

Legislating for new technology: the textual performance of expectations, actors and accountabilities in regenerative medicine

Abstract

This working paper undertakes a textual analysis of the Advanced Therapy Medicinal Products Regulation which passed into law in the European Union (EU) in 2007, using the analytic concept of performativity. The document is significant for the development of regenerative medicine in the EU and globally. Drawing on concepts from socio-legal studies and innovation studies, the text is analysed in terms of its style and narratives, and substantively in terms of: scientific-industry structure; production and technology; expectation and vision; risk; rights and responsibilities; and actors - regulatory actors, participants in regenerative medicine, and the public. The analysis shows a tension between standardisation and imprecision in the conceptual fabric of the legislative text, and reveals a number of 'elephants in the room' – including the concept of regenerative medicine itself. The reasons for the imprecision and conspicuous absences are discussed. Such texts combine material significant to key concerns of recent theorising of innovative technologies, such as technology expectations, sector-building and the stabilisation of technology. Referring to philosopher John Austin's well-known work on 'how to do things with words', Austin's concept of the 'conventional consequences' of a performative text is referred to in order to argue that legislative texts are a special class of document which should be accorded a more prominent place in studies of the governance and emergence of new technological zones and sectors.

Keywords: law; innovation studies; regenerative medicine; shaping of technology; textual discourse analysis

Legislating for new technology: the textual performance of expectations, actors and accountabilities in regenerative medicine

INTRODUCTION

The discursive linguistic construction and representation of innovative scientific domains and new biomedical technological sectors is an important motor force in their emergence and steering, as has been extensively noted, especially in Science & Technology Studies (STS). This insight is applicable generally in the field of study of the interaction of the social and the material: 'What turns a piece of stuff into a social object is its embedment in a narrative construction' (Harré, 2002). Political governance processes are pursued through a wide variety of narratives which construct biomedical 'stuff' as potentially valuable constituents of future healthcare and the sociomedical world. The development of regulatory policy is one of the key vehicles through which national states and supranational governance agencies seek to steer the direction that biomedical technologies might take. Regulatory policy is drafted, debated and argued in socio-linguistic forums, and it is ultimately codified as legislative text published in formal documents. The texts that societies' political processes create as legislation are codified in a peculiar and distinct class of document. Conventionally regarded as part of a government process that involves setting of rules, monitoring, accrediting, surveillance and so on, I have argued elsewhere that, at least in the case of the regulation of innovative technology, such governance activity has a constructive and shaping action as well (Faulkner, 2008, 2009).

Legislative texts, *par excellence*, work through the performative use of language. Law is comprised of codified language and it relies particularly on the performative nature of language in practice. Performative, 'illocutionary' speech acts have the effect of producing what the philosopher Austin termed 'conventional consequences', namely such principle-based social relationships as rights, commitments, permissions, prohibitions and obligations (Austin, 1962). English language typically uses the terminology of 'shall', 'may', 'may not' and 'shall not' for conveying such societal rules, guidance and expectations. It is a matter of everyday observation to note that there is a preponderance of such performative terminology in legal texts.¹

In this paper, I analyse and discuss the performativity of one recently ratified legislative text that bears on the now widely recognised domain of regenerative medicine. I will focus primarily on the question of *what* does this text do - and not do - in and for the domain to which it is addressed? Second, I ask *how* - by what methods and in what terms - does it accomplish what it does accomplish? The framing of issues examined in

the paper is guided by bringing together a number of related concerns that have been prominent in Science & Technology Studies (STS) and innovation studies in recent years. These concerns focus especially upon issues of understanding the multiple, inter-related driving forces that produce and shape new technologies or technoscientific sectors as 'emerging' into potentially stabilised structures of scientific and socioeconomic practice. Regenerative medicine is widely envisaged as being in a state of emergence in this way.

The paper examines the intersections between 'legal' and 'social' spheres. The value of such an approach has been promoted and conceptualised, in socio-legal studies, through a 'law in action' concept that goes beyond legal-theoretical analysis (Lange, 2005, 2006, 2007). In the field of science and medicine, linguistic innovativeness is endemic, as the viral dissemination of the prefix *bio* demonstrates (biomedicine, biosociality, biocitizenship, bioprospecting and so on), along with the naming of new fields of expertise such as proteomics. Socio-legal studies' analysis in biotechnology has pointed to the interaction and co-construction of legal definitions and the social world: '... although there have been various legal or administrative definitions of biotechnology.... these definitions are themselves immersed in the economic, scientific, or political strategies that constitute biotechnologies' (Pottage, 2007), and from the perspective of legal theory, 'formal legal categorizations are themselves unstable symptoms of complexity' (Pottage, *op.cit.*). Thus attention to the emerging legislative lexicon of regenerative medicine, and the sites of its use, is one means of gauging the place in society at the present time of its diverse set of activities and actors and how their relationships are being configured.

In a cognate line of analysis, recent STS study of regulatory policy has demonstrated similar legal/social interaction in pointing to the innovative, constructive nature of the developing societal regulation of hybrid and converging technologies (Brown et al, 2006; Faulkner, 2009) in defining technological zones (Barry, 2001 & 2006). I use the term technological 'zone' in this paper to refer to potentially emergent, stabilisable socio-technological fields. The rationale for this is essentially that the term 'sector' implies too much product-based stability, and concepts of interorganisational field or innovation network do not give sufficient credence to technology itself as an actor-agent (Faulkner, 2009 gives a more detailed discussion). In parallel, recent work in innovation studies has pointed to the need to give more attention to the roles of 'institutional' actors including states - and thus law-making processes and products - in shaping the emergence of new technologies or technological zones. Such zones may be legitimised partly through technical standardisation and state regulatory policymaking. It is clear, therefore, that the formulation of legislation as a performative force in states' attempts to steer innovation agendas has been a somewhat neglected dimension in the understanding of

how new technologies might be shaped, especially in the context of the contemporary era of the regulatory state (Majone, 1994), where the role of state institutions in socioeconomic innovation and governance processes is coming under increasing scrutiny.

The steering of scientific and technological innovation is a key activity of societies' contemporary governance efforts globally. An array of emerging biomedical technologies is under development, supported by a barrage of visionary promises of a revolution in healthcare practices and a reconfiguration of the place of medicine in society. In some fields, such as molecular-level prenatal genetic diagnosis, it is possible to glimpse the shape of things to come as the sciences of prediction and their social and medical implications are starting to challenge the basic therapeutic and diagnostic paradigms of societies' healthcare practices. Underpinning such developments, national and regional bio-economies jockey for position in a global competition of scientific R&D and product development. 'Regenerative medicine' has become one of the most prominent slogans amongst the strategists and practitioners of these innovative sciences, technologies and healthcare products. Because some of the emerging technologies involve manipulation of viable human and animal materials at the cellular level they have become controversial, with human embryonic stem cells and human-animal hybrids having provoked particular attention and, as is well known, various political interventions in societies worldwide. Social, ethical and religious values have been challenged by the emergence of these technologies and global transactions in a new field of bioethics have become integral to the shaping and direction of the regenerative medicine field.

Legislative texts, of course, are not simply the repository of sets of prohibitive or enabling laws – the scope of their performance is much richer than this. The analysis to be presented in this paper will show that such texts may be seen to encapsulate a diverse array of world-views, visions of the future, invocations of key actors, introductions of constraints and opportunities, rules about acceptable behaviour, assumptions about a regional economy, ethics, and so on. Legislative documents thus constitute one – particularly salient one - of the many different types of social spaces and physical forms in which are inscribed society's expectations and perceived risks about an emerging field such as regenerative medicine.

Expectation; Actor and Institution; Technology

The part played by visions and expectations in the emergence of new technologies has recently attracted a great deal of attention from scholars in Science & Technology Studies

(Borup et al, 2006). Future-oriented visions and expectations, like the performativity of legal statute, are seen as fundamentally 'generative' (Brown & Michael, 2003). This work has noted, for example, that expectations and concerns about risks may be intense during the early stages of a technology, which we can note is often the stage at which policymakers' attention is turning toward the legislative implications of emerging developments. Just as the collectivisation of shared expectations may reach a point where they become *de facto* obligatory, a legislative text, in representing the culmination of a large process of negotiation and development of shared meanings about participation in a regulatable domain, clearly may solidify expectations in a manner that *actually is* obligatory in terms of a society's law-making.

In examining the accomplishments of a specific piece of legislation in the domain of regenerative medicine, therefore, it is likely that expectations will be evident in a variety of ways, which will include an expression of a vision of future healthcare, a configuring of participant actors and of institutional provisions, and a delineation of the technology itself. In broad terms the alignment of such a set of active components may be termed a 'sociotechnical regime' (cf. Berkhout et al 2003; Markard & Truffer, 2008). In this paper, I suggest that societal legitimation through an embedding in legislation should be considered as one defining feature of sociotechnical regimes or technological zones, a feature in which the role of the state is seen as more to the fore than firm or technology-based conceptualisations have recognised. Equally, attention to legislation should be incorporated into attempts to extend the notion of expectation dynamics to zone-shaping forces such as agenda-setting and techno-scientific network dynamics (cf. van Merkerk & Robinson, 2006), the forces that frame problems to which technologies might be the solution, and the outlining of the 'rules of the game' which define who may participate in a technological zone on what terms. 'The law' may clearly have a role in shaping, stabilising and locking-in to regimes the principles of emergent interactions of actors such as researchers, institutes, materials suppliers, healthcare institutions, regulators and manufacturers.

