arrival of profit-seeking actors. At the same time, it was during these debates that conflicting values between non-profit and commercial players were extrapolated. In addition to tensions between players in the tissue engineering field, also institutional conflict within the Commission affected the course of events with the SANCO Directive, and its relation with the Enterprise regulation. The latter is discussed in the next chapter. Two critical developments should be noted here that form the analytical backdrop for understanding the institutional tensions between these players. One refers to the role of the European Commission vis-à-vis the European Parliament. As has been analysed before in relation to human genetics (see Salter & Jones 2002), the stance of the European Parliament has consistently been more sceptical towards new technological developments, reflected in its positioning in regulatory decision-making. For example EP resolutions on ethical and legal grounds date back to the early 1990s, with several attempts to introduce a legally binding ban on the cloning of human beings. Unlike Commission officials, MEPs are 'naturally sensitive to the cultural response of their national constituencies' (2002: 332). A second institutional and political context is provided by neighbouring policy areas at EU level, and more specific the EU's research funding programmes. The debate on funding research on human embryonic stem cells under Framework Programme 6 for example (see for more on this Salter 2005b, 2006) is of paramount importance in reflecting on the tissue engineering case in the broader policy context. Here bio-economic

parameters come to the fore again. As has been argued, the EU's struggle over the future of contested therapies in regenerative medicine, including tissue engineering and stem cell science, can be considered part of a global contest for national ànd EU advantage. As such a wedge is created between ambitions of science and cultural values, creating 'cultural biopolitics' (Salter 2006) in which the operation of biopower is targeted at the control of the values that permit or proscribe the development of health technologies.

10 The Enterprise regulation: reconstructing ethics

This section makes the transition from the SANCO Directive to the Enterprise Regulation. As an opening note it should be emphasised that the legislative instrument for the marketing of tissue engineered products was altered during the policy shaping process. Instead of a Directive, as was broadly anticipated, the Commission chose a Regulation as more appropriate tool. This was a reflection of the need for a quick but uniform solution for the regulatory gap left behind by the SANCO Directive.

The SANCO legislation is very clear in its legislative basis, stating explicitly that the aim of this Directive is quality and safety standards, whereas 'this Directive does not have as its primary objective the placing on the market of tissues and cells of human origin.' (DG SANCO 2004).

While the SANCO Directive is based on the public health article (art 152) of the Amsterdam Treaty, the initiative by DG Enterprise has the promotion of the single market as main aim (art 95). One important concern for industry is the particularities of this health article, as it implies that Member States are not prevented from 'maintaining or introducing more stringent protective measures' (European Commission (EC) 1997: art 152, al 4(a)). In other words the Directive prescribes basic safety criteria, while any Member State can adopt more protective measures and install higher safety standards on the use of human tissues and cells when they feel the need to. This means that this health article does not provide for harmonisation across Member States (A-EU5, 2003). Commercial developers have expressed concerns over this legal basis, as they fear that Member States will indeed raise their safety controls in order to exclude certain products from entering their national markets:

> The article I think under which DG SANCO operates only sets minimum criteria and so the risk gets from industry's point of view that each country could say: yeah, yeah, we'll work with the minimum but we also want to put additional controls for our country in there. And so you could

> end up with, again, you wouldn't have a pan European system... It just means you don't really have a free market anymore.
> (Product safety manager for multinational company M2, 2003)

In this situation commercial developers, and other actors active in the tissue engineering sector, have to comply with the quality and safety requirements under the SANCO Directive, but are confronted with a regulatory lag in relation to authorisation for commercialisation of their products in Europe.

To 'correct' this regulatory ambiguity, DG Enterprise is preparing regulation that defines the process of authorisation for tissue engineered products, with requirements for obtaining manufacturing license, scientific assessment of new products, and post-marketing surveillance to keep track of possible adverse effects of these products. While tissue engineered products can only be placed on the market after fulfilling the quality and safety requirements under the SANCO Directive, the Enterprise regulation aims to guarantee free movement of products within the single market by harmonising the rules for authorisation. In this respect DG Enterprise has to work with a dual objective, where first and foremost the highest level of safety protection for patients has to be guaranteed before an effective internal market can be created. [61]

While the Enterprise legislation is still under development, and final outcomes are as yet unknown, some emerging themes can be observed. One notable trend is the increased role of commercial developers in shaping the legislation. DG Enterprise has traditionally been 'close' to industry because of its mandate and objective in promoting trade. In the health domain a longstanding relation was established with companies and trade associations, in the context of DG Enterprise's involvement in controlling medical devices and pharmaceuticals in the EU.

Focusing on the legislative documents and proposals issued so far, several other observations can be made. One of these is the highly debated question of the very definition of tissue engineering, which is discussed here in relation to

[61] As later expressed in the final legislative document by DG Enterprise: 'While taking account of the fact that any regulation on the manufacture and distribution of medicinal products must be fundamentally aimed at safeguarding public health, this aim must be achieved by means that do not impede the free movement of medicinal products within the Community' (DG Enterprise 2005: 4).

the in- or exclusion of animal cells. This definition issue is related to the scope of the legislation, and in how far tissue engineered product should be part of a medicinal product approach. As we have seen in chapter 2, regulatory policy development in this field is shaped by continuous debate over the most appropriate approval route for these products, with medical devices and medicinal product Directives considered the most viable Community options. The final proposal for the Enterprise Regulation, adopted by the Commission in November 2005, places tissue engineering under the medicines umbrella, where the EMEA deals with authorisation of these products for the single European market. In this task the agency is assisted by a new expert Committee for Advanced Therapies (CAT) with specific expertise to evaluate tissue engineered products. The early development of the Enterprise Regulation is dominated by discussions over whether this is the most appropriate construction, what exact expertise is needed to evaluate the technology, and what the practical implications are of this centralised system (especially for the many SMEs in the sector). However, these issues are not further explored in this chapter. Instead, I focus on the drawing of boundaries around the definition of tissue engineering, which highlights significant divergence from the SANCO debate in relation to ethical considerations.

This chapter explores in how far the highly contested role of ethical considerations, and with that the regulatory scope, during the SANCO debate are influential in the way the Enterprise Regulation was build, or which alternative frames are called upon in this specific initiative. I empirically approach this by analysing the diverse consultation rounds and expertise calls that led to the final proposal for a Regulation in November 2005, analysing the role of the key players in this exercise, and discussing how the boundaries are constituted around drawing this Regulation against the backdrop of the SANCO debate.

The last section of this chapter gives a reflective account of the implications of 'regulating ethics' in comparing the two legislative initiatives, thereby also drawing conclusions about the viability of the bio-society.

10.1 Shifting frames: on animal cells

The emerging debate on xenogeneic tissues and cells is vibrant and relevant. The potential authorisation of animal material for circulation on the single European market has far reaching implications for the health and safety of European citizens, for risk management approaches in the EU, and for 'public trust' in products as well as the Commission's competence in European governance of innovative technologies.

This discussion starts with the observation that the SANCO Directive does not address animal sources in any sense. Although this Directive covers the procurement stage, this concerns *human* tissues and cells. Community legislation for the procurement of animal cells is currently absent. In the legislation currently in development for the marketing of tissue engineered products, the Enterprise Regulation, animal cells do play a role. This section provides further details by focusing on the different consultation rounds that the Commission organised over the last years. Here a remarkable change in focus has taken place in stakeholders' stances towards these cells, where different boundaries are drawn around the desirability of their inclusion in Community legislation.

10.1.1 Strict exclusions and 'realpolitik'

In June 2002, DG Enterprise launched a web-based consultation entitled 'Consultation document: Need for a legislative framework for human tissue engineering and tissue-engineered products' (DG Enterprise 2002). With this document stakeholder input was sought on a future regulatory framework to cover the marketing procedure for tissue engineered products. One main issue addressed was the definition and scope of tissue engineering, pointing out the need to produce 'a scientifically valid and legally sustainable definition of tissue engineering, and tissue engineered products, in order to underpin a legislative framework and to provide a sound basis for demarcation between tissue engineered products on the one hand and medical devices, pharmaceutical products and cell therapy on the other' (DG Enterprise 2002: 2). More specific

at this stage the Commission suggested excluding xenogeneic organs, tissues and cells from the tissue engineering domain.

Stakeholders were divided over the question whether xenogeneic tissues and cells should be covered under the new legislation. Some government officials were in favour, arguing how largely the same issues (most notably with respect to risk) were at stake in comparing tissue engineering with xenogeneic products, while others opposed on the basis that it would add additional complexity to an already complex subject. Some respondents felt that it was simply too early for xenogeneic products to contemplate regulation. An interviewee who took part in this consultation exercise explained how a pragmatic view had to be taken, where it was a question of 'realpolitik' to move the regulation forward:

> I think what we've said mainly for UK at the present moment is that because there is a need to make progress here, let us leave xenotransplantation out of this, that was our response on there [i.e. to the Enterprise consultation] because if you bring xenotransplantation in we'll spend three or four years in Europe arguing about this, and that's a difficult one... And then I think the UK view there was partly pragmatic. We're saying that OK there are areas there which need to be sorted out, but if we're to make progress then realpolitik says we've got to go for the biggies, you know the easiest way of getting this forward. If you were to put xenotransplantation in then this is going to delay us for another two or three years. I'm not sure that the time is right yet and equally there may be other ways of taking this forward. So let's separate these out. If you try too wide a directive you'll just have all the problems of '98 repeated, so let's go in rather narrow and focused so at least we achieve something.
> (Regulatory professional in national government agency R2, 2003)

In contrast, most companies were largely in favour of including xenogeneic material. Their representatives in trade bodies on the other hand were more cautious, pointing out ethical sensitivity and scientific uncertainty around the therapeutic use of viable xenogeneic cells. On this basis they suggested to exclude products based of animal material, with the notable exception of animal derived material ('ancillary elements') used during culturing and processing in tissue engineering applications:

> However, xenogeneic viable material should not be confused with animal derived materials currently being used as part of human tissue

> product manufacturing processes, such as mouse feeder cells in skin cell expansion for treating severely burned patients. In such cases, we would propose a certification scheme specifically focussing on safety, and which could be extended to include other biological materials used during manufacturing and not yet covered by the medical device or the medicinal products regulations, such as cytokines, bovine serum, etc... Taking this into account, the definition of tissue engineered products should allow for the ancillary use of animal (or theoretically also plant) derived material.
> (EuropaBio 2002: 5).

For years the culturing of human cells had been based on using certain animal-derived materials, such as bovine or horse serum, bovine collagen and other additives or growth factors of animal origin. It was argued that these concern so called non-viable animal derived components. Thus the definitions under which the proposed Regulation excluded animal material mainly referred to xenotransplants; living animal organs, tissues or cells.

10.1.2 'In principle' exclusions

Two years later a second consultation round took place (DG Enterprise 2004b). Again matters of definition and scope were addressed. The most striking difference in this document concerned the use of animal material. Similar to the earlier consultation document, the Commission proposed that 'in principle' xenogeneic tissues and cells should be excluded from the tissue engineering Regulation. However a change in wording and intention was witnessed here: the Commission stated that xenogeneic tissue engineered products may be developed in the future, implying that there could be a need to regulate this more complex category of products. Because of safety and ethical issues surrounding this material, and the still early stages of development, 'for the time being' an exclusion should remain in force. The proposal is explicit though in that 'this would not exclude the use of xenogeneic cells or tissues used for the production of human tissue engineered products, as long as these xenogeneic materials are not present in the *final* product.' (DG Enterprise 2004b: 6). This final product clause was highly debated. Many respondents highlighted that unintentionally traces of animal-derived material (bovine serum, collagen, or via the use of xenogeneic scaffolds) could be left behind in the final product. Thus in practice this provision would not work. Some respondents suggested in this

respect that legislation should ensure that any xenogeneic materials present in the final product are not viable (DG Enterprise 2004a).

Furthermore the proposal mentioned the need to accommodate future developments in the tissue engineering sector, including reassessment of the scope of application, where it was concluded that 'the opportunity to include xenogeneic tissues within the scope of the Regulation could thus be re-examined some time after its entry into force, based on a reassessment of the market situation' (DG Enterprise 2004b: 6).

In a 'joint industry comments' document issued in August 2004, it became clear that industry was less than impressed with the latest proposal. It questioned the definition of 'material of animal origin' and alerted the Commission to not exclude tissue engineered products for which certain manufacturing steps involve the use of viable material of animal origin (such as murine 3T3 fibroblasts for skin cell cultures). Industry continued to argue that 'in fact, many human tissue engineered products are produced using some viable animal material during the production and have a long history of safety' (EUCOMED et al. 2004: 2).

Still the Commission was of the view that 'in principle' xenogeneic material should be excluded from the scope of the legislation.

10.1.3 Complicated exclusions

In May 2005, DG Enterprise published a third and final web-based consultation paper, together with the details of the full proposal for a Regulation, outlining the regulatory strategy (DG Enterprise 2005f). As in previous proposals, xenogeneic materials were out of the scope of legislation, although in this version a subtle alteration was added: excluded were 'tissue engineered products derived *exclusively* from cells or tissues of animal origin', whereas it was subsequently stated that 'nonetheless, this Regulation should apply to human tissue engineered products for which tissues and cells of animal origin are used in the manufacture without being present in the final product, or, if present, only in trace amounts and without being viable.' (DG Enterprise 2005c:

9). Note here how the last part of the sentence on non-living 'trace amounts' was added in accordance with industry concerns over the difficulties in excluding the presence of animal material altogether.

10.1.4 Animal cells in – embryonic stem cells out

A major shift occurred in respondents' views on this Commission position, as can be read from the responses to this consultation round in summer 2005 (DG Enterprise 2005b). Two main points are worth illustrating here, both related to how the proposed Regulation deals with different cell sources. One concerned the use of animal cells, while the other addressed embryonic stem cells.

Arguably the most striking set of responses concerned the exclusion of xenogeneic products. Earlier consultation rounds had generally led to the conclusion that it was too early and too controversial to consider regulating xenogeneic tissue engineered products, although some hints were made over the years towards less rigid definitions and restrictions. This consultation revealed a rather more extreme step, where a majority of the respondents challenged the exclusion of this material on a number of grounds. First it was argued that several products based on animal material are already covered under Community legislation, such as cell therapy medicinal products based on animal cells by the legislation on medicinal products (since 2003) and medical devices incorporating (non viable) animal cells by the legislation on medical devices (already since 1993). On this basis it would not make sense to make an exception for xenogeneic cells under the proposed regulation. Furthermore respondents pointed out that xenogeneic tissue engineered products are already in clinical development in Europe, with more applications in the pipeline, and excluding these from the proposed regulation would have a negative impact on innovation in this field. Next it was brought up how it may be difficult to argue that xenogeneic tissue engineered products are totally excluded from the Regulation, while arguably even more controversial products (e.g. based on embryonic stem cells) are not. Finally by excluding these products, no Community legislation at all would apply to xenogeneic tissue engineered products, meaning that harmonisation would not be achieved, with a fragmented market as likely result (DG Enterprise 2005g: 4-5). Based on

these arguments, it was suggested to include xenogeneic tissue engineered products in the scope of the proposal.

The second main issue concerned embryonic stem cells. Several respondents called for a complete ban on the use of embryonic sources for the manufacturing of advanced therapies. They argued how the Regulation should be unambiguous that Member States are not forced to accept products which contradict their ethical position. The response of the Commission to this issue was extremely defensive. At the same time the responsibility for this sensitive domain was passed on to the SANCO Directive which had addressed embryonic stem cell use more than once in the preceding years. The Commission reply read:

> The Commission takes due note of this concern on such an important issue. However, it should be borne in mind that this matter was extensively debated during the adoption of the European Directive on the quality and safety of human tissues and cells. In this context, the European Parliament, representing citizens, and the Council of the European Union, representing Member States, have recognised that there is, to date, no consensus in Europe upon which harmonised decisions could be taken on the use or prohibition of embryonic stem cells. Thus, decisions on such use or prohibition should, and will remain, a national responsibility (DG Enterprise 2005g: 3).

Furthermore it was repeated, 'to avoid any misunderstanding', that the Regulation would not interfere with decisions made by Member States on the use or prohibition of any specific type of cells.

It was remarkable that the embryonic stem cell issue was only brought up during the third consultation stage, just before final adoption of the proposal. According to some, it was a well-maintained strategy of DG Enterprise to avoid this contested issue, in order to not delay the legislation any further - also given the earlier experience and repetitious debate during the SANCO Directive. An EC official within DG Enterprise who was involved in the earlier stages of the proposal indeed admitted that all effort was undertaken to prevent the embryonic stem cell debate from reviving. The main argument put forward was that the SANCO Directive already deals with this issue, which would imply that DG Enterprise could stay clear of this ethically charged domain. During the time

of interviewing this respondent, the plan was still to have a Directive on tissue engineered products:

> If we develop tissue engineered product on the basis of embryonic stem cells then we will have some problems [laugh]... I refuse to mention this in my [Enterprise] Directive. But somebody may raise the finger and say. And my point is very simple on this. It's to say: OK, we take the Directive from SANCO... on procurement etcetera. We say the procurement is done by them. So give them the problem. If they solve the problem there, then it's over for us.
> (EC official in DG Enterprise A-EU3, 2003)

This line of argument was also communicated in the stakeholders' consultation responses, though perhaps in less explicit terms, where 'the problem of embryonic stem cells' was referred to the SANCO domain that manages the procurement of cells, rather than considering it part of the remit of the product legislation under DG Enterprise. As such, the boundary drawing around the scope of the regulation was aimed at boxing out ethically contested elements.

More than three years after the first consultation round was organised, the Commission presented the final 'Proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004'. This proposal was adopted on 16 November 2005 (DG Enterprise 2005e).

In this proposed Regulation also ethical aspects are mentioned. At first reading these do not seem to include anything new, compared to the provisions of the SANCO Directive. Along the lines of this Directive the Commission is of the opinion that products based on human tissues and cells should be founded on the philosophy of voluntary and unpaid donation, anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient. Respect for fundamental human rights is mentioned, followed by citing the subsidiarity principle where the use or non-use of specific cell sources remains Member States decision. But whereas the SANCO Directive explicitly stated how this also applies to the use of embryonic stem cells, the Enterprise Regulation is phrased in a slightly different way:

> The proposed Regulation does not interfere with national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products based on such cells (DG Enterprise 2005f: 10).

The explicit mention of any specific type of *human or animal cells* reflects the recent debate on including xenogeneic sources under the heading of tissue engineering. Furthermore the reference to sale or supply of products based on these cells is interesting in the context of the Enterprise aim, based on Treaty article 95, to promote a single European market. Thus harmonisation of regulation and the common market objective are threatened by the subsidiarity principle which leaves the use of contested cell sources to national level decision-making. This means that a marketing authorisation granted for a xenogeneic tissue engineered product would be valid only in the Member States where this authorisation does not contradict national legislation.

In this respect there was also another notable change in comparison to earlier drafts. In the final proposal the definition of 'tissue engineered product' was extended to now also include animal tissues and cells:

> Article 2: Definitions
>
> Tissue engineered product means a product that:
> – contains or consists of engineered cells or tissues; and
> – is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue;
>
> A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices. (DG Enterprise 2005f)

In the week before the final proposal went public, trade association EuropaBio convened an industry meeting as a last lobbying opportunity and to discuss the proposed Regulation (Geesink 2005). Members of the Commission and Parliament and several research and industrial representatives presented their views on the proposal issued earlier that year. An official from DG Enterprise explained the general outline of the Regulation. MEP Liese, rapporteur for the SANCO Directive, gave his vision on possible issues for discussion in

Parliament. This meeting gave some preliminary insights on what was to be expected next with the Regulation entering the co-decision procedure. Most relevant was the discussion on ethical considerations in relation to different cell sources.

DG Enterprise official Rossignol first addressed 'the embryonic stem cell issue' which was also brought up during the last consultation round:

> It is clear for us that, first, this debate already took place in the context of the adoption of the Tissue and Cells Directive, which will apply to the donation and procurement of cells used in these products. It is very clear that the competence on the use or non-use of any type of cells, including the use of embryonic stem cells, for ethical reasons is a national responsibility. This proposal should by no means and will not interfere this national competence. So this proposal is, to sum it up, neutral related to these stem cells or issues (Rossignol 2005).

Thus a discourse was presented where the responsibility for embryonic stem cells lies with the SANCO Directive that deals with procurement, while national Member States have a final say in authorising or banning products based on these cells. Slightly more complicated is the use of xenogeneic cells and materials in tissue engineered products. The EC official refers to the different consultation rounds, where respondent of the last one were most explicit in their plea for inclusion, based on already existing legal provisions and on their current use across Europe:

> Xenogeneic tissue engineered products are already, according to experts, in clinical development in several parts of the EU. So there's also the issue of why to exclude these products in a proposal which, as I said, is neutral towards more controversial products like embryonic stem cells. So there was also a question of logic. So we discussed the need to re-include these products (Rossignol 2005).

MEP Liese, rapporteur of the SANCO Directive, agreed with this position, but also pointed out how the European Parliament, whose turn it will be next, might have a different opinion:

> I share the view that it was very illogical to say that xenotransplantation, that xenogeneic therapies are excluded from the scope, but to be not so clear in the embryonic stem cells. You can have different opinions on xenotransplantation, and I anticipate some problems with agreement there with the group in Parliament – maybe they want to ban it or so –

> but I think you cannot ignore that there are already scientists doing clinical trials with animal cells transplanting to human beings... With embryonic stem cells we are not yet in the state of clinical trials, which is why I think the industry could be more relaxed if it's covered or not, and the Parliament will definitely look at this in detail (Liese 2005).

In the discussion session at the end of this meeting the responsible EC official expressed that 'we should not underestimate the political debate on the use of animal cells' (Rossignol 2005).

10.2 The final downfall of the bio-society

As demonstrated so far, gradually the boundaries around the definition and scope of tissue engineering were expanded, where the final Commission proposal considers animal cells part of tissue engineering, and hence of the scope of the legislation. What did not change though were the risk management requirements as set out in the proposal. Here there is talk of long-term patient monitoring and traceability of donors, products and starting materials on which these products are based. But it is well recognised that the use of xenogeneic material does not only pose risks to the individual patient but to society at large by the potential for disease transmission. The proposal does not mention any impacts on the environment or for public health at large.

Interestingly in this respect, an impact assessment study carried out for the Commission in relation to the proposed Regulation dedicates a paragraph to 'potential environmental impacts'. Tissue engineered products could have such an impact through their production process or use. Human cells are considered 'low risk' in this study, but special attention is given to 'ancillary reagents', such as growth media, growth factors, hormones or antibiotics used during the culturing or production process. It is discussed here how 'contamination with higher risk organisms than the human cells used might occur during the production process' (Bock et al. 2005: 53). Given these circumstances, the study states:

> Currently there are no data on potential hazards of hTEPs [human tissue engineered products] to the environment. Due to low production volumes and the rather structural than metabolically mode of action of hTEPs it

> can be assumed that risks will be low. However, these assumptions need to be assessed thoroughly and the inclusion of environmental risk assessment in the proposed regulatory options should be considered on that basis (Bock et al. 2005: 53).

Although the impact study argues that 'environmental risks are considered to be relatively low, because of the low production volume, the use of readily biodegradable substances, the very limited survival of human cells outside controlled laboratory conditions, and strict production conditions' (2005: 53), an environmental risk assessment would have to give more clarity on the potential hazards of tissue engineered products.

The proposed inclusion of animal cells in tissue engineering technologies puts this need in a different context, both in terms of safety and ethical considerations. As also expressed by Glasner and Rothman:

> How would potential benefits and risks of harms be conveyed to subjects when it comes to what is known and unknown regarding transgenic applications, such as the possible introduction of animal pathogens into humans? (Glasner and Rothman 2001)

Lifting tissue engineering from the medical domain into an environmental context presumes different requirements for risk management. An influential approach in this respect is that of precaution, which also relates to uncertainty of risks and effects. The precautionary principle covers 'those specific circumstances where scientific evidence is insufficient, inconclusive or uncertain and there are indications through preliminary objective scientific evaluation that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the chosen level of protection' (Commission of the European Communities (CEC) 2000: 9-10). Although originally only mentioned in relation to environmental issues in the Treaty, the precautionary principle covers a broader range of circumstances to be covered by EU policy. Precaution as risk management tool for tissue engineering has been suggested by one interviewee as possible approach:

> So while we may say, in the short term, a particular piece of tissue manipulation has worked, in terms of some outcome measures, what we just don't know in the longer term is whether that reconnection actually

> causes other problems. And you're then into a decision as to whether the risks are outweighed by the benefits and for a short-term benefit from a patients, in terms of solving their disease, the fact that may cause cancer, five, ten, fifteen years down the line, for example, because you've upset a gene regulatory mechanism. It's a difficult one to answer as to whether it's worth while. You know you can take up precautionary line and say: well we shouldn't do anything until we know for certain what the benefits and the harms are, but I figure on an individual level and there's potential for an individual to consent... although it's, you know, it's very difficult for them to actually know what they are presenting to, but we don't know what the potential harms are and there's lot of ambiguity about what those risks are.
> (Academic scientist in public health involved in clinical ethics committee O3, 2003)

Still the assumption here is that of risk for the individual patient, where public health is not (directly) affected. This notion becomes problematic when tissue engineered products contain animal material.

