Stretching and challenging the boundaries of law: varieties of knowledge in biotechnologies regulation

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Abstract

The paper addresses the question of adaptation of existing regulatory frameworks in the face of innovation in biotechnologies, and specifically the roles played in this by various expert knowledge practices. We identify two overlapping ideal types of adaptation, first the stretching and maintenance of a pre-existing legal framework, and second a breaking of existing classifications and establishment of a novel regime. We approach this issue by focusing on varieties of regulatory knowledge which, contributing to and parting of political legitimacy, in principle enable the making of legally binding decisions about risks and benefits of technologies. We base the discussion around two case studies, one of animal biotechnology ethical regulation, the other of 'advanced therapy' medicinal product regulation, both in the context of European Union frameworks. Specifically we explore the knowledge configurations constituting expert committees and other institutional formations of expert regulatory knowledge in their political context. We show that where sectoral and moral boundaries are challenged, different modes of regulatory knowledge beyond scientific forms – legal, procedural, moral, economic and industrial – can shape regulatory innovations either by maintenance of regimes through commensuration and stretching, or through differentiation and separation creating new frameworks. We conclude that establishing an essential techno-scientific difference between pre-existing and novel technologies does not in itself require new regulatory structures, and that the regulatory strategy that is followed will be determined by a combination of different forms of knowledge.

1. Introduction

The emergence of new biotechnologies brings many kinds of governance challenges for which traditional types of governance, including law-making, are not always sufficient. Law is often seen as unable to keep up with the rapid developments involved, facing difficulties dealing with technical uncertainties and rapid scientific evolution. Furthermore, issues of classification between different domains of nature, science, materials and products have become a key part of the regulation of bioscience and biotechnology in contemporary societies. In this paper we focus on law-making and its difficulties of addressing issues related to new technologies by focusing on the concept of 'regulatory knowledge' and its role in law-making. We understand law-making as both the negotiating processes of drafting a framework for making legal decisions (such as authorizing and licensing), and the interpretive process geared towards 'implementing' regulations.

Two different strategies of law-making appear evident, with varying degrees of intentionality in practice. A first strategy involves commensuration, an analogical legislative strategy, including new provisions in an existing legal framework. A second strategy is to develop new legal frameworks. Both strategies require consideration of the strength and usefulness of existing classificatory

systems. The development of new legal frameworks is typically informed by expert stakeholders claiming specialist knowledge or accompanied by the institution of expert committees that develop standards within these new frameworks. In this paper we are interested in the reasons for maintaining, stretching, or breaking the pre-existing legal framework and the role that expertise plays in this. To what extent can processes of commensuration stretch and thus maintain the pre-existing legal framework and when is breaking of existing classifications necessary, or what knowledge-related factors engender such legal fracturing? By answering this research question, we intend to come to a broader understanding of the concept of regulatory knowledge and its role in the construction and re-construction of law. We argue from case studies that regulatory knowledge encompasses more than scientific knowledge only, and thus that the concept should be broadened to include other forms of knowledge that are mobilized in processes of design and implementation of law. We do so by exploring various legislative strategies and practices involving the institution of expert committees and the workings of other expert knowledge actors as vehicles or channels of regulatory knowledge.

We approach the research question by combining a legal perspective with Science and Technology Studies (STS) perspectives. We believe that either single disciplinary perspective risks bypassing or simplifying relevant elements of problem-definition deriving from the other discipline. Our initial assumption is that an answer can be found in a detailed exploration of the process of law-making and a critical analysis of the various roles variously defined experts play in this process in providing knowledge of multiple forms that is required for law-making innovations in adapting and reacting to new biotechnologies.

2. Perspectives and methodology

Multiple forms of knowledge enter into the formation and adaptation of regulatory regimes. As Demortain points out in the introduction to this special issue, there is a need to analyse forms of knowledge that are 'more synthetic, situated and experiential', compared to the more often investigated analytic and quantitative forms of scientific , often risk-related, regulatory knowledge (Demortain, 2017). Alongside this, it is important to understand the collective actors and institutional forums that are implicated in the knowledge domains of law-making. One legal analysis on this point argues that the characteristics of the emergence of new biotechnologies require flexibility and strong public participation to come to agreed ethical principles guiding governance, but that these are elements that the rule of law *per se* cannot provide (Rial-Sebbag and Cambon-Thomsen, 2012). However, in legal studies, alternatives for law-making in these fields are explored by developing new

legislative approaches (Van der Burg and Brom, 2000). An interactionist approach to law provides such an alternative. This approach understands law as flexible as it is responsive to the needs of society (Fuller, 1969; Selznick, 1992). Such responsiveness can be established by broad participation of both experts and the public (Poort, 2013). Broad participation in its turn, in principle enlarges the democratic legitimacy of law-making in democratic societies. Democratic legitimacy, therefore, brings in a (additional) reason for involving a range of experts in law-making. At the same time, it can be noted that flexibility itself is not an undisputed good, because it counteracts the need to establish clear rules of engagement for participants in particular sectors or technologies - actors involved need to 'know where they stand'. A common strategy to shape law-making to deal with the tensions and uncertainties typical of innovative biotechnologies such GM foods or nanotechnology is involving claimed and acknowledged experts in decision-making processes. For example, in the EU-regulation on GMOs (EC 2001/18), an important role is given to the European Food and Safety Authority (EFSA) who are assigned to perform an environmental risk analysis on which licensing can either be granted or not. In terms of legitimacy, involving experts is seen in a legal perspective to bring in a substantive justification of legal decisions as experts are taken to 'know more' about the subject than the law-maker. Their robust knowledge is seen to be able to legitimate decisions. Furthermore, societally validated experts may be seen to bring in an element of neutrality, refrain from normative judgments and build their claims on facts, observation and rational arguments. In other words, experts can be accorded and claim a high level of accountability. In summary, a strong reliance on the role of scientific and technical experts in addressing complex legislative issues is apparent (Poort 2013, chapter 2).