The exact text of techno-scientific legislation is pored over in fine detail not only by lawyers but also by many of those engaged in developing technologies, by scientists engaged in R&D activities, by companies' regulatory affairs managers and strategy leaders from large companies, by (in the case to be considered here) hospital R&D managers, and by regulation and business consultants who provide advice to smaller companies. Indeed, a number of such participants in a new field are likely to interact with each other and regulatory policymakers in issue networks and policy networks attempting to influence the design of rules of engagement for the emerging field, which are eventually solidified into a legal document, as has been the case for the document

discussed here. Legislative texts, therefore, are 'enacted' and 'acted on' by a range of more or less organised stakeholders, contributing to the shaping of an emerging set of practices and social meanings in the regulatable field.

This paper, therefore, concerns itself with how expectations and visions, formulations of legitimate participants and their inter-relationships, and the scope of new technology, are inscribed and actively expressed in one text. It explores the interpretation of this text in terms of the over-arching concept of the steering of innovation of a zone of biomedical technology.

METHODOLOGY: DOING DOCUMENTS AND TEXTS

The legislative document and text that I examine here is a Regulation for 'Advanced Therapy Medicinal Products' produced in the European Union (European Parliament and Council of the European Union, 2007). It is one of many possible vehicles into which representation of the visions, institutions and technologies of regenerative medicine has been built, and is undoubtedly of major significance for the field.

The conceptual convergence noted above between socio-legal studies and STS applies also to methodology. Qualitative empirical socio-legal research methods increasingly have taken up techniques of discourse analysis. Likewise, policy discourse analysis is a strategy for examining how policy discourses congeal to make some particular perspectives more prominent than others. In STS, in the field of genetics, discourse analytic techniques have been used to analyse governance initiatives, asking: 'what sorts of social relations (these) policy documents are a part of; the authorial identity that they assume; and the dominant forms of representation of science, the economy and patients that they embody' (Kerr, 2003). Critical discourse analysis draws attention to technical devices of genre and style as well as the substance of texts, having been applied for example to a British government 'Green Paper' on environmental policy (Fairclough, 1995). Similarly, concepts from literary theory may be applied to understanding the rhetorical construction of implied authorship and readership in texts produced in formal organisations, which may make particular sorts of claims to authority or factuality (Atkinson & Coffey, 2004). Drawing on these instances of textual and discourse analysis, therefore, it is possible to approach a legislative text as a document whose methods and content can be interrogated. We can ask what techniques it deploys – rhetoric, metaphor, and narrative; we can ask what subjects and objects the text assumes or conjures up; we can ask in the case examined here, what are the socioeconomic, ethical and technological aspects of regenerative medicine that are highlighted, and which downplayed; and we can ask how the document as a social entity is positioned as an actor performing cross-

national scientific, industrial and medical government.² Given that the creation of biomedicine is a collective and social enterprise, analysis can attend to how the legislation conceives of participants in the field and how participants, both regulators and regulated, are construed as relating to the regulation that the document enacts.

The methodology used here, therefore, is to treat the document primarily as a vehicle of discourse and conveyor of meanings, susceptible to detailed interpretation via various forms of structural, stylistic and content analysis. It does not, primarily, attempt to treat the text as a document in the valuable way recently advocated by Prior (Prior, 2003 & 2008), who draws on actor-network theory to advocate an approach that goes beyond treating documents as 'containers of content', to treat them as 'active agents' (Prior, 2008). It is clear that, given the appropriate research study, the document in question in this paper could be analysed in this way, to examine how it can 'influence episodes of social interaction' or 'schemes of social organization' (Prior, 2008). One could, for example, observe how the document is used in meetings of, say, the regulatory affairs department of a regenerative medicine company, or in the interaction between healthcare policymakers and industry representatives. Whilst this type of analysis is not the main aim of this paper, some remarks will nevertheless be made especially about the way it works with schemes of social organisation – taken here to be patterns of relationships between social and technological actors - which have produced the document, and which are its regulatory objects.

The legislative text to be considered is a rich, highly condensed source of data. Needless to say, the text is the outcome of a massive collective effort involving literally hundreds of people over several years, many of whom were acting in some or other organisational or representative capacity – thus bringing even more people, institutions and interests into the process of producing it. Many phrases, clauses or paragraphs have been the subject of intense debate, conflict, proposals, counter-proposals and numerous amendments. Short phrases and even single words can have large significance. In general, the text differs in what might be called its summative quality from the discursive and repetitive nature of many policy documents whose intention is to discuss and persuade audiences of particular concepts, strategies and proposals which might be applicable to a policy domain (cf. Iannantuono & Eyles, 1997). The document crystallises the fine-grain detail of a socio-political process and its outcome at a certain point in time.

Under the European Union's political 'co-decision' procedure, different administrative units, committees and working groups of the tripartite political system have all contributed to the process that has resulted in the text: the European Commission (which proposes legislation), the European Parliament (which debates it) and the Health

Council of Europe (which debates and finally votes on it, representing the political positions of Member States). The centrality of the text itself to the process is indicated, for example, by the record of the Working Group on Pharmaceuticals and Medical Devices, a group under the auspices of the Council, whose deliberations proceeded by a succession of notes of member states' agreement and disagreement with the proposed wording of each draft article in the text, appended to the evolving draft text of the legislation itself (the author obtained copies of the successive versions of this annotated text through the European Union's formal transparency rules). In legal terms, the resulting Regulation is a *lex specialis* introducing additional provisions referring to but not being overridden by existing EU Directives on the production and marketing of pharmaceuticals – medicines for human use.

The analysis that I present uses the English-language version of the text, which is translated by the European Commission into 21 other languages. It is published by the European Union in both paper and online form in the *Official Journal of the European Communities (OJ)* (European Parliament and Council of the European Union, 2007). The analysis proceeded via searching for a wide variety of terms partly derived from intimate knowledge of the field over a period of about six years' study. Passages containing sought-for words were scrutinised for other, related terms. For example, a search for an obvious term such as 'risk' would lead to a search for the perhaps less obvious 'concern'. I also used thesaurus look-up to identify possible terms, and scrutinised the text by reading it repeatedly to locate other related and cognate concepts and terms. In interpreting the text, frequency of occurrence of terms has some meaning but must be considered alongside position in the document as a whole and conceptual significance in the field. Conspicuously absent words or phrases, or absent themes also may 'speak volumes'. In the case to be considered, the document has some hierarchical organisation and narrative structure, which is described. One might expect a legislative text to be relatively lacking in discursive techniques of persuasion that are used in other types of policy-oriented text – such as rhetoric and storylines. My analysis shows the extent to which this is and is not so.

As noted above, the analysis is animated by a set of questions arising from a guiding interest in the relationship between innovation and regulation/regulatory policy. I can now formulate these analytic concerns in terms of a more specific set of operationalisable questions. These questions include: do actors in this scientific and regulatory field orient themselves to a real or imagined regenerative medicine industry or sector? Which types of regulatory and other actors take or are given responsibility for regenerative medical technologies, and what relationships of power or accountability do they have to each other? What relationships between users and producers of these technological products

are envisaged? How does regulatory discourse represent the involvement in innovation of patients, the wider society, and publics? How is the materiality of technological products construed by regulatory discourse?

The paper proceeds with a summary of the issues that the Regulation addresses and a brief overview of the main points of the history of its negotiation, before presenting the textual analysis that addresses the questions above.

Summary of the history and main issues of the EU's Advanced Therapies Medicinal Products (ATMP) Regulation

The Advanced Therapy Medicinal Products Regulation (European Parliament and Council of the European Union, 2007) evolved through consultations and negotiations which began seriously in 2002, following earlier failures of attempts to include human tissue products in EU medical devices regulation. The initiative to create the Regulation was driven at least as much by industry stakeholders as by the European Commission. The Regulation was voted on and approved by the European Parliament and Council of Europe, under the co-decision procedure, in 2007, with implementation of pan-European and national Member State provisions due by the end of 2008. The European Commission's stated priorities in negotiating this new Regulation, were outlined by the Director of the Commission's Directorate (DG) of Enterprise and Industry as being to 'Guarantee a high level of health protection; Harmonise and facilitate market access; Foster competitiveness; and Provide overall legal certainty' (Lalis, 2006).

The consultation document for the Regulation portrayed 'a coherent ensemble' of tissue engineering, cell therapy, and gene therapy (European Commission, 2005), jointly distinguished by four stated main characteristics: Innovative manufacturing; Scarce scientific and industrial expertise; Traceability & risk management; and the primary participation of small and medium-sized enterprises (SMEs), hospitals and tissue banks. The concept of 'advanced therapy' was invented in large part in order to align tissue engineering, for which regulation was lacking, with some other therapies which were already subject to pharmaceutical regulation. The draft ATMP Regulation thus brought tissue engineering (TE) into the jurisdiction of the pharmaceutical regulatory regime. This was 'justified legally' on the grounds of these therapies: having properties for treating or preventing disease; being used with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action (this means: working in the same way as drugs); and 'in accordance with the jurisprudence of the European Court of Justice on the matter...are capable of having a significant effect on the actual functioning of the body'. The Regulation thus

enacts a form of regulatory pharmaceuticalisation. This move has been analysed in detail elsewhere (Faulkner, 2008 & 2009). Figure 1. illustrates the initial framing of the 'advanced therapy' concept in relation to existing European directives, showing the bringing together of the three types of therapy.