The inclusion of xenogeneic material in tissue engineering constructs poses several questions of an ethical nature. One of these concerns the level of risk. The trade-off of individual benefit against societal risk is problematic in this domain, as it has implications for the ways in which new medical technologies are evaluated (Welsh and Evans 1999). Whereas the assessment of medical therapies is usually based on considerations of individual risk and benefit, rather than implications for public health and society at large, the use of xenogeneic sources changes this balance towards a broader type of risk assessment needed to encompass the level and extent of both risk and uncertainty. More specific, ethical considerations underlie thinking about unknown risks of a public character and how to assess and manage these risks. One of the implications of dealing with infectious risk to the public, is that the acceptability of risk has to be determined via a public mechanism, rather than on individual patient basis. Furthermore the classical model for informed consent, which is currently based on individual consent for medical interventions, needs to encompass third parties that could be affected. It also requires monitoring and surveillance of not just individual patients but also their close contacts, which raises moral issues about the processes of informed consent (most notably the option to 'drop out' at any point in time) and medical confidentiality (Vanderpool 2002). In addition, this will extend the individual life span, as this type of risk is not a one-off event, thus creating intergenerational

risk and effects over time. In terms of risk management and regulation this means that iterative strategies have to be developed, also to control effects of cross-species mutations and the introduction of new infectious diseases in the human population over time (Bach et al. 2002). Thus the focus of decision-making and regulatory policy changes alongside the shift from individual to collective risk. Also, rather than focusing on a regulatory framework driven by technical considerations, more broad types of risk assessment are needed to accommodate the ethical and social implications of this technology.

As discussed previously, technological risks have become more difficult to assess. Modern technology has created risks that are more complicated and uncertain, more far reaching and invisible, more intense and uncontrollable. To capture these dimensions, more complex types of risk assessment are required (Krimsky 2000). Technocratic risk assessment needs to be extended to encompass the broader societal concerns raised by the far-reaching effects of technological risk and uncertainty (Scoones 2001). In this context, scientific expert knowledge is not sufficient anymore to inform and legitimise regulatory policy, especially in highly contested technological domains. It has been argued that political decisions should be based on expert knowledge ànd social judgement.

This is also where the relationship with broader questions of norms, ethics and values comes to the fore. An important notion concerns the management of socio-political and ethical concerns related to tissue engineering technology. As discussed, these concerns have been largely deprived of in accounts of R&D actors. In contrast, the debate on the SANCO Directive was dominated by ethical concerns. But policy shaping is typically concerned with delivering implementable solutions to narrowly defined science-based problems (judicial default mode). As has also been demonstrated in relation to other innovative technologies, most notably in dealing with GMOs and human genetics, in the institutional management of risk often a functional separation is made between technical assessment versus socio-political and ethical dimensions. In order to institutionally manage complexity and uncertainty in technological risk assessment, responsibilities for policy and regulatory choices are divided up between different expert bodies, while 'moral considerations are allocated to

other areas of professional expertise and social and economic issues are deemed best dealt with by consumer choice and market response' (Scoones 2001:19).

Two observations can be made here. One relates to the role of 'ethical expertise' in Community policy making, while the other concerns the current inability of the EU to manage ethical concerns in the context of regulatory policy.

As discussed in relation to the SANCO Directive, advisory group EGE was to some extend influential in shaping the legislation on human tissues and cells. While the Commission diverged from the Group's advice to limit tissue procurement to public sector institutes, this only happened after prolonged lobby-work by industrial players wanting to establish a level playing field with tissue banks. A subsequent Opinion specifically focused on tissue engineering was rather exotic though, where for example the use of animal cells was not addressed, nor any social impacts of the technology on patient access or availability of products. This chapter has outlined the problematic nature of including animal cells in the current legislative format. As discussed in earlier chapters, under clinical and commercial risk, issues around cost-effectiveness and lack of reimbursement have been mentioned as important stumbling blocks for further development of the technology, affecting both producers and consumers. As such these issues have a large impact on society and economy, and on how the bio-society and bio-economy deal with innovative technology.

On the other hand the EGE Opinion did emphasise areas of potential future concern, such as patentability of starting materials for tissue engineered products. So far this issue has not been taken up in either of the two legislative initiatives. Given EGE's mandate as the official representative of bioethical values at EU level, and aim to take on the role of guardian of the civil rights society (see also: Salter and Jones 2002a) in expressing EU citizen's concerns, perhaps this is more indicative of the technocratic stance of the Commission in relation to these issues than reflecting lack of public concern.
A second notion concerns the way in which the EU treats ethics. In the debate on the SANCO Directive we have seen the continuous boundary-work over

11 Regulating tissue engineering futures?

> Sometimes we try to regulate the future and it's complicated.
> (Official at European Commission DG SANCO A-EU5, 2003)
>
> The problem - very acutely for the industry and the regulators, is that this field is a field where the science has progressed faster than the legislation and I suspect that's a truism across technical, social and ethical aspects of this field.
> (Industrial scientist at multinational consultancy company M-EU8, 2003)

This previous chapters have focused on the policy shaping and decision-making process of the SANCO Directive and the Enterprise Regulation. In earlier chapters the complexity and uncertainty around risks of the technology were emphasised, and the problematic nature of regulating risk in this context. Not discussed so far is how the Commission attempts to deal with this uncertainty and complexity in its regulatory policies. An underlying framework for considering this ambiguity is by analysing the two legislative initiatives in terms of tensions between clarity and flexibility.

It can be argued that both the SANCO Directive and the Enterprise Regulation had to juggle between clarity and flexibility. Clarity was needed over which regulatory approach would be appropriate for tissue engineering, where decades of debate focused on whether this technology could be integrated with existing legislative frameworks on medical devices and pharmaceuticals or if a specific legal framework was needed. The proposed and, respectively, adopted legislations so far give clarity for manufactures and their invested interests in providing a strict but unified framework for tissue engineering, covering quality and safety aspects of starting materials and the marketing authorisation of products. Clarity is also needed for patients in order to provide equal access to treatments. Finally regulators are helped with a classification system that is less ambiguous than in the previous situation. On the other hand flexibility is needed and a tailored approach because of the specific nature of tissue engineered products. Also flexibility is needed to keep up to date with the fast moving scientific and technological developments in this field. But related to flexibility in order to catch up with the rapid evolvement is the need to cope with the

exploring the margins of what is legally possible in terms of incorporating ethical concerns in Community regulation. This has been shown to be an elaborate and complicated affair, which significantly shaped the content and progress of the Directive – with risks of stalling in the final stages in Parliament. A trading zone was created in which cultural values have to compete with a moral economy in which 'ethics' has become subject to trade in exchange for political consensus.

In the light of the proclaimed need to also take normative, political and ethical considerations into account when deciding on the social acceptability of risks, it has been proven impossible to define uniform decisions that are acceptable within the whole Community. Given the diverging positions of Member States on the authorisation or prohibition of embryonic cell sources, consensus at EU level, and thereby the possibility for governance, is lacking. The EU has to balance here between universal European-wide agreed criteria and national concerns. Values are generally locally produced and maintained, and the European regulatory state is not equipped, nor mandated, to manage this diversity and interfere with decisions at this level (subsidiarity). Regulating ethics at this level is thus a socio-political oxymoron.

To sum up, my case study of tissue engineering regulation by and in the EU adds to an understanding of the limitations of the institutional governance of risk and the complexity in managing moral dilemmas at this level. As such the bio-society has to look for alternative models in order to become a reality.

different risks associated with the diverse types of tissue engineered products. As a Commission official explains this dilemma in relation to the SANCO Directive:

> So there is the concern that how fast is moving the advances in tissue engineering. So when we consult and create a new regulation of tissue engineering you have to consider that from year to year things are moving very fast... we should have to find a more flexible way for it. Flexible way, but from the other side have to ensure to the population the basic criteria of quality and safety. So I think that in the definition of tissue engineering everybody has to take into account all these principles. So it's not only a question of scientific definition but also a question of other interests because we cannot forget one thing where we talk about regulation; that we are not working with scientific definitions. We are working with legal definitions who have practical consequences. (EC official in DG SANCO A-EU5, 2003)

Balancing between clarity and flexibility is furthermore complicated by the inevitable regulatory lag. In the light of the Enterprise Regulation, which became part of the strictly controlled medicinal product approach, this Commission official explains:

> There are many, many other things that I cannot plan at this moment. So the idea is to have a legislation that is quite flexible. And this goes against the spirit of the pharmacy, where... you have the tendency to want to fix all the details of the rules of what has to be done for checking, etcetera - where at this moment I am not able to describe what will be in ten years from now necessary. And don't forget that a directive - if you want to change it you need at least three years of working on it. So we will be always running after, if we try to be precise, we will always be running after the development and impairing the development (EC official in DG Enterprise A-EU3, 2003)

In order to provide flexibility, the comitology procedure became integral part of both legislative initiatives. Comitology is a peculiar instrument, and an often overlooked exponent of the EU expert system. 'Comitology committees' are made up of civil servants as experts representing the Member States, and assist the Commission in exercising its implementing functions. After it has been decided what should be legislated (so after the Parliament and Council have adopted legislation), the Commission is authorised to work out how this should be done, with a mandate to fill in technical and detailed requirements. The work of the comitology committee includes taking decisions on the detail of the implementation of Community laws and the adaptation or updating of

Community legislation in order to take account of technical developments (European Institute of Public Administration (EIPA) 2000). This procedure is used for measures relating to protection of the health or safety of persons, animals and plants. It also plays a decisive role in shaping the implementation phase of tissue engineering regulation.

Taking up detailed rules in a central Directive or Regulation reduces the flexibility needed to adapt regulatory requirements. Both the SANCO and Enterprise legislations are limited to fundamental issues and basic requirements, with additional instruments of technical requirements via comitology and standard development or guidelines for the more specific aspects - for example in relation to safety testing. The main reason for recourse to comitology in the SANCO Directive was to act quickly upon new scientific insights, most notably in the face of emerging risks of transmission of communicable diseases.

The decision on what to include under the basic framework of the legislation and what goes to comitology, is a very political one. As the following interviewee explains, involved as advisor in the draft SANCO Directive and future member of the comitology committee:

> The problem with the Directive is that one never knows if you have a Directive. I think that the first message is that the Directive is a good move... to have minimum regulations... so a very important document for starting towards this. The second point is this will be out of importance if afterwards the comitology developing the technical annexes does not do a very good job. So the secret lies both in the main text of the Directive but also from the work that will be done in committee in the comitology process, in setting up the technical annexes which are the core of the safety and quality of the products.
> (Director national transplantation agency and advisor SANCO R-EU6, 2003)

But while the regulatory lag in tissue engineering might be eased by arrangements for a flexible regulatory approach, this flexibility also constitutes uncertainty.

Furthermore, what is subject to comitology is not uncontroversial. During the debate on the SANCO Directive MEPs fought over which provisions would

remain in the main legislative text, which is dealt with under co-decision, and what is left to Member States representatives under comitology. This mainly concerned issues around donation. This points towards another problematic notion, which is that comitology is not a very democratic procedure.

The comitology procedure has been criticised over the years, most notably over the issue of what should be decided in a legislative or implementation procedure, and where to draw the line between the two. Furthermore the complexity of the system and lack of transparency of the committee structure has fuelled fears of these committees as a Trojan horse, by which national interests are carried into the implementation process of Community law (Neuhold 2001). The two extracts below reflect some of the concerns:

> Committees are seen as embodying the most opaque and even secret part of EC decision making. They are considered to be the most intransparent aspect of the EC system of governance (European Institute of Public Administration (EIPA) 2000: 94).

> Comitology: short hand for national bureaucratic influence, lack of transparency and accountability of industry, academic and bureaucratic experts (Altenstetter 2004: 12).

The 'comitology debate' concentrates on the question in how far comitology committees affect the EC implementation process, how they are controlled and by whom (Neuhold 2001). Some speak of 'government by committee' in this respect (European Institute of Public Administration (EIPA) 2000: 75). Concerns are expressed that comitology procedures give extensive law-making powers to invisible and largely unaccountable committees made up of Commission officials and civil servants from Member States (EurActiv 2006). As a system, the comitology procedure has raised issues of democratic legitimacy of the EC policy process, with the committees reflecting the 'democratic deficit' and 'bureaucratic and technocratic bias' of the EC system, given the committee members are not elected on a democratic basis and the meetings are not open to the public.[62] Yet others see institutional conflict between different EU institutions. As also visible in discussions on the SANCO Directive, especially the European Parliament (EP) has expressed critiques that

[62] Although it should be noted that public access to documents has improved since the revised comitology decision of 1999 (EFTA, 2002).

comitology is used as a strategy of the Council to circumcise the participation of the EP within decisions (Neuhold 2001).

Opposed to viewing comitology as democratic deficit, it has also been argued that these fora mainly deal with technical issues, retaining their legitimacy by efficiently producing quality output (Majone 1994). One study demonstrated that these committees mainly manage routine matters (European Institute of Public Administration (EIPA) 2000). Still, some are concerned that the members of comitology committees are involved in more than technical issues and also find politically sensitive subjects on their way (notable examples being biotech regulation and BSE). A provisional statement in my study is that in the case of the SANCO Directive strongly opposing views became explicit between the Parliament and Council over the question what is considered 'technical detail' suitable for comitology versus what are the politically sensitive issues that need to be dealt with under the democratic scrutiny of co-decision. The explosive discussion on embryonic stem cells demonstrates that the demarcation between 'technical' and 'ethical' detail is difficult to achieve.

During the co-decision procedure it is decided which provisions are suitable for a comitology approach. With the innovative character of tissue engineering it can be argued though whether comitology is the most appropriate tool to deal with new insights. The innovative character of tissue engineering, but with that the associated risks, determines in how far new developments can be suited under this approach. There is a thin line between adjusting technical requirements and using comitology as a backdoor for accommodating potentially more risky and more controversial developments in this domain. For example, the current Enterprise proposal includes xenogeneic cells, with the argument of legalistic consistency and current (though experimental) practice. Interviewees have pointed out how in the future tissue engineering can include a much more diverse range of products than currently on the market. From currently available and relatively simple applications of tissue engineered skin, cartilage and bone, a 'slippery slope' could lead to including potentially more risky future applications under the tissue engineering heading. Embryonic stem cells and animal cells have already been addressed in this respect. Furthermore, 'to complicate matters further, it is quite likely that some TEPs

[tissue engineered products] might be used as vehicles for gene therapy, or cells in the product might have been genetically engineered.' (Lloyd-Evans 2004: 54). By extending the definition of tissue engineering, as witnessed in the Enterprise Regulation, it becomes difficult to control potentially controversial applications.

In other words, while the comitology procedure has been developed as a tool to manage complexity and uncertain risks, which became especially relevant in the post-BSE era, this same procedure raises questions about the legitimacy of the current regulatory system in the EU, technocratic versus democratic principles, and the difficulties in drawing boundaries between technical details and ethical concerns.

In this context it is important to further analyse the comitology developments for the SANCO Directive and Enterprise Regulation, which are currently being negotiated. Future research should address this matter.

Conclusion: boundaries of risk and regulation in a political economy of medicine

The political economy of tissue engineering regulation is crucial to understanding technological innovation in the EU. This research analyses these developments in terms of a tension between the bio-society and bio-economy. It addresses questions on risk and safety, clinical application and commercial activities, and relates these themes to social and ethical considerations in policymaking. Such matters are central to discussions about the development and regulation of European biotechnology. To open up these questions requires addressing the risk domains of such technologies. At present, as shown, there is a risk gap that is not met by EU regulation. The research concludes that the ethical questions raised by tissue engineering cannot be answered at an EU level, for reasons of realpolitik.

This thesis started with the introduction of two guiding concepts, bio-economy and bio-society, which are key to understanding the shaping of a regulatory regime in tissue engineering. I have argued how economic imperatives and ambitions to drive the EU further towards a global competitive player in the 'knowledge-based bio-economy' created a strong underlying framework for stimulating biotechnological innovation and the life sciences. Tissue engineering became a significant component in this ambition. Since the 1980s this economic paradigm has created tensions with quests for bio-societal values such as sustainability, leading to calls for awareness of social as well as technological aspects of the applied life sciences. In this pre-genomic era, a model was presented based on the assumption it was indeed possible and desirable to create 'a society based on the conscious management of self-organising systems for the sustenance and enrichment of human life and purposes' (Green 1984: 9).

However, social demands were overshadowed by enthusiasm for biotechnological solutions by most European governments, with increasing amounts of budget and political willpower dedicated to expanding the new life sciences as guardians of the global economy and world well-being.

While public concern over biotech applications increased, the EU's technology policy only started to change after the BSE crisis, the controversy over GMOs and the discussion on biotechnology patents (Borras 2003). During the last decade the innovation agenda has opened up to include questions of risk and social sustainability. Social and ethical considerations became instrumental in creating a common vision; science had to deliver what 'the people' need in compliance with an acceptable ethical consensus. This setting provides a backdrop for analysing the demands for technological innovation as well as socio-political and ethical considerations to be taken into account in the development of regulatory policy for tissue engineering. The example of a typical tissue engineering product cycle (Apligraf) as discussed in chapter 1 gives a flavour of the diverse technoscientific, clinical, commercial, regulatory, social and ethical aspects of biotechnological innovation in this domain.

But as also described, the European Commission, as main legislative body at this level, played a dual role in both stimulating biotechnological innovation and in regulating the field. This led to frictions in institutional and ideological aims. Whereas the promotion of trade is considered a long-term strategic goal of the EU, health and safety regulation is a rather novel challenge.

Until recently health policy was a matter of exclusive member state autonomy and concern. The Treaty of Amsterdam (1997) was the first piece of communal legislation that made public health protection a formal Community objective in its own right. More specifically it expressed the need for community wide legislation on human tissues and cells, which provided a starting point for further policy developments as discussed in this thesis. At the same time this Treaty reflects the dual legal basis of Community action, where article 152 on public health had to be integrated with the one covering completion of a single European market (article 95).

The Community is now one of the key actors in European health and safety regulation, as also witnessed in the case of tissue engineering, and funding is secured in support of the explicit significance of biotechnology applications in the health domain. For example in the latest Framework Programme (FP7) the healthcare market was declared a strategic part of the bio-economy.

These developments are partly covered in social scientific discussions about the impact of the life sciences and the dynamics of health technology innovations at European level and scale. In addition to an extensive body of knowledge on agricultural biotechnology applications, some social scientific literature has focussed on more recent policy developments in the EU health domain. For example the rise of a European regulatory state has been described for pharmaceuticals (Abraham and Lewis 2000, 2002) while processes of Europeanisation have also been analysed for medical devices (Altenstetter 1996, 2004). Also the EU management of human genetic technologies has gained scholarly attention (Salter and Jones 2002) and more recently several studies have been published on the role of human embryonic stem cells in developing European policy (Salter 2005, 2006). My case study of tissue engineering regulation adds to the increasing understanding of health technology applications in multilevel governance. By drawing on understandings in the political economy of medicine, and analysing implications for conceptual discussion within science and technology studies (STS) about boundary work and regulatory science, this thesis has focused on elements of risk and regulation, and on the shaping of a regulatory regime in tissue engineering. The main set of findings can be summarised under general headings reflecting differentiated notions of risk; the reproduction of perceived risk, uncertainty and the translation from risk to regulation; negotiations over the boundaries between techno-science and socio-politics, including the role of moral arguments in EU regulatory policy; stakeholder participation in regulatory science; and finally the overall implications of these developments for reconfiguration of understandings in the social scientific and STS literature.

Below I revisit these main findings and outline the implications and value of my approach for fellow academics and policymakers wanting to understand the dynamics of novel health technologies at EU level.

Differentiated notions of risk

Exemplified by developments in genetics and the creation of the human genome project, risk has become a key focus of attention, where the human body has been redefined as a field of risk (see also: Gabe 1995; Rose 2001). Risk has also entered political debate in the EU, and represents in many ways the much wider political and social concern about the governance of science in the EU (Borras 2003). Political discourse has centred on risks associated with new biomedical technologies, with various strategies developed to control risk. Here regulatory efforts were targeted at potential hazards while at the same time problems arose of lack of scientific knowledge about these new sciences and technologies.

An important starting notion that has informed my analysis in this context includes the notion of 'risk', which is operationalised in the following way. First of all, a main concern for the conceptual use of the term 'risk' in my study relates to the understanding of risk perception as a socially constructed concept. My notion of risk departs from the politics of risk definition, based on the assumption that 'whoever controls the definition of risk controls the rational solution to the problem at hand '(Slovic 1999: 689). In tissue engineering there is no such thing as 'the definition of risk' though, as broad variability exists between different professional groups on how to frame risk issues, highlighting 'the contested nature of who is defining what as risk and how' (Adam et al. 2000: 4). These different frameworks of risk are important because they dictate which 'solutions' are constructed in the policy process, e.g. which risk management strategies are considered valuable and feasible, and what information is needed and useful in reaching a decision. It also has implications for the legitimacy of different viewpoints in the policy process. By analysing the key dimensions of the construction of risk in tissue engineering, and the different dimensions and values attached to variations in risk, risk framing is linked to policy implications. The construction of risk discourses is tied in with the expression of a technological, political or social acceptable solution. Thus the definition of risk is at the same time the definition of a solution.

Second, and in contrast with many traditional approaches in risk analysis, my understanding of 'risk' is not limited to narrow techno-scientific parameters. A technical approach of risk does not take into account the complex and socio-political nature of phenomena, including political dimensions (such as conflict or discrepancy over definition of what risks are and how they should be managed) or ethical concerns (including values in judgement of risk). By focusing on underlying values in risk assessment and risk decisions, the starting point of analysis is a concern with the perceiver of risk, rather than with risk as a phenomenon in itself (which, in technical terms, is usually expressed as probability in one way or another).

Moreover, in this thesis I have demonstrated the interrelations between conventional notions of risk – often expressed in safety terms, 'from the laboratory side of things' - to the broader arena of innovation where also clinical and commercial concerns determine the perception of risk. By tying together these three distinct domains of laboratory, clinic and market practice I underline the significance of studying risk within a broader framework. This has implications for risk assessment and risk management studies of innovative technologies, as these tend to fail to take into account both the contingency and uncertainty around 'the definition of risk' and the differentiation in risk perceptions underlying these analyses.

The main research question addressed here concerns how and to what extent expert definitions of risk are articulated in tissue engineering R&D and in which ways they are framed and differentiated. My research has sought to unravel the dimensions of different types of risk as perceived by professional actors (scientists, clinicians and manufacturers) involved in the research and development stages of tissue engineering, thus representing a model of the early innovation process or front-end stage where products emerge from laboratory to clinic into the commercial cycle. Based on these accounts I developed a three-tier typology of risk around domains of laboratory, clinic and market, which I labelled technological, clinical and commercial risk. These different risk domains were described in chapters 4 to 6.

Technological risk covers concerns related to the processing and manufacturing of human tissue and cells, and reflects an overall concern with safety (chapter 4). The first main set of technological risks are related to cell sourcing and handling, including disease transmission, contamination and infection. Disease transmission refers to the transmission of (infectious) diseases between humans (such as HIV and hepatitis), but also potential transgenic transfer and the introduction of novel human and animal viruses (zoonoses) into the human population. Contamination and infection of the tissues and cells can take place during the production and manufacturing process, and can include contamination of the source material.
Both disease transmission and infection are mentioned as dominant technological risks, especially, and initially, in relation to the use of donor material. Autologous applications, on the other hand, are seen as relatively safe and 'risk-free' and as such unproblematic from both a technological and patient perspective. But closer inspection of the cell culturing process reveals how autologous cell sources also inhibit a problematic frame, most notably by the inclusion of xenogeneic material.

A broad second category of safety concerns is related to the cell behaviour during the processing and manufacturing of tissue engineered constructs, and after implantation in the human body. This includes (immune) rejection by the body, but also problems with controlling the cell growth (unwanted cells, cell modification, uncontrolled cell proliferation and differentiation) to prevent tumour formation or other unwanted effects such as the 'travelling' of cells through the body to places where they can cause harm. Also the interplay between cells and their supporting materials, so-called cell-scaffold interactions, and bio-incompatibility are issues addressed under this heading. Furthermore there are concerns with the limited shelf-life of many of these products and both the quality and quantity of cells needed to be effective, e.g. to produce a sufficient amount of quality living cells for transplantation into the patient (cell viability). Other factors include toxicity of processing materials, such as growth factors and antibiotics added during the culturing process and to support the cells during transport, and problems with the sterility and final testing of the product.