In Science and Technology Studies (STS), on the other hand, the role of scientific expertise in decision making concerning technological issues is problematized by in-depth analysis of case studies and various models that explore and define the different roles experts might claim and be accorded (for example, Collins and Evans, 2002; Jasanoff, 2003; Liberatore and Funtowicz, 2003). Assumptions of neutrality and lack of bias are questioned, and 'technical' advice or decisions are typically analysed as in fact 'political'. Different forms of specialized expertise and the socioeconomic sources of their authority are highlighted. Indeed, concerns about the status of claims to scientific expertise are frequently voiced in public (and parliamentary) debate and this is a major topic of interest in STS studies. Thus STS studies can contribute equally to an exploration of the role of specialists or 'experts' and their multiple claims to and demonstrations of knowledge in law-making processes. Ironically, where the role of experts in legal studies seems to be idealized or simplified, the complexity of law-making in much STS seems to be relatively overlooked, with notable exceptions (for example, Jasanoff, 2015; Latour, 2012); Faulkner 2012b).

In both perspectives, the involvement of scientific or technical experts is connected to knowledge-claims. From the legal perspective, scientific experts play an important role in bringing in knowledge that the legislator lacks or is lacking in general. The STS perspectives criticize the limited understanding of scientific experts by showing the complexities related to knowledge claims and pinpointing different types of knowledge. We, therefore, consider both perspectives relevant for coming to a full, rounded understanding of the concept of regulatory knowledge. There are certain forms of knowledge that require or allow regulatory intervention (Demortain, this volume). Combining legal and STS perspectives, we can say that the standards of scientific regulatory knowledge when aligned with collectively negotiated processes that promote political legitimacy enable the making of legally binding and societally acceptable decisions about novel technologies.

In this discussion, therefore, we want to explore the role of multiple forms of regulatory knowledge, knowledges shaping regulatory decisions and law-making. We believe that these are relevant for creating insights into the reasons for maintaining, stretching, or breaking a legal framework in ways that become accepted as legitimate. Starting from first principles, non-scientific types of knowledge such as legal knowledge and what might simply be called 'societal knowledge' may be important parts of 'regulatory knowledge' broadly defined, in any given sector or instances of novel technology. Whereas, different types of scientific knowledge, for example developmental biology, zoology or bio-engineering, may be relevant for making legal decisions, one can also consider other knowledge forms such as 'ethics' or specialized knowledge of moral values, 'economic' knowledge and practical, administrative or 'procedural' knowledge for example about bureaucratic or political processes and 'rules of the game'. We aim to show in this paper that these types of knowledge may be as relevant for strategies of law-making as different types of scientific knowledge. Clearly, the regulatory challenges presented by biotechnology are more far-reaching than merely fitting these developments into current legal frameworks. In the EU environment, it also requires re-establishing the relation between national regulation and EU-regulation which together form the current legal framework. Both (may) use different categorizations and have various backgrounds as well as roots in legal systems. Consequently, the new technologies and applications of these technologies may challenge the categorizations and systems of the law in novel ways. For example, Mahalatchimy et.al. have analysed and compared the regulation of human tissues for medical use in the context of 'advanced therapies' in the UK and in France (Mahalatchimy et.al., 2012). Whereas the challenges in France are primarily explained from the human-rights perspective, the UK regulatory challenges were captured mainly through licensing procedures. The influence of EU-regulation in each system differed. The balance between EU-regulation and the national legal framework, consequently, needs

to be re-established as soon as new rules require implementation, as new developments in technology emerges as the influence of both can be different in each legal system.

Different forms of knowledge may be enshrined in different legal regimes, for example the EU-Directive on cultivation of GM-crops (2015/412) adopted in 2015 enables EU Member States to prohibit or restrict cultivation of GM-crops on their territory, but they can only do so on considerations *other than safety,* as safety measurements are already regulated in Directive 2011/18. Understanding the background and basis of these boundaries is relevant for shaping new regulatory frameworks or fitting the new technological developments into the existing one by commensurative strategies. Thus, regarding 'legal' knowledge being a type of regulatory knowledge, legal principles need to be taken into account to assure predictability and legal clarity (Fuller, 2001; Dworkin, 1993) and existing frameworks cannot be bypassed.

Evidence about and representation of society's concerns (societal knowledge) is also in principle required for law-making and, thus can be understood as constituting part of the sum of regulatory knowledge. Societal knowledge we take to refer to the values and concerns among different groupings within society as these are relevant for debate and possible acceptance of technologies. 'Social facts', scenarios and visions for development are equally relevant for law-making (Poort, 2013, chapter 2). Societal knowledge provides insights into the context in which both the law or regulatory framework and the new technology will function and develop. These issues typically are characterized by both a lack of consensus on scientific and biological facts as well as on social values. We return to a discussion of these and other different forms of 'regulatory' knowledge in discussing two case studies, below. We note at the outset that scientific specialists in particular fields may deploy these other forms of regulatory knowledge, or claims to such knowledge, to varying degrees, as well as their discipline-based technical expertise.