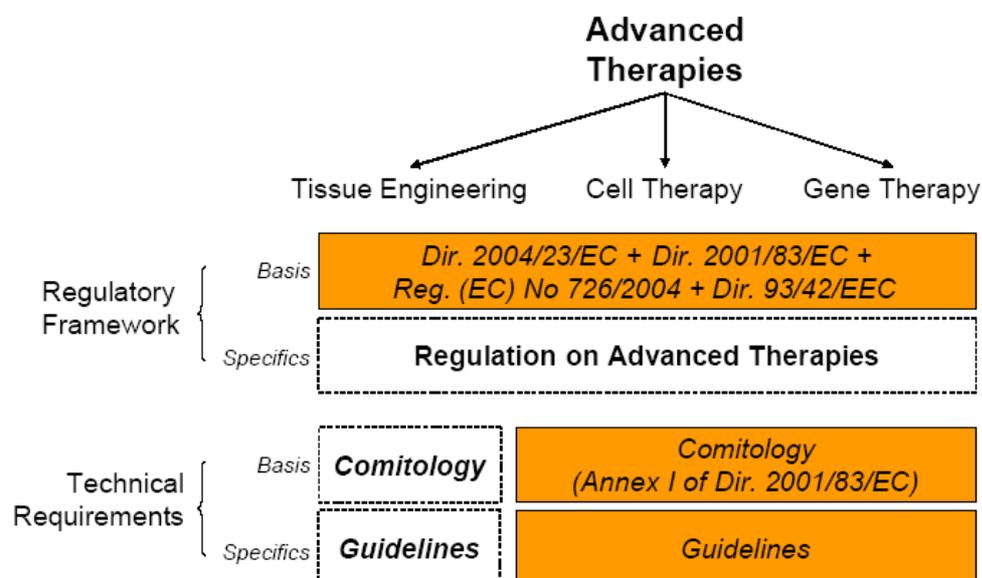


Figure 1. The original European Commission conceptualisation of an Advanced Therapies Regulation (note at this point *not* Advanced *Medicinal* Therapies). The 'Dir'ectives and 'Reg'ulations in the top bar refer to existing Directives on human tissue and cell banking, medicines and medical devices.

Source : European Commission DG Enterprise and Industry (2005)

The main features of the ATMP when finally ratified and published can be regarded as the following, which is a distillation of a range of commentators' interpretations of the key aspects.

- the 'scope' of tissue engineering as a technology is defined, alongside cell therapy and gene therapy;
- EC/EU centralised authorisation for products is introduced;
- A new expert scientific-technical Committee for Advanced Therapies (CAT) is created, based in the European Medicines Agency (EMA);
- 'Pre-certification' of new products is introduced;
- a substantial licensing fee-waiver for small companies is introduced;
- hospital one-off individually prescribed products are excluded from the requirements of the Regulation (though must still meet equivalent safety and quality standards);
- there should be 30 year traceability of each starting material and patient;

- postmarketing follow-up surveillance rules are introduced;
- 'technical requirements' such as preclinical and clinical data requirements are delegated to 'comitology' ('technical' committees outside the parliamentary process) for future development.

The text of the legislation shows, in abbreviated form, the position reached on each of these points. As previous analysis has shown, the contents of the ATMP have been, and in some respects continue to be, controversial. The most controversial points have concerned: the so-called 'hospital exemption'; the 'pharmaceutical' designation of TE products and the treatment of combination products (i.e. combining features of pharmaceutical and medical device 'modes of action') especially with regard to the respective powers of the pharmaceutical and medical device regulatory evaluation procedures; the ethics of inclusion/exclusion of certain types of tissues/cells, especially human embryonic stem cells and human-animal hybrids and manipulations that might affect the germ line; the definition of the 'scope' of advanced therapy medicinal products; the role of national regulatory authorities; the composition of the new Committee for Advanced Therapies; the ownership and responsibility for compiling and retaining surveillance data on patients/products. The medical device industry, in particular, has made many attempts to resist pharmaceuticalisation, with some success, although concerns continue about the coverage of regulations for specific types of device product, where 'regulatory gaps' are seen to remain.

Formal aspects of the text of the ATMP Regulation

It can be noted at the outset that the format of the Regulation is as a textual document (many contemporary documents contain sounds, images, diagrams, and so on (Prior, 2008,)) but this document is comprised wholly of textual language. The legal pronouncements themselves are prefaced by 31 paragraphs most of which set out the issues raised and the principles of justification on which the Articles of the legislation itself are allegedly based. Many of these formed parts of the 'Explanatory Memorandum' which was part of the earlier draft versions of the Regulation, and which is a usual part of draft legislation put forward by the European Commission. They can be regarded as outlining a European Union world-view on regenerative medicine products. Thirty 'Articles' follow, laying out the legal framework and provisions themselves, followed by the statement that 'This Regulation shall be binding...and directly applicable in all Member States', thus distinguishing itself from a Directive, which requires transposition into national legislation. This section is followed by four Annexes, which deal, first, with types of cell and tissue 'manipulation'; second, a list of 30 items which must be included in written descriptions of any product characteristics; third, a list of 14 items of

information required to be included in the outer packaging of any product; and fourth, a list of required information to be included in any package leaflet.

In the analysis and presentation of textual extracts from the Regulation these different materials are identified as 'J' (Justification), 'A' (Article), or 'Annex' as appropriate. The text as a whole can thus be regarded as having an overall narrative structure characterised by an extensive though condensed statement of issues to be addressed and factors seen as relevant to the case in hand, followed by the legal provisions that are intended to provide measures to meet them. The Articles of the Regulation are divided into the following 'chapters' (a full list of the Article headings, by number, is given in Table 1; the prefatory Justification paragraphs do not have headings):

ATMP Regulation: Article Chapter headings:

-
1. Subject matter and definitions
 2. Marketing authorisation requirements
 3. Marketing authorisation procedure
 4. Summary of product characteristics, labelling and package leaflet
 5. Post-authorisation requirements
 6. Incentives
 7. Committee for Advanced Therapies
 8. General and final provisions
-

As can be seen from this list, the emphasis of the Regulation is on provisions for placing new products in the healthcare marketplace, describing them to users and patients, following up results of their clinical use, supporting innovating companies or other establishments, and creating an institutional regulatory framework. The paper now proceeds to analyse the text of the document, following the guiding interest and questions outlined above.

ANALYSIS

In this section, I analyse the text according to the main concerns that have been identified in the introduction to this paper, namely expectations and visions, rules of engagement for participants and the relations between them, and the scope of the material technology of regenerative medicine. First, I examine the way in which the text deploys concepts that might invoke a vision of regenerative medicine as an industrial/R&D sector.

(A) Concepts of scientific-industrial structure and organisation

Of interest to an analysis of regenerative medicine is the way in which a new techno-scientific sector is constructed and apprehended by interest-driven actors who might contribute to the production of actual medical products. In the case of the text analysed here, therefore, one can examine the way in which the European Union document refers to concepts which might denote the contours and constitution of a regenerative medicine field. A number of terms have thus been analysed. Questions that should be asked here are: are the definition and boundaries of a regenerative medicine field clear, suggesting that it has a clear identity amongst political and socioeconomic actors and governments? what are the existing sectors that impinge upon the new field? are the fields that are evoked depicted as forming a 'coherent ensemble'? This analysis is presented below.

SECTOR (6 occurrences; Location J5, J10, J15; A22 x3). This term is not prominent in the text. The main uses are to refer to existing, widely recognised industrial and R&D sectors. The only mentions in the legislative Articles (A22) all refer to possible conflict of interest of members of a new Committee for Advanced Therapies. Of the scientific-industrial fields that could be referenced, the two referred to are the biotechnology sector and the medical devices sector. 'The public and non-profit sector' also receives one mention. No regenerative medicine sector is identified by name in the text. Advanced therapy products are aligned with biotechnology in a statement made early in the text, in a paragraph that goes on to note the specificity of the regulatory data requirements of emerging ATMPs: 'Advanced therapy medicinal products should be subject to the same regulatory principles as other types of biotechnology medicinal products' (J13). Examples are: 'the internal market in the **biotechnology sector**' (J5); 'areas bordering on other **sectors** such as biotechnology and medical devices (J10); 'Member States should be urged to take all necessary steps to encourage a **strong public and non-profit sector involvement** in the procurement of human cells or tissue' (J15); and 'members and alternates of the Committee for Advanced Therapies shall have no financial or other interests in the biotechnology **sector** and medical device **sector** that could affect their impartiality' (A22).

FIELD (4 occurrences; Location J1, J10, J23, J29). All the occurrences of this term are in the Justification section of the text, the term perhaps being too imprecise for use in the legislating sections. It appears to be used in a broader and less clearly-defined way (even) than 'sector'. Examples are: '**This nascent field** of biomedicine offers new opportunities..' (J1); 'expertise, which goes beyond the **traditional pharmaceutical field**' (J10), and unspecified uses of '**this field**'. However, its use in J1, the primary foundation-laying justificatory claim, arguably underpinning the whole Regulation, is

notable in conjuring up 'this nascent field', albeit without dignifying it with a distinct name of its own.

AREA/AREAS (8 occurrences; J11 x2, J21, J24, A21 & A23). This term is used mainly for 'scientific areas', and, as one might expect, in a flexible and multi-faceted way. The use in the Articles is in the section on the new Committee for Advanced Therapies: '... beyond the traditional pharmaceutical field and covers **areas bordering** on other sectors such as biotechnology and medical devices' (J10); 'The composition of the Committee for Advanced Therapies should ensure appropriate coverage of the **scientific areas** relevant to advanced therapies, including gene therapy, cell therapy, tissue engineering, medical devices, pharmacovigilance and ethics. Patient associations and clinicians with scientific experience of advanced therapy medicinal products should also be represented' (A22).