Whereas technological risk is mainly concerned with the safety of tissue engineered products, **clinical risk** considers safety as part of a more complex and elaborate trajectory of performance testing, taking into account the efficacy of these products over a longer period of time. Clinical risk is about perceptions of risk related to clinical evidence available for these products (chapter 5). The main issues under this heading are the question of efficacy of tissue engineered applications (if they actually 'work'), what clinical evidence is available and how to interpret this, and what tools are needed to evaluate the efficacy and safety of the technology on the long-term.

Chapter 5 started with the perceived lack of clinical evidence currently available for most advanced tissue engineered products that have entered the clinic. Clinical efficacy is relevant in the final stages of the innovation process, in getting marketing approval or reimbursement for products, but also earlier in the trajectory. Assessment of these products is problematic already in the pre-clinical stage, where new therapies are tested in the laboratory and in animal studies to determine their safety (and toxicology) before entering human trials. Especially the relevance of animal models has been questioned, because of the dependence of tissue engineering technology on the performance of cells and tissues in the human body. A case study of one particular advanced tissue engineering application, autologous chondrocyte implantation (ACI), illustrates many elements of the debate on efficacy and safety testing in this area. One of the main conclusions here, which also affects clinical practice and policy development, is that the existing models for assessing efficacy and safety – most notably the golden standard of the randomised controlled trial – are not adequate to evaluate experimental therapies such as tissue engineering. Furthermore, and this connects to the third category in the risk typology, issues around clinical efficacy also translate into cost- and reimbursement trouble. The development costs for tissue engineered products are generally high. For example tissue engineered applications in wound care (for the treatment of diabetic ulcers or burns) have to compete with a variety of clinical alternatives, some of which have an established safety profile, and most of which are generally cheaper and/or easier in use. Thus in addition to safety and efficacy, cost-efficacy plays a more prominent role in the evaluation of this particular technology. Cost - rather than value for money, as advertised by many developers - becomes an 'added' stumbling block for the introduction of these

products into the clinic and marketplace, but also in gaining long-term experience and gathering outcome data on clinical efficacy. Most notably, demonstration of efficacy is needed in some countries to get marketing approval for tissue engineered applications, depending on the regulatory framework, which puts pressure on developers to collect efficacy data and conduct cost-benefit studies. But marketing authorisation is not sufficient, and regulation is only a stepping stone to gaining reimbursement for these products by national insurance and healthcare providers. While regulatory initiatives can be set and negotiated at European level, the health insurance system in Europe is not standardised: Individual EU Member States have separate national arrangements for their respective health care systems, whether public or private, leading to a wide array of care and reimbursement options. To date, tissue engineered products are not generally reimbursed in any European country, mainly due to lack of cost-effectiveness data. Many of the tissue engineered products are still in early stages of development and the small biotech companies involved do not have the resources for large, long-term clinical trials to provide information on the cost-effectiveness of the treatment compared to conventional alternatives (EC 2004).

This brings us to **commercial risk**, which refers to concerns about the market and business climate for tissue engineering, and includes factors to do with cost and marketability of tissue engineered products (chapter 6). A main commercial risk is cost and cost effectiveness, to be understood as part of 'fourth hurdle' strategies representing the increasing need for manufacturers to demonstrate the economic value of their product before they are able to obtain marketing approval and reimbursement. Lack of reimbursement is an economic risk for commercial developers, but the limited uptake by national health service systems has broader implications in the potential for social and health inequalities. While it seems like manufacturers are most affected by fourth hurdle policies, implications for patients include the limited availability of potentially beneficial technology. As such commercial risk affects both producers and consumers. These issues have a large impact on society and economy, and on how the bio-society and bio-economy deal with innovative technology.

But commercial risk also has a broader connotation. These developments need to be placed in the context of an unstable and vulnerable commercial environment of predominantly small start-up biotech companies that do not have the means or expertise to successfully commercialise and launch products in a climate of fading investors' confidence and lack of regulatory controls. This is especially pressing in the case of autologous applications, the main focus of R&D efforts by European developers, where issues around scaling up and a complicated competitive environment have led to disappointment over commercial potential and market performance. Furthermore these developments are taking place against a socio-political background of diminishing public confidence in biotech more general. Especially in Europe concerns over controversial technologies such as GMOs and health scares such as BSE have led to a risk-aware (if not risk-averse) climate with increasing safety controls.

In chapters 4 to 6 it was demonstrated how different risk frames are defined and redefined by professional R&D groups in this domain in terms of quality and safety, therapeutic effectiveness and in relation to cost efficacy and marketability of products. Whereas these chapters discussed the three branches of the risk typology in relatively segregated format, in chapter 7 the risk perceptions across these different domains are reviewed in order to accommodate the constitution of different values attached to the risk objects and to elicit alternative dimensions in the perception and acceptability of risk. The biological components that become starting materials for tissue engineered products serve as powerful boundary objects in this respect. Thus I have interpreted the classifications of risk with the introduction of a 'risk hierarchy' and 'risk balance'. The **risk hierarchy** is a reclassification of risk in terms of the particular source material used for tissue engineered constructs. More specific, autologous applications are generally considered 'less risky' than products based on allogeneic material. As demonstrated though, this perception becomes problematic with the inclusion of xenogeneic material in the cell culturing and manufacturing process for both the autologous and allogeneic engineering routes. Furthermore I have argued how the particular cell source determines not only scientific endeavours but also drives clinical concerns and commercial strategies. It is here that the risk hierarchy becomes a more

dynamic model, where risk in techno-scientific terms takes on a different meaning and value in clinical and commercial domains. Furthermore, risks related to particular cell sources have led to different regulatory scenarios, where initially a distinction was made between autologous and allogeneic cell sources in regulatory controls, while subsequently this distinction was abandoned. In order words the ambiguity in this particular risk frame resounds in the regulatory debate and policy shaping around tissue engineering.

But in addition to risk variability per domain, interviewees took into account the population affected and the short versus long-term effects in both perceived risks and benefits of these applications, underlining the importance of the levels of aggregation and the time-scale involved. A second dimension of risk described in chapter 7 is what I have called the '**risk balance**'. The risk balance is about acceptability of risk, where perceived risks of tissue engineering are differentiated into levels and degrees of risk for particular applications, subsets of populations, and the envisaged effects over time. The risk balance thus takes into account the specific therapeutic purpose of the tissue engineering application (over a spectrum from life saving to merely cosmetic) across stages of the innovation process, and is concerned with both risks and benefits of the technology - and the trade-off between the two in determining acceptability of risk. It has been argued that tissue engineering technology will always imply a certain level of 'residual risk' as demands for a zero risk society are considered unrealistic. But this residual risk is not a generic category, as the risk balance also looks at the population at risk and the final risk-receiver, where acceptability is dependant on whether potentially harmful effects are limited to individuals or the society as a whole (e.g. individual versus collective risk) and in how far these risk are extended over time (inter-generational risk). Thus also the risk balance is a socially constructed notion.

The content of the balance of risk and the hierarchy of risk provide the context for risk management approaches, making the transition to the social world of regulation as discussed in subsequent chapters. But by making the transition from risk assessment to risk management, one could argue that some consensus is needed on the definition of risk, as this dictates policy solutions to risk-based problems. In other words, some negotiated common framework was

to be articulated, in which interested individuals and institutions adopt a similar or at least compatible conceptualisation of the risk issue in question. As such, tissue engineering is typically treated as a generic technology for regulatory purposes. But many interviewees have argued how a specific and alternative type of risk assessment is needed, to accommodate both the developing character of the technology and the associated (unknown) risks, with its diverse current and future applications.

A risk-based approach in tissue engineering is problematic for policy purposes given the large heterogeneity of applications currently on the market and in experimental stages of development. Regulatory policy has to balance between covering the current product portfolio, of applications 'out there' at this moment in time, and of envisaged products potentially entering the market in the near future. Risk assessments require looking at the range of future options, and the potential benefits and risks of each. Regulation has to be able to incorporate the diverse and innovative nature of products, and be flexible enough to adapt to technological progress to prevent itself from running out of date. As a developing innovation, tissue engineering is an interesting case for the conflict between the level of certainty that industry needs in terms of consistent rules and predictable evaluation, while at the same time flexibility is needed in the evaluation of safety and efficacy of these products, given their complexity and broad range of applications (Bartlett Foote 2002). Therefore one particular concern in the development of a regulatory framework is the difficulty of foreseeing the consequences of a technology during early stages of development, and designing control mechanisms for when the potential harmful consequences of the technological innovation become visible for society. This is furthermore complicated by the fact that significant risks might develop that have not been seen in healthcare before. Here notions of uncertainty and complexity pose difficulties to regulators trying to cover future outcomes of innovative therapies.

The reproduction of perceived risk, notions of uncertainty and the 'translation' from risk to regulation

An underlying perspective in the evaluation of perceptions of risk in tissue engineering concerns the unknown character of many of these risks. With progressing innovation and change in Western society, new forms of uncertainty are created, and with them uncertain risks (Nowotny et al. 2001). While it has been demonstrated that many interviewees express views about the ability of controlling risk, for example via the implementation of quality control systems and safety standards in laboratories and manufacturing units, tissue engineering is an example par excellence of a technology with many 'unknown unknowns'. Uncertain risks spring from the inherent unpredictability due to complexity.

Many of these uncertain risks are of a technological nature, where it is unknown what effects and potential harm can be expected from, for example, the use of donor cells in terms of disease transfer. Interviewees have stressed how the behaviour of living cells in the body and of biological materials in general are difficult to estimate. But this technological uncertainty also constitutes socio-political and institutional ambivalence.

Tissue engineering technology is indicative of the emergence of a new discourse of both scientific and political uncertainty. Political and institutional strategies in this context have focused on risk as dominant discourse, where expert knowledge and scientific rationality would overcome the various challenges of the technology and its diverse applications in terms of safety and socio-political controversy. At the same time a political and regulatory discourse has arisen which had to deal with ethical ambivalence and moral dilemmas created by tissue engineering technology. The notion of risk was for a long time based on probabilities and associated with rational decisions. This study has underlined the social constructive character and 'plural rationalities' of risk, where different actors draw overlapping but also competing boundaries around the diverse risk domains and around what is considered 'regulatable'. Furthermore the notion of uncertain risks has drawn attention to the 'puzzling lack of sureness' that has become dominant in so many contemporary techno-

scientific domains. But tissue engineering is not just a case of scientific uncertainty which complicates regulatory policymaking; it also shows overlap with political and, arguably, social uneasiness on how to go about assessing this novel technology. Where uncertainty has been described as arising from a situation of incomplete scientific information, which has constituted precautionary approaches in diverse (environmental) policy domains, socio-political uncertainty was witnessed in the analysis of the regulatory debate on tissue engineering. This uncertainty was driven by different boundary drawing exercises around moral dilemmas regarding cell sources; a situation which was 'solved' in the case of the SANCO Directive by recourse to a legal framing of ethical concerns around embryonic stem cells via the subsidiarity approach. Uncertainty as such relates to boundary drawing in domains of risk, although it can be argued that risk and uncertainty can be considered separate dimensions in a spectrum, with the notion of uncertain risk as more appropriate depiction in the case of tissue engineering. This uncertainty relates to science and technology, and extends to the political and social (Gottweis 2005).

The question of dealing with complexity and uncertain risk at EU level is pervasive. The precautionary principle has been used in this respect as one pragmatic but highly criticised approach in biotech governance of several agricultural applications. The case of tissue engineering added an additional – and equally controversial – solution by means of the comitology system, which has gained considerably less scholarly attention in the social scientific literature. The management of uncertainty in EU policy as such has been problematised broadly, but the discussion about this uncertainty takes place far away from the EU stage. The notion of uncertain risk as described in this thesis - reflecting concerns by scientific, clinical and commercial stakeholders alike – has not entered the policymaking circles and public debate about risk management approaches for tissue engineering applications, which is a missed opportunity in the context of future development of highly innovative but contested health technologies.

But pragmatic approaches provide only part of the solution. An equally strong interpretation informing my analysis is the problematic nature of EU governance and the questionability of the very notion of risk regulation.

First of all, moving from perceptions of risk to risk regulation implies a different concept and scope, and involves a different set of actors. Risks are redefined and attributed a different value when entering the policy domain. Typically, risks are characterised in terms of probability, as the possibility of unwanted or adverse effects occurring. Deeply rooted in this concept of risk is the understanding of a causal relationship between action and effect, and the need and indeed ability to avoid or modify undesirable outcomes, which discriminates risk from danger (Vos 1999). Risk is thus both a descriptive and normative concept. Furthermore, risks can not be separated from the contexts in which they occur. Thus rather than treating it as an almost 'stand alone' or independent concept, the meaning of risk takes a different form and shape in a regulatory context, where perceptions of risk have to be translated into systematic means of risk assessment for regulatory purposes. Most notably, when risk forms the basis of regulation the notion of acceptable risk is becoming increasingly important. This is also where a new set of actors comes in, as regulatory risk is the domain of regulators, policy advisors and experts. These actors are faced with particular difficulties in interpreting risk and determining the level of acceptable risk – not the least because of ambiguity about the definition of acceptable risk.

Regulation, then, is often understood as a fundamentally political-economic concept, interpreted as a way in which governments attempt to manage the tension between protecting the public and allowing producers to trade and make their products profitable. My research has discussed regulation from a multilevel governance perspective, where tensions became visible between different institutional actors interacting in a highly complex environment; the socio-political context ('bio-politics') and the strong economic undercurrent have been analysed in this respect.

These developments are set in a risk society (Beck 1992) where risks have become more global, unknowable in advance and collective in their incidence. Perceptions of increasing risk have called for more elaborate regulation to maximise safety and protect consumers and citizens against potentially risky substances. The globalised character of increasingly uncertain risks also

means that nation states are no longer perceived to be the best risk managers (Irwin and Michael 2003).

With the increased interference in health and safety regulation, EU institutions are faced with conducting risk assessment and risk management tasks that were previously decided upon in the national context. This poses several regulatory difficulties, most notably in the relationship with individual Member States. One such issue concerns the impact of regulation in the light of the transfer of powers from national to European level, and the EU competence in dealing with risk and safety of innovative technologies. This includes legal questions about rule implementation and highlights most notably the principles of subsidiarity and proportionality, which have been particularly influential in tissue engineering regulation.

The risk society has created a regulatory society, where regulatory action involves the assessment of risks associated with specific substances or products and based on this are regulatory decisions on how to manage these risks. While adopting a framework of risk as the basis for regulatory action has remained largely unquestioned, the type of risk involved in these provisions has stirred debate (Newell 2002a, 2002b). Risk is not a generic category, and some have argued that the selection of particular risk issues reflects the willingness of the state to accept responsibility for certain problems (Levidow et al. 1996). The level of acceptable risk forms a typical basis for regulatory action, but it also constitutes a very difficult notion to translate into policy because of the social constructive and dynamic character of what is perceived as acceptable risk at one point in time and space. Thus acceptable risk is both a political and regulatory tool, both a scientific concept and a policy objective, belonging to the domains of both risk assessment and risk management. The acceptability of risk then becomes a regulatory instrument in determining which risks society can take on, and which as such implicitly harbours a ranking of norms and values (Vos 1999). In this way, risks cannot be isolated from social and political questions about acceptable levels of risk and uncertainty.

In this thesis I have discussed how the regulation of risk, especially in the health and safety domain, encompasses estimations of both a scientific and

social value, both of which are subject to ongoing change and adaptation. I have also questioned the conventional approaches in risk analysis, pleading for a rethinking of existing models and assumptions in this field based on my tissue engineering case study.

First of all, risk as related to modern technologies needs to consider the complexity, uncertainty and ambiguity inherent in the interaction of modern technology, society and the environment. Yet many conventional risk assessment strategies are ill-equipped to take into account these diverse criteria in the face of uncertainty and indeterminacy, as they are usually based on the assessment of a limited number of criteria where technical assessments are seen to be sufficient (Krimsky and Golding 1992). In other words, more complex types of risk assessment are required (Krimsky 2000). Further, in this context the need has been expressed for an extension of technocratic risk assessment to encompass the broader societal concerns raised by the far-reaching effects of technological risk and uncertainty (Scoones 2001). Society requires a 'broader' socio-political and economic assessment of the risk of its technologies.

A second set of understandings that my case study adds to existing literature relates to the assumed linear relation between risk and regulation. Many theories on risk regulation follow a science-based approach. Also interpretations that question the politicised nature of risk regulation, and/or the functional distinction between risk assessment and risk management (as many 'regulatory science' theorists claim), are based on the assumption of a linear relation between risk and regulation. In this context, the 'regulatory regime' concept is too reductionist and one-dimensional. It fails to enable an understanding of the more complex dynamics of tissue engineering technology. More in particular, I argue in this thesis that the identification of risks does not lead to straightforward solutions in the regulatory domain. My study has demonstrated the problematic nature of this assumption by focusing on risk domains as constructed by R&D actors, while subsequently analysing the regulatory 'transfer'. Here it becomes clear that many risks are not 'regulatable'. Put simply: on the way from risk to regulatory policy certain risks get lost in translation, thereby leaving behind a '**risk gap**'. Resembling notions of a

regulatory lag, there is a gap between the expression of technological, clinical and commercial risks and a regulatory solution. I make this argument more explicit by briefly rehearsing the developments around the two regulatory initiatives analysed in this research: the SANCO Directive and Enterprise Regulation.

The objective of the SANCO Directive is to cover quality and safety aspects of human tissues and cells, thereby taking technological risk as the focal point of departure. The Enterprise Regulation covers the marketing of products, but not the commercial risks associated with their therapeutic use. While introducing opportunities for commercialisation of products in the single European market, the main commercial risk concerns of cost-effectiveness and reimbursement are excluded from the EU policy domain. Decisions on the organisation of healthcare systems are left to Member State level in accordance with the principles of subsidiarity and proportionality. Furthermore, in the latest proposal for a Regulation by DG Enterprise, decisions on the criteria for clinical efficacy (in this study described under clinical risk) were referred to comitology. The implications of this construction are as yet unknown.

These examples imply that technological risk is to some extent addressed in the EU regulatory domain. However, EU policy does not tackle the particular boundary objects within this domain (the different biological materials), in part because it does not disaggregate the risk hierarchy. An early proposal for the Enterprise Regulation discussed the possibility of a two-tier approach for autologous and allogeneic cell sources, based on the perceived diverging levels of risk. This proposal was fiercely criticised by stakeholders on the basis of its inconsistency. For reasons of 'regulatability' this two-tier model was abandoned in favour of an 'all cell sources count' approach. Therefore, limitations exist in translating 'R&D risks' into regulatory policy.

To get to grips with these developments I used the notion of '**regulatable risk**' in this thesis, arguing that for regulators and policymakers risks have to be manageable and 'regulatable' in order to enter the policy domain. I demonstrate how particular risk frames and definitions are adopted for inclusion in policy and practice, while others are neglected or downplayed as not being suitable for

control and management. In this way the transition - and often taken for granted fluent cause or linear logic - from risk assessment to risk management is redefined. I consider this in terms of boundary drawing and the articulation of particular powerful or dominant risk discourses, where certain arguments are fore grounded and others 'boxed out' in favour of what is perceived to be belonging to the 'regulatable' domain. The notion of political culture is invasive in this context, where I used the case of tissue engineering as example of the evolution of a regulatory object through several passages.

Negotiated boundaries between techno-science and socio-politics, and the role of moral arguments in EU regulatory policymaking

My concern with perceptions of risk can be understood as an early manifestation, where I argue that a broader conceptual approach towards 'risk' is needed to encompass political implications and the mobilisation of policy networks in understanding dynamics between risk and regulation.
In the proclaimed 'risk society', and following from this my suggested entrance of the 'regulatory society', technological risks have become more difficult to assess. To this effect calls were made for broader types of risk assessment, to encompass the broader societal concerns raised by the far-reaching effects of technological risk and uncertainty. More participative styles of governance would be needed, where expert knowledge and social judgements go hand in hand. In this research I have outlined how technological and ethical frames are part of the same package of arrangements. In this section I recapitulate the main developments in relation to the role of ethical imperatives.

An important notion addressed in this thesis concerns the inclusion of (and implications of dealing with) socio-political and ethical concerns related to tissue engineering technology. Risk is intrinsically connected to moral concerns of tissue engineering technology, as it incorporates diverging views about acceptability and the distribution of risk over different levels; it raises questions about accountability and responsibility and about what is justifiable. Especially in the face of uncertainty about implications and long term risks and safety, ethical considerations around tissue engineering technology are paramount.

Interestingly though, as made explicit in chapter 7, only a small but narrowly defined selection of issues featured in interviewees' accounts. When asked about potential ethical concerns around use or implications of tissue engineering technology, the majority of core R&D constituencies expresses how in their view tissue engineering largely stays clear from ethical or moral dilemmas. Some interviewees, mostly clinicians, have discussed the problematic nature of clinical trial design and gaining proper informed consent. Others have referred to possible religious concerns, but this was phrased in relation to xenotransplants rather than the inclusion of animal derived material in tissue engineered applications. There is one large domain though over which interviewees do worry: the use of human embryonic stem cells in (future) tissue engineered applications. Although scientifically largely uncontroversial, according to these interviewees, the impact of embryonic stem cells therapies in the public eyes is foregrounded as shared concern. These considerations provide the backdrop for interpreting the shaping of EU regulatory policymaking, where the value of these particular concerns has followed different tracks.

Socio-political and ethical issues are relevant in the face of policy shaping, where the main concern is with delivering implementable solutions to narrowly defined science-based problems (judicial default mode). Also in tissue engineering a technical rather than ethical framework is called upon in attempts to reduce uncertainty and complexity in this domain, although large variability exists in the ways in which 'ethics induced' ambiguity is managed institutionally across the different regulatory initiatives. Thus attempts are undertaken to exclude ethical concerns from 'science-based' regulation. But as also illustrated in this research, these debates represent a complex mix of arguments where technical and ethical considerations of risk and safety are intimately connected. This research departs from the assumption that ethical considerations cannot be segregated from techno-scientific assessments for regulatory purposes, thus questioning the current institutional set-up of tissue engineering regulation in the EU.

This is not a straightforward assumption though. As has also been demonstrated for other innovative technologies (see for example: Levidow and Carr 1997; Salter and Jones 2002b), the regulatory process of tissue engineering swings between technical and social concerns. This development is also echoed in the institutional management of risk, where technical risk assessment is treated as a separate task from socio-economic or ethical analyses. By separating these dimensions, the role of the independent and objective expert advice becomes more prominent.

Of conceptual relevance in this respect is the point that ethical concerns can be considered as transgressing boundaries of risk domains, while also shaping the regulatory domain. Moral issues are not fixed but fluid and hybrid, not static but permeable; they remain open for negotiation and reconsideration, and as such for continuous boundary drawing. In this situation it is particularly difficult to achieve closure, and ethical arguments are powerful boundary objects in regulatory policy shaping, where organised interests are gathered around specific ethical objections and legal possibilities. This is accomplished by including or excluding particular items and selective agenda-setting, thus entering the politicised domain of risk regulation of tissue engineering in the EU and of drawing boundaries around the social and political acceptability of the technology.

In contrast to the limited awareness of R&D actors, during the policy shaping process many concerns have been expressed over the ethical and health implications of the use of human tissues and cells, and of its manufactured offspring. In the debate on the SANCO Directive we have seen the continuous boundary-work over exploring the margins of what is legally possible in terms of incorporating ethical concerns in EU regulation. This has been shown to be an elaborate and complicated affair, which significantly shaped the content and progress of the Directive – with risks of stalling in the final stages in Parliament.

A trading zone was created in which cultural values have to compete with a moral economy in which 'ethics' has become subject to trade in exchange for political consensus. Reflecting on this course of events, I have argued how ethics has become a 'political toy' that was tossed from one corner to the other.

The EU trading zone for ethical considerations was enlarged in an attempt to unite (national represented) moral concerns with socio-political considerations and pragmatic policymaking, resembling tensions between cultural biopolitics and the moral bio-economy.

The main ethical concerns were over the use of embryonic stem cells (ESCs) and of therapeutic cloning techniques in order to retrieve these cells, while during the comitology procedure also reproductive cells stirred debate. It can be argued that one reason for the delay of this Directive was exactly over these cells sources, as the Parliament tried to use the Directive as a tool to prohibit embryonic stem cell research and therapeutic cloning (Liddell and Wallace 2005). When these provisions were discarded, because the Commission felt it was not competent to legislate upon ethical matters, the focus of attention in the Parliament shifted towards making sure that at least the Directive would include principles of voluntary unpaid donation. This was another ethically fuelled issue, where again matters of safety had to prevail over ethical considerations. This time the Parliament 'won', as the final Directive stipulates how donors should not be paid (although some room was left to Member States to decide upon 'compensation' for donation), but this victory was part of a package deal between Parliament and Council in order to move the much needed Directive forward, rather than stalling the legislation and going into a conciliation procedure.