In light of these guiding principles, we take an approach that regulatory knowledges of the types outlined above are likely to be relevant for pinpointing the reasons for and factors affecting *maintaining, stretching, or breaking pre-existing legal frameworks,* and conversely, study of the dynamics of legal framework innovations will inform understanding of the roles of regulatory knowledges and expertise. We will draw on two case studies of biotechnological innovations to explore the dimensions of regulatory knowledge and the role of experts in the negotiating phase of law-making as well as the role of experts in the framework of legal decision-making (especially licensing aspects). In doing so we build on previous study by each author, developing them further by focusing on the parts played by knowledges and various kinds of experts. We therefore present two

case studies that, as we shall show, highlight not only scientific knowledge but also other knowledge resources mobilised in regulatory and law-making processes. Regulatory regimes tend to be characterized by distinct patterns and types of knowledge and expertise, and our case studies in two substantive innovative scientific domains help us understand more thoroughly how different expertise informs the sociopolitical processes of both regulatory design and regulatory practice. Taking our case studies in turn, therefore, we refer first to research on regulating Advanced Therapy Medicinal Products (ATMP) within the EU. We show that commensuration as a legislative strategy of analogy is central (Faulkner, 2012a) to law-making in this case. Commensuration is a strategy of 'making things the same' by 'classifying technologies by drawing attention to the aligning of otherwise distinct cognitive or practical domains', including in this instance notable non-scientific knowledge domains. By doing so, the regulatory framework is stretched so that applications of new technologies may fit in. In other words, flexibility is created. In this research, additionally, a moral challenge to the scope of the Regulation was important to the legal debate, and the resolution of this evoked a particular form of regulatory knowledge that we discuss below. Our second case study is on the regulation of animal biotechnology in Denmark, the Netherlands, and Switzerland. In this threefold comparison the focus is on the role of expert committees in drafting the law. To what extent are expert committees institutionalised What kinds of experts are involved? What was their role in law-making? To what extent did they build on pre-existing legal frameworks or develop new ones? Following our presentation of the case studies, in section 4, we discuss the roles of various kinds of experts and knowledges in law-making that the cases display. In this discussion we touch upon socio-legal studies undertaken in the context of the concept of regulatory knowledge, pinpointing the benefits of a combined legal and STS approach. Furthermore, we discuss the implications of the previous sections for the concept of regulatory knowledge.

3. Two Case Studies

In this section, we describe the two case-studies mentioned above that illustrate the challenges of regulating new technologies, pointing out the different types of, and roles played by, different forms of knowledge mobilized in practical and policymaking regulatory work, and the actors that embody them.

The Advanced Therapy Medicinal Products (ATMP) Regulation and the Tissue-Engineered Products case

The ATMP Regulation[1] applies broadly in the field of 'regenerative medicine' (although the Regulation itself does not mention this term), widely envisaged as being a revolutionary medical development, and including various cell, tissue, medical device and gene therapy innovations that are the subject of huge worldwide research and public investment. From a legal perspective it is a *lex specialis*, amending an existing Directive, and this is significant, signaling as it does the relationship to an existing, 'inherited' piece of legislation. Here, we consider the ATMP Regulation in two aspects, first examining key points from the negotiation of the Regulation through the EU political process and the forms of knowledge deployed in this process, and secondly considering its subsequent implementation through various regulatory institutional forms and actions and their claimed expert knowledge practices. Different forms of regulatory expertise and its institutional organization are shown in each case.

First, one of the purposes of the ATMP regulation was to make legal provision for placing on the market tissue engineered (TE) technologies with medical product application. TE technologies typically combine manufactured biomaterials with living, viable human tissues or cells. The manufactured part would be classified as a 'medical device' for regulatory purposes, requiring the application primarily of various branches of engineering and biomaterials knowledge. The TE technology was widely believed to fall into a 'regulatory gap'. During the late 1990s and early 2000s, multiple different definitions of TE technology were circulated and this was crucial to the development of regulatory activity that has attempted to classify the technology and define a clear regulatable domain for it. In this context, it was widely believed amongst the relevant expert medical device regulatory and policy actors that a specific, *standalone* regulatory regime for this class of products was appropriate and would be put in place. In other words, a breaking of the inherited legislative regime was envisaged, due to the technological mateial itself being portrayed as radically different from those regulated under existing medicines and 'devices' regimes. However, this proposal for a separate TE regulatory authority was not implemented. The reason for this lay in a commensurating (stretching and maintaining) strategy that emerged from the European Commission.

In order to understand this switch from a breaking model to a maintaining model it is necessary to know that within the European Commission's then DG Enterprise, which was leading the development of new regulation, there was a division of technical regulatory expertise applicable to

[1] 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, OJ L 324 (ATMP Regulation).

medical products between pharmaceutical and medical device domains,organized into separate sections. An advisory Medical Devices Expert Group (MDEG), representing EU member states, comprised engineers from a variety of specialisations, device experts from national authorities, physicians, and technical product assessors for example with specialist knowledge in metals, plastics and bio-materials. Unlike medical devices, however, pharmaceuticals were already represented by central EU regulatory expertise in the form of the Committee for Medicinal Products for Human Use (CHMP) in the then European Medicines Evaluation Agency (EMEA), comprising a wide variety of technical expertise including Member State nominated representatives for biochemistry, drug safety assessment, pharmacology, toxicology, and medical specialisms such as cardiology, The initial responsibility for developing regulation lay with the medical devices section, but this was superseded by the pharmaceutical section, amidst controversial debates about the material classification of the nature of the products themselves. The pre-existence of the central EMEA, with no equivalent for medical devices, as well as the powerful influence of pharmaceutical industry lobbying were certainly instrumental in this change of direction. Therefore, an initial principle based on the riskiness of the *provenance* of the biomaterials used was superseded by one based on the *mode of action* of the products (Faulkner, 2012b). This pulled TE into a stretched pharmaceutical framework, commensurating a 'coherent ensemble' comprising tissue engineering, cell therapy and gene therapy as 'ATMPs'. However, this was not a move arising purely from scientific or technical regulatory knowledge, as shown for example by the explanatory preamble to the Regulation which asserted that one of the rationales for the 'coherence' of the 'ensemble' was the claim that: 'Advanced therapy products are usually developed by innovative small and medium-sized enterprises, highly-specialised divisions of larger operators in the Life Science sector (biotechnology, medical devices and pharmaceuticals), hospitals or tissue banks. They are subject to rapid and often radical innovation' (EU Monitor, 2005) – an economic, sectoral, rather than scientific knowledge claim, produced in-house from DG Enterprise. The EC's 'public consultation' with claimed expert stakeholders from different medical products sectors, was also key to this shift, enhancing the legitimacy of the outcome. That the technical debate focused to a large extent around the biomedical materials and how they act biologically – pharmaceuticals by metabolic and chemical action, and devices by mechanical or physical action – shows the deployment of regulatory knowledge as 'politics (or economics) by other means' (cf. Bloor et al, 2013). This, allied with the pre-existing central EMEA shows that the commensurating strategy was co-produced through an interaction of institutionalised political power and scientific-technical product ambiguities. The primary outcome was a new Committee for Advanced Therapies (CAT) instituted within the European Medicines Agency, which nevertheless acknowledges the sectoral conflicts in the process