Those with a concern or interest in the ethical aspects of these technologies may be surprised to see ethics referred to as a 'scientific area' here. In fact, whilst clinicians and patients' associations are given specific representation by *membership* of the new committee, 'ethics' is not represented by dedicated members such as philosophers of ethics or bioethicists, but rather it is expected that this dimension will be represented willy-nilly by the collective membership. (On the other hand, those who would see the committee as an example of technocratic decision-making policy might be surprised to see ethics mentioned at all, and indeed its ill-defined inclusion was the subject of conflict in negotiations). In the light of debates about policy and sociological issues of lay and alternative expertise and expert patients, the reference to patient associations with 'scientific experience' is also worthy of note. Given the high degree of attention to issues of the composition of this committee during negotiations, this cannot simply be attributed to sloppy drafting of the text.

An issue of the availability of technical expertise was a major point of debate in the negotiation of the Regulation in 'this area'. 'Open consultation with all interested parties...should be carried out in order to allow a pooling of the **limited expertise in this area...**' (J21).

MEDICINE; REGENERATIVE MEDICINE (0 occurrences). These terms do not appear in the text as reference to broad institutionalised fields of healthcare-related activity. The term 'innovative medicines' is used once: 'scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies...' (A23- Tasks of the Committee for Advanced Therapies). Otherwise all uses of the term 'Medicine' are in institution names or the names of official bioethical codes.

INDUSTRY (1 occurrence, J21). The term 'industry' is used only once in the entire text, in a way that does not define it, in relation to the demographics of the composition of the new committee: '...Open consultation with all interested parties, in particular Member State authorities and **the industry**, should be carried out...' (J21).

Overall then, concepts of the field of medicine or science to which the Regulation is oriented are vague and loosely defined in this key document, emphasizing the lack of a clear identity for any technological zone or emerging sector. Although the text is explicit about creating the category of advanced therapy products, which is not used elsewhere in the world in biomedical regulatory policy, it does not propose that this amounts to the status of a sector itself, nor does it use the term regenerative medicine, unlike hundreds of research institutes worldwide and a growing number of the multinational medical and healthcare product companies.

(B) Concepts of the production and technology of advanced therapies

Alongside the terms that might define the fields of regenerative medicine, the ATMP Regulation uses language that characterises the nature of the socioeconomic processes that may create innovative healthcare products, and which defines the possible scope of those products themselves. In such a techno-scientific field we can examine the deployment of terms such as 'science', 'technology', 'process', 'product', and 'engineered'. The most glaring analytic comment that can be made here is that while the terminology of specialised knowledge production ('science') is used consistently through the document, the concept of technology is hardly used at all.

TECHNOLOGY/IES (2 occurrences, apart from use of term biotechnology and one reference to the European Group on Ethics in Science and New Technologies (EGE)). For example: 'market access for **these innovative technologies**' (J9); and: 'a procedure that provides for sufficient flexibility, so as to easily accommodate the rapid evolution of **science and technology**' (J13). Usages of **SCIENCE/SCIENTIFIC** (39 occurrences; 18 in Js, 21 in As) begin with the first Justification claim: 'new scientific progress...' (J1), supported by several further references to scientific evolution, through references to 'scientific evaluation' of the products under consideration, to the 'scientific areas' mentioned in the previous section, and a set of references to scientific advice, scientific consensus and scientific qualifications in the Articles concerning marketing authorisation, certification and the working of the Committee for Advanced Therapies. Examples include: 'ensure a high level of scientific evaluation of these medicinal

products in the Community,...' (J9); 'ensure scientific consistency and the efficiency of the system,...' (J12); 'The names and scientific qualifications of all members (of the Committee) shall be made public...' (A21).

PRODUCT (227 occurrences). This term is ubiquitous in the document, emphasizing that the regenerative technologies in question are framed by this legislation primarily as commercialisable commodities in a competitive marketplace in biomedical knowledge and saleable healthcare goods provision. A key reference to advanced therapies is provided in the text: 'a **given product** based on genes, cells or tissues' (twice, in J24 and A17) in connection with the scientific product assessment process, emphasizing the generic nature of the envisaged technologies. The term **REGENERATIVE** is not used, although there is an early invocation of ATMPs that are 'presented' (i.e. by manufacturers making claims about a product) as being aimed at: '**...restoring, correcting or modifying physiological functions**' (J2). The purpose of this early ground-laying paragraph is to make it clear that products acting by pharmacological, immunological or metabolic means will fall into the jurisdiction of biological medicinal products. Where the product is a complex one including a medical device component, rules are laid down for providing information to enable assessment of it: '**... applications for the authorisation of an advanced therapy medicinal product containing medical devices, bio-materials, scaffolds or matrices** shall include a description of the physical characteristics and **performance of the product** and a description of the **product design methods.**' (A7).

PROCESS (5 occurrences). This term appears only in the Justification section, two in cross-references to the Tissues and Cells Directive (European Parliament and Council of the European Union, 2004) and one reference to the processing of personal data, so the number referring to the *production process* is very small: '**... prepared industrially or manufactured by a method involving an industrial process.**' (J6); 'guidelines specific to advanced therapy medicinal products should be drawn up, so as to properly reflect **the particular nature of their manufacturing process**' (J17).

In view of the discussion around some tissue and cell therapy technologies as to whether they are products or services (for example knee cartilage cell therapy, which is already available) it is interesting to note that the term **SERVICE** does not appear at all. This is an absence shared with the term **HEALTHCARE** with which it could be considered closely aligned, as in the concept of a national healthcare service. It can be noted nevertheless that the healthcare/hospital site is an important one in terms of the current efforts to develop regenerative tissue and cell-based technologies.

TISSUE ENGINEERING/ENGINEERED (15 occurrences; J1, J3, J11, J13, J28, A2 x6 ('Definitions'), A4, A21, A29 x2). **GENE THERAPY** (9 occurrences, J1,J3,J11,J13, A2 x2, A4, A21, **CELL THERAPY** (9 occurrences; J1,J3,J11,J13, A2x3,A4, A21). Most references to Tissue Engineering terms are to 'tissue engineering products' and their definition. Most notable, indeed fundamental to the Regulation and signalled by its very early appearance in the text, is the question of defining tissue engineering, as one of the three advanced therapies. Unlike gene therapy and cell therapy : '... **a legal definition of tissue engineered products remains to be laid down**'.. ' (J3). In the Articles, these terms are mostly mentioned in A2, the Definitions section, where clarifications are provided of the regulatory approach for products with potentially ambiguous definitions, for example a product that is both tissue engineered and a cell therapy.

BIOTECHNOLOGY (7 occurrences; J1,J5,J9,J10,J13 A21, A22). The initial vision setting out the type of technology being formulated in the legislation employs this term: 'cellular and molecular biotechnology' (J1). The term is used, as seen in the previous section, to denote an established industrial/commercial sector, but it is also used to frame the type of material technology in question by establishing advanced therapies *as* 'biotechnology medicinal products'. The strength of this framing move is evident in the suasive use and repetition of the phrase in J9 and J13: '**other modern biotechnology medicinal products** currently regulated at Community level are already subject to a centralised authorisation' (J9); 'Advanced therapy medicinal products should be subject to the same regulatory principles as **other types of biotechnology medicinal products**' (J13).

Controversy about ethical issues in the negotiation of the legislation concerned especially embryonic stem cells and the possible development of products using human-animal hybrids. In fact, the eventual Regulation is non-prescriptive about the starting materials of advanced therapy products, the subsidiarity principle being invoked so that members states that wish to introduce their own principles may do so. The term **EMBRYONIC** appears only once. An original proposal to exclude animal-based products from the scope of the regulation was challenged by many stakeholders, and thus the text is non-prescriptive about this too. The prefix **XENO** (xenotransplantation, xenogeneic, i.e. animal, cross-species) does not appear, but: '(The Regulation at) ...Community level should not interfere with decisions made by Member States on whether to allow the use of... embryonic stem cells, or animal cells' (J7). **ANIMAL** does appear (8 times; A2x2, A25, Annex II, Annex IIIx2, Annex IV), including specific indication that this material is permitted: 'A tissue engineered product may contain cells or tissues of human or animal origin...' (A2). This is a reversal of the original proposal from the Commission to exclude such material.

ENGINEERED (13 occurrences; J3, J13, A2 x8, A4, A29 x2); **MANIPULATION** (4). These terms are used primarily to accomplish the establishment of a legal definition of tissue engineered products (in A2): ‘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’ (A2)... ‘Cells or tissues shall be considered ‘engineered’ if they fulfil at least one of the following conditions: — the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved... — the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor (A2). Specific manipulations are listed that do not amount to substantial manipulation. These include cutting, centrifugation, irradiation, cell separation, and cryopreservation (Annex 1).

Overall, the discourse of regenerative medicine’s technologies is dominated in this legislation by the concept of marketisable products, a usage that is strongly and rhetorically aligned with the biotechnology sector, which figures large in the economic strategy of the European Union, as in other advanced industrial countries and regions. ‘Market access’ terminology is used rather than mention of healthcare or health services. The legislation also accomplishes a legal definition of the particularity of tissue-engineered products, and has eschewed a service-based framing of the regenerative medicine enterprise. On ethical issues of the composition of products, the text confirms a non-prescriptive approach to the types of materials used, leaving this to Member States under the subsidiarity principle (patients are given the right to information about the composition of products – see below). The rhetorical appeal to the authority of science is evident throughout the text, and it appears that the conceptualisation of commodity *products* dominates any possible use of concepts of *technology* per se. The aim to achieve legal clarity in the definition of ‘engineered’/‘substantially manipulated’ products may await the experience of legal case decisions and the actions of the Committee for Advanced Therapies and the European Medicines Agency.