Thus the main ethical issues during the SANCO debate concerned the inclusion or exclusion of specific cell sources, and the nature of donation. Interestingly, one of the areas not discussed in any length concerns the role of xenogeneic material as another potentially contested cell source. While xenotransplantation was mentioned in the initial proposal for the Directive, no reference was made to so called non-viable animal sources, such as the bovine serum used during cell culturing. Nor were these animal-derived substances put on the agenda at any point during the debate. A similar silence occurred over genetically modified tissues or cells, where the Commission felt it was too early to consider this material, or the techniques used to engineer particular cell sources, as a realistic clinical option that should be addressed at this stage. In other words, while ESCs and therapeutic cloning, and to some extent

reproductive cells, were at centre stage during the debate, other potentially controversial cell sources and techniques did not enter the discussion at all. That is, so far. In the proposal building stages of the Enterprise Regulation, analysed in chapter 10, the focus of attention changes slightly, where in addition to embryonic material also xenogeneic and other cell sources enter the debate.

Furthermore, in this context I have addressed the role and position of ethical advisory bodies. The most important of these is the European Group on Ethics in Science and New Technologies (EGE), an influential specialist advisory body reporting directly to the President of the European Commission. This group has issued several opinions with relevance to tissue engineering. Most notably, the EGE gave the creation of tissue engineering regulation a significant push by stating in their 1998 expert Opinion that there was an 'urgent need to regulate the conditions under which human tissues circulate within the European Market' (EGE 1998). In its Opinion on ethical aspects of tissue banking the EGE addressed a range of ethical considerations, including commercialisation and the need to keep the tissue domain under control of public health institutions and non profit-making organisations. This Opinion was influential in initiating and to some extent steering the policy debate. However, the EGE's principle on the non-profit character of tissue establishments was controversial, and the Commission diverged from this advice in drafting the SANCO Directive. This only happened after prolonged lobby-work by industrial players wanting to establish a level playing field with tissue banks. Furthermore, the most specific Opinion from the EGE came after the final SANCO Directive was published: a report on the ethical aspects of human tissue engineering (EGE 2004). While this Opinion specifically focused on tissue engineering technologies, it was rather exotic. For example the use of animal cells was not addressed, nor any social impacts of the technology on patient access or availability of products. On the other hand this EGE Opinion did emphasise areas of potential future concern, such as patentability of starting materials for tissue engineered products. So far this issue has not been taken up in either of the two legislative initiatives. Given EGE's mandate as the official representative of bioethical values at EU level, and aim to take on the role of guardian of the civil rights society in expressing EU citizen's concerns (see also: Salter and Jones 2002a),

perhaps this is more indicative of the technocratic stance of the Commission in relation to these issues than reflecting lack of public concern.

I have considered these developments in the context of a shuffle from bio-society to bio-economy. The foregrounding of ethical issues and social impact of tissue engineering technology could indicate a silent move towards notions of the bio-society. The debate in Parliament over ethical concerns reflects varying democratic positions in Member States, which is problematic at EU level. This points towards an underlying notion; the inability of the EU to deal with the impact of contested technologies. Regulating ethics at this level has proved difficult and is bound by legal constraints as formulated in Treaties. As such, the EU as a European regulatory state (Majone 1994) is not a state of European values. This threatens the bio-society, where different stances towards the desirability and impact of tissue engineering result in boxing out these concerns altogether. I demonstrated this point by analysing the debate on ESCs and the incorporation of 'less controversial' ethical concerns around donation into the final version of the SANCO Directive. I discussed how 'ethics' have become part of a significant trading zone in the EU regulatory cycle, where cultural values and (national) norms compete with economic imperatives and other represented interests. As such, this episode of the regulatory cycle resembles biotechnological developments that have been described in terms of 'cultural biopolitics' in parallel to 'moral economies' (Salter 2006). In the new global knowledge economy of tissue engineering dynamic discourses of cultural values about the desirability of techno-scientific innovations are accompanied by a moral economy in which these values can be traded and exchanged. As such, the trading of values facilitates negotiation and the achievement of a political compromise.

As a conclusion in this context I have set out the limitations of 'regulating ethics' at EU level in my particular case study of tissue engineering. In the light of the proclaimed need to also take normative, political and ethical considerations into account when deciding on the social acceptability of risks, it has been proven impossible to define uniform decisions that are acceptable within the whole Community. Given the diverging positions of Member States on the authorisation or prohibition of embryonic cell sources, consensus at EU level,

and thereby the possibility for governance, is lacking. The EU has to balance here between universal European-wide agreed criteria and national concerns. Values are generally locally produced and maintained, and the European regulatory state is not equipped, nor mandated, to manage this diversity and interfere with decisions at this level. Encompassing ethics is problematic in the absence of a 'European moral state'. Regulating ethics at an EU level, I have argued, is a socio-political oxymoron.

These findings can be extrapolated to other settings, as tissue engineering is but one example of a contested innovative technology entering the European stage. The problematic notion of moral arguments and European values has been addressed in relation to other technologies, most notably in relation to human embryonic stem cells (Salter 2005, 2006) and genetically modified crops (Welsh 2005). In the context of the latter, it is argued that the biotech revolution challenges established ethical systems and principles. My analysis adds to this discussion by pointing out the problematic nature of 'regulating ethics' in a multilevel governance environment, where the political economy of tissue engineering science has important implications for continued and future applications. Some have argued in this respect that the boundaries between politics and science are less well defined than assumed, whilst the science/commerce boundary becomes increasingly important (Welsh et al 2005). Analysing how this market context became a primary concern in my study brings an additional dynamic into existing understandings in the social scientific literature that have mostly focused on the relation between science and politics, thereby downplaying the problematic consequences of the relationships between neo-liberal capitalism and science.

Thus this thesis analysed the strong economic imperative underlying these developments and the mechanisms of a neo-liberal market in an increasingly global setting. In this context regulation is only a partial solution, where for commercial developers product reimbursement is the main concern. But also described in this thesis is the vulnerability of an upcoming industry in the context of fourth hurdle policies, which so far has failed to market profitable products. As such, technologies spill across fields and markets. I have discussed several policy implications in this context, such as the quest for new

business models (based on value for money rather than cost, a desire mostly expressed by commercial developers). Related to this are the need for novel methods to evaluate clinical efficacy and the issue of access to potentially beneficial but safe and acceptable technological innovations. In terms of safety considerations, one element is worth reiterating here for its far reaching implications for the management of technological risk. This concerns the distributive character of risk in relation to the acceptability of tissue engineered applications, and the question of who bears responsibility for controlling these risks. This relates in particular to the role of 'the state' vis-à-vis other actors involved in regulatory decision making and control. The case of tissue engineering has demonstrated that 'the state' (in the multilevel governance notion also including the European representation of the nation-state) only takes partial responsibility for the risks associated with tissue engineered products. Furthermore the control mechanisms currently being developed are not up to standard to accommodate the diversity in uncertain risks associated with this technology, nor do they reflect the potential level and scale of these risks. This became most explicit in the way in which the Commission tried to manage concerns around the use of xenogeneic material in tissue engineered applications.

As demonstrated in chapter 10, the boundaries around the definition and scope of tissue engineering were gradually expanded, where the final Commission proposal considers animal cells part of tissue engineering - and hence of the scope of the legislation and legal remit of Community action. What did not change though were the risk management requirements as set out in the proposal. These describe long-term patient monitoring and criteria for traceability of donors, products and starting materials on which these products are based. But it is well recognised that the use of xenogeneic material does not only pose risks to the individual patient but to society at large by the potential for disease transmission. The proposal does not mention any impacts on the environment or for public health at large (forms of collective risk), effectively presenting tissue engineering as medical technology which applies to individual patients. As discussed, this notion becomes problematic when tissue engineered products contain animal material; lifting tissue engineering from the medical domain into an environmental context presumes different

requirements for risk management and has implications for the ways in which new medical technologies are evaluated (Welsh and Evans 1999).

One of the implications of dealing with infectious risk to the public, is that the acceptability of risk has to be determined via a public mechanism, rather than on an individual patient basis. The classical model for informed consent, which is currently based on individual consent for medical interventions, needs to encompass third parties that could be affected. It also requires monitoring and surveillance of not just individual patients but also their close contacts, which raises moral issues about the processes of informed consent (most notably the option to 'drop out' at any point in time) and medical confidentiality (Vanderpool 2002). In addition, this will extend the individual life span, as this type of risk is not a one-off event, thus creating intergenerational risk and effects over time. In terms of risk management and regulation this means that iterative strategies have to be developed, also to control effects of cross-species mutations and the introduction of new infectious diseases in the human population over time (Bach et al. 2002). Thus the focus of decision-making and regulatory policy changes alongside the shift from individual to collective risk. Lack of acknowledgement of this issue in current regulatory efforts is highly problematic and should be addressed in future evaluations.

Stakeholder participation in regulatory science

An underlying conceptual concern in this thesis encompasses a political analysis of who is involved in regulatory decision making, and what this means for representation of interests in relation to broader concerns that enter the debate on tissue engineering regulation. This relates to the role of socio-political and ethical arguments vis-à-vis technical concerns in regulatory policymaking, but more specific to the configuration of actors involved in this exercise. Focusing on participants in regulatory decision-making gives insight into the ways in which different subjects are being prioritised in terms of risk and safety, where underlying value systems are made explicit and where diverse institutional tensions exist between these different actors and what they represent. These tensions occurred for example amongst institutional players

and professional stakeholders, between technical and ethical values they represent, in commercial and public health objectives, and last but not least between risk perceptions and what is considered as belonging to the regulatable domain.

I have studied stakeholder participation in reference to the gradual broadening of the scope of legislation. Two interrelated trends are visible here: one from regulating traditional tissue banking activities to also include manufactured products based on human tissues and cells, while the other focuses on the relation between the SANCO Directive on quality and safety and the new Regulation that was being developed around the same time by DG Enterprise, and which covers the marketing of these products. These trends imply a shift in the involvement of different stakeholder groups in the policy shaping process. This had a direct influence on 'opening up' a Directive that was originally developed to just accommodate traditional tissues and cells.

During the development of the SANCO Directive conflicts of interests were most visible between actors in traditional tissue banking culture, which has typically been associated with local and hospital based practices on a national level, versus commercial developers in an increasingly multinational tissue engineering sector. This can be considered in the light of a growing regulatory reach (Welsh and Evans 1999) and stronger move towards Europeanisation of tissue and cell regulation, where the SANCO Directive represents the shift from local production to commercialisation on trans-national scale. Also it underlines the tensions between public health and competitiveness agendas. This is furthermore complicated by internal politics and bureaucratic competition within the Commission, which has also shaped the scope and means of the SANCO Directive.

In the chapters on regulation (9 and 10) I described how industrial representatives successfully lobbied for a 'level playing field' with other parties in the tissue domain, thereby widening the scope of the Directive from traditional tissue banking activities to also allow other institutions in procurement activities. This was important for companies in order to directly access their starting materials for product manufacturing. With this the tissue

banking monopoly was broken down. The industry involvement also had other implications, as it opened up discussion about 'tissue banking values' over the nature of donation, which had always been linked to arguments of non-profit. This also explains the discussions in Parliament over ethical considerations, as these were mostly based on perspectives of public-health protection and patient safety – the very aim and legal basis of the SANCO Directive. These traditional values were called into question by the arrival of profit-seeking actors. At the same time, it was during these debates that conflicting values between non-profit and commercial players were extrapolated. In addition also institutional conflict within the Commission affected the course of events with the SANCO Directive, and its relation with the Enterprise regulation.

Two critical developments should be noted here that form the analytical backdrop for understanding the institutional tensions between these players. One refers to the role of the European Commission vis-à-vis the European Parliament. As has been analysed before in relation to human genetics (see Salter & Jones 2002), the stance of the European Parliament has consistently been more sceptical towards new technological developments, reflected in its approach to regulatory decision-making. A second institutional and political context is provided by neighbouring policy areas at EU level, and more specific the EU's research funding programmes. The debate on funding research on human embryonic stem cells under Framework Programme 6 for example (see for more on this Salter 2005b, 2006) is of paramount importance in reflecting on the tissue engineering case in the broader policy context. Here bio-economic parameters come to the fore again. As has been argued, the EU's struggle over the future of contested therapies in regenerative medicine, including tissue engineering and stem cell science, can be considered part of a global contest for national and EU advantage. As such a wedge is created between ambitions of science and cultural values where the operation of biopower is targeted at the control of the values that permit or proscribe the development of health technologies.

Thus the participants in regulatory science are involved in continuous boundary drawing between different value and belief systems (such as public health and commercial concerns – tissue banking and industry). Boundaries are

constructed around the regulatory world itself, thereby excluding certain risks, while also within the regulatory domain boundary demarcation takes place in negotiating the scope of the legislation. In the SANCO Directive this is witnessed in attempts to establish fixed boundaries around the legal remits of the EU in regulating tissues and cells, thereby ruling out ethical concerns. In the Enterprise Regulation an opposite trend is visible. Here the scope of the legislation is not narrowed down to purely 'technical' matters (versus socio-political and ethical stances) but are technical definitions of the technology extended in order to accommodate more recent innovation, including tissue engineered products based on animal cells. Thereby the legislative scope is widened to allow potentially controversial cell sources entering the European market.

Implications for the reconfiguration of understandings in the social scientific and STS literature

Overall, my case study of tissue engineering regulation by and in the EU adds to an understanding of the limitations of the institutional governance of risk and the complexity in managing moral dilemmas at this level. As such the bio-society has to look for alternative models in order to become a reality.

On a policy level I have outlined the need for alternative models in the assessment and management of risk, for new means of clinical evaluation, for informed consent at collective scale and the voiced desire for business models that reflect the innovative character of tissue engineering technologies. Also diversity and uncertainty in risk regulation have been critically reviewed, where the relevance was expressed of an integrated approach in styles of European governance to include social and ethical considerations alongside techno-scientific dimensions.

Boundary work has been used as conceptual framework in this research to understand the role of techno-scientific actors and knowledge in policy advice, and as tool to gain insight in demarcating domains of risk and regulation. The boundaries of these domains, as I have demonstrated, are flexible and

contingent, and continuously negotiated and reproduced in the political and institutional context of determining what is considered regulatable at EU level. Changing mechanisms of in- and exclusion are paramount, as became clear from my analysis of risk perceptions across different domains and of the role of ethical principles in regulatory policy-shaping of tissue engineering, and it is at these cross-sections where boundaries become fluid and permeable, rather than fixed.

My study has revealed several additions to the boundary work approach as originally put forward by Gieryn (1983, 1995). While traditional notions have focused on the **construction of boundaries in the science domain**, in my analysis I have extended this notion beyond demarcations of science from 'non-science' as spatial markers for cognitive authority. In this research I am concerned with the 'narrow' techno-scientific actors, but also with clinicians, manufacturers, regulators, politicians, patient groups, advisors and other experts with a stake in tissue engineering. This means I move away from Gieryn (and other)'s exclusive focus on science as domain of demarcation.

It has been recognised how the boundaries of science are ambiguous, and its borders flexible and contextually contingent. However, negotiations over these borders do not limit themselves to the dichotomy of science versus such non-sciences as technology, policy, politics and regulation. My aim in this research has not been to determine if tissue engineering is a science, or what kind of science. Rather, I am concerned with the perceptions of professional actors (the 'inhabitants' of the social world of tissue engineering) on demarcating the domain over several important issues including risk, regulation, expertise and ethical concerns. I demonstrated how 'the science' of tissue engineering constitutes many differentiated boundaries *within* and *across* each of these domains, most notably in relation to ambiguous definitions of risk, negotiated boundaries of uncertainty and in carving out what is considered the regulatable domain. The boundaries of tissue engineering are not just ambiguous, flexible and dynamic – as argued in Gieryn's original account – but also continuously reconstructed by different actors, often inconsistent and heavily contested.

A useful vehicle to analyse these interactions is provided by Star and Griesemer (1989) with their notion of 'boundary objects'. I used **boundary objects** in my work to underline the importance of different organised interests between domains of risk and regulation, thereby extending the limited social world concept of 'pure' science in itself and focusing on professional spheres of interaction that are not wrapped up in traditional disciplinary thinking. The social worlds and sub-worlds as defined in my research are understood in terms of practices and shared beliefs between actors within and between different stages of innovation. For example R&D actors constitute one such social world, further differentiated in technological, clinical and commercial 'subworlds', while regulatory policy activity can be conceived as another dominant social world, where technical and ethical frames represent different ideologies and activities that it is made up of. The boundaries of these social worlds are set by temporary and thus fluid or hybrid understandings of the issues at stake, and are negotiated and at many times contested. For example I have demonstrated how 'trading zones' (or 'pidgin zones') are created in professional group alliances during the discussion of ethical principles in regulation.

In addition to my attempt to overcome the 'science versus non-science' limitations of many current approaches, a second main addition to existing literature concerns the **complex institutionalised character of boundary work**. Studying the institutional context of EU decision making adds complexity to the environment in which boundary work takes place, mainly driven by the many uncertainties at this level. The tissue engineering domain is surrounded by technological, clinical, commercial, political and social uncertainty, which is reflected in boundary drawing exercises in these respected areas. In this context Shackly and Wynne (1996) have introduced the concept of a 'boundary ordering device' to allow actors to negotiate uncertainty across social worlds. This proved useful for my study, also in relation to the role of authority of scientists as policy advisors, which connects boundary work to regulatory science. Thus my research extends this approach by pointing out the problematic nature of the broader socio-political and institutional setting at multi-level governance.

By focusing on the complex dynamics of EU policymaking interactions become explicit between different heterogeneous professional groups with their own institutional affiliations, practices and ambitions. Here decision-making and policy outcomes are troubled by political and social uncertainty, and by a 'regulatory science' that thrives on value-laden rather than the ideal typical science-based mode of action. In this highly fluid institutional and epistemic sets of relations that forms the backdrop for a context-bound negotiated regulatory science, the relationship between science and politics is once again challenged and notions of what is considered problematic (e.g. how issues are framed, as moral or technical; in terms of defining risk and acceptability, what is subject to regulation, etc) remain open to debate. The involvement of diverse interest groups as described in this thesis gives boundary work a temporal dimension, where most notably risks associated with boundary transgression are a feature of society in late modernity (as described in extensis by Giddens 1990 and Beck 1992). As Glasner (1998) argued, the boundary between laboratory and society is necessarily transgressed when the risks of new technologies only become knowable in the future.

A third consideration in my adaptation of boundary work approaches concerns the dominant preoccupation with **'the politics' versus 'the science' demarcation**, and how science and policy are defined and distinguished. The boundaries between these domains are important because whether a question is classified as scientific or political shapes judgements about who should resolve it (Hilgartner 2000). Some critical reflection is in place here though.

One observation here relates to framing technology in terms of moral controversy, which is a particular interesting site for social scientific investigations of boundary work as it is at these crossroads of conflict that assumptions about the characteristics of science are articulated and reconstructed. But when science controversies are framed as a moral dispute, rather than 'merely' technical or political, the boundaries between science and politics are subject to different forms of boundary-work: 'where disputes critical to science lie outside its domain of authority, scientists may seek to blur rather than demarcate boundaries among political, ethical and scientific spaces' (Kelly 2003: 344). The claiming of territories and conflict over boundaries between

most notably technical versus ethical stances are important drivers for the debate on tissue engineering regulation, and has been empirically addressed in this research.

A second observation in this politically charged notion of boundary work reflects my concern with 'what's left out'. In addition to the science/politics boundary which has traditionally gained substantial scholarly attention (see for example Guston 1999) I have pointed out the value of studying economic imperatives and the context of innovation in a neo-liberal market environment. Rethinking the boundaries between science and capital/commerce and studying these developments from a political economy perspective in medicine adds another dynamic to the abundant literature that takes the science/politics boundary as focal point of analysis.

Thus my analysis on the shaping of a regulatory regime has added a political economy component to STS studies on boundary-work, and has used elements of governance theories in order to understand stakeholder positions and interest representation at EU level. Complex configurations between national and supra-national players, within and between different EU level institutions and their representatives demand an analysis which puts emphasis on long-term tensions between bio-economy and bio-society and the ways in which these are interwoven with more recent responsibilities of the Commission for public health protection.

This brings us to the notion of **regulatory science**, where again the boundaries between science and politics, or of academic science versus regulatory science (Jasanoff 1990), are problematised. Regulatory science refers to 'forms of knowledge and understanding developed in response to the requirements of government and industry in the context of the regulatory process' (Irwin and Michael 2003: 45). It brings together the relation between regulatory policy and scientific expertise, and the role of scientific evidence and uncertainty in decision making. Also the relation between innovation and regulation, and the operation of science in 'separate' areas of academic, government and industry activity are implications of regulatory science (Leydesdorff 2001).

Expertise is a key notion in accounts of regulatory science, which I have addressed in several ways. I have discussed the role of scientists as prominent actors in providing knowledge and input into the policy process, resembling notions of scientific experts as a fifth branch of government (Jasanoff 1990). I have also considered scientific expertise as problematic in terms of accountability and credibility, where an increasing part of government is conducted by technical experts, who are contrary to their political executives not elected. This is especially pressing when it concerns supranational regulatory institutions in the EU that operate on an even more distant level of democratic participation (Abraham and Lewis 2000). While recognising the importance of expert knowledge in policymaking, especially in complex science domains, at the same time these bodies have been criticised for their 'closedness', shielding them from external scrutiny (Irwin and Michael 2003). Furthermore my study supports existing understandings that expert knowledge is not value-free but conditioned by the social context of research that gives limitations in their technical assessment (Krimsky and Golding 1992). Scientists do not limit their judgements to purely scientific matter and the case study of tissue engineering adds to the body of knowledge stating how especially biotechnology has raised moral and ethical issues which call for more than purely scientific understanding (see for example Levidow and Carr 2005). Controversy and disagreement amongst scientists have demonstrated not just the contested nature of objective science, but also the normative assessments in which scientists engage.

Regulatory science is a restricted domain where wider public groups are effectively excluded from discussion (Rothstein et al 1999). Many scholars in this tradition have called for more participatory styles of governance, stemming from the assumption that broadening the circle of participants in European governance (NGO's, 'the public') will lead to inclusion of (more) social and ethical concerns on the agenda and new methods of engagement by institutions of the EU. Also the role of institutionalised ethical advisory bodies such as EGE is relevant in this respect. While recognising the limited participation in the regulatory science of tissue engineering (which is mainly driven by scientific experts, industrial representatives and technocratic networks of Brussels-based regulators), my study has also expressed the need

to look beyond the usual processes of decision-making by the grand institutions of the EU (Council, Commission and Parliament).

Whereas many academics have focused on expert authority as part of the policy cycle, I have drawn attention to an often overlooked exponent of the EU expert system, namely **comitology**. Comitology is a peculiar system of EU expert committees made up of civil servants that represent Member States and Commission officials. These committees assist the European Commission in working out the technical details for implementation of new legislation. This provides flexibility in regulatory approach, as new insights can be included in implementation measures via these committees, rather than changing the main text of Directives via the co-decision procedure. This is relevant for a complex and novel technology such as tissue engineering, where, for example, requirements for new safety tests can be incorporated more easily in risk management approaches (see chapter 11).

Comitology is also a highly criticised system. One critical issue reflects concerns over what should be decided in a legislative or implementation procedure, and where to draw the line between the two. Furthermore the complexity of the system and lack of transparency of the committee structure has fuelled fears of these committees as a Trojan horse, by which national interests are carried into the implementation process of Community law (Neuhold 2001).

Thus the comitology procedure has raised issues of democratic legitimacy of the EC policy process, with the committees reflecting the 'democratic deficit' and 'bureaucratic and technocratic bias' of the EC system, given the committee members are not elected on a democratic basis and the meetings are not open to the public. Yet others see institutional conflict between different EU institutions. Also visible in discussions on the SANCO Directive, MEPs have continuously expressed dissatisfaction that comitology is used as a strategy of the Council to circumcise the participation of the European Parliament within decisions.

In other words, while the comitology procedure has been developed as a tool to manage complexity and uncertain risks, which became especially relevant in the post-BSE era, this same procedure raises questions about the legitimacy of the current regulatory system in the EU, technocratic versus democratic principles, and the difficulties in drawing boundaries between technical details and ethical concerns. In this context it is important to further analyse the comitology developments for the SANCO Directive and Enterprise Regulation, which are currently being negotiated. Future research should address this matter. For scholars interested in the problematic relation between EU expert systems and democratic participation, the comitology system provides an excellent and as yet under-explored area of investigation.

A final conceptual implication of my study worth reiterating here concerns notions of **regulation and innovation**. An important observation in this respect is the increasingly global character of regulation and innovation (Irwin and Michael 2003). Regulatory requirements are not limited to national boundaries, and as also demonstrated in the case of tissue engineering, national governments have to harmonise their frameworks in line with EU level regulation. With companies targeting global rather than local markets for their products, national governments become part of a larger and international network of trade and exchange, which means that also regulatory systems become globalised. This affects the content and level of expertise needed, and the scientific evidence to underpin regulatory decisions.