by allowing for some representation of medical devices expertise when 'combination products' (cells + device) are presented.

Alongside this example of pharmaceutical regulatory knowledge dominating a new field through regulatory policy committees and interest representation, the debate of the proposed ATMP Regulation through the European Parliament provided examples of different forms of regulatory expertise and different concerns, including moral issues. The public health parliamentary committee (called ENVI) that led the debate of the ATMP Regulation was led by a MEP with Christian religious convictions who, together with another MEP with similar convictions, attempted to exclude from the Regulation certain types of human material, notably human embryonic stem cells. Such matters were termed 'the ethical issues' in the debate (Faulkner et.al. 2006). It is notable that both these MEPs were in fact medically qualified, the former as an anaesthetist and the latter as a physician, thus qualifying them as bringing to the debate technical medical expertise deemed relevant to the regulatory case at hand. This movement, however, was successfully opposed by a majority which was led by a Social Democrat *lawyer* MEP, who drew on her knowledge and legal expertise in the working of parliamentary process to turn the majority to the social ethics of patients' access to future healthcare therapies as the overriding principle. In terms of regulatory knowledge, therefore, we can see a form of practical, procedural political 'nous' (know-how based on experience) form of knowledge, allied with 'legal' knowledge, being mobilized here.

Turning to the implementation of the ATMP regulation, it is notable that much of the expert committee CAT's work has been on classification of proposed products and that this has proved much less clear-cut than anticipated. A high degree of uncertainty continues to exist around the workability of the definitional boundaries between tissue engineered and cell therapy products. At the same time, conflicts over the relatively light representation of medical device expertise, and over the high degrees of uncertainty in the developing science base have produced pressures for a high level of engagement with stakeholders with expertise relevant to regulation , taking the form of a large number of consultative mechanisms and 'soft' interactions with the regulatory agency and committee. The constitution of the CAT is noteworthy in terms of the regulatory expertise represented. In particular, it was assumed that a scientific and technical membership would be able to act on ethical aspects and, therefore, there is no professional ethicist representative nor 'members of the public', although there are two seats for patient group representation. Otherwise, individual members' regulatory expertise is quite complex, typically combining a disciplinary knowledge such as pharmacology or molecular and cell biology, or clinical disciplines such as

obstetrics/gynaecology, with 'regulatory science' knowledge such as clinical trial design and medicines evaluation methodology.

Again, although the knowledge-base of the constitution of the CAT is almost entirely scientific and technical, it and its members act in ways that go beyond those boundaries. Exemplifying the soft regulatory knowledge debates, an 'EMA/CAT-Notified Body Collaboration Group' was established, bringing together pharma medicinal and device bioengineering expertise (Notified Bodies are technical organisations assessing safety, risk etc. of medical devices in the EU system). The primary remit of this was to provide 'overview, coordination and (identify) the need for any update of any process and guidance for consultation of a notified body for medical devices during an assessment undertaken by the CAT'. Another example of what has been called this 'institutional proliferation' process (Faulkner, 2012a) is a novel linking by the EMA between the CAT and scientific learned societies. The first such meeting, formulated as a 'workshop', which was attended by some 200 people, was between the CAT and the European Society for Gene and Cell Therapy. This and other similar consultative developments, highlight both the scientific uncertainty in the emerging field, (arguably) a democratisation of scientific expertises, and a strategy of containing conflict through a form of *inter-institutional* commensuration. In such institutional processes, it is clear that there is an entangling of a range of scientific, clinical and regulatory knowledge forms in 'political' debates involving disciplinary and sectoral interest, another example of the entanglement of regulatory knowledges and interest-driven political strategy.. However, overall the overarching pharmaceutical regulatory regime has been preserved, albeit in a context of uncertain and contested scientific knowledges in interaction with regulatory policy development.

Regulating animal biotechnology: a comparison between Switzerland, Denmark and the Netherlands

Poort, in our second case study, compared the regulation on animal biotechnology in three different European countries: Switzerland, Denmark and the Netherlands. By use of these case studies, Poort intended to identify alternative strategies for regulating complex issues in the field of biotechnology. One of the focus-points in her research was to what extent the moral challenges were addressed in regulatory processes. In the context of this paper, we focus on the analysis that relates to expert involvement in regulatory practice. In all three countries, during the legislative procedure various expert committees were involved. It would exceed the extent of the paper to go into detail about all

these committees and various roles they have played.[2] Therefore, we limit ourselves to discussing regulatory practice in which decisions on the use of animal biotechnology are made on a case-by-case basis. In all three countries, animal biotechnology was regulated by a licensing procedure. Animal biotechnology brings in novelties regarding risks and safety requirements as well as challenges to the moral status of animals. For both types of novelties it seemed clear that a standalone regulatory regime was required, separated from the existing regulations on animal experiments, as was the case with the initial vision for tissue-engineered medical products described in the ATMP case above, although moral issues were not the critical driver in that case.