(C) Future-oriented concepts: expectations and vision

Given the growth of interest in the generative capacity of technology expectations, it is of interest to examine what instances of such phenomena might appear in a legislative text such as the ATMP Regulation. There are two lines of analysis here. First, it is possible to note what terms of novelty, innovation, hope and healthcare futures are embodied in the

textual performance of the legislation. Second, it is of course the case that regulation of the sort being enacted here is future-oriented. Thus it is of interest to analyse what provisions for the unpredictable development of the technology and its associated projected benefits and risks might be incorporated in the text.

PROGRESS (2 occurrences; J1, A25). The first justificatory statement of the Regulation has been referred to earlier in this analysis. While many concepts are compacted into it, the notion of progress is perhaps the most powerful, the term itself being used as well as several other terms denoting the expectation of future development, related both to techno-scientific knowledge and the potential for medical treatment. Here it is in full: 'New scientific **progress** in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engineering. This **nascent field** of biomedicine **offers new opportunities** for the treatment of diseases and dysfunctions of the human body' (J1). The future orientation is also emphasized in the other use of 'progress', where evaluation of the Regulation itself by the European Commission is built in to its own terms: 'the impact of **technical progress** on the application of this Regulation' (A25). The term **EVOLUTION** (2 occurrences; J13, A24) is used almost synonymously to denote progress: 'As science **evolves** very rapidly in this field...' (access to scientific advice should be enabled; J23), and: (establishing technical requirements for preclinical and clinical data) 'should be done through a procedure that provides for sufficient flexibility, so as to easily accommodate the rapid **evolution** of science and technology'(J13).

HOPE, EXPECTATION, VISION. None of these terms themselves appear, though of course their meaning is implicit in the concepts of progress and evolution noted above. **OPPORTUNITIES** appears once. The term **FUTURE** is used only in a procedural sense ('future application for clinical trials'), and not at all to denote a concept of, say, 'the future' of biomedicine or healthcare. The term **INNOVATION** does not appear, and the concept of **NOVELTY** is not prominent (1 occurrence), being used only as another term in the set concerning the almost goes-without-saying expectation of techno-scientific progress: 'Because of the novelty, complexity and technical specificity...' (J5).

The *future-orientation* and *open-endedness* of the unpredictable development of regenerative medicine are emphasized in the provisionality of much of the legislative text and measures introduced for review of its own operation. There are numerous examples in the legislating Articles: 'By 30 December 2012, the Commission shall publish a general report..., which shall include comprehensive information on the different types of advanced therapy medicinal products...the Commission shall **assess the impact of technical progress** on the application of this Regulation...' (A25 'Report and Review').

Similarly: 'In order **to take into account scientific and technical developments**, the Commission should be empowered to adopt any necessary changes regarding the technical requirements for applications for marketing authorisation...' (J26). The latter statement points to one of the many controversial issues in the development of the legislation, a criticism that is frequently made in the political process of the European Union, namely the power given to the Commission and its executive bodies, through 'comitology' ('technical' committees that operate without parliamentary scrutiny) to make decisions that some stakeholders see as having a political dimension.

The concept of techno-scientific progress, in summary, is one of the fundamental framing devices of this legislative text. An assumption of rapid progress of science has led to major provisions for open-endedness in 'technical' aspects of the Regulation. It is difficult to interpret the flexibility or narrowness of the technological pathway that is implied by the legislative text. On the one hand, the assumption of progress is allied with an openness to a future development of different types of advanced therapy products, while on the other hand the criterion of 'substantial manipulation' (discussed in section B above) does create a principle by which the legislation can be invoked, albeit a principle that may be contested in case of particular products or services. Thus the position of the text as conveying expectations that are 'generative' is mixed: on the one hand mechanisms are enacted that will allow products to be assessed and potentially approved, on the other hand such products are not framed as falling within a clear sectoral identity other than the very broad 'biotechnology' sector. The textual framing of expectations of these technologies thus emphasizes the product-focused, formative point at which regenerative medical technology finds itself.

(D) Concepts of risk, health, and safety

As noted in the previous section, the framing of different projected forms of risk and benefit is one of the dynamics that constitute a technological zone such as cell and tissue engineering (cf. Faulkner et al, 2008). Risk is itself a future-oriented concept that is part of the architecture of expectations that are built into an emerging technology. Modes of risk assessment are integral to the pathway that the technology might take into the world of sociomedical practice. Thus the establishment of risk assessment procedure is an important aspect of the social legitimation function that legislation may aim to help accomplish. In the legislation under consideration here, some rules to govern the technical assessment of risk to health are laid down, whilst provision is also made for standards to be formulated for the type of data that should be produced in order that health risks can be assessed, this process being an open-ended one due to the unpredictable nature of the future development of the technology. The legislation thus

exemplifies the phenomenon of 'risk regulation' (Hood et al, 2001; Faulkner et al, 2008). The concept of risk therefore links the strand of analysis pursued here on technology expectations and the strand on the legal definition of the nature of the material technology.

Safeguarding human health was stated to be one of the key principles underlying the ATMP Regulation, along with economic aspects and legal clarity. It is thus interesting to note that the term **HEALTH** is used only 4 times (J2, J15, J20, A19), all in the context of public health/human health. However, this is a case where the word-count analysis does not indicate the significance of the concept, for example: '... **the essential aim of any rules governing their (ATMPs) production, distribution and use must be to safeguard public health**' (J2). The single reference to HEALTH in the Articles is to the granting of a fee reduction to small companies or hospitals applying for marketing authorisation if the case for 'public health interest' is strong.

RISK (9 occurrences; (J20 x2, A14 x5, A16, A21). The term **BENEFIT** does not appear.. The majority of references to the term risk itself are to 'risk management' and the putting in place of frameworks for monitoring and control. Article 14 is titled '**Post-authorisation follow-up of efficacy and adverse reactions, and risk management**'. For example, 'Where there is particular cause for **concern**, the Commission shall, on the advice of the Agency, require as part of the marketing authorisation that a **risk management system designed to identify, characterise, prevent or minimise risks...**' (A14). The evaluation of the performance of medical products in the healthcare products industry is typically conceived as being concerned with quality, safety and efficacy. Quality and safety can be regarded as concerned primarily with preclinical assessment of the production process and test regimes such as toxicology or tumorigenic testing, while efficacy is primarily a matter for 'postmarketing' assessment of clinical performance of a product in patients' medical treatment. An important point here in relation to tissue-engineered technologies relates to their perceived particularity: '**data necessary to demonstrate the quality, safety and efficacy** of the product, may be highly specific...(while already in existence for cell and gene therapy) they need to be established for tissue engineered products' (J13). These terms appear repeatedly in the text, frequently as a trio. **QUALITY** (17 times – 10 Js, 7 As) assessment is included as part of a 'compulsory' assessment procedure, aligned with 'modern biotechnology medicinal products'. And 'the type and amount of quality, preclinical and clinical data necessary to demonstrate the quality, safety and efficacy' (J13) may be specific to a technology', and the text makes provision for 'technical requirements' to be developed 'through a procedure that provides for sufficient flexibility, so as to easily accommodate the rapid evolution...' (J13).

SAFETY (14 times: 10 Js, A14, A23 x2, Annex II) in one instance is linked to a non-compulsory promotion of donation as opposed to commercialised sourcing of human tissue/cells: 'as voluntary and unpaid cell and tissue donations may contribute to **high safety standards** for cells and tissues' (J15). Safety principles are presented as leading to data monitoring requirements: 'A system allowing complete traceability of the patient as well as of the product and its starting materials **is essential to monitor the safety...**' (J22). 'Preclinical safety data' should be included in manufacturers' descriptions of any product (Annex II). **EFFICACY** is mentioned rather less overall (8 times: J9, J10, J13, J20, A14 x2, A23 x2), consistent with the greater emphasis given in pharmaceutical regulation to pre-marketing assessment, compared to the medical device regime – though here efficacy assessment plans should be provided at the time of product authorisation: 'Follow-up of **efficacy** and adverse reactions is a crucial aspect of the regulation' (J20)... 'the applicant shall detail...the measures envisaged to ensure the follow-up of efficacy...and of adverse reactions thereto' (A14). The provision for dealing with **ADVERSE** clinical events (6 occurrences) is linked to efficacy. Apart from provisions for efficacy that also cover adverse reactions, patients are enrolled (softly) into the regime at this point: '**the patient should be expressly asked to communicate any adverse reaction** which is not mentioned in the package leaflet to his doctor or pharmacist' (Annex IV).

Various types of risk assessment typical of the pharmaceutical regime are thus built into the text, along with provisions for future detailing of data requirements specific to particular (tissue-engineered) technologies. As will be seen below, there is an attention here to issues of public confidence in the new ATMP regime, given a perception that the health risks of the products potentially under consideration are generally deemed to be novel and high. There is an increased provision for assessment of clinical outcomes and long-term traceability, though unlike premarket assessment this is not a centralised role of the new regulatory committee. The organisation of and access to technical risk assessment expertise is thus constituted as part of the regenerative medicine zone envisaged here for the European Union.