This development puts pressure on traditional notions of innovation, which are generally based on commercial and economic output. Successful innovation, in these terms, is expressed as the marketing of products. Arguably a difference exists though between innovation on the one hand and scientific and therapeutic progress on the other. Also the link between innovation, progress and regulation is much more contingent. As demonstrated with the international development of pharmaceuticals, the relationships between innovation, regulatory science and progress may be more complex and controversial than often assumed (Abraham and Reed 2002). In a discourse of technological innovation and scientific progress promises are often created which translate into beneficial treatment for patients - an assumption on which also regulators

base their evaluation. Tissue engineering is illustrative for a technological development which is presented as highly innovative, but which so far has failed to successfully commercialise and deliver profitable and beneficial therapeutic alternatives. As such neo-liberal market science does not translate easily into products - in the same way that big science did not translate into big products. Furthermore the accessibility of these novel constructs for (future) generations of patients is at best unknown. As such a gap exists between the optimistic visions of science and the more uncertain and unstable market environment in which the fruits of scientific enterprise have to perform. In a similar way the boundaries between research and treatment are reconstructed, which has policy implications in a global setting. In the context of the construction of an 'economy of hope' around technological innovations, and more so when these innovations are linked to therapeutic promises, policymakers and industrial developers should be aware of the complex dynamics underlying the innovation process and potential negative implications of failing expectations for future experimental endeavours.

Further Research Is Needed (FRIN)!

This research suggests three principal areas of future study. First, an obvious extension is to examine the implementation phase of the SANCO Directive and the further legislative development of the Enterprise Regulation. The importance of the comitology procedure for the implementation of these legislative initiatives has already been discussed. Furthermore, it would be valuable to research the role of the embryonic stem cell debate on the subsequent development of tissue engineering as technological innovation and in its impacts on bio-society.

Second, so far the regulatory science of tissue engineering has been limited to a small group of dominant interested parties (including scientific experts, policy advisors, regulators and commercial developers and their representatives). Of relevance is an analysis of ways in which this domain can become less exclusive. Central to this concern is the importance of participation by 'stakeholder groups', such as medical professionals and patient representatives, in this process. Equally interesting is the monitoring of 'public' representatives such as EGE in this process.

Finally, an important theme for research is the way in which tissue engineering may become a 'controversy in the making'. Manufacturers in particular have hinted at the risk of a controversy, which could potentially contaminate the tissue engineering sector as a whole. Issues of liability have been mentioned in this respect, where a link could be made with corporate governance strategies in order to control risk. Furthermore, with the SANCO Directive we have witnessed how ethical concerns have come to dominate the 'democratic part' (Parliament) of the legislative cycle. When the boundaries of regulatory science are extended to encompass techno-scientific as well as socio-political aspects, a possible shift from a dominant bio-economy to a bio-society may become a viable option.

Bibliography

Abels, G. 2002. Experts, citizens, and Eurocrats - towards a policy shift in the governance of biopolitics in the EU. *European Integration Online Papers: http://eiop.or.at/eiop/eiop/pdf/2002-019.pdf* 6(19), pp. 1-26.

Abraham, J. and Lewis, G. 2000. *Regulating medicines in Europe: Competition, expertise and public health*. London: Routledge.

Abraham, J. and Lewis, G. 2002. Citizenship, medical expertise and the capitalist regulatory state in Europe. *Sociology* 36(1), pp. 67-88.

Abraham, J. 2002. A social science framework for the analysis of health technology regulation: the risks and benefits of innovative pharmaceuticals in a comparative context. *Health, Risk & Society* 4(3), pp. 305-324.

Abraham, J. 2002. Regulatory science as culture: contested two-dimensional values at the US FDA. *Science as Culture* 11(3), pp. 309-335.

Abraham, J. and Reed, T. 2002. Progress, innovation and regulatory science in drug development. *Social Studies of Science* 32(3), pp. 337-369.

Adam, B. et al. 2000. *The risk society and beyond. Critical issues for social theory*. London Thousand Oaks: SAGE.

Alper, J. 2002. The rise of the European bioentrepreneur. *Nature Biotechnology* 20(suppl), pp. BE3-5.

Altenstetter, C. 1996. Regulating healthcare technologies and medical supplies in the European Economic area. *Health policy* 35(1), pp. 33-52.

Altenstetter, C. 2004. Regulatory Governance of Medical Devices in the European Union - Beyond Theories of European Integration. *Paper prepared for Fifth European Conference on Health Economics, London 2004, 8-11 September*, p. 32pp.

Alvarez, O. M. et al. 1998. A novel treatment for venous leg ulcers. *J Foot Ankle Surg* 37(4), pp. 319-324.

Amsterdamska, O. 2005. Demarcating epidemiology. *Science, Technology & Human Values* 30(1), pp. 17-51.

Asselt, M. B. A. v. and Vos, E. XX. The precautionary principle and the uncertainty paradox. *Journal of Risk Research*.

Atala, A. 2004. Tissue engineering and regenerative medicine: concepts for clinical application. *Rejuvenation Res* 7(1), pp. 15-31.

Atkinson, P. et al. 2003. *Key themes in qualitative research: continuities and changes*. Walnut Creek, CA: AltaMira Press.

Bach, F. H. et al. 2002. Uncertainty in xenotransplantation: individual benefit versus collective risk. In: Sherlock, R. and Morrey, J.D. eds. *Ethical issues in biotechnology*. Lanham: Rowman & Littlefield Publishers, pp. 341-349.

Bader, A. 2005. *Presentation during EuropaBio Industry Hearing on Advanced Therapies, 9 November 2005, Brussels*. EuropaBio. Available at: <URL: http://www.europabio.org/events/IndustryHearing/presentations/Stakeholder%20-%202%20-%20Bader.pdf> [Accessed: Nov 2005]

Banta, M. N. and Kirsner, R. S. 2002. Modulating diseased skin with tissue engineering: actinic purpura treated with Apligraf. *Dermatol Surg* 28(12), pp. 1103-1106.

Bartlett Foote, S. 2002. MTLF Summit: defining a regulatory process for combination products: the emergence of tissue engineering.

Beck, U. 1992. *Risk Society: Towards a New Modernity*. London: SAGE.

Bentley, G. et al. 2003. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Br* 85(2), pp. 223-230.

Bentley, G. and Minas, T. 2000. Treating joint damage in young people. *BMJ* 320(10 June), pp. 1585-1588.

Bijker, W. et al. 1987. *The social construction of technological systems. New directions in the sociology and history of technology*. Cambridge, MA ; London: MIT Press, p. 405pp.

Blume, S. S. 1992. *Insight and Industry - On the dynamics of technological change in medicine*. Cambridge MA: MIT Press.

Blume, S. S. and Geesink, I. 2000. Vaccinology: an industrial science? *Science as Culture* 9(1), pp. 41-72.

Bock, A.-K. et al. 2005. *Human tissue-engineered products: Potential socio-economic impacts of a new European regulatory framework for authorisation, supervision and vigilance. Report by the European Commission's Joint Research Centre (Institute for Prospective Technological Studies). Technical Report EUR 21838 EN. Brussels, November 2005.* European Commission's Joint Research Centre (Institute for Prospective Technological Studies). Available at: <URL: ftp://ftp.jrc.es/pub/EURdoc/eur21838en.pdf> [Accessed: Nov 2005]

Bock, A. K. et al. 2003. Human tissue-engineered products: today's market and future prospects - synthesis report EUR 21000 EN. Institute for Prospective Technological Studies IPTS and Joint Research Centre EC. pp. 1-55

Bonassar, L. and Vacanti, C. 1998. Tissue engineering: the first decade and beyond. *Journal of Cellular Biochemistry Supplements* 30(31), pp. 297 - 303.

Borras, S. 2003. *The innovation policy of the European Union - from government to governance*. Cheltenham: Edward Elgar.

Bouchie, A. 2002. Tissue engineering firms go under. *Nature Biotechnology* 20, pp. 1178-1179.

Brannigan, M. C. 2001. Ethical Concerns in Tissue Engineering: An Opportunity for Preventive Ethics. *A Report from the Pittsburgh Tissue Engineering Initiative, PTEI* Internet: http://www.ptei.org/news/article_02.html.

Branwyn, G. 1998. Foreskin farming. *Wired* 6.02, p. 4.

British Sociological Association (BSA) 2002. BSA Statement Of Ethical Practice. *http://www.britsoc.co.uk/equality/63.htm.*

Brittberg, M. et al. 1994. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med* 331(14), pp. 889-895.
Brittberg, M. et al. 2001. Autologous chondrocytes used for articular cartilage repair: an update. *Clin Orthop* (391 Suppl), pp. S337-348.

Brittberg, M. et al. 2003. Articular cartilage engineering with autologous chondrocyte transplantation. A review of recent developments. *J Bone Joint Surg Am* 85-A Suppl 3, pp. 109-115.

Bronson, J. G. 2003. Tissue Transplantation and Engineering: What's Happening? *Orthopedic Technology Review* 5(5).

Brown, N. and Michael, M. 2001. Switching between science and culture in transpecies transplantation. *Science, Technology & Human Values* 26(1), pp. 3-22.

Brown, N. and Michael, M. 2004. Risky Creatures: institutional species boundary change in biotechnology regulation. *Health, Risk and Society* 6(3), pp. 207-222.

Brown, N. and Webster, A. 2004. *New Medical Technologies and Society: Reordering Life*. Cambridge.

Brown, N. et al. 2006. Regulating Hybrids – 'cleaning up' and 'making a mess' in tissue engineering and transpecies transplantation *Social Theory and Health* 4(1), pp. 1-24.

Brown, P. et al. 2001. Human cell- and tissue-based products: progress, promise and regulatory issues. *Journal of Commercial Biotechnology* 7(4), pp. 287-298.

Brownlee, C. 2001. The mechanics of tissue engineering. *Modern Drug Discovery MDD* 4(12), pp. 34-38.

Bud, R. 1993. *The Uses of Life: A History of Biotechnology*. Cambridge: Cambridge UP.

Cambridge Consultants Ltd (CCL) 2003. Tissue engineering: does it have a commercial future? *Press release, online at: http://www.cambridgeconsultants.com/cgi-bin/printable.pl*, pp. 1-2.
Caporaso, J. A. and Levine, D. P. 1992. *Theories of political economy*. Cambridge: Cambridge University Press.

Carr, S. and Levidow, L. 2000. Exploring the Links Between Science, Risk, Uncertainty, and Ethics in Regulatory Controversies About Genetically Modified Crops. *Journal of Agricultural and Environmental Ethics* 12(1), pp. 29-39.

Chapekar, M. S. 1996. Regulatory concerns in the development of biologic-biomaterial combinations. United States Food and Drug Administration. *J Biomed Mater Res* 33(3), pp. 199-203.

Chapekar, M. S. 2000. Tissue engineering: challenges and opportunities. *J Biomed Mater Res* 53(6), pp. 617-620.

Chignon, T. 2003. Initiatives to Harmonize Regulations of Human Tissue/Cell Products in the European Union. *RAPS RA Interactive: emerging technologies, emerging regulations*, pp. 1-4.

CIGNA 2005. CIGNA healthcare coverage position: Wound Healing: Tissue-Engineered Skin Substitutes and Growth Factors. *Online at: http://www.cigna.com/health/provider/medical/procedural/coverage_positions/medical/mm_0068_coveragepositioncriteria_woundhealing.pdf*, pp. 1-18.

Clarke, A. E. et al. 2003. Biomedicalization: Technoscientific transformations of health, illness, and U.S. biomedicine. *American Sociological Review* 68(2), pp. 161-194.

Clinica 2003. European Commission moves human tissue products from devices to biotech unit. *Clinica* (1085).

Coffey, A. and Atkinson, P. 1996. *Making sense of qualitative data*. London: Sage.

Cogle, C. R. et al. 2003. An overview of stem cell research and regulatory issues. *Mayo Clin Proc* 78(8), pp. 993-1003.

Collins, H. and Evans, R. 2002. The third wave of science studies: Studies of expertise and experience. *Social Studies of Science* 32(2), pp. 235-296.

Colman, A. and Burley, J. C. 2001. A legal and ethical tightrope. Science, ethics and legislation of stem cell research. *EMBO Rep* 2(1), pp. 2-5.

Commandeur, P. et al. 1996. Public Debate and Regulation of Biotechnology in Europe. *Biotechnology and Development Monitor* (26), pp. 2-9.

Commission of the European Communities (CEC) 2000. Communication from the commission on the precautionary principle. COM (2000) 1, 02022000.Brussels: European Commission. pp. 1-29

Commission of the European Communities (CEC) 2001. Communication from the commission: Towards a strategic vision of life sciences and biotechnology. Consultation document COM(2001) 454 final. Brussels: European Commission. pp. 1-32

Conrad, P. 2005. The shifting engines of medicalization. *Journal of Health and Social Behaviour* 46(March), pp. 3-14.

CORDIS. 2005. *FP7 Office website* Available at: <URL: http://cordis.europa.eu.int/fp7> [Accessed: May 2006]

Council of the European Union 2003. Common guidelines: Common position adopted by the Council with a view to the adoption of a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *Interinstitutional File: 2002/0128 (COD). 10133/03. Brussels, 14 July 2003*, pp. 1-39.

Council of the European Union 2003. Common Position (EC) No 50/2003 of 22 July 2003 adopted by the Council, acting in accordance with the procedure referred to in Article 251 of the Treaty establishing the European Community, with a view to adopting a directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *Official Journal C 240 E , 07/10/2003*, pp. P. 0012 - 0024

Council of the European Union 2003. 2512th Council meeting Employment, social policy, health and consumer affairs. Luxembourg, 2 and 3 June 2003. Provisional version 9688/03 (Presse 152). *Human tissues and cells - Public deliberation*, pp. 7-8.

Cox, M. 2003. Progress on regulations for human-derived therapeutic products. *Med Device Technol* 14(1), pp. 32-34.

Crabtree, B. and Miller, W. 1992. *Doing qualitative research*. London: Sage.

Crouch, C. 1997. *Political Economy of Modern Capitalism*. London: Sage.

Curran, M. P. and Plosker, G. L. 2002. Bilayered bioengineered skin substitute (Apligraf): a review of its use in the treatment of venous leg ulcers and diabetic foot ulcers. *BioDrugs* 16(6), pp. 439-455.

Danish Medicines Agency 2004. The safety and quality of tissues & cells by the Danish Medicines Agency (Laegemiddelstyrelsen). *Annex. 08-12-2004*, pp. 1-8.

De, S. K. et al. 2002. Wound treatment with human skin equivalent. *J Am Podiatr Med Assoc* 92(1), pp. 19-23.

De Marchi, B. and Ravetz, J. R. 1999. Risk management and governance: a post-normal science approach. *Futures* 31, pp. 743-757.

De Marchi, B. 2003. Public participation and risk governance. *Science and Public Policy* 30(3), pp. 171-176.

Denker, H. 1999. Embryonic stem cells: An exciting field for basic research and tissue engineering, but also an ethical dilemma? *Cells Tissues Organs* 165(3-4), pp. 246-249.

Department of Health (DoH) 2001. A code of practice for tissue banks providing tissues of human origins for therapeutic purposes. London: Medicine Controls Agency Department of Health.

Department of Health (DoH) 2002. Human bodies, human choices: the law on human organs and tissue in England & Wales - A consultation report. London: Department of Health.

Department of Health (DoH) 2003. Code of Practice on the import and export of human body parts and tissue for non-therapeutic uses. London: Department of Health.

Department of Health (DoH) 2003. Human Bodies, Human Choices: Summary of responses to the consultation report. London: Department of Health. p. 44

DG Enterprise 2001. Guideline MEDDEV. 2.1/3 Rev. 2: Demarcation between Directive 90/385/EEC on Active Implantable Medical Devices and Directive 93/42/EEC on Medical Devices and Directive 65/65/EC relating to Medicinal Products and Related Directives. pp. 1-16.

DG Enterprise. 2002. *Consultation document: Need for a legislative framework for human tissue engineering and tissue-engineered products* Enterprise DG, European Commission (EC). Available at: <URL: http://pharmacos.eudra.org/F2/advtherapies/docs/Questionnaire_2002.pdf> [Accessed: Aug 2005]

DG Enterprise. 2004a. *DG Enterprise consultation: Summary of contributions proposal for a harmonised regulatory framework on human tissue engineered products* DG Enterprise, European Commission (EC). Available at: <URL: http://pharmacos.eudra.org/F2/advtherapies/docs/Summaryofresultsfinal2004.pdf> [Accessed: Aug 2005]

DG Enterprise. 2004b. *Proposal for a harmonised regulatory framework on human tissue engineered products: DG Enterprise consultation paper.* DG Enterprise, European Commission (EC). Available at: <URL: http://pharmacos.eudra.org/F2/advtherapies/docs/Consultation_document_2004.pdf> [Accessed:

DG Enterprise. 2005a. *Consultation paper Human Tissue Engineering and beyond: Proposal for a community regulatory framework on advanced therapies.* DG Enterprise, European Commission (EC). Available at: <URL:

http://pharmacos.eudra.org/F2/advtherapies/docs/ConsultationPaper-AdvancedTherapies-2005-May-04.pdf> [Accessed: Nov 2005]

DG Enterprise. 2005b. *Contributions to the May 2005 Consultation paper Human Tissue Engineering and beyond: Proposal for a community regulatory framework on advanced therapies.* DG Enterprise, European Commission (EC). Available at: <URL: http://pharmacos.eudra.org/F2/advtherapies/Stakehcom2005.htm> [Accessed: Nov 2005]

DG Enterprise. 2005c. *Human tissue engineering and beyond: Proposal for a community regulatory framework on advanced therapies. Proposal for a regulation of the European Parliament and of the Council on Advanced Therapies and amending Regulation (EC) No 726/2004* DG Enterprise, European Commission (EC). Available at: <URL: http://pharmacos.eudra.org/F2/advtherapies/docs/DraftRegulation-Advanced%20Therapies-2005-May-04.pdf> [Accessed: Aug 2005]

DG Enterprise. 2005d. *Impact assessment SEC (2005) 1444: Annex to the Proposal for a Regualtion on Advanced Therapy Medicinal Products. Commission staff working document {COM(2005) 567 final}. Brussels, 16 November 2005.* DG Enterprise, European Commission (EC). Available at: <URL: http://pharmacos.eudra.org/F2/advtherapies/docs/SEC_2005_1444_EN.pdf> [Accessed: Nov 2005]

DG Enterprise. 2005e. *Press release IP/05/1428: Commission unveils new rules to support gene, cell or tissue based therapies. Brussels, 16 November 2005.* DG Enterprise, European Commission (EC). Available at: <URL: http://pharmacos.eudra.org/F2/advtherapies/docs/IP-05-1428_EN.pdf> [Accessed: Nov 2005]

DG Enterprise. 2005f. *Proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 {SEC(2005) 1444}. COM(2005) 567 final 2005/0227 (COD). Presented by the Commission, adoption of the Commission proposal on 16 November 2005.* DG Enterprise, European Commission (EC). Available at: <URL: http://pharmacos.eudra.org/F2/advtherapies/docs/COM_2005_567_EN.pdf> [Accessed: Nov 2005]

DG Enterprise. 2005g. *Summary of results of the May 2005 Consultation paper Human Tissue Engineering and beyond: Proposal for a community regulatory framework on advanced therapies.* DG Enterprise, European Commission (EC). Available at: <URL: http://pharmacos.eudra.org/F2/advtherapies/docs/2005Consultation-Outcome-2005-11-18.pdf> [Accessed: Nov 2005]

DG Enterprise European Commission (EC) 2004. Proposal for a harmonised regulatory framework on human tissue engineered products: DG Enterprise consultation paper. *Online at:*

http://pharmacos.eudra.org/F2/advtherapies/docs/Consultation_document_2004.pdf, pp. 1-17.

DG Research 2001. Stem cell research at European level - meeting report.Brussels: European Commission (EC). pp. 1-86

DG Research. 2005. *New perspectives on the knowledge-based bio-economy. Conference report 15-16 September 2005.* European Commission. Available at: <URL: http://www.efi.fi/attachment/f5d80ba3c1b89242106f2f97ae8e3894/065c24ec0778a68329e3ccdf6c9879c9/kbbe_conferencereport1.pdf> [Accessed: May 2006]

DG Research and Life Sciences Directorates European Commission (EC) 2002. Stem cells: Therapies for the future? Brochure.Luxembourg: Office for Official Publications of the European Communities. pp. 1-36

DG SANCO 2002. Proposal for a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (2002/C 227 E/28) COM(2002) 319 final — 2002/0128(COD). Submitted by the Commission on 19 June 2002. Health and Consumer Protection, European Commission (EC). *Official Journal of the European Communities*, pp. C 227 E/505-521.

DG SANCO 2002. Proposal for a Directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells. COM/2002/319 final, 2002/0128(COD). Presented by the Commission. Brussels, 19 June 2002. 2005(Aug 2005), pp. 1-64.

DG SANCO 2002. Quality and safety standards for human tissues and cells. *Press release. Health and Consumer Protection European Commission (EC). Brussels, 19 June 2002.*

DG SANCO 2002. Summary report of the 18th meeting of the Scientific Committee on Medicinal Products and Medical Devices. Held on 1st.October 2001 in Brussels, Adopted on 18 January 2002. *Directorate C - Scientific Opinions. C2 - Management of scientific committees; scientific co-operation and networks. Doc.SANCO/SCMPMD/2001/0007 Final*, pp. 1-5.

DG SANCO 2003. Amended Proposal for a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells. COM(2003) 340 final 2002/0128 (COD), presented by the Commission pursuant to Article 250 (2) of the EC Treaty.Brussels: Health and Consumer Protection, European Commission (EC). pp. 1-55

DG SANCO 2003. Commission non-food Scientific Committees (under the responsibility of the Health and Consumer Protection Directorate General): Summary of the objectives and activities for risk assessment in the main areas of activity and evaluation of future needs. *Directorate C - Scientific Opinions C2*

- *Management of scientific committees; scientific co-operation and networks SANCO.C2 - D/370080*, pp. 1-29.

DG SANCO 2003. Common Position (EC) No 50/2003 of 22 July 2003 adopted by the Council, acting in accordance with the procedure referred to in Article 251 of the Treaty establishing the European Community, with a view to adopting a directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Health and Consumer Protection, European Commission (EC). *Official Journal C 240 E , 07/10/2003*, pp. P. 0012 - 0024.

DG SANCO 2003. Common position adopted by the Council with a view to the adoption of a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Interinstitutional File: 2002/0128 (COD) 10133/03 SAN 133 CODEC 783 OC 372.Brussels: Health and Consumer Protection, European Commission (EC).

DG SANCO 2003. Communication from the Commission to the European Parliament pursuant to the second subparagraph of Article 251 (2) of the EC Treaty concerning the common position of the Council on the adoption of a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells /* SEC/2003/0906 final - COD 2002/0128 */.Brussels: Health and Consumer Protection, European Commission (EC).

DG SANCO 2003. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003: setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. *Official Journal* L 33/30-40.

DG SANCO 2003. Draft Report on the proposal for a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells - COM (2002) 319 - C5-0302/2002 - Provisional 2002/0128 (COD).Brussels: Committee on the Environment Public Health and Consumer Policy, European Commission (EC).

DG SANCO 2003. Final Report on the proposal for a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (Enhanced cooperation between committees) - FINAL A5-0103/2003.Brussels: Committee on the Environment, Public Health and Consumer Policy, European Commission (EC).

DG SANCO 2003. Human tissues and cells - European Parliament legislative resolution on the proposal for a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (COM(2002)

319 - C5-0302/2002 - 2002/0128(COD)). Minutes - P5_TA-PROV(2003)0182. A5-0103/2003.Brussels: Health and Consumer Protection, European Commission (EC).

DG SANCO 2003. Opinion of the European Economic and Social Committee on the "Proposal for a Directive of the European Parliament and of the Council setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells" (COM(2002) 319 final - 2002/0128 (COD)). Health and Consumer Protection, European Commission (EC). *Official Journal C 085 , 08/04/2003*, pp. P. 0044 - 0051.

DG SANCO. 2003. *Public health: human tissues and cells* Health and Consumer Protection, European Commission (EC). Available at: <URL: http://europa.eu.int/comm/health/ph_threats/human_substance/tissues_en.htm > [Accessed: Aug 2005]

DG SANCO 2004. Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. Health and Consumer Protection, European Commission (EC). *Official Journal of the European Union*, pp. L 91/25-39.

DG SANCO. 2004. *Conclusions - Expert meeting on EU coding system for tissues and cells. Luxembourg 30 April 2004.* Available at: <URL: http://europa.eu.int/comm/health/ph_threats/human_substance/documents/ev_040430_01_en.pdf> [Accessed: April 2006]

DG SANCO 2004. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Health and Consumer Protection, European Commission (EC). *Official Journal of the European Union* (7/2/2004), pp. L 102/148-158.