In the Dutch context it was entirely the moral challenges that portrayed *animal biotechnology* as being different from *animal experiments*. These moral challenges that animal biotechnology brought in were incentives to break with the existing legal framework for experiments and draft a separate regulatory framework in the Animal Health and Welfare Law in 1997 and to appoint the dedicated Dutch Ethics Committee on Animal Biotechnology (CAB). The CAB consists of nine experts from various fields such as social science, biotechnology, medical science and ethics, however it is notable that there is no specific representation of legal expertise. The CAB was assigned to advise on cost-benefit evaluation in concrete cases as well as to give advice on how to address the novel challenges to the moral status of animals. In regulatory practice, however, the CAB has had a prominent role in licensing. Officially, the Minister was responsible for licensing taking into account the advices of the CAB. The Minister made draft decisions building on the CAB's recommendations. These draft decisions were open to public objections in a public consultation procedure officially organized by the Minister. In regulatory practice, the CAB chaired these public consultation procedures. After these hearings, the CAB may or may not revise its recommendations and send it again to the Minister. Building on these recommendations, the Minister then decided whether or not to grant a license. In reality, it was the CAB that decided as the Minister, without exceptions, adopted the advice of the CAB.

The moral challenges acted as strong incentives for breaking with the existing regulatory framework, which became most visible, when in 2009, the Dutch Minister decided that the CAB's task was fulfilled: the moral status of 'animal' in light of animal biotechnology did not require further exploration. From that time on, animal biotechnology has been regulated within the existing regulatory framework of animal experiments by use of some additional provisions (Poort, 2013). The Dutch case here, therefore, provides an interesting example of both separation and commensuration. In the first instance, the moral challenges are incentives to develop a standalone regulation for animal

[2] For more thorough analysis which includes the legislative procedure, we refer to Poort, 2013, chapter 5, 6 and 7.

biotechnology. At the same time, as soon as these moral challenges were crystallized, the legislator seemed to adjust to existing regulation. In other words, an ultimate strategy of commensuration is preferred. Commensuration here has several benefits as it makes the licensing procedure relatively easy: adapting to inherited regulations is more efficient as similar institutions and experts can be consulted.

The role of moral values in portraying animal biotechnology provides a good example of the Dutch legal culture in which no explicit distinction is made between law and morality and in which different types of rule-setting are intertwined (Poort, 2013, Chapter 7). The Dutch legal culture is not only one of clear-cut rules, but leaves room for alternative dynamics and soft interactions in regulatory practice. The role of the CAB illustrates an integrated process of rule-setting in which both scientific knowledge and societal knowledge are balanced in a cost-benefit analysis.

In Switzerland, both moral challenges and novelties in risks and uncertainties were relevant for regulating animal biotechnology in a distinct regulatory framework drafted in the Gene Technology Law (2004). In this framework, both the Swiss Ethics Committee on Non Human Gene Technology (ECNH) and the Swiss Federal Expert Committee for Biosafety (SECB) were assigned to advise the Swiss Minister on cost-benefit evaluations in concrete cases either on the moral impact of issues concerning non-human gene technology, although in separate sections. The ECNH consists of twelve members from different fields of expertise including biotechnology, social science, medical science, ethics, and law. The ECNH was established in 1998, but was given a specific mandate in the licensing procedure on biotechnological procedure with animals by the Gene technology Law (GTL) in 2004. Given that it is an ethics committee, as such, it is perhaps surprising that there is only a single professional ethicist. The SECB on the other hand consists of around 16 members who have scientific expertise in the areas of biotechnology, gene technology, the environment and health, and represent various protection and exploitation interests. The SECB is a permanent federal advisory committee that advises the Federal Council on drafting of laws, ordinances and recommendation concerning licenses taking into account the protection of people and the environment in the biotechnology and gene technology sector. In Switzerland, the Biotechnology Section of the Federal Office for the Environment is responsible for licensing. The consultation process starts with a round focused on biosafety risks in which the SECB is consulted. After this round of consultation, the ECNH is consulted on moral challenges related to the biotechnological procedures. The ECNH is not obliged to advise on each license application. The ECNH, therefore, restricts itself to controversial or new issues raised by particular applications (Errass, 2006).

In Switzerland a clear distinction is made between scientific knowledge and the moral challenges involved. The consultative mechanisms regulated in the GTL contain distinct sections in which different expert stakeholders are involved with different tasks. This approach gives room to perform according to the expertise they have: the ethical experts have a more signaling function with 'soft' interactions, while the scientific experts can advise according to the standards as put down in the regulatory framework.

Thus Swiss case shows an approach to animal biotechnology which combines both strategies of commensurating and breaking the existing regulatory framework. The high degree of uncertainty and controversies that continues to exist are excluded from the current decision-making process in licensing, while at the same time these issues are not excluded from the broader (political and public) debate (Poort, 2013, Chapter 6). On the one hand, the legislator seem to adapt to existing structures of licensing and risk evaluation reflected in the terms of references of the SECB who need to be consulted for each licensing application. On the other hand, by drafting a distinct regulation on gene technology, the complexity of gene technology is acknowledged. At the same time, the 'ethical debate' and the signaling function of the ECNH are 'soft' mechanisms outside the regulatory framework as the ECNH is not obliged to advise in each licensing procedure.

In Denmark, biotechnological procedures with animals are regulated in the Act on the Cloning and Genetic modification of Animals (2005). In this Act, the exclusive purposes for using animal biotechnology are listed. By listing these purposes a differentiation between biotechnology and experiments with animals is made. Remarkable is, however, that despite this differentiation between biotechnology and experiments, the same institution is appointed to decide upon licensing: the Animal Experiment Directorate. The Animal Experiment Directorate consists of eleven members which contains one judge as chairman, five scientists and five members of animal protection organizations, although no formal or professional ethics expertise is represented, nor range of their possible viewpoints.Due to this assembly, various viewpoints, which extend well beyond elaborations on the scientific aspects, can be brought forward during the licensing procedure.