(E) Actor concepts: regulatory actors; institutional participants; users, patients and publics

Regulatory actors

The regulatory actors and the proposed institutional arrangements that they will enact, as one would expect, are mentioned repeatedly in the text. So, for example, **THE AGENCY**, i.e. the European Medicines Agency, which is given responsibility for ATMPs

by the Regulation, is mentioned 40 times (9 times in Justification, 31 in Articles, demonstrating its pre-eminent position in the legal acts). For example, the Committee for Advanced Therapy (see below) should prepare: 'a draft opinion on the quality, safety and efficacy of each advanced therapy medicinal product for final approval by **the Agency's** Committee for Medicinal Products for Human Use' (J10). As noted in the introductory summary of the ATMP Regulation, the Regulation creates a new **Committee for Advanced Therapies** (CAT), within the institutional boundaries of the European Medicines Agency. This is described in detail (referred to by name 37 times). The first mention gives its rationale: 'The evaluation of advanced therapy medicinal products often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers areas bordering on other sectors such as biotechnology and medical devices. For this reason, it is appropriate to create, within **the Agency, a Committee for Advanced Therapies** (CAT), which should be responsible for preparing a draft opinion...of each advanced therapy medicinal product for final approval by the Agency's Committee...' (J10). Notable here is the hierarchical relationship created between the new CAT and the existing pharmaceutical standing committee. This relationship is made explicit later in the text: 'Where the scientific opinion on an advanced therapy medicinal product drawn up by the Committee for Medicinal Products for Human Use (CHMP) ...is not in accordance with the draft opinion of the CAT, the CHMP shall annex to its opinion a detailed explanation of the scientific grounds for the differences' (A9 para.4).

I have noted above the position of advanced therapies in relation to the pharmaceutical and medical device domains. Further insight into the positioning of advanced therapy can be gained by examining the deployment of references to the respective regulatory regimes for these domains. Thus the Standing Committee for Medicinal Products for Human Use (**CHMP**), the primary committee of the European Medicines Agency, appears regularly (13 times). **NOTIFIED BODIES**, the organisations that perform premarket assessments of medical devices, are mentioned less frequently (6 times), all referring to the case of 'combined' ATMPs, i.e. products that have an advanced therapy element combined with a medical device component. For example: 'The application for a marketing authorisation for a combined advanced therapy medicinal product shall include, where available, the results of the **assessment by a notified body** ...of the medical device part...' (A9). This usage emphasizes the secondary status of the medical device regime accorded by the regulatory text to this class of technologies.

Aside from the regulatory bodies, a number of other institutional authorities in the regenerative medicine domain are configured in the text. **AUTHORITIES** (5 occurrences): 'Open consultation with all interested parties, in particular **Member State**

authorities and the industry...' (J21). Apart from this reference, the others are to '**competent authorities**', in other words the regulatory institution in each member state mandated to implement European directives and regulations on medicines and/or medical products.

The set-up of regulatory arrangements in its various institutional parts is described quite consistently through the document as a **SYSTEM** (19 times). The term is used to denote the overall framework of arrangements as well as sub-system arrangements. For example: 'To ensure scientific consistency and the efficiency of **the system**, the Agency should ensure the coordination between the Committee for Advanced Therapies and its other Committees...' (J12); and: '**a system** of evaluation and certification of the resulting data by the Agency, independently of any marketing authorisation application..' (J25), and: 'require as part of the marketing authorisation that a risk management **system** designed to identify, characterise, prevent or minimise risks..' (A14). A requirement for '**traceability systems**' is also described in a section devoted to it (A15).

So the configuration of regulatory actors emphasizes the centralised authority of the EU's pharmaceutical regulatory set-up and the location of regenerative medicine in this. The maintenance of a role for the medical device regime signals the sectoral tension over claims for jurisdiction of this emerging biomedical zone. The text makes rhetorical appeals to administrative rationality with its claims to establish a 'system' of regulation composed of technical committees with memberships created through a mixture of routes of member state representation and cross-appointment from the pharmaceutical Agency.

Institutional participants

The text contains evidence of assumptions about how a new field of regenerative medical technology might be constituted in terms of its institutional actors. A wide range of participants are potentially involved, but the actors conjured up in the legislative text are defined in somewhat abstract terms. The terms **FIRM** and **COMPANY** do not appear nor, surprisingly, does the term **ESTABLISHMENT**, as in 'tissue establishment', the designation created in 2004 for organisations holding banks of tissues or cells (European Parliament and Council of Europe, 2004). **HOSPITAL and SMALL AND MEDIUM-SIZED ENTERPRISES** (SMEs) (5 times) do appear, some distinction, not formal, being made between producers and consumers of products: 'Studies necessary to demonstrate the quality and nonclinical safety...are often carried out by **small and medium-sized enterprises**' (J25); 'the **hospital, institution or private practice** where the product is *used*' (in relation to traceability – A15) appears. In general, participants are

defined more by reference to their position as actors seeking approval for their new products, or by their consumption of them, rather than specifics of the type of institution. Thus the terms (marketing authorisation) **APPLICANT** (8 times) and (marketing authorisation) **HOLDER** (13 times) are widely employed. **MEMBER STATES** (18 times), as one would expect, are widely invoked, drawing attention to the national state level of stakeholder interest in the regenerative medicine zone.

Aside from the regulatory actors, therefore, the institutional participants are invoked sketchily, and primarily in abstract terms by reference to their position as applicants for or recipients of decisions through the centralised authorisation procedure.

Users, patients and publics

In general users, patients and publics of regenerative medicine do not figure large in the legislative text. The term **MEDICAL PRACTITIONER** is mentioned twice, and **MEDICAL PROFESSIONS** once. It is assumed that a stringent regulatory policy will be beneficial to the interaction between scientific/medical practice and patients, the Justification text including the intent to: 'ensure a high level of scientific evaluation of these medicinal products in the Community, **to preserve the confidence of patients and medical professions** in the evaluation and facilitate Community market access...' (J9). References to the **PATIENT** mostly concern traceability and references to clinical approaches to individual treatment (16 times; J6, J9, J19, J22, A4, A12, A13, A15 x2, A21, A28, Annex II, Annex III, Annex IV x2). There are two mentions of patients as having rights or involvement in regulatory activity, namely the right to know the composition of ATMPs (interestingly, there is no such right in the case of pharmaceutical drugs), and an assertion that the labelling of products should be developed with the involvement of patients as to matters such as readability and legibility ('consultations with target patient groups..'). Representation of **patients associations** on the new Committee for Advanced Therapies is also established. In case of adverse reactions to a treatment '**the patient should be expressly asked to communicate any adverse reaction** which is not mentioned in the package leaflet to his (*sic*) doctor or pharmacist' (Annex IV). The reason for the relatively high number of mentions in the Annexes is that these deal with clinical effects on patients and information supplied to them via labelling and packaging.

The **PUBLIC**, in the sense of the constituency of people who occupy the public sphere or who constitute 'the general public', do not appear in the text, nor does **CITIZEN**. The only occurrences of the term 'public' are in the contexts of 'public health', 'public sector' (as a source of investment), 'public calls for expression of interest' in order to identify clinician and patient association representatives for the authorisation committee (CAT),

and the publicising - 'making public' – of information about, first, the membership of the CAT, and second a requirement for Member States to communicate any national restrictions on types of cell or tissue, which in turn shall be 'made publicly available' by the European Commission.

The public of regenerative medicine is thus constituted as an abstract, remote presence rather than as an active participant or even 'scientific citizen'. Public health is highlighted and the conventional rhetoric of public confidence and the confidence of the medical professions is associated with the role of scientific evaluation of the technologies. Some rights and responsibilities are given or at least offered to patients as individual actors, and a minimum of representation on the central committee is granted to organised patient groups.

(G). Concepts of rights, responsibilities and empowerments

As noted in the introduction to this paper, legislative texts commonly proceed with a host of performative vocabulary, and the ATMP Regulation is no exception in this respect. In this section I briefly summarise the deployment of this terminology and comment in more detail on the vocabulary that indicates the relationships and responsibilities of participants in the production of regenerative medicine products and their regulation. The authority of the European Union's politico-legal process is signalled in the very first paragraph of the text outlining the measures that are being put in place: 'Subject definition' (Chapter 1, Article 1): 'This Regulation **lays down specific rules** concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products'.

A summary of the law-creating language is indicated by the constant occurrence of terms such as **SHOULD** (53 occurrences) and **SHALL** (109). Similarly, the concept of the necessity of the measures being put in place is emphasized: **ENSURE** (19); **NECESSARY** (21); and **REQUIREMENTS** (21). Terms of **AUTHORISED/-AUTHORISATION** (46 occurrences, 11 in the Justification, 35 in the Articles) appear throughout the text: 'products subject to centralised authorisation procedures', 'requirements for manufacturing or importation', and 'advice on post-authorisation activities'. Conversely, terms of enablement and permission are much less prominent. For example, **ALLOW** appears four times, though one mention being particularly important: 'The regulation of advanced therapy medicinal products at Community level should not interfere with **decisions made by Member States on whether to allow** the use of any specific type of human cells,...' (J7). This is a key usage, because it refers to the subsidiarity principle that permits member states to exercise sovereign rights over the

provenance of cells and tissues which might be made available to their citizens. **EMPOWERED** is used only three times, twice for the European Commission, once for the European Medicines Agency.