DG SANCO 2004. Opinion of the Commission pursuant to Article 251 (2), third subparagraph, point (c) of the EC Treaty, on the European Parliament's amendments to the Council's common position regarding the proposal for a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells amending the proposal of the Commission pursuant to Article 250 (2) of the EC Treaty. /* COM/2004/0080 final - COD 2002/0128 */. Commission of the European Communities, Brussels, 5.2.2004, COM(2004) 80 final - 2002/0128 (COD).Brussels: Health and Consumer Protection European Commission (EC). pp. 1-4

DG SANCO 2004. Technical requirements for the donation procurement and testing of human tissues and cells. Draft 3/08/2004. .Brussels: Health and Consumer Protection, European Commission (EC). pp. 1-22

DG SANCO. 2005. *Contributions of the Open Consultation on Draft Technical Requirements for Tissues and cells* Available at: <URL:

http://europa.eu.int/comm/health/ph_threats/human_substance/oc_tech_cell/oc_tech_cell_contributions_en.htm> [Accessed: April 2006]

DG SANCO 2005. Technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. Draft 29/03/05.Brussels: Health and Consumer Protection, European Commission (EC). pp. 1-16

DG SANCO. 2005. *Tissues and cells Regulatory Committee. Summary Report 29 June 2005: T&C Reg.Com/2005/1/Minutes* Health and Consumer Protection European Commission (EC) Available at: <URL: http://europa.eu.int/comm/health/ph_threats/human_substance/documents/ev_20050629_mi_en.pdf> [Accessed: April 2006]

DG SANCO. 2005. *Tissues and cells Regulatory Committee: Summary Report of the Written procedure* Available at: <URL: www2.europarl.eu.int/.../comitologie/droit_information/2005/COM-AC_DI(2005)CMT-2005-4471_EN.doc> [Accessed: April 2006]

DG SANCO 2006. Commission Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. *Official Journal L 038, 09/02/2006*, pp. P. 0040 - 0052.

DG SANCO. 2006. *Website European Commission: public health: risk assessment* DG SANCO, European Commission. Available at: <URL: http://europa.eu.int/comm/health/ph_risk/risk_assess_en.htm> [Accessed: April 2006]

DG SANCO. 2006. *Website European Commission: public health: risk assessment: scientific committees* DG SANCO, European Commission. Available at: <URL: http://europa.eu.int/comm/health/ph_risk/committees/former_committees_en.htm> [Accessed: April 2006]

DG SANCO. 2006. *Website Scientific Committee on Emerging and Newly-Identified Health Risks. European Commission: public health: risk assessment: scientific committees* DG SANCO, European Commission. Available at: <URL: http://europa.eu.int/comm/health/ph_risk/committees/04_scenihr/04_scenihr_en.htm> [Accessed: April 2006]

DG SANCO: SCMPMD. 2001. *Opinion on the State of the Art Concerning Tissue Engineering. Doc.SANCO/SCMPMD/2001/0006 Final* Scientific Committee on Medicinal Products and Medical Devices, European Commission SANCO DG. Directorate C - Scientific Opinions. C2 - Management of scientific committees; scientific co-operation and networks. Available at: <URL: http://europa.eu.int/comm/food/fs/sc/scmp/out37_en.pdf> [Accessed: August 2005]

Dickenson, D. 2002. Commodification of human tissue: implications for feminist and development ethics. *Developing World Bioeth* 2(1), pp. 55-63.

Dickenson, D. 2005. Human tissue and global ethics. *Genomics, Society and Policy* 1(1), pp. 41-53.

Dietz, T. et al. 1989. Definitions of Conflict and the Legitimation of Resources: The Case of Environmental Risk. *Sociological Forum* 4(1), pp. 47-70.

DoH Medical Devices Agency (MDA) 2002. A Code of Practice for the Production of Human-derived Therapeutic Products. London: Department of Health.

DoH Medical Devices Agency (MDA) and DoH Medicine Controls Agency (MCA) 2003. UK's answer to the EU Commission's Consultation Document on the need for a Community Framework on Human Tissue Engineered Products. *Internal document Department of Health.*

DoH Medicine Controls Agency (MCA) 2001. A Code of Practice for Tissue Banks Providing Tissues of Human Origins for Therapeutic Purposes. London: Medicine Controls Agency, Department of Health.

Douglas, M. and Wildavsky, A. 1982. *Risk and Culture: An essay on the Selection of Technical and Environmental Dangers.* Berkeley CA: University of California Press.

Douglas, M. 1992. *Risk and blame: essays in cultural theory.* London: Routledge.

Dresser, R. 2001. Ethical issues in embryonic stem cell research. *Jama* 285(11), pp. 1439-1440.

Drug information online PDR. 2002. *PDR Drug information for APLIGRAF®* Drug information online:. Available at: <URL: http://www.drugs.com/PDR/Apligraf.html> [Accessed: August 2005]

Drummond, M. F. 1980. *Principles of economic appraisal in health care.* Oxford: Oxford University Press.

Drummond, M. F. 2003. The use of health economic information by reimbursement authorities. *Rheumatology (Oxford)* 42 Suppl 3, pp. iii60-63.

Duncker, E. 2001. Symbolic communication in multidisciplinary cooperations. *Science, Technology & Human Values* 26(3), pp. 349-386.

Dworkin, G. and Kennedy, I. 1993. Human tissue: rights in the body and its parts. *Med Law Rev* 1(3), pp. 291-319.

Eaglstein, W. H. et al. 1999. Acute excisional wounds treated with a tissue-engineered skin (Apligraf). *Dermatol Surg* 25(3), pp. 195-201.

Eaglstein, W. H. and Falanga, V. 1997. Tissue engineering and the development of Apligraf, a human skin equivalent. *Clin Ther* 19(5), pp. 894-905.

Eaglstein, W. H. and Falanga, V. 1998a. Tissue engineering and the development of Apligraf, a human skin equivalent. *Cutis* 62(1 Suppl), pp. 1-8.

Eaglstein, W. H. and Falanga, V. 1998b. Tissue engineering and the development of Apligraf a human skin equivalent. *Adv Wound Care* 11(4 Suppl), pp. 1-8.

Eaglstein, W. H. and Falanga, V. 1998c. Tissue engineering for skin: an update. *J Am Acad Dermatol* 39(6), pp. 1007-1010.

EFTA 2002. The European Economic Area: decision shaping and participation in committees. *EFTA Bulletin. European Free Trade Association* 1 - 2002, June.

EGE. 1998. *Ethical aspects of human tissue banking. Opinion no 11 of the European group on ethics in science and new technologies (EGE) to the European Commission. 21 July 1998.* European Group on Ethics in Science and New Technologies (EGE). Available at: <URL: http://europa.eu.int/comm/european_group_ethics/docs/avis11_en.pdf> [Accessed: April 2006]

EGE. 2000. *Ethical aspects of human stem cell research and use - Opinion no. 15 of the European group on ethics in science and new technologies (EGE) to the European Commission. 14/11/2000* European group on ethics in science and new technologies (EGE). Available at: <URL: http://europa.eu.int/comm/european_group_ethics/docs/avis15_en.pdf> [Accessed: Aug 2005]

EGE. 2002. *Ethical aspects of patenting inventions involving human stem cells. Opinion no. 16 of the European group on ethics in science and new technologies (EGE) to the European Commission.* EGE. Available at: <URL: http://europa.eu.int/comm/european_group_ethics/docs/avis16_en.pdf> [Accessed: Aug 2005]

EGE. 2004. *Report of the European Group on Ethics on the ethical aspects of human tissue engineered products* European Group on Ethics in Science and New Technologies (EGE). Available at: <URL: http://europa.eu.int/comm/european_group_ethics/docs/humantissueprod.pdf> [Accessed: Aug 2005]

EGE. 2006. *Website of the European Group on Ethics in Science and New Technologies* Available at: <URL: http://europa.eu.int/comm/european_group_ethics/index_en.htm> [Accessed: May 2006]

Elmalem, S. 2002. In search of a regulatory framework for human tissue and cell-based products in Europe. *Thesis for the post-graduate diploma (DESS) of International Drug Development and Registration, France.*

EMEA: CPMP 2001. Points to consider on the manufacture and quality control of human somatic cell therapy medicinal products.

CPMP/BWP/41450/98.London: EMEA Committee for Proprietary Medicinal Products (CPMP). pp. 1-11

EMEA: CPMP 2003. Note for guidance on the use of bovine serum in the manufacture of human biological medicinal products. CPMP/BWP/1793/02.London: Committee for Proprietary Medicinal Products (CPMP). pp. 1-8

EMEA: CPMP 2004. CPMP Biotechnology Working Party Work programme 2004-2005. EMEA/CPMP/BWP/5092/03.London: EMEA Committee for Proprietary Medicinal Products (CPMP). pp. 1-8

EMEA: CPMP 2004. Note 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) (2004/C 24/03). EMEA. *Official Journal of the European Communities* C 24/6-19.

EMEA: CPMP 2004. Points to consider on xenogeneic cell therapy medicinal products. Adopted 17 Dec 2003, EMEA CPMP/1199/02.London: EMEA Committee for Proprietary Medicinal Products (CPMP). pp. 1-24

EMEA. 2006. *Website: About the EMEA - Structure* European Medicines Agency. Available at: <URL: http://www.emea.eu.int/htms/aboutus/emeaoverview.htm> [Accessed: April 2006]

Enoch, S. et al. 2005. Informed consent should be obtained from patients to use products (skin substitutes) and dressings containing biological material. *J Med Ethics* 31(1), pp. 2-6.

EP news. 2003. *Press release: Quality and safety standards for human tissues and cells: MEPs want strong ethics. April 10th, 2003* Available at: <URL: http://www.europarl.org.uk/NEWS/items2003/april10.htm> [Accessed: April 2006]

Epstein, S. 1995. The Construction of Lay Expertise: AIDS Activism and the Forging of Credibility in the Reform of Clinical Trials. *Science, Technology & Human Values* 20 (4 - Special Issue: Constructivist Perspectives on Medical Work: Medical Practices and Science and Technology Studies), pp. 408-437.

Eriksson, L. 2004. From persona to person: the unfolding of an (un)scientific controversy. *PhD thesis Cardiff University*, 298pp.

EUCOMED 1999. Industry Position on Human Tissue Product Regulation.Brussels: EUCOMED.

EUCOMED 2000. Summary of the EUCOMED diner-debate on human tissues. 29 November 2000, Dorint Hotel, Brussels.

EUCOMED 2002. Third Eucomed educational visit: Exploring breakthrough human tissue technologies. *Press Release Issue 06/02* Brussels, 18 April 2002.

EUCOMED 2003. Quality and safety of human tissues and cells: Eucomed position on Commission Proposal for a Directive, The European Medical Technology Industry Association. *Eucomed Position Paper on the Commission report to the Council and Parliament on Medical Devices* 5(3).

EUCOMED 2003. DG Enterprise - Tissue engineering - Industry letter to Commissioner Liikanen - May 2003 (29/01/2004), Joint letter asking the European Commission for a regulation covering marketing authorisation aspects of tissue engineered products - 13/05/2003. *Internet: http://www.europabio.org/pages/workgroups_detail.asp?wo_id=55.*

EUCOMED 2003. EuropaBio & Eucomed comments on Common Position by the Council (14 July 2003) of the Sanco Directive on "Setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells" - 2002/0128 (COD). *Internet: http://www.europabio.org/pages/workgroups_detail.asp?wo_id=55*, p. 3.

EUCOMED 2005. Human tissue engineered products - Commission's initial proposal on advanced therapies is inadequate. *Press release* Brussels, 25 May 2005.

EUCOMED 2005. Human tissue-engineered products: Eucomed calls for new stand-alone EU regulation. *Press release. Brussels, 14 April 2005.* Online: http://www.eucomed.be/docs/Eucomed_Press_Release_04.05.pdf.

EUCOMED 2005. Eucomed position paper on the proposal for a community regulatory framework on advanced therapies of 04 May 2005. *Online position paper: http://www.eucomed.be/docs/EUCOMED_POSITION_PAPER_HTP_June05.pdf*, pp. 1-3.

EUCOMED 2005. What is human tissue engineering? *EUCOMED Newsletter: Medical Technology Focus* 44(July/August 2005).

EUCOMED 2005. What regulatory approach for novel technologies? *EUCOMED Newsletter: Medical Technology Focus* 44(July/August 2005).

EUCOMED. 2006. *Human tissue engineering vademecum* Available at: <URL: http://www.eucomed.org/upload/pdf/tl/vademeca/human_tissue_vademecum.pdf> [Accessed: May 2006]

EUCOMED et al. 2004. Joint industry comments on Proposal for a harmonised regulatory framework on human tissue engineered products: DG Enterprise consultation paper. *Online document: http://www.europa-bio.be/positions/hTEPs0804.pdf*, pp. 1-10.

EurActiv 2003a. Council adopts common position on human tissues and cells proposal. *Internet EurActive.com: http://www.euractiv.com/cgi-bin/cgint.exe/1311261-413?204&OIDN=1505984&-home=search.*

EurActiv 2003b. EP Committee adopts position on safety of human tissues and cells. *Internet EurActive.com: http://www.euractiv.com/cgi-bin/cgint.exe/1311261-413?204&OIDN=1505062&-home=search*.

EurActiv 2003c. Human tissues and cells issue high on EU agenda. *Internet EurActive.com: http://www.euractiv.com/cgi-bin/cgint.exe/1311261-413?204&OIDN=1504562&-home=search*.

EurActiv 2003d. MEPs drop ethical aspects from position on human tissues directive. *Internet EurActive.com: http://www.euractiv.com/cgi-bin/cgint.exe/1311261-413?204&OIDN=1506575&-home=search*.

EurActiv. 2006. *Comitology - online dossier* Available at: <URL: http://www.euractiv.com/Article?tcmuri=tcm:29-117454-16&type=LinksDossier> [Accessed: April 2006]

EuropaBio. 2002. *EuropaBio position paper and response to DG Enterprise consultation document on the need for a legislative framework for human tissue engineering and tissue-engineered products. 30 Sept 2002* Available at: <URL: http://www.europabio.org/pages/workgroups_detail.asp?wo_id=55 or http://www.europabio.org/upload/articles/article_212_EN.doc> [Accessed: Nov 2005]

EuropaBio. 2003. *EuropaBio (revised) position paper on Council common position of DG Sanco Directive (October 2003). EuropaBio & Eucomed comments on Common Position by the Council (14 July 2003) of the Sanco Directive on "Setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells" - 2002/0128 (COD)* Available at: <URL: http://www.europabio.org/articles/article_258_EN.pdf> [Accessed: April 2006]

EuropaBio. 2003. *Information and Position Paper: Human stem cell research: a novel technology that will benefit patients. October 2003* Available at: <URL: http://www.europabio.org/upload/articles/article_254_EN.doc> [Accessed: Oct 2004]

EuropaBio. 2004. *Comments from EuropaBio on Commission consultation paper provisions for micro, small and medium-sized enterprises (SMEs), establishing the circumstances in which SMEs may pay reduced fees, defer payment of the fee, or receive administrative assistance. 8 December 2004* Available at: <URL: http://www.europabio.org/positions/SMEprovisions.pdf> [Accessed: Nov 2005]

EuropaBio et al. 2004. *Joint industry comments on Proposal for a harmonised regulatory framework on human tissue engineered products - DG Enterprise consultation paper. 13 August 2004* Available at: <URL: http://www.europabio.org/positions/hTEPs0804.pdf> [Accessed: Nov 2005]

EuropaBio. 2004. *EuropaBio Feedback on Commission's Consultation Paper on Tissue Engineered Products Legislation. 29 April 2004* Available at: <URL: http://www.europabio.org/positions/Posengineering.doc> [Accessed: Nov 2005]

EuropaBio. 2005. *EuropaBio Position paper on the proposal for a Community Regulatory Framework on Advanced Therapies of 04 May 2005* Available at: <URL: http://www.europabio.org/positions/CRF-AdvTherapies-offmod.pdf> [Accessed: Nov 2005]

EuropaBio and EUCOMED. 2005. *Why human cell & tissue-engineered products (hTEPs) need a specific and separate Regulation. Joint industry paper. 29 March 2005* EuropaBio
EUCOMED. Available at: <URL: http://www.europabio.org/documents/Ebio-Eucomedhteps.pdf> [Accessed: Nov 2005]

European Commission (EC) 1993. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. *Official Journal of the European Communities* L 169/1.

European Commission (EC) 1997. Treaty of Amsterdam amending the Treaty on European Union, the Treaties establishing the European Communities and related acts. *Official Journal OJEC, C 340, 10 November 1997* ISSN 0378-6986.

European Commission (EC) 1998. Commission communication on the Community marketing authorisation procedures for medicinal products (98/C 229/03). *Official Journal of the European Communities* C 229/4-17.

European Commission (EC) 2001a. Directive 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the Community code relating to medicinal products for human use. *Official Journal of the European Communities* 28.11.2001 L 311 EN, pp. 67-128 (162pp).

European Commission (EC) 2001b. European Governance: A White Paper. *Brussels, 25.7.2001 COM(2001) 428 final. Online publication: http://europa.eu.int/eur-lex/en/com/cnc/2001/com2001_0428en01.pdf.*

European Commission (EC) 2003a. Communication from the Commission to the European Parliament pursuant to the second subparagraph of Article 251 (2) of the EC Treaty concerning the common position of the Council on the adoption of a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells /* SEC/2003/0906 final - COD 2002/0128 */.

European Commission (EC) 2003b. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. *Official Journal of the European Communities* L 33/30-40 EN, pp. 30-40.

European Commission (EC) 2003c. Report from the Commission on European Governance. *Luxembourg, ISBN 92-894-4555-6. Online: http://europa.eu.int/comm/governance/docs/comm_rapport_en.pdf.*

European Commission (EC) 2004. European Commission focuses on human tissue engineering potential. *Press release, 22 January 2004. Brussels IP/04/85.*

European Commission: EESC 2002. Opinion of the European Economic and Social Committee on the "Proposal for a Directive of the European Parliament and of the Council setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells" (COM(2002) 319 final — 2002/0128 (COD)). *Official Journal of the European Union* 2003/C 85/44, pp. 44-51.

European Institute of Public Administration (EIPA) 2000. Governance by committee: the role of committees in European policy making and policy. *Research Paper 00/GHA. Maastricht, May 2000.*

European Parliament (EP) 2003a. Amendments 32-159 Draft report Liese to Provisional draft report on the proposal for a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (COM(2002) 319 – C5-0302/2002 – 2002/0128(COD)).Brussels: Committee on the Environment Public Health and Consumer Policy, European Parliament. p. 83

European Parliament (EP) 2003b. Debates of the European Parliament Sitting of Monday 15 December 2003: Human tissues and cells. *Internet: http://www.europarl.eu.int/.*

European Parliament (EP) 2003c. Final Report on the proposal for a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (COM(2002) 319 – C5-0302/2002 – 2002/0128(COD)). FINAL A5-0103/2003, 25 March 2003. Amendments to a legislative text by European Parliament Brussels: European Parliament. pp. 1-76

European Parliament (EP) 2003d. Human tissues and cells. European Parliament legislative resolution on the Council common position adopting a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (10133/3/2003 – C5-0416/2003 – 2002/0128(COD)). A5-0387/2003 - Rapporteur: Peter Liese. Texts adopted at the sitting of Tuesday 16 December 2003, P5_TA-PROV(2003)12-16 PROVISIONAL EDITION PE 339.903, EP - Adopted amendments in second reading (EU Parliament).Brussels: European Parliament. pp. 32-42

Fahey, C. 1998. Experience with a new human skin equivalent for healing venous leg ulcers. *J Vasc Nurs* 16(1), pp. 11-15.

Falanga, V. J. 2000. Tissue engineering in wound repair. *Adv Skin Wound Care* 13(2 Suppl), pp. 15-19.

Faulkner, A. 1997. 'Strange bedfellows' in the laboratory of the NHS? An analysis of the new science of health technology assessment in the United Kingdom. In: (ed) . Sociology of Health and Illness Monograph No. 3. In: Elston, M.A. ed. *The sociology of medical science and technology. Sociology of Health and Illness Monograph.* Vol. 3. Oxford: Blackwell, pp. 197-223.

Faulkner, A. et al. 2003. Human tissue engineered products--drugs or devices? *BMJ* 326(7400), pp. 1159-1160.

Fielding, N. 1993. Qualitative interviewing. In: Gilbert, N. ed. *Researching social life.* London: Sage, pp. 135-153.

Fischer, F. 1990. *Technocracy and the politics of expertise.* Newbury Park, Calif; London: Sage.

Flick, U. 1998. *An introduction to qualitative research.* London: Sage.

Frey, R. G. 2002. On the ethics of using animals for human benefit. In: Sherlock, R. and Morrey, J.D. eds. *Ethical issues in biotechnology.* Lanham: Rowman & Littlefield Publishers, pp. 287-297.

Fujimura, J. 1992. Crafting science: standardised packages, boundary objects, and 'translation'. In: Pickering, A. ed. *Science as practice and culture.* Chicago: University of Chicago Press, pp. 168-211.

Fujimura, J. 1996. *Crafting Science: A Socio-History of the Quest for the Genetics of Cancer.* Cambridge MA: Harvard University Press.

Funtowicz, S. O. and Ravetz, J. R. 1993. Science for the post-normal age. *Futures* 25(7), pp. 739-755.

Furness, P. 2004. Transplanting Human Tissue: Ethics, Policy, and Practice. *BMJ* 328(7437), pp. 469-a-.

Gabe, J. 1995. Health, medicine and risk: The need for a sociological approach. In: Gabe, J. ed. *Health, medicine and risk: sociological approaches.* Oxford: Blackwells, pp. 1-17.

Ganchoff, C. 2004. Regenerating movements: embryonic stem cells and the politics of potentiality. *Sociology of Health & Illness* 26(6), pp. 757-774.

Geesink, I. 1998. *Tissue engineering, the hybrid character of a technology [Tissue engineering: het hybride karakter van een technologie].* Master's thesis, University of Amsterdam UvA.

Geesink, I. 2005. *Report of the EuropaBio Industry Hearing on Tissue Engineering and Advanced Therapies. Radisson SAS Brussels, 9 Nov 2005* EuropaBio. Available at: <URL: http://www.europabio.org/events/IndustryHearing/REPORT%20of%20Hearing-051206.pdf> [Accessed: Dec 2005]

Gelijns, A. C. and Rosenberg, N. 1995. The changing nature of medical technology development.*Sources of Medical Technology: Universities and Industry*. Institute of Medicine, pp. 3-14.

Genzyme. 2002. *Epicel package insert* Available at: <URL: http://www.genzymebiosurgery.com/pdfs/epicel_package_insert.pdf> [Accessed: 2 Feb 2005]

Genzyme. 2004. *Carticel product label package insert. 65001 Revision 07/2004.* Genzyme. Available at: <URL: http://www.carticel.com/pdfs/carticel_product_label.pdf> [Accessed: Aug 2005]

Genzyme. 2005. *Carticel product information online: http://www.carticel.com/home.asp* Genzyme. Available at: <URL: http://www.carticel.com/home.asp> [Accessed: Aug 2005]

Genzyme. 2006. *Epicel website* Available at: <URL: http://www.genzymebiosurgery.com/prod/burn/gzbx_p_pt_burn.asp> [Accessed: Feb 2006]

Giddens, A. 1990. *The Consequences of Modernity*. Cambridge: Polity Press.

Gieryn, T. F. 1983. Boundary-work and the demarcation of science from non-science: strains and interests in professional ideologies of scientists. *American Sociological Review* 48(6), pp. 781-795.

Gieryn, T. F. 1995. Boundaries of science. In: Jasanoff, S. et al. eds. *Handbook of Science and Technology Studies.* Thousand Oaks: SAGE, pp. 393-443.

Gieryn, T. F. 1999. *Cultural boundaries of science: credibility on the line.* Chicago: University of Chicago Press.

Gilbert, G. N. and Mulkay, M. 1984. *Opening Pandora's box: a sociological analysis of scientist's discourse*. Cambridge: Cambridge University Press.

Gilbert, N. 1993. *Researching social life*. London: Sage.

Glasner, P. 1998. Patrolling the boundaries or tracing the contours: cartographic metaphors and the human genome project. In: Wheale, P. et al. eds. *The social management of genetic engineering.* Aldershot, Brookfield USA, Singapore, Sydney: Ashgate, pp. 29-43.

Glasner, P. and Rothman, H. 2001. New genetics, new ethics? Globalisation and its discontents. *Health, Risk & Society* 3(3), pp. 245-252.

Gottweis, H. 2002. Stem Cell Policies in the United States and in Germany: Between Bioethics and Regulation. *Policy Studies Journal* 30(4), pp. 444-469.

Gottweis, H. 2005. Governing genomics in the 21st century: between risk and uncertainty. *New Genetics and Society* 24(2), pp. 175-193.

Green, D. 1984. Towards a 'bio-society'? In: The Commission of the European Communities in association with the journal Futures ed. *The FAST report (1984). Eurofutures – the challenges of innovation*. Vol. chapter 1. London Butterworths, pp. 7-60.