However, despite the possibilities of this broad assembly, the relevant knowledge for licensing is in practice restricted to merely scientific aspects. The moral challenges as well as the social impact do not have a role in licensing: no distinct ethics committee for licensing is appointed. According to the members of the Directorate, the moral challenges were already dealt with during the legislative process. During the legislative process, the Danish Animal Ethics Council was consulted about the

moral impact of animal biotechnology. Their advices on the moral status of animals are reflected in the differentiation in specific research purposes for which licenses are allowed.

The only main difference in licensing between animal biotechnology and animal experiments, therefore, is a different form that scientists have to fill in, in which the limitation to four research purposes is listed. The benefits of adapting to an existing and well-functioning regulatory framework is that the Animal Experiment Directorate has, during the years, developed standards on how to deal with the licensing applications. These standards concern requirements on how to protect animal welfare and health. The Directorate has adapted these standards for animal biotechnology licensing too. As a result, the licensing procedure was not problematic and did not lead to heated debates. The standards as developed in context of animal experiments could additionally provide safeguards in animal biotechnology. Notably, it was the scientists of the committee that played the dominant role. The regulatory strategy here is, thus, one of commensuration in which the boundaries are stretched in such way that additional scientific knowledge is included. Commensuration as such ensures that the acknowledged experts have a decisive say in licensing. This strategy is both efficient and ensures sufficient knowledge and thus legitimacy. At the same time, this strategy also makes it difficult to give room to continuous moral challenges in which other types of knowledge may be required. The Danish legal culture, however, is not designed in such a way that alternative strategies have room to stimulate continuous debate on moral or social challenges or in 'soft' interactions. In this sense, the regulatory process *per se* has been de-politicised. Regulation needs to be straight-forward and consist of clear standards. Morality and social concerns can have a role in the broader political process leading to legislation, but are separated into different institutional arenas matters in light of concrete legal decision-making (Ross, 2004).

4. The role of experts and knowledge in regulatory strategies

Our case studies show the roles of different knowledges and expertise being mobilized in different patterns of regulatory and legal flexibility and innovation. Our discussion assesses the extent to which flexibility can be stretched and the knowledge-related factors leading to maintaining existing regimes or instituting new, separate ones. Rial-Sebagg et. al. criticize the limits of the legal frameworks lacking flexibility and lacking broad participation when dealing with new technology developments (Rial-Sebbag and Cambon-Thomsen, 2012). Their criticism points to a need to adapt ethical principles in regulating technology. In other words, regulatory knowledge includes knowledge of the ethical principles involved. Additionally, they note the need to develop strategies anticipating

the emergence of new technologies. Flexibility conflicts with the traditional legal principles such as legal clarity and predictability. In legal theory, therefore, an important point of debate involves whether flexibility can be integrated in the regulatory framework. Rial-Sebbag et.al. argue that this need for flexibility cannot be found in the legal; however, institutionalizing ethics offers an alternative. Poort, on the other hand, has analyzed regulatory strategies in which flexibility was established in the legal domain; by the use of open norms that require further interpretation in regulatory practice (soft mechanisms). Likewise, Faulkner has pointed to the deployment of a variety of legislative drafting tactics in the ATMP Regulation, which make for substantive flexibilities, future-oriented open-endedness and legally protected spaces for institutional responsiveness to techno-scientific innovations (Faukner, 2012c).

In the previous section we have illustrated, through two case-studies, two common strategies on how to deal with the emergence of new technologies which both include societally acknowledged experts and various forms of regulatory expertise. First of all, in the ATMP (tissue engineered product) case we observed a strategy of commensuration by which new technologies are fitted in the current legal framework (maintaining though stretching the inherited legal framework). Second, the comparative study on regulating animal biotechnology showed besides commensuration, also a second strategy: drafting new regulations (breaking the legal framework). The usual starting-point for legislators, though not all stakeholders, is to see whether new technologies can fit in the current legal framework and whether the same expert structures can be re-assigned. For example, when regulating animal biotechnology in Denmark, legislators have appointed the same expert committee which was already responsible for licensing of animal experiments. The reason to appoint the same committee was that the members of this committee were seen as the experts in the field: Why not make use of their expertise (maintaining)? At the same time, research on genetic modification of animals is regulated in a different regulatory framework than animal experiments as the technologies were found to differ on a fundamental level and to challenge different boundaries (breaking). Furthermore, genetic modification brings in novel risks that may not be covered in the current regulatory framework. In the Netherlands and in Switzerland, new expert committees were institutionalized due to these differences on the more fundamental levels and the lack of knowledge about future risks (Poort 2013). The need to include insights about the moral challenges were an incentive to appoint a different type of expert committee with a different task and composition. Both the Netherlands and Switzerland introduced ethics committees to deal with the differences on the more fundamental level. Ethics as such is seen as a specific kind of expertise and a specific type of knowledge required to make legal decisions. In the ATMP case, a new multidisciplinary scientific and evaluative regulatory committee was created as detailed above, but located within an existing over-

arching committee and regulatory institution, with broader expertise (for example including a non-science lawyer), responsibility and authority.