The term **RIGHTS** is mentioned four times, all in the same justificatory paragraph: 'This Regulation respects the **fundamental rights** and observes the principles reflected in the Charter of Fundamental Rights of the European Union and also takes into account the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine Convention on Human Rights and Biomedicine' (J8). The text thus refers to rights as one of the bases for the legislation, rather than putting in place rights that participants might have in the production, regulation or consumption of advanced therapy products. One of the most controversial aspects of the debate of the Regulation in the European Parliament was the so-called 'ethical issues'. These were rather narrowly defined to refer to issues of the materials from which advanced therapies might be made or derived, such as human embryonic stem cells, on which there was a great deal of disagreement between the EU political parties and other divisions. As noted above, the final text uses subsidiarity to enable Member States to set their own principles here. The term **ETHICS** appears only twice, in references to representation on the products authorisation committee (CAT) and to ethical requirements for clinical trials. The European Group on Ethics of New Technologies (EGE) is referred to as one of the bodies whose 'Opinion' has been taken into account – an example of the many instances of intertextuality in the document. The term **BIOETHICS** does not appear.

Responsibilities, therefore, are created in abundance by the text whilst few rights and permissions are established. Aside from a non-compulsory commitment to voluntary unpaid donation of human material, the most controversial ethical issues are devolved to national states.

DISCUSSION

The paper has analysed the content and textual method of a new piece of legislation that is important to the future development of biomedical technologies globally. I have suggested that legislation such as that examined here should be accorded a more prominent place in theoretical understanding of the shaping and emergence of new fields of science and technology. As the analysis has shown, legislative text can enshrine expectations about a new technology and provide social legitimation for its producers and products, as well as at least partly accomplishing its stakeholders' aims of introducing a set of principles for controlling and monitoring the technology and

configuring an institutional set-up for the application of technical standards and monitoring systems.

The analysis has drawn together parallels between recent work in innovation studies, socio-legal studies and STS. The way in which a new techno-scientific sector might be constructed has been identified as an important and neglected area for contemporary research efforts in science & technology policy research and innovation studies emanating from evolutionary economics approaches (Malerba, 2006; Nelson, 2008). It also figures increasingly large in STS studies that focus on the mechanisms of early-stage lock-in of technology trajectories (van Merkerk & van Lente, 2005). A constructivist position answers affirmatively the law-in-action question 'should social, political and economic dynamics be considered not just as "factors" in law's environment, but as building blocs in the constitution of law?' (Lange, 2006). The analysis presented here shows both that political and economic dynamics are inscribed into law, and that the law enacts political, economic and technological features of an emerging biomedical zone – in selective ways.

Documents with consequences

A legislative text is a particular class of document, and is utilised in flexible ways in a variety of circumstances by various socioeconomic actors, as Prior argued: 'once a text or document is sent out into the world there is simply no predicting how it is going to circulate and how it is going to be activated in specific social and cultural contexts' (Prior 2008). This statement can be examined in the light of legislative documents. Whilst it is valuable in pointing to the flexible 'activation' of documents, it may in this light be a slightly over-general statement about the social mobilisation to which a document is susceptible. There may not be such a free market in the active consumption of legislative texts as other texts. To adapt terms from STS, legislative documents may be regarded as having a summative and distilling quality that leads to a measure of lock-in to a limited range of possible societal uses, effects and functions, in this case related to obvious framings of technology and actors, and the social position of the document itself in a political and legal system.

Taking the concept of documents as actors influencing or involved in 'episodes of interaction' and 'schemes of social organisation' - 'actors that can be recruited into schemes of organized activity and regarded by others as allies, enemies, or perhaps

simply instigators of further actions' (Prior, 2008:827), it is clear that the legislative text considered here enacts schemes of organisation that are, in effect, designs for future social, economic and regulatory relationships comprising the regulated and regulating actors constituted in the text. However, even this formulation does not quite capture the way in which the legislative text acts. Rather than presenting 'designs for' future organisation, because of its status as a legal statute, following an accepted political procedure, the document should be seen as *accomplishing* the new organisation that it sets out in its text (though, of course, without implementing it into the variability of actual practices) – it is more forceful, societally legitimate and effect-producing than a mere proposal or plan of action, and more path-defining than many other types of documents produced through lesser degrees of socio-political negotiation. It is more powerful in creating and shaping Austin's 'conventional consequences'. As Austin put it, such illocutionary acts 'take effect' rather than merely bringing about a certain state of affairs (Austin, *op.cit.*).

The power of conventional consequences here is supported by the issue-framing and legislative action of the text. Just as, for example, the discourse of environmentalism provided legitimacy for policies that protect public good over individual economic interests in human genetics policy (Jones & Salter 2003), in this case the discourse of safety assessment and risk management performs a legitimating function. This is achieved partly through the densely structured institutional embedding of the legislation in the political fabric of the EU, and partly through framing of a risk agenda and the corresponding legal framework erected by the document itself.

Elephants in the room

It is instructive to note some conspicuous absences revealed in the conceptual content of the legislative text under consideration. I suggest that three of the most conspicuously invisible large mammals in the regulatory room described by the ATMP Regulation are firstly the public, secondly bioethics, and thirdly, regenerative medicine itself. How might we account for these large absences? A number of issues present themselves. Evidence of the absence of regenerative medicine has been clear in the analysis. 'This area', 'the industry' and so on, are clearly and possibly deliberately indeterminate evocations of the domain of activity treated in the legislation. This point is discussed further in the following section. In the case of 'the public', it is the case that the negotiation of the regulatory text included phases of 'public consultation' managed by European Commission officials (European Commission, 2005). However, the 'publics' that took part consisted primarily of national regulatory authorities, trade associations, tissue and cell banking organisations, lawyers, patients associations and the like – no

voice of, say, general consumers organisations or individual 'members of the public'. Thus it is clear that the concept that the text mobilises is one of an abstract, presumed public, envisaged especially in the conventionally supposed relationship between regulation and 'public confidence'. In the case of ethics or bioethics, I described how the EU negotiation process had resulted in a narrow definition of 'ethical issues' that were essentially excluded from the regulation, with an indeterminate *representation of* ethics figured into the 'scientific areas' in the composition of the new specialist advanced therapy committee (CAT). Thus it may be that the absence of *bioethics*, as opposed to just 'ethics', one of the most significant developments in the governance of biomedical innovation over the last 20 years (Salter & Jones, 2002; Hedgecoe & Martin, 2003), is omitted exactly because it is - or claims to be - a field of specialist expertise that would require explicit representation in the product assessment process if recognised as a legitimate discourse in the field at all.

Standardisation, imprecision and legal certainty

One of the main stated aims of the text discussed here was to provide 'legal clarity' for the field, but it has been noted that policymaking may work best when categories and boundaries are flexible, because this allows policymakers to build consensus and deflect criticisms (e.g. Jasanoff, 1990). This discussion shows that such an analysis holds for a legislative text as well as the policymaking process that in part produces it. Thus the vagueness and looseness of the deployment of many key concepts in the ATMP Regulation suggests that although it is a summative legal text, its legal formality harbours possibly productive flexibility that allows for a wide variety of different actors to orient themselves in the text (and in the law) and to engage themselves in the actions that the text mandates. But even aside from this sociological insight, the administrative-rational goal of legal certainty appears mythical – in both the anthropological and everyday sense. The development of this legislation was thus partly fuelled by an urge to 'fill the gaps' in the EU's legislative jigsaw of biomedicine (devices, drugs, genes, blood, whole organs and so on), but even on its own terms gaps remain – for example, a 'Recast' of medical device regulation announced by the European Commission in 2008 will attend to technologies incorporating nonviable tissues/cells, which the legislation analysed here does not cover.

The standardisation of *terminology* is greater in some aspects of the text considered here than in others. Unsurprisingly, the degree of standardisation and concentration of terminology is greater for the legal Articles than for the rationale-building preceding justificatory segments. For example, the activity-defining terminology of sectors, areas, fields and so on is relatively loose and non-controlled, while on the other hand the more

abstract focus on products and applicants and users nevertheless appears much clearer – fewer alternative terms are deployed.

Standardisation is also expressed in the case considered here as *Europeanisation*. The concept of a technological zone that I have drawn on involves the building of technical standardisation, which the ATMP text provides a backbone for. The legislative regulation of technology is one of the routes through which the integrative European project is being attempted (cf. Callon, 2004). Although not an explicit term in the text, inter-national standardisation through '*harmonisation*' between national states is of course one of the aims of the European Union political project.

The document describes a regulated future in which regenerative medicine products might be created in or brought to the European marketplace and into healthcare practice safely and with economic benefit. Embedded in this discursive future is an obvious ideological expectation of progress (cf. Kerr, 2003). But this regulated future makes allowances for a variety of uncertainties associated with unpredictable developments, anticipated to be scientific and technological. Thus the regulatory text frames an intentional imprecision of innovation-dependent *open-ended futures*, and sets up courses of action to respond to them, which go beyond the *already-envisaged futures*.

CONCLUSION

In this paper I have unpicked the performativity of a single legislative document, showing in it a mixture of presences and absences, clarities and imprecisions. I have argued that such documents are an important device in the regulatory state's toolbox for shaping, locking-in and legitimating the zone of regenerative medicine. We have been examining a document enshrining stakeholders' expectations which accomplishes its own conventional consequences, in the form of participants' rights and obligations and the open-ended scope of the technology itself. This type of document should thus be accorded a more prominent place in theorising the innovation of new biomedical and other sociotechnological zones. The analysis shows that by and large the authorship of the legislative text prefers the flexibility of neutral, abstract, de-contextualising concepts to more substantive concepts, so the boundaries of the networks of action producing regenerative products remain undefined. The discussion shows, finally, that a legislative text accomplishes much more than just legislation. Legal documents also perform non-legal acts.