Griffith, L. G. and Naughton, G. 2002. Tissue engineering--current challenges and expanding opportunities. *Science* 295(5557), pp. 1009-1014.

Guston, D. H. 1999. Stabilizing the boundary between US politics and science: the role of the Office of Technology Transfer as a boundary organization. *Social Studies of Science* 29(1), pp. 87-111.

Habermas, J. 2003. *The Future of Human Nature*. Oxford: Polity Press.

Halffman, W. 2003. *Boundaries of regulatory science. Eco/toxicology and aquatic hazards of chemicals in the US, England, and the Netherlands, 1970 - 1995.* Amsterdam: Doctoral Thesis University of Amsterdam, Department of Science Dynamics.

Hancher, L. and Moran, M. 1989a. *Capitalism, culture and economic regulation.* Oxford: Clarendon.

Hancher, L. and Moran, M. 1989b. Organizing regulatory space. In: Hancher, L. and Moran, M. eds. *Capitalism, Culture, and Regulation*. Oxford: Clarendon, pp. 271-299.

Hanft, J. et al. 2003. Are tissue replacements cost effective? *Podiatry Today* 16(7), pp. 64-70.

Hardingham, T. et al. 2002. Tissue engineering: chondrocytes and cartilage. *Arthritis Res* 4 Suppl 3, pp. S63-68.

Harrison, P. E. et al. 2000. The in Vitro Growth of Human Chondrocytes. *Cell and Tissue Banking* 1(4), pp. 255-260.

Hedgecoe, A. 2003. Terminology and the construction of scientific disciplines: the case of pharmacogenomics. *Science, Technology and Human Values* 28(4), pp. 513-537.

Helen, I. 2004. High-tech medicine, life enhancement and the economy of hope. *Science Studies* 17(1), pp. 3-19.

Henon, P. R. 2003. Human embryonic or adult stem cells: an overview on ethics and perspectives for tissue engineering. *Adv Exp Med Biol* 534, pp. 27-45.

Hilgartner, S. 2000. *Science on stage - expert advice as public drama.* Stanford: Stanford University Press.

Ho, A. D. et al. 2005. Stem cells and ageing. *EMBO Reports* 6(S1), pp. S35-S38.

Hogan, S. 2005. *Presentation during EuropaBio Industry Hearing on Advanced Therapies, 9 November 2005, Brussels.* EuropaBio. Available at: <URL: http://www.europabio.org/events/IndustryHearing/presentations/Authoritie%20-%206%20-%20hogan.pdf> [Accessed: Nov 2005]

Hogle, L. F. 2003. Life/Time Warranty. Rechargeable cells and Extendable Lives. In: Franklin, S. and Lock, M. eds. *Remaking life & death: toward an anthropology of the biosciences.* Sante Fe / Oxford: School of American Research Press / James Currey, pp. 61-96.

Holm, S. 2002. Going to the Roots of the Stem Cell Controversy. *Bioethics* 16(6), pp. 493-507.

Holm, S. 2003a. The ethical case against stem cell research. *Camb Q Healthc Ethics* 12(4), pp. 372-383.

Holm, S. 2003b. Regulating stem cell research in Europe by the back door. *J Med Ethics* 29(4), pp. 203-204.

Holm, S. 2004. Stem cell transplantation and ethics: a European overview. *Fetal Diagn Ther* 19(2), pp. 113-118.

Hood, C. et al. 2001. *The Government of Risk: Understanding Risk Regulation Regimes.* Oxford: Oxford University Press.

Horlick-Jones, T. and Sime, J. 2004. Living on the border: knowledge, risk and transdisciplinarity. *Futures* 36, pp. 441-456.

Hospital - Robert Jones and Agnes Hunt Orthopaedic Hospital 2005. Website OsCell: http://www.oscell.enta.net/.

Hüsing, B. et al. 2003. Human Tissue Engineered Products – Today's Markets and Future Prospects. Final Report for Work Package 1: Analysis of the actual market situation – Mapping of industry and products. Karlsruhe, Germany: Fraunhofer Institute for Systems and Innovation Research. p. 122

Indech, B. 2000. The International harmonization of human tissue regulation: Regulatory control over human tissue use and tissue banking in select countries and the current state of international harmonization efforts. *Food & Drug Law Journal* 55, pp. 342-372.

Irwin, A. 1995. *Citizen Science: a study of people, expertise and sustainable development.* London: Routledge.

Irwin, A. and Wynne, B. 1996. *Misunderstanding science? The public reconstruction of science and technology.* Cambridge: Cambridge University Press.

Irwin, A. et al. 1997. Regulatory Science: Towards a Sociological Framework. *Futures* 29(1), pp. 17-31.

Irwin, A. et al. 1998. Regulatory Science and the European Control of Agrochemicals. In: Bal, R. and Halffman, W. eds. *The Politics of Chemical Risk: Scenarios for a Regulatory Future*. Dordrecht: Kluwer, pp. 231 - 250.

Irwin, A. and Michael, M. 2003. *Science, Social Theory and Public Knowledge*. Buckingham: Open University Press.

Jasanoff, S. 1990. *The fifth branch: science advisers as policymakers*. Cambridge, MA: Harvard University Press.

Jasanoff, S. 1995a. Procedural Choices in Regulatory Science. *Technology in Society* 17(3), pp. 279-293.

Jasanoff, S. 1995b. Product, Process, or Programme: Three Cultures and the Regulation of Biotechnology. In: Bauer, M. ed. *Resistance to New Technology*. Cambridge: Cambridge University Press, pp. 311 - 331.

Jasanoff, S. 2005a. *Designs on Nature: Science and Democracy in Europe and the United States*. Princeton, NJ: Princeton University Press.

Jasanoff, S. 2005b. In the democracies of DNA: ontological uncertainty and political order in three states. *New Genetics and Society* 24(2), pp. 139-155.

Jessop, B. 1995. The Regulation Approach, Governance and post-Fordism: Alternative Perspectives on Economic and Political Change? *Economy and Society* 24(3), pp. 307-333.

Jette, J. 2004. Healing its wounds: a year after bankruptcy, Organogenesis claims a profit. *The Patriot Ledger at SouthofBoston.com* 30 November 2004.

Joerges, C. and Neyer, J. 1997. From Intergovernmental Bargaining to Deliberative Political Processes: The Constitutionalisation of Comitology. *Eur Law J* 3(3), pp. 273-299.

John, P. 1999. Policy networks. *Draft paper - Contribution to the Blackwell Companion to Political Sociology, edited by K. Nash and A. Scott* Online: http://website.lineone.net/~peter.john/polnet2.html.

Kanavos, P. et al. 2000. Can economic evaluation guidelines improve efficiency in resource allocation? The cases of Portugal, The Netherlands, Finland, and the United Kingdom. *Int J Technol Assess Health Care* 16(4), pp. 1179-1192.

Kearnes, M. et al. 2006. *Governing at the Nanoscale: People, policies and emerging technologies*. London: Demos, pp. 1-89.

Kelly, S. 2003. Public Bioethics and Publics: Consensus, Boundaries and Participation in Biomedical Science Policy. *Science, Technology & Human Values* 28(3), pp. 339-364.

Kent, J. 2005. Making Connections - Linking Ethics and Regulation in the Social World of Tissue Engineering. *Regulatory Affairs Focus (RAPS journal)* Oct 2005.

Kent, J. et al. 2006. Towards Governance of Human Tissue Engineered Technologies in Europe - Framing the case for a new regulatory regime. *Technological Forecasting and Social Change* 73(2006), pp. 41-60.

Kirsner, R. S. 1998. The use of Apligraf in acute wounds. *J Dermatol* 25(12), pp. 805-811.

Kleijwegt, T. 2003. *Regulation of tissue engineered medical products in member states of the European Union.* Master's thesis, Universiteit Utrecht.

Koh, C. J. and Atala, A. 2004a. Therapeutic cloning applications for organ transplantation. *Transpl Immunol* 12(3-4), pp. 193-201.

Koh, C. J. and Atala, A. 2004b. Tissue engineering, stem cells, and cloning: opportunities for regenerative medicine. *J Am Soc Nephrol* 15(5), pp. 1113-1125.

Krimsky, S. 1991. *Biotechnics and society: the rise of industrial genetics.* Westport: Praeger Publishers.

Krimsky, S. 2000. Risk assessment and regulation of bioengineered food products. *Int. J. Biotechnology* 2(1/2/3), pp. 231-238.

Krimsky, S. and Golding, C. 1992. *Social Theories of Risk.* Westport, CT: Praeger.

Kruip, S. ed. 2003. *Quality and safety of human tissue and cells* Brussels, EP:

Langer, R. S. and Vacanti, J. P. 1999. Tissue engineering: the challenges ahead. *Sci Am* 280(4), pp. 86-89.

Lash, S. 2000. Risk culture. In: Adam, B. et al. eds. *The risk society and beyond. Critical issues for social theory.* London Thousand Oaks: SAGE, pp. 47-62.

Lavik, E. and Langer, R. 2004. Tissue engineering: current state and perspectives. *Appl Microbiol Biotechnol* 65(1), pp. 1-8.

Lebessis, N. and Paterson, J. 1997. The future of European regulation - A review of the workshop 11th of June 1997. *EC Forward Studies Unit Working paper online: http://europa.eu.int/comm/cdp/working-paper/future_of_european.pdf*, p. 29pp.

Levidow, L. and Carr, S. 1997. How biotechnology regulation sets a risk/ethics boundary. *Agriculture and Human Values* 14(1), pp. 29-43.

Levidow, L. and Carr, S. 2000. Unsound science? Transatlantic regulatory disputes
over GM crops. *Int. J. Biotechnology* 2(1/2/3), pp. 257-273.

Levidow, L. and Carr, S. 2005. Precautionary expertise for European Union agbiotech regulation. *Science and Public Policy* 32(4), pp. 258-259.

Levidow, L. et al. 1996. Regulating Agricultural Biotechnology in Europe: Harmonisation Difficulties, Opportunities, Dilemmas. *Science and Public Policy* 23(3), pp. 135 - 157.

Levidow, L. et al. 1997. European Biotechnology Regulation: Framing the Risk Assessment of a Herbicide-Tolerant Crop. *Science, Technology & Human Values* 22(4), pp. 472-505.

Lewicki, R. J. et al. 2003. *Making sense of intractable environmental conflicts.* Washington: Island Press.

Lewis, R. 2005. Stem cell ... an emerging portrait: struggling to sharpen the lines that define embryonic stem cells. *The Scientist* 19(13), pp. 14-18.

Leydesdorff, L. and Etzkowitz, H. 2001. The transformation of university-industry-government relations. *Electronic Journal of Sociology* 5(4), p. 16.

Liddell, K. and Wallace, S. 2005. Emerging regulatory issues for human stem cell medicine. *Genomics, Society and Policy* 1(1), pp. 54-73.

Liese, P. 2005. *Presentation during EuropaBio Industry Hearing on Advanced Therapies, 9 November 2005, Brussels.* EuropaBio. Available at: <URL: http://www.europabio.org/events/IndustryHearing/index.htm> [Accessed: Nov 2005]

Lindahl, A. et al. 2001. Health economics benefits following autologous chondrocyte transplantation for patients with focal chondral lesions of the knee. *Knee Surg Sports Traumatol Arthrosc* 9(6), pp. 358-363.

Lindahl, A. et al. 2003. Cartilage repair with chondrocytes: clinical and cellular aspects. *Novartis Found Symp* 249, pp. 175-186; discussion 186-179, 234-178, 239-141.

Lloyd-Evans, M. 2004. Regulating tissue engineering. *Materials Today, Internet: www.materialstoday.com/pdfs_7_5/lloyd-evans.pdf* 7(5), pp. 48-54.

Lock, M. 2001. The Alienation of Body Tissue and the Biopolitics of Immortalized Cell Lines. *Body & Society* 7(2), pp. 63-92.

Loughlin, K. 2002. Representing medicine: innovation and resistance in 1950s Britain.*Innovations in health and medicine: diffusion and resistance in the twentieth century.* London, New York: Routledge, pp. 129-144.

Löwy, I. 1992. The strength of loose concepts - boundary concepts, federative experimental strategies and disciplinary growth: the case of immunology. *Hist. Sci* xxx, pp. 371-396.

Luyten, F. P. 2003. Presentation to Public Hearing on the proposal for a directive of on setting standards of quality and safety for the donation,

procurement, testing, processing, storage, and distribution of human tissues and cells, Brussels, January 2003. Online at http://www.eutop.de/ct/Download/Luyten.ppt.

Lysaght, M. J. 1995. Product development in Tissue Engineering. *Tissue Engineering* 1(2), pp. 221-227.

Lysaght, M. J. and Hazlehurst, A. L. 2004. Tissue Engineering: The End of the Beginning. *Tissue Eng* 10(1-2), pp. 309-320.

Lysaght, M. J. et al. 1998. An economic survey of the emerging tissue engineering industry. *Tissue Eng* 4(3), pp. 231-238.

Lysaght, M. J. and Reyes, J. 2001. The growth of tissue engineering. *Tissue Engineering* 7(5), pp. 485-493.

Macdonald, K. and Tipton, C. 1993. Using documents. In: Gilbert, N. ed. *Researching social life.* London: Sage, pp. 187-216.

MacKenzie, D. and Wajcman, J. 1999. *The social shaping of technology.* Second ed. Buckingham Philadelphia: Open University Press.

Majone, G. 1994. The rise of the regulatory state in Europe. *West European Politics* 17(3), pp. 77-101.

Majone, G. 1996. *Regulating Europe.* New York: Routledge.

Majone, G. 1997. The new European agencies: regulation by information. *Journal of European Public Policy* 4(2), pp. 262-275.

Majone, G. 1999. The Regulatory State and its Legitimacy Problems. *West European Politics* 22(1), pp. 1-24.

Majone, G. 2003. The politics of regulation and European Regulatory institutions. In: Hayward, J. and Menon, A. eds. *Governing Europe.* Oxford: Oxford University Press, pp. 297-312.

May, C. 2005. Narratives of evaluation. *Presentation at final international conference for Innovative Health Technologies (IHT). 27 October 2005, Church House, Westminster, London.*

Maynard, A. and Cookson, R. 2001. Money or your life? The health-wealth trade-off in pharmaceutical regulation. *J Health Serv Res Policy* 6(3), pp. 186-189.

McCartney, M. 1996. Bio-engineered tissues move toward the clinic. *Lancet* 348(9025), p. 466.

McIntire, L. V. et al. 2002. WTEC Panel Report on Tissue Engineering Research.Maryland: International Technology Research Institute, World Technology (WTEC) Division.

Medical Research Council (MRC) 2001. Trial management guide.

Medical Research Council (MRC). 2005. *Trial types explained* Medical Research Council MRC. Available at: <URL: http://www.ctu.mrc.ac.uk/TypesTrial.asp> [Accessed: March 2005]

Miller, W. and Crabtree, B. 1992. Primary care research: a multimethod typology and qualitative road map. In: Crabtree, B. and Miller, W. eds. *Doing qualitative research*. London: Sage, pp. 3-28.

Moran, M. 1998. Explaining the rise of the market in healthcare. In: Ranade, W. ed. *Markets and health care: a comparative analysis*. London: Addison Wesley Longman Limited, pp. 17-33.

Moran, M. 1999. *Governing the health care state - a comparative study of the United Kingdom, The United States and Germany*. Manchester: Manchester University Press.

Moran, M. 2001. The rise of the regulatory state in Britain. *Parliamentary Affairs* 54(1), pp. 15-31.

Moran, M. 2003. *The British regulatory state: high modernism and hyper-innovation*. Oxford: Oxford University Press, p. 240.

Moreno-Borchart, A. 2004. Building organs piece by piece: Accomplishments and future perspectives in tissue engineering. *EMBO reports* 5(11), pp. 1025–1028.

Naughton, G. K. 2002. From lab bench to market: critical issues in tissue engineering. *Ann N Y Acad Sci* 961, pp. 372-385.

Nerem, R. M. 2000. The challenge of imitating nature. In: Lanza, R.P. et al. eds. *Principles of tissue engineering*. San Diego: Academic Press, pp. 9-15.

Neuhold, C. 2001. Much ado about nothing? Comitology as a feature of EU policy implementation and its effects on the democratic arena. *Paper to be presented at the ECPR Workshop: Governance and Democratic Legitimacy. 6-11 April 2001, Grenoble*, pp. 1-36.

Newell, P. 2002a. *Biotechnology and the Politics of Regulation* Institute of Development Studies (IDS). Available at: <URL: http://www.ids.ac.uk/ids/bookshop/wp/wp146.pdf> [Accessed: Sept 2005]

Newell, P. 2002b. Globalisation and the International Governance of Modern Biotechnology. Mapping Paper. *Globalisation and Poverty paper. Online: http://www.gapresearch.org/governance/PNMappingpaperfinal.pdf*, p. 17pp.

NICE 2000. *Guidance on the Use of Autologous Cartilage Transplantation for Full Thickness Cartilage Defects In Knee Joints. Technology Appraisal Guidance no.16.* London: National Institute for Clinical Excellence.

NICE 2005. *Technology Appraisal Guidance 89: The use of autologous chondrocyte implantation for the treatment of cartilage defects in knee joints.* London: National Institute for Clinical Excellence.

Nicholson, D. 2002. The effects of local context on the development of obstetric ultrasound scanning in two Scottish hospitals. *Innovations in health and medicine: diffusion and resistance in the twentieth century.* London, New York: Routledge, pp. 21-36.

Niese, D. 2005. *Presentation during EuropaBio Industry Hearing on Advanced Therapies, 9 November 2005, Brussels.* EuropaBio. Available at: <URL: http://www.europabio.org/events/IndustryHearing/presentations/Stakeholder%20-%205%20-%20Niese.pdf> [Accessed: Nov 2005]

Nightingale, P. and Martin, P. 2004. The myth of the biotech revolution. *Trends Biotechnol* 22(11), pp. 564-569.

Nowotny, H. et al. 2001. *Re-thinking science: Knowledge and the public in an age of uncertainty.* Cambridge: Polity Press.

OECD 1982. Biotechnology: International trends and perspectives. In: Bull, A.T. et al. eds. Paris: Report by the Organisation for Economic Co–operation and Development (OECD). pp. 1-78

Ogus, A. I. 1994. *Regulation: Legal form and economic theory.* Oxford: Clarendon Press.

Organogenesis 2003. Apligraf - prescription information.

Organogenesis 2005a. Apligraf website. *http://www.apligraf.com/.*

Organogenesis. 2005b. *Prescribing information: Apligraf* Organogenesis. Available at: <URL: http://www.apligraf.com/PDF/prescribing_information.pdf> [Accessed: August 2005]

Pang, F. 2002. Design, analysis and presentation of multinational economic studies: the need for guidance. *Pharmacoeconomics* 20(2), pp. 75-90.

Parenteau, N. 1999. Skin: the first tissue-engineered products. *Sci Am* 280(4), pp. 83-84.

Paul, J. E. and Trueman, P. 2001. 'Fourth hurdle reviews', NICE, and database applications. *Pharmacoepidemiol Drug Saf* 10(5), pp. 429-438.

Persidis, A. 1999. Tissue engineering. *Nat Biotechnol* 17(5), pp. 508-510.

Peterson, L. 1996. Articular cartilage injuries treated with autologous chondrocyte transplantation in the human knee. *Acta Orthop Belg* 62 Suppl 1, pp. 196-200.

Peterson, L. 2002. Technique of Autologous Chondrocyte Transplantation. *Techniques in Knee Surgery* 1(1), pp. 2-12.

Peterson, L. et al. 2002. Autologous chondrocyte transplantation. Biomechanics and long-term durability. *Am J Sports Med* 30(1), pp. 2-12.

Peterson, L. et al. 2003. Treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: results at two to ten years. *J Bone Joint Surg Am* 85-A Suppl 2, pp. 17-24.

Petit-Zeman, S. 2001. Regenerative medicine. *Nat Biotechnol* 19(3), pp. 201-206.

Pinch, T. J. and Bijker, W. 1987. The social construction of facts and artifacts: or how the sociology of science and the sociology of technology might benefit each other. In: Bijker, W. et al. eds. *The social construction of technological systems. New directions in the sociology and history of technology*. Cambridge, MA ; London: MIT Press, pp. 17-50.

Prelle, K. et al. 2002. Pluripotent stem cells--model of embryonic development, tool for gene targeting, and basis of cell therapy. *Anat Histol Embryol* 31(3), pp. 169-186.

Purvis, J. 2003. *Speech by John Purvis MEP - European Parliament 9th April 2003* Available at: <URL: http://www.scottishtorymeps.org.uk/archive/purvis/issues/speeches/speech18.htm> [Accessed: April 2006]

Rajan, K. S. 2003. Genomic capital: public cultures and market logics of corporate biotechnology. *Science as Culture* 12(1), pp. 87-121.

Reiss, M. J. and Straughan, R. 1996. *Improving nature? The science and ethics of genetic engineering*. Cambridge: Cambridge University Press.

Renn, O. 1992. Concepts of risk: A clarification. In: Krimsky, S. and Golding, C. eds. *Social Theories of Risk*. Westport, CT: Praeger, pp. 53-79.

Rhodes, R. A. W. 1997. *Understanding Governance: Policy Networks, Governance, Reflexivity and Accountability*. Buckingham: Open University Press.

Richards, T. 2000. Stem cell research. *BMJ* 321(7274), pp. 1427-1428.

Rogers, E. M. 1995. *Diffusion of innovations*. Fourth ed. New York: The Free Press.

Romeo-Casabona, C. M. 2002. Embryonic Stem Cell Research and Therapy: the Need for a Common European Legal Framework. *Bioethics* 16(6), pp. 557-567.

Rose, N. 2001. The Politics of Life Itself. *Theory Culture Society* 18(6), pp. 1-30.

Rossignol, N. 2005. *The new proposed regulation. Presentation during EuropaBio Industry Hearing on Advanced Therapies, 9 November 2005, Brussels.* EuropaBio. Available at: <URL: http://www.europabio.org/events/IndustryHearing/presentations/authorities%20-1-%20rossignol.pdf> [Accessed: Nov 2005]

Rothstein, H. et al. 1999. Regulatory science, Europeanization and the control of Agrochemicals. *Science, Technology & Human Values* 24(2), pp. 241-264.

Royal Society 2000. Stem cell research and therapeutic cloning: an update. Policy document 12/00.London: Royal Society. pp. 1-8

Salter, L. 1988. *Mandated Science: Science and Scientists in the Making of Standards.* Dordrecht: Kluwer Academic Publishers.

Salter, B. 2001. Who rules? The new politics of medical regulation. *Social Science & Medicine* 52(6), pp. 871-883.

Salter, B. and Jones, M. 2002a. Human genetic technologies, European governance and the politics of bioethics. *Nature Reviews Genetics* 3(October 2002), pp. 808-814.

Salter, B. and Jones, M. 2002b. Regulating human genetics: the changing politics of biotechnology governance in the European Union. *Health, Risk & Society* 4(3), pp. 325-340.

Salter, B. 2004. Cultural biopolitics, bioethics and the moral economy. *Working paper 1 Global Biopolitics Research Group*, pp. 1-18.

Salter, B. 2005a. Bioethics and the global moral economy: the cultural politics of human embryonic stem cell science. *Working paper 3 Global Biopolitics Research Group*, pp. 1-25.

Salter, B. 2005b. The global politics of human embryonic stem cell science. *Working paper 2 Global Biopolitics Research Group*, pp. 1-28.

Salter, B. 2006. Cultural politics, human embryonic stem cell science and the European Union's Framework Programme Six In: Webster, A. ed. *Innovative Health Technologies: new perspectives, challenges and change.* London: Palgrave Macmillan.

Sarangi, S. and Candlin, C. 2003. Categorization and explanation of risk: a discourse analytical perspective. *Health, Risk & Society* 5(2), pp. 115-124.

Schonfeld, W. H. et al. 2000. An economic assessment of Apligraf (Graftskin) for the treatment of hard-to-heal venous leg ulcers. *Wound Repair Regen* 8(4), pp. 251-257.

Schutte, E. 2002. Regulatory barriers to tissue-engineered products. *Med Device Technol* 13(2), pp. 27-29.

Schutte, E. 2003. Industry Position on Proposed Directive (representing Eucomed), Presentation at public hearing Quality and safety of human tissue and cells, European Parliament Brussels, 29 Jan 2003. Online at: http://www.eutop.de/ct/Download/Schutte.ppt.

Scoones, I. 2001. *Science, policy and regulation: challenges for agricultural biotechnology in developing countries. IDS Working Paper no 147* Institute Of Development Studies (IDS) Available at: <URL: http://www.ids.ac.uk/ids/env/PDFs/ian%20SCIENCE-jul20.pdf> [Accessed: Sept 2005]

Shackley, S. and Wynne, B. 1996. Representing Uncertainty in Global Climate Change Science and Policy: Boundary-Ordering Devices and Authority. *Science, Technology & Human Values* 21(3), pp. 275-302.