In general, we can say, if the issue appears to be, or is successfully argued to be, 'too different', a new framework is designed. Being 'different' can be characterized by uncertainties and unknown consequences and risks, but it may not necessarily need to. Being 'different', or 'too different', can also be based on sufficient scientific knowledge, social knowledge, or other forms of knowledge. Based on this knowledge, the new technology or entity is classified as being 'different', or, indeed, sufficiently similar to existing entities. Such difference or similarity may be seen to pertain to substantive characteristics inherent in the technology, its moral meanings or its anticipated features or consequences in society and the economy. Qualifying a technology or an entity produced or created by a new technology as being different or 'substantially equivalent' to use a product regulators' term, in such ways, implies that it is compared with another technology or entity for its commensurability, and raises of course the political issue of which stakeholder actors are able to achieve such qualification in given regulatory domains. There are no clear directions on what it means to be 'too different', which means that stakeholders' power, resources and claimed expertise become crucial, pointing to the key role of forms of regulatory knowledge beyond the scientific and technological. Besides, as is clear in both our cases, the two ideal-type strategies are not mutually exclusive: a combination of the two strategies is used though tending one way or the other; new law, existing institutions; inherited, adapted law, new institutions.

Similarly, it has been noted in related fields that there has been a need for novel 'hybrid' institutional arrangements when dealing with issues that concern hybrid trans-species entities (Brown and Michael, 2004). Although commensuration seems most pragmatic, the process of commensuration seems frequently to complicate regulation even more. Stokes (2012) argues that adapting existing regulation may contribute to an easy but possibly premature acceptance of (nano)technology. At the same time, she questions whether the current regulations offer enough safeguards against possible harm, emphasizing that adapting old regulatory frameworks to new risks may result in 'deeply-seated issues of ill-fitting regulatory orientations' (Stokes, 2012, p.98). Following Hisschemoller and Hoppe, it is like addressing an unstructured problem as if it is structured, using old structures that were used to address other issues (Hisschemoller and Hoppe, 1995). Applying old regulatory measures to new regulatory problems risks bypassing fundamental debate about the desirability and applications of new technology innovations. Furthermore, we can doubt whether the old rules can address new risks that come along with the new technology. The

evidence of 'soft' or informal interactions with a range of different scientific expertise, around the formal legislative and regulatory work, shows a learning process in which legal innovation and scientific-biotechnological innovation are co-produced. The intervention of legal knowledge, industry sector knowledge, economic knowledge, and knowledge of political procedure are also all exemplified in our case studies. Such participative interactions, in the context of democratic societies at least, builds legitimacy for the legal and regulatory enterprise.

Each regulatory system has different cultural and industrial sectoral backgrounds, classification systems and participants' expectations. Every attempt to fit a new technology into a pre-existing framework, will re-challenge old classifications and established relations between legal systems, and the associated knowledges embedded in these systems and mobilized by their range of participants. We draw similar conclusions in the contexts of the ATMP and the Danish case of regulating animal biotechnology. In the case of products to be covered by the ATMP Regulation, a new commensurating regime was instituted, but this was done under the umbrella of the existing pharmaceutical legislation. Stretching of the pharmaceutical regime and its associated sciences and technological knowledge to embrace tissue engineered products and combination products including a 'device' component has indeed led to continuing problems of conflict with the expectations and sectoral knowledge and expertise of medical device industry producers. In Denmark, the authority that is responsible for animal experiments was also appointed to decide on licensing concerning animal biotechnology. Their task did not change, the members were further assigned for tasks reviewing in a licensing procedure, building on a risk assessment. The members could easily adjust to existing standards that function in animal experiment practice. The implementation of the new licensing procedure was, therefore, unproblematic. In both the the Danish and ATMP case studies, expert organizations, forums and committees play an important role in the regulatory regimes. Either new expert committees are institutionalized (as the ATMP) or existing ones are appointed to deal with the novel technologies (as in animal biotech). These expert committees either have an advisory role beyond scientific regulatory knowledge in the legislative procedure, or have a role in the case-by-case review procedure which is commonly implemented when dealing with technology issues. A review procedure gives room in principle to identify all interests, engage stakeholders and to reflect upon all risks on a case by case basis. However, in the Danish case study, the expert committee, consisting of members with different scientific backgrounds either representing different interests, merely focused on risk assessment following a technological perspective. As was argued, the fundamental ethical challenges were already dealt with in the legislative procedure. Expertise, for that matter, remains focused on the scientific. In the ATMP case the expert CAT committee's primary role has been to classify types of medical product so that the required test and trial data can be

defined, to produce opinions on safety and efficacy of products, and to recommend or deny market authorisations. However, as has been seen, the committee has acted far more widely than this technical remit, arguably deploying 'political' knowledge for example in instigating multi-stakeholder meetings both to present the current state of regulatory rules and associated guidance and to develop them through the contributions of multiple scientific experts in a field of high scientific uncertainty and contested interests. This high degree of stakeholder engagement undoubtedly builds political legitimacy for the evolving regulatory guidance that is co-produced in 'implementing' the ATMP legal framework.

Both our case studies yield examples of the relationship between the deployment of scientific knowledge and ethics expertise. This relation deserves specific commentary. Regulatory practice that we have described shows us that institutions involved in the legal review procedure are designed in such a way that decision-making builds on scientific knowledge focusing on safety requirements (Holmberg and Ideland, 2012), but that, at the same time, these institutions (officially) include room for discussion about ethical desirability. As soon as new technologies give rise to moral concerns and public debate, either ethics committees are installed and institutionalized, or a strategy for handling ethics is designed. The novel nature of the technology clearly plays an important role. In the Dutch case, the biotechnological procedures with the use of animals were regulated in a new regulatory framework because of both the lack of scientific knowledge about risks and the moral complexity. The terms of reference of the ethics committee were to advise on a case-by-case basis about the moral concerns as well as to identify the moral status of animals. In Switzerland both a Committee on Biosafety and an Ethical Committee on Non-Human Gene technology were involved in licensing on the use of animals in biotechnological procedures. In the ATMP case, specialist ethics was not enrolled into the new Committee for Advanced Therapies, however the ATMP Regulation set up patient group membership of the committee and expected ethical aspects to be discussed also by the range of scientific expertise constituted. Although the functioning of certain committees has been criticized for its lack of a thorough moral analysis (Poort et. al., 2013), the acknowledgment of moral complexity as such plays a role in institutionalizing novel expert committees, also in the field of ethics itself. Although we can identify several similarities in the three approach to animal biotechnology, we also noticed differences in approach: the role of ethics committees, the role of scientific experts, the room for fundamental debate and the reasons for choosing a certain strategy. These differences cannot be explained by the differences in knowledge gaps as those case studies concern similar technologies in a similar time period with equal access to scientific knowledge. It seems that in such cases another feature is of importance for deciding whether or not to draft new regulation or fit into the existing legal framework: legal knowledge.

Legal knowledge implies knowledge about the legal system, the legal categorizations and the background of a legal framework. In the comparative study on animal biotechnology, it became clear that also the legal culture in which a new technology is regulated is relevant for maintaining, stretching or breaking the existing legal framework. For example, in the Netherlands, in which there is more room for alternative regulatory mechanisms, the legislator has chosen a more radical breaking with the existing legal framework than in Denmark. In Denmark, instead, a licensing procedure similar to animal experiments was followed with only small additions to the existing framework. This strategy is in line with the Danish pragmatic approach to regulation, in which rules have to be clear-cut and provide clear standards. The Dutch legal culture leaves more room for open-endedness and flexibility in 'soft' interactions. Equally, at EU level in the case of the 'political' negotiation of the ATMP Regulation, the crucial role was described of a lawyer MEP's expertise, in turning the debate on principles of social morality, drawing on knowledge of the informal dimensions of the legislative process in the EU policymaking environment. As Stokes convincingly states, when adapting to old rules, also the broader policy setting with all its values, goals, intentions and priorities are adapted. When a new technology mismatches this broader setting, new regulatory frameworks may be designed. Brown et. al. point out that new technologies challenge old legal classifications as well as relations between legal systems (Brown et al, 2006). Each legal system has its own types of classifications as well as its own interpretations of how best to protect from risks and how to ensure safety.

The examples in this paper illustrate that a range of knowledges are instrumental in the negotiation and adaptation of law for innovative, challenging technologies. These include articulation of moral values, scientific facts and societal and economic consequences that may be relevant for legal decision-making (Poort, 2013) and that knowledge of these is such that experts can be designated to bring it into the legal process. It is argued that experts *soi disant* are involved when dealing with issues in which the legislator lacks knowledge. The lack of knowledge and expert consensus is also explained by the complexity of the issue at stake introducing diverse types of uncertainties. Reasons for scientific expert involvement concern the neutrality that they may be claimed to bring in. Besides, scientific experts are consulted as they are seen to 'know more' about issues at stake than legislators or regulatory policymakers, thus enabling the affordance of political legitimacy that goes beyond the simply technical or scientific.. Our cases show that new institutional arrangements often involve new expert forums or committees that focus on a specific novel aspect of the new technology. Therefore, different types of expertise are introduced too. Our cases demonstrate that regulatory expertise that can be promoted as shaping the case at handis not coterminous with scientific expertise, but also implies societal , moral and other forms of expertise. Furthermore, specialist regulatory forums may

adjudicate on the scope of the law that they enact, thus performing a boundary-defining function – defining what is and what is not commensurable with a new legal territory.

At first sight, we may conclude that most relevant for deciding whether the existing framework can be maintained or whether new regulatory measures are required, is either the lack of scientific knowledge or scientific knowledge that portrays the new technology as being (very) 'different' from existing standards and modes. Scientific experts are organized or consulted for various reasons: neutrality, objectivity, either 'knowing more', or to demonstrate their representation for reasons of credibility of the regulation process. A perceived gap of knowledge, which cannot be bridged by existing regulatory frameworks and existing institutions, is of particular importance for exploring new regulatory measures, because this leaves the ground open for various types of knowledge, stakeholders' interests and their own knowledges to be deployed. This analysis teaches us that the dynamics such as debate about social and cultural desirability of new technologies, and their industrial organisation is equally important. Therefore, ethics committees and ethics representation, economic analysis and societal debate additionally may play an important role in any given innovative technological field, although it is difficult to discern any systematic pattern of relationships between the framing of expertise and the maintaining/breaking strategy chosen in any given case.

The ways in which expert knowledges are selectively mobilized in processes of legal or regulatory innovation, therefore, have important consequences for the development of innovative techno-scientific fields and the industries that take them up. Major steering principles are built into the rules of engagement in a field, for example in our ATMP case, allowing the controversial human embryonic stem cell-based products in the name of possible eventual public health gains, and shaping the regenerative medicine regime in a pharmaceutical frame, thus encouraging new products fitting a 'medicines' rather than a 'devices' paradigm.

5. Conclusion

Genetically modified animals are different from natural animals; hybrid embryos are different from human embryos; cybrid embryos are different from hybrid embryos; cloning is different from breeding; cell therapy products are different from tissue engineered products. Such constructs of qualification of being 'different' have both social, economic and legal consequences, which are shaped through the mobilisation of a variety of modes of regulatory knowledges, which we have highlighted. Both legal classifications and social/economic boundaries are challenged, which may, or

may not, lead to the conclusion that new regulatory frameworks are needed: the traditional legal classifications no longer hold and adaptation or innovation will be required. We have analysed this phenomenon by following both an STS approach and a legal approach to understand the concept and practices of regulatory knowledge and the role of experts in decision-making.

An STS approach emphasizes how actors in regulatory processes interact politically while bringing specialist knowledge in various forms and intellectual bases into the governance domain. In particular, the malleable, indeterminate status of regulatable objects means that alternative solutions