NOTES

1. Austin distinguished several types of performative, illocutionary utterance. His 'exercitive' type most closely corresponds to the legislative mode considered here. Amongst words of this type he gave: 'permit'; 'authorize'; 'sanction'; and 'appoint' (Austin, 1962).
2. It almost goes without saying that the legislation considered here inhabits a complicated landscape of other documents – legislative, consultative, proposal-making and so on. In concentrating on the text of this one document I have chosen for reasons of space not to analyse this detailed intertextuality, which can be regarded as one dimension of the authority to which the text lays claim.

REFERENCES

- Atkinson P. & Coffey A. 2004. Analysing documentary realities. In: Silverman, David (ed.). 2004 *Qualitative research : theory, method and practice / edited by David Silverman* (London, SAGE): 56-75.
- Austin, J.L. (1962). *How to Do Things With Words*. (London, Oxford University Press).
- Barry, A., (2001). *Political Machines: Governing a Technological Society*. The Athlone Press, London.
- Barry, A. (2006). Technological Zones. *European Journal of Social Theory*, 9(2): 239-253.
- Berkhout F., Smith A., Stirling A. (2003). *Sociotechnological regimes and transition contexts*. Working paper 2003/3.
<http://www.sustainabletechnologies.ac.uk/PDF/Working%20papers/FB1.pdf>

GBRG working paper, January 2010. Alex Faulkner, Centre for Biomedicine & Society, KCL

Borup, Mads; Brown Nik; Konrad, Kornelia; Van Lente, Harro. (2006). The sociology of expectations in science and technology. *Technology Analysis & Strategic Management*, 18 (3&4): 285 – 298.

Brown, N. and Michael, M. (2003). A Sociology of Expectations: Retrospecting Prospects and Prospecting Retrospects, *Technology Analysis and Strategic Management*, 15 (1): 3-18.

Brown, N.; Faulkner, A.; Kent, J; Michael, M. (2006). Regulating Hybrids: 'Making a Mess' and 'Cleaning Up' in Tissue Engineering and Transpecies Transplantation. *Social Theory & Health*, 4(!): 1-24.

Callon M. (2004). Europe wrestling with technology. (Review of Barry, A. *Political Machines*, 2001). *Economy and Society* 33, 1, 121-134.

European Commission (2005). *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*. 2005/0227(COD). EC, Brussels 16.11.2005.

European Commission DG Enterprise and Industry (2005) Consultation paper - *Human Tissue Engineering and beyond: proposal for a Community regulatory framework on Advanced Therapies*. Brussels, 04 may 2005.

European Parliament and Council of the European Union (2004) Directive 2004/23/EC 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 *Official Journal L 102*, 7.4.2004.

European Parliament and Council of the European Union (2007). Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal L 324/121-137*, 10.12.2007.
<http://register.consilium.europa.eu/pdf/en/07/st03/st03627.en07.pdf>.

Fairclough, N. (1995) *Critical Discourse Analysis: The Critical Study of Language* (Harlow: Addison Wesley Longman).

Faulkner A. (2009) Regulatory policy as innovation: constructing rules of engagement of a technological zone for tissue engineering in the European Union, *Research Policy*, online: doi: 10.1016/j.respol.2009.01.017.

GBRG working paper, January 2010. Alex Faulkner, Centre for Biomedicine & Society, KCL

Faulkner A. (2009) *Medical Technology into Healthcare and Society: a sociology of devices, innovation and governance*, Basingstoke: Palgrave Macmillan (published 5.11.2008)

Faulkner A, Geesink I, Kent, J, FitzPatrick D (2008) Tissue-engineered technologies: scientific biomedicine, frames of risk and regulatory regime-building in Europe, *Science as Culture*, 17, 2, 195-222.

Faulkner A. (2008). Unconventional Medicine? Turning Tissue Engineered Technologies into Pharmaceuticals in the European Regulatory Regime. In: Greco G.N. (ed.). *Tissue Engineering Research Trends*, New York: Nova Science Publishers, pp281-296.

Kent, J., Faulkner, A., Geesink, I., & FitzPatrick, D. (2006). Towards Governance of Human Tissue Engineered Technologies in Europe: Framing the case for a new regulatory regime. *Technological Forecasting and Social Change*, 73, 41-60.

Harré, R., 2002. Material Objects in Social Worlds. *Theory, Culture & Society* 19, 5-6, 23-33.

Hedgecoe A, Martin P. (2003). The Drugs Don't Work: Expectations and the Shaping of Pharmacogenetics. *Social Studies of Science*, 33: 327-364.

Hood C, Rothstein H, Baldwin R. (2001). *The government of risk: understanding risk regulation regimes*. Oxford, Oxford University Press.

Iannantuono A; Eyles, J. 1997. Meanings in policy: a textual analysis of Canada's 'Achieving Health For All' document. *Social Science & Medicine*, 44, 11: 1611-21.

Jasanoff, S. (1990) *The Fifth Branch: Science Advisors as Policymakers* (Cambridge, MA: Harvard University Press).

Jones, M.; Salter, B. (2003) The governance of human genetics; policy discourse and constructions of public trust. *New Genetics and Society*, 22, 1: 21-41

Kerr A. (2003) Governing genetics: reifying choice and progress. *New Genetics & Society*, 22(2): 143-158.

Lalis, G. (2006). *Genes, Cells and Tissues: Commission proposal on Advanced Therapies*. Presentation to BIO (Biotechnology Industry Organization) International Convention, Chicago, April 2006. <<http://www.europabio.be/AdvancedTherapies.htm>> (Accessed April 2007).

GBRG working paper, January 2010. Alex Faulkner, Centre for Biomedicine & Society, KCL

Lange, Bettina. (2005). Researching Discourse and Behaviour as Aspects of Law in Action, in: R. Banakar and M. Travers (eds.), *Theory and Method in Socio-Legal Research*, Oxford, Hart Publishing, pp. 175-194.

Lange, Bettina (2006) Social Dynamics of Regulatory Interactions: An Exploration of Three Sociological Perspectives, in: M. Freedman (ed.) *Law and Sociology*, Oxford, Oxford University Press, pp. 141-164.

Lange, Bettina (2007) How to conceptualize law in European Union integration processes? - Perspectives from the literature and empirical research, in: Gessner, Volkmar (ed.) *European Ways of Law*, Hart Publishing, Oxford, pp. 255-276

Majone G., 1994. The European Community as a Regulatory State. *European Community Law* 1, 321-419.

Malerba, F., 2006. Innovation in sectoral systems: What we know...and what we would like to know. Presentation to SPRU 40th Anniversary Conference, September, 2006, University of Sussex, UK.

Markard J and Truffer B. (2008). Technological innovation systems and the multi-level perspective: Towards an integrated framework. *Research Policy*, 37(4): 596-615.

Nelson RR. (2008) Factors affecting the power of technological paradigms. *Industrial and Corporate Change*, 17(3): 485-97.

Pottage A. (2007) The Socio-Legal Implications of the New Biotechnologies. *Annual Review of Law and Social Science*, 3: 321-344. (doi: 10.1146/annurev.lawsocsci.3.081806.112856)

Prior L. (2003) *Using documents in social research*. London: Sage.

Prior L. (2008) Repositioning documents in social research. *Sociology*, 42, 5: 821-836.

Harré R. (2002). Material Objects in Social Worlds. *Theory, Culture & Society*, 19 (5-6): 23-33.

Salter, Brian and Mavis Jones (2002) 'Human Genetic Technologies, European Governance and the Politics of Bioethics', *Nature Reviews Genetics* 3(10): 808-14.

GBRG working paper, January 2010. Alex Faulkner, Centre for Biomedicine & Society, KCL

van Merkerk, R.O. and van Lente, H. (2005) Tracing emerging irreversibilities in emerging technologies: The case of nanotubes. *Technological Forecasting and Social Change*, 72, 9: 1094-111.

van Merkerk, R.O., and Robinson, D.K.R. (2006) Characterizing the Emergence of a Technological Field: Expectations, Agendas and Networks in Lab-on-a-chip Technologies, *Technology Analysis & Strategic Management*, 18(3/4): 411-28.

Table 1

Headings of the ATMP Regulation's legal Articles (A1-A30 referenced in the text)

1. Subject matter
 2. Definitions
 3. Donation, procurement and testing
 4. Clinical trials
 5. Good manufacturing practice
 6. Issues specific to medical devices
 7. Specific requirements for advanced therapy medicinal products containing devices
 8. Evaluation procedure
 9. Combined advanced therapy medicinal products
 10. Summary of products characteristics
 11. Labelling of outer/immediate packaging
 12. Special immediate packaging
 13. Package leaflet
 14. Post-authorisation follow-up of efficacy and adverse reactions, and risk management
 15. Traceability
 16. Scientific advice
 17. Scientific recommendation on advanced therapy classification
 18. Certification of quality and non-clinical data
 19. Reduction of the fee for marketing authorisation
 20. Committee for Advanced Therapies
 21. Composition of the Committee for Advanced Therapies
 22. Conflicts of interest
 23. Tasks of the Committee for Advanced Therapies
 24. Adaptation of Annexes
 25. Report and Review
 26. Committee procedure
 27. Amendments to regulation EC 726/2004 (tissue and cells banking etc.)
 28. Amendments to Directive 2001/83/EC (medicines for human use)
 29. Transitional period
 30. Entry into force
-