Shen, J. T. and Falanga, V. 2003. Innovative Therapies in Wound Healing. *J Cutan Med Surg.*

Sharp, L. 2000. The Commodification of the body and its parts. *Annual Review of Anthropology* 29, pp. 287-328.

Sheridan, B. 2001. *EU biotechnology law & practice: regulating genetically modified & novel food products.* Bembridge: Palladian Law Publishing ltd.

Sibbald, R. G. et al. 2001. Cost-effectiveness of Apligraf in the treatment of venous leg ulcers. *Ostomy Wound Manage* 47(8), pp. 36-46.

Silverman, D. 1997. *Qualitative research: theory, method and practice.* London: SAGE publications.

Sittinger, M. et al. 1999. Joint cartilage regeneration by tissue engineering. *Z Rheumatol* 58(3), pp. 130-135.

Skalak, R. and Fox, C. F. e. 1988. Tissue Engineering. Proceedings for a Workshop held at Granlibakken, Lake Tahoe, California, February 26-29, 1988. *Alan Liss, New York.*

Slovic, P. 1999. Trust, Emotion, Sex, Politics, and Science: Surveying the Risk-Assessment Battlefield. *Risk Analysis* 19(4), pp. 689-702.

Slovic, P. 2000. *The perception of risk.* Ebbw Vale: Earthscan publications.

Smith, D. and Hellman, K. B. 2003. Regulatory Oversight and Product Development: Charting the Path. *Tissue Eng* 9(5), pp. 1057-1058.

Smith&Nephew 2005. TransCyte product description. *Online: http://wound.smith-nephew.com/uk/Product.asp?NodeId=2053. Accessed 2 Feb 2005.*

Sottile, V. et al. 2003. In vitro osteogenic differentiation of human ES cells. *Cloning Stem Cells* 5(2), pp. 149-155.

Star, S. L. and Griesemer, J. 1989. Institutional ecology, 'translations' and coherence: amateurs and professionals in Bekeley's Museum of Vertebrate Zoology 1907-39. *Social Studies of Science* 19, pp. 387-420.

Stirling, A. et al. 1999. *On Science and Precaution In the Management of Technological Risk: An ESTO Project Report* European Science and Technology Observatory (ESTO), European Commission. Available at: <URL: ftp://ftp.jrc.es/pub/EURdoc/eur19056en.pdf> [Accessed: Sept 2005]

Stock, G. 2003. From regenerative medicine to human design: what are we really afraid of? *DNA Cell Biol* 22(11), pp. 679-683.

Stock, U. A. and Vacanti, J. P. 2001. Tissue engineering: current state and prospects. *Annu Rev Med* 52, pp. 443-451.

Streit, M. and Braathen, L. R. 2000. Apligraf--a living human skin equivalent for the treatment of chronic wounds. *Int J Artif Organs* 23(12), pp. 831-833.

Suarez-Villa, L. 2001. The rise of technocapitalism. *Science Studies* 14(2), pp. 4-20.

Suarez-Villa, L. 2003. Technocapitalism and the Governance of Innovation: An Organizational Perspective.*SSTNET European Sociological Association 6th Conference*. Murcia, Spain.

Sutherland, F. W. and Mayer, J. E., Jr. 2003. Ethical and regulatory issues concerning engineered tissues for congenital heart repair. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 6, pp. 152-163.

Sylvester, K. G. and Longaker, M. T. 2004. Stem cells: review and update. *Arch Surg* 139(1), pp. 93-99.

Taylor, R. S. et al. 2004. Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle. *BMJ* 329(7472), pp. 972-975.

Technology Evaluation Center (TEC) 2003. Autologous Chondrocyte Transplantation of the Knee. *Assessment Program* 18(2), pp. 1-80.

Temenoff, J. S. and Mikos, A. G. 2000. Review: tissue engineering for regeneration of articular cartilage. *Biomaterials* 21(5), pp. 431-440.

TERG 2003. TERG survey of regulatory authorities in the European Union. *Data collected as part of IHT project on Tissue Engineering Regulation and Governance, between November 2002 and March 2003.*

Thuesen, A. 2001. Graftskin (Apligraf®) for diabetic foot ulcers. *School of Pharmacy and Allied Health Sciences: Drug information service* 5(1), pp. 1-3.

Tienhoven, E. A. E. v. et al. 2001. Pre-clinical safety assessment of Tissue Engineering Medical Products (TEMPs) - an investigation on assays and guidelines for biocompatibility testing.Bilthoven: RIVM report 640080 002/2001. p. 33

Trent, J. F. and Kirsner, R. S. 1998. Tissue engineered skin: Apligraf, a bi-layered living skin equivalent. *Int J Clin Pract* 52(6), pp. 408-413.

Vacanti, J. P. and Vacanti, C. 2000. The history and scope of tissue engineering. In: Lanza, R.P. et al. eds. *Principles of tissue engineering.* San Diego: Academic Press, pp. 3-7.

Van der Sluijs, J. et al. 1998. Anchoring Devices in Science For Policy: The Case of Consensus Around Climate Sensitivity. *Social Studies of Science* 28(2), pp. 291-323.

Van Valkenburgh, J. 1996. Circumcision yielding skin for ulcerous feet. *The Commercial Appeal.* May 7, 1996.

Vanderpool, H. Y. 2002. Critical ethical issues in clinical trials with xenotransplants. In: Sherlock, R. and Morrey, J.D. eds. *Ethical issues in biotechnology.* Lanham: Rowman & Littlefield Publishers, pp. 351-357.

Vanhemelrijck, J. 2005. *Presentation during EuropaBio Industry Hearing on Advanced Therapies, 9 November 2005, Brussels.* EuropaBio. Available at: <URL: http://www.europabio.org/events/IndustryHearing/index.htm> [Accessed: Nov 2005]

Vaughan, E. and Seifert, M. 1992. Variability in the framing of risk issues. *Journal of Social Issues* 48(4), pp. 119-135.

Veulemans, N. 2005. *Presentation during EuropaBio Industry Hearing on Advanced Therapies, 9 November 2005, Brussels.* EuropaBio. Available at: <URL: http://www.europabio.org/events/IndustryHearing/presentations/Stakeholder%20-%204%20-%20Veulemans.pdf> [Accessed: Nov 2005]

Viola, J. et al. 2003. The emergence of tissue engineering as a research field. *Report EEC-9815425 prepared for the National Science Foundation*, pp. 1-128.

Vos, E. 1999. *Institutional frameworks of community health and safety legislation: committees, agencies and private bodies.* Oxford: Hart.

Waldby, C. 2002. Stem cells, tissue cultures and the production of biovalue. *Health: An Interdisciplinary Journal for the Social Study of Health, Illness and Medicine.* 6(3), pp. 305-323.

Warwick, R. M. and Kearney, J. N. 2002. Safety of human tissues and cells for transplantation. In: Polak, J.M. et al. eds. *Future strategies for tissue and organ replacement.* London: Imperial College Press, pp. 381-419.

Wassenaar, C. et al. 2001. Tissue Engineered Medical Products (TEMPs): A prelude to risk management. Netherlands: RIVM National Institute of Public Health and the Environment.

Waymack, P. et al. 2000. The effect of a tissue engineered bilayered living skin analog, over meshed split-thickness autografts on the healing of excised burn wounds. The Apligraf Burn Study Group. *Burns* 26(7), pp. 609-619.

Welsh, I. 2005. Values, Science and the European Union: Biotechnology and transatlantic relations. In: Manners, I. and Lucarelli, S. eds. *Peace and War: Values in EU Global Action*. London: Routledge.

Welsh, I. et al. 2005. Another Science for Another World? Science and Genomics at the London social Forum. *Working Paper 70. Cardiff School of Social Sciences, Cardiff University. http://www.cf.ac.uk/socsi/publications/workingpapers/pdf-files/wrkgpaper70.pdf.*

Welsh, I. 2000. *Mobilising modernity: the nuclear moment.* London: Routledge.

Welsh, I. and Evans, R. 1999. Risk, regulation and surveillance: Social and technological dimensions of change in the science of xenotransplantation. *New Genetics and Society* 18(2/3), pp. 197-218.

Wilkinson, S. 2000. Commodification Arguments for the Legal Prohibition of Organ Sale. *Health Care Analysis* 8(2), pp. 189-201.

Williams, D. 2001. Clarity and Risk: The Challenges of the New Technologies. *Medical Device Technology* 12(9), pp. 12-14.

Williams, D. 2003. The Japanese Approach to Tissue Engineering. A report of the Royal Academy of Engineering Mission to Japan.London: Royal Academy of Engineering. p. 61

Woolgar, S. and Pawluch, D. 1985. How Shall We Move beyond Constructivism? *Social Problems* 33(2), pp. 159-162.

Wynne, B. 1992. Carving out Science (and Politics) in the Regulatory Jungle. *Social Studies of Science* 22(4), pp. 745-758.

Wynne, B. 1995. Public understanding of science. In: Jasanoff, S. et al. eds. *Handbook of Science and Technology Studies*. Thousand Oaks: SAGE, pp. 361-388.

Wynne, B. 1996. May the sheep safely graze? A reflexive view of the expert-lay knowledge divide. In: Lash, S. et al. eds. *Risk, Environment and Modernity: Towards a New Ecology*. London: Sage.

Wynne, B. 2001. Creating public alienation: Expert cultures of risk and ethics on GMOs. *Science as Culture* 10(4), pp. 445-481.

Young, F. E. 2000. A time for restraint. *Science* 287(5457), pp. 1424-.

Zwanziger, L. L. 2003. Biology, ethics, and public policy: deliberations at an unstable intersection. *Anat Rec* 275B(1), pp. 185-189.

Appendices

Appendix 1: Glossary of technical terms

Allogeneic (allogenous): taken from different individuals of the same species (donor), lends itself to off-the-shelf availability, but may require engineering immune acceptance.

Allograft (homograft): a tissue or an organ transplant between individuals of the same species, but genetically non-identical.

Autograft: a tissue or an organ transplanted into a new position within or on the same individual.

Autologous: taken from the same individual (patient's own), immune acceptable, and does not lend itself to off-the-shelf availability.

Autologous somatic stem cells: cells from a site in the patient's own body, and not the reproductive organs, that have the capacity to produce the different cells in a cell lineage.

Biocompatibility: the ability of a material or device to function with an appropriate host response in a specific application

Biocompatible material: a material that can function in a biologic environment without known or significant detrimental effects on either the material or the living system.

Biodegradable material: a material that breaks down when placed in a biologic environment.

Biomaterial: a substance which is compatible with the physiology of the body; typically designed for use in tissue engineering.

Biopsy: removal of tissue from living object.

Biomimetic: able to replicate or imitate a body structure (anatomy) or function (physiology).

Bone morphogenetic proteins (BMPs): important cell-cell signaling molecules first identified by their ability to induce cartilage and bone formation; growth factors often used to promote differentiation of osteogenic precursor cells into osteoblasts.

Cell lineage: all the types of cells that can develop from a single stem cell, in the context of one type of tissue.

Chondrocytes: cartilage cells

Collagen: Insoluble protein which accounts for 25% to 30% of the total protein in animal organisms; major element of skin, bone, cartilage, teeth, blood vessels, tendons etc.

Differentiation: the development of cells with specialized structure and function from unspecialized precursor cells, which occurs in embryonic development and in the subsequent replacement of certain types of cell from persisting unspecialized stem cells.

Epidermis: scarf skin, the outer layer of the skin covering the exterior body surface

ESCs: embryonic stem cells; stem cells derived from embryos

Extracellular matrix: a material outside and between body cells which is the main mediator of cell-to-cell signals and which is important for effective healing of wounds.

Fibroblasts: cell shape of connective tissue, in skin equivalents fibroblasts are associated with the dermis (while the epithelial layer consists of keratinocytes).

Growth factors: molecules produced by cells and found in extracellular matrix that affect the behaviour, growth, and division of body cells; active proteins which are able to stimulate tissue formation.

In vivo: within the living organism (body) or natural system.

In vitro: outside of the living organism or natural system; in the test tube/laboratory, usually referring to artificial experimental systems such as cultures.

Keratinocytes: skin cells of the epithelial layer

Matrix: an intricate network of natural or synthetic fibres that aids in the reinforcement and development of tissues by supplying a scaffold on which cells may grow, migrate and proliferate.

Osteoblast: bone-forming cell that secretes the bone matrix.

Osteoclast: large, multinucleate cell that destroys bone or any other matrix during bone formation and remodelling.

Osteoinductive: promoting bone growth.

Phenotype: the expression of structure, function, or behaviour of an organism or cell.

Procurement: obtaining cells and tissues from human patients or cadavers

Scaffold: a three-dimensional biocompatible construct (may be seeded with cells) that serves as a temporary implantable tissue; generally fated to biodegrade and be replaced by natural tissue.

Stem cell: undifferentiated cell in embryo or adult which can undergo unlimited division and give rise to one or several different cell types. Stem cells can have different characteristics: totipotent means able to produce an entire being; pluripotent is able to produce all tissues and self-renew indefinitely (like with embryonic stem cells); multipotent implies the ability to produce many cell types and self-renew over the lifetime of the being and over many subsequent generations if transplanted (like with haematopoietic stem cells); and progenitor cells, like neural stem cells, are able to produce restricted numbers of cells and with limited to no capacity of self-renewal.

Xenogeneic: cell source from a non-human species for use in humans, requires engineering immune acceptance.

Xenotransplantation: Surgically removing an organ or tissue from one species and transplanting it into a member of a different species; a xenotransplant is cultured in a (genetically changed) animal.

Appendix 2: Timelines EU tissue engineering regulation

Timeline SANCO Directive
Key dates in the development of Directive 2004/23/EC

2 Oct. 1997	Treaty of Amsterdam: article 152
21 Jul. 1998	EGE opinion on ethical aspects of human tissue banking
June 2000	Porto expert meeting
1 Oct. 2001	SCMPMD state of the art Opinion on tissue engineering
6-7 Feb. 2002	Malaga expert and national representatives meeting
7-8 Feb. 2002	Malaga EU Ministerial Seminar
19 Jun. 2002	Proposal for a Directive presented by Commission
1 Jul. 2002	President of Parliament refers proposal to the Committee on the Environment, Public Health and Consumer Policy in the European Parliament (responsible standing committee)
2 Oct. 2002	Dr Peter Liese appointed as rapporteur
11 Dec. 2002	European Economic and Social Committee (EESC) opinion on proposal
29 Jan. 2003	Public hearing on proposal: stakeholders' views
20 Feb. 2003	Public hearing on proposal: patient perspectives
25 Mar. 2003	European Parliament: tabled legislative report, 1st reading or single reading
10 Apr. 2004	European Parliament: legislative opinion, 1st reading or single reading
28 May 2003	European Commission: modified legislative proposal
2 Jun. 2003	Discussion of report in the Council
11 Jul. 2003	Council: statement on common position
22 Jul. 2003	Council: common position
11 Aug. 2003	Commission: communication on the common position
4 Nov. 2003	European Parliament: tabled legislative report, 2nd reading

14 Nov. 2003	European Parliament: draft report by the committee responsible
16 Dec. 2003	European Parliament: decision at 2nd reading
5 Feb. 2004	Commission: opinion on the EP amendments to the common position
3 Mar. 2004	Council adopts Directive
31 Mar. 2004	Legislative final act
7 Apr. 2004	Date of entry into force of Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Publication in the Official Journal of the European Communities.
30 Apr. 2004	Expert meeting on EU Coding System for tissues and cells (comitology)
29 Jun. 2004	EGE Opinion on ethical aspects of human tissue engineered products
Aug – Oct 2004	Open consultation technical requirements for Directive annex 1 (comitology)
29 Mar. 2005	Draft technical requirements (annex 1) for the coding, processing, preservation, storage and distribution of human tissues and cells (comitology)
June 2004	Open consultation technical requirements for Directive annex 2 (comitology)
29 Jun 2005	Tissues and cells Regulatory Committee - Summary Report (comitology)
8 Feb. 2006	Implementing legislative act: Commission Directive 2006/17/EC (comitology)
1 Mar. 2006	Entry into force Commission Directive 2006/17/EC (comitology) Transposition: 11 November 2006
7 Apr. 2006	Implementation date for SANCO Directive

Timeline DG Enterprise Regulation
Key dates development of legislative document

Jun - Sept. 2002	First consultation round: Public web consultation on the need for Community legislation
Feb. 2003	Publication of responses to web consultation
13 May 2003	Joint industry letter to Commissioner Liikanen (after industry meeting)
28 Apr. 2003	Report market study DG JRC-IPTS
11 Jul. 2003	Expert meeting Member States representatives
7 Aug. 2003	Expert meeting Member States representatives
9 Sept. 2003	Expert meeting Member States representatives
23 Sept. 2003	Formal consultation 25 Member States regulatory authorities
Oct. 2003	Final synthesis report study DG JRC-IPTS
Nov. 2003	Tissue engineering dossier moves from medical device section (G4) in DG Enterprise to the Biotechnology Unit
Feb. 2004	Second consultation round announced
19 Feb. 2004	Expert meeting Member States representatives
16 Apr. 2004	Multi-stakeholder meeting Brussels; Commission presents draft proposal for regulatory framework
29 Apr. 2004	Formal consultation 25 Member States regulatory authorities
30 Apr. 2004	Deadline second consultation round on draft proposal
23 Jun 2004	Industry meeting with Commission
July 2004	Commission publishes summary of responses second consultation round
13 Aug 2004	Joint industry comments on Commission proposal for regulation
4 May 2005	Third consultation round launched
20 May 2005	Industry meeting with Commission

25 May 2005	Expert meeting Member States representatives
1 June 2005	Formal consultation 25 Member States regulatory authorities
7 June 2005	General stakeholders meeting Brussels
20 June 2005	Deadline for input third consultation round
9 Nov. 2005	EuropaBio industry hearing
16 Nov. 2005	Commission and Council adopt initial legislative document
13 Dec 2005	Co-rapporteur appointed: Locatelli Pia Elda (PSE)
14 Dec. 2005	Rapporteur appointed: Mikolášik Miroslav (PPE-DE)
11 May 2006	European Parliament hearing on Advanced Therapies
1 June 2006	Council debate planned
13 Sept. 2006	European Parliament scheduled report for 1st or single reading by Standing Committee
24 Oct. 2006	European Parliament Part session scheduled for 1st or single reading

Appendix 3: List of interviewees

Codes of interviewees and date of interview
Total of 69 interviews (including follow-up).

POLICY ADVISORS and EXPERTS

A-EU1 - 131103
Conservative MEP involved in SANCO Directive

A-EU2 - 060104
Regulatory affairs professional in consultancy firm advising multinational industry, A-EU2, 2004

A-EU3 - 110603
Official in DG Enterprise, European Commission

A-EU4 -151003
Medical director national transplantation agency in Europe, expert advisor on DG SANCO Directive

A-EU5 - 290803
Official in DG SANCO, European Commission

A-EU6 - 121103
European expert advisor to DG Enterprise, scientist, head of UK tissue engineering centre

A-EU7 - 121203
Expert at European Medicines Agency

A-EU8 - 021203
Representative European Association of Tissue Banks

A-EU9 - 021203
Member European Group on Ethics in Science and New Technologies (EGE)

A-EU10 - 231105
Official in DG Enterprise, European Commission
(follow-up)

A-EU11 - 241105
Official in DG SANCO, European Commission
(follow-up)

CLINICIANS

Cl-EU1 - 101203
Clinician in trauma surgery working on autologous chondrocyte implantation with commercial affiliation

Cl-EU2 - 251103
Academic clinician in vascular surgery

Cl-EU3 - 251103
Clinician in orthopaedic surgery and director of specialist medical centre for autologous chondrocyte implantation

Cl-EU4 - 160303
Clinician in woundcare management in burns hospital with commercial affiliation

Cl-EU5 - 151203
Clinician involved in start-up company for osteoarthritis treatment with academic affiliation

Cl-EU6 - 170603
Medical specialist in woundcare management involved in quality assurance, academic and clinical affiliation

Cl1 - 100203
Clinical scientist in academic centre for health services research

Cl2 - 030303
Clinician in UK academic hospital working with autologous cartilage implantation, with commercial affiliation

Cl3 - 180303
Clinician in wound healing in UK university hospital

Cl4 - 250503
Clinician in burns unit of UK academic hospital

Cl5 - 140703
UK academic clinician in autologous chondrocyte implantation, with commercial affiliation

Cl6 - 081203
UK clinician in vascular surgery

CONSUMER AND PATIENT GROUPS

Co1 - 190303
Nurse in wound care based in UK hospital, involved in professional wound care society

Co2 - 240303
UK clinician in wound healing and professional member of national consumer organisation for diabetes

Co3 -190503
Representative and founder of consumer organisation for people with burn injuries

Co4 - 210503
Representative of organisation for cardiac patients

Co5 - 170603
Representative national Health Authority concerned with patient safety

MANUFACTURERS

M-EU1 - 221003
Clinical scientist in multinational industrial setting involved in quality insurance for clinical and regulatory affairs

M-EU2 - 110603
Consultant and representative of European industry association for medical devices EUCOMED

M-EU3 - 270104
Scientist in charge of quality control and process management for multinational tissue engineering company

M-EU4 - 120603
Quality assurance and regulatory affairs manager in multinational tissue engineering company, involved in diverse industry representation bodies and regulatory policy development

M-EU5 - 120603
Corporate affairs manager in multinational company, involved in European biotech association and regulatory policy development

M-EU6 - 090204
Regulatory affairs manager in multinational company

M-EU7 - 111103
Pharmacovigilance manager in multinational company for autologous tissue engineering applications (mainly cartilage)

M-EU8 - 230703
Industrial scientist at multinational consultancy company, advising industry on high tech and cell therapies

M-EU9 - 130603
Regulatory affairs manager of multinational company producing autologous cartilage product

M-EU10 - 161203
Director of multinational company in Europe producing autologous tissue engineering applications including cartilage

M-EU11 - 130204
Regulatory affairs manager of multinational company, representative several industrial associations

M-EU12 - 251005
Spokesperson European Association for Bioindustries EuropaBio
(follow up)

M-EU13 - 161105
Commercial provider of tissue engineering product in US, representative of European trade association
(follow-up)

M-EU14 - 091205
CEO of multinational tissue engineering company in Europe
(follow-up)

M1 - 170203
CEO and regulatory affairs specialist in tissue engineering company

M2 - 120303
Scientific manager corporate product safety assurance for multinational company, involved in EU regulatory policy

M3 - 020403
Industry consultant and representative national healthcare industry body

M4 - 050805
Customer relations officer US-based multinational manufacturer of allogeneic TE woundcare products (Apligraf helpline)

REGULATORS

R-EU1 - 231003
Director of national government agency for medicinal and biological products, involved as expert in EU regulatory activity for DG Enterprise and national representative in CPMP (EMEA)

R-EU2 - 120603
Medical director of tissue bank involved in standard setting

R-EU3 - 130603
Scientific expert in legislation and standard setting of medical technology and tissue engineering, based in advisory body for national government department of public health, involved in EU regulatory activity

R-EU4 - 171203
Head of national regulatory agency for medicine and European policy advisor in regulation of human tissue.

R-EU5 - 111103
Regulatory affairs professional for national government agency in medical devices and human tissue, background in multinational industry, involved in policymaking.

R-EU6 - 111103
Medical director of national transplantation agency, involved in EU regulatory activity for SANCO Directive

R1 - 111202
Representative national tissue bank association, involved in national and EU regulatory activity

R2 - 140503
Regulatory professional in national government agency for medical devices and pharmaceutical products, involved in EU and national policy

R3 - 020603
Regulatory professional for national government department of health, involved in national and EU policy development on tissue banking and expert SANCO Directive

SCIENTISTS

S1 - 140103
Academic research scientist in tissue engineering lab with industrial links

S2 - 040503
Academic scientist in lab for stem cells and biomaterials

S3 - 170203
Academic research scientist in tissue engineering centre

S4 - 030303
Academic research scientist in clinical care and cartilage repair

S5 - 030403
Academic research scientist in wound healing and clinical management, professor in tissue engineering and cell therapy

S6 - 200503
Academic research scientist in university centre for tissue engineering and biomaterials

S7 - 200603
Academic research scientist in UK tissue engineering lab with industrial links

S8 - 171103
Academic research scientist in cardiovascular TE applications in hospital

S-EU1 - 201103
Research scientist in connective tissue research working in university setting with multinational industry

S-EU2 - 120104
Academic research scientist in biomaterials and tissue engineering involved in European tissue engineering society

OTHER

O1 - 200503
Policy advisor in purchase and supply office of national healthcare provider, involved in assessment of medical products including tissue engineering

O2 - 170603
Legal professional in regulation of biotechnology

O3 - 211003
Academic scientist in public health and ethics

O4 - 281103
Clinical scientist involved in evaluation of medical technology based in academic department of medical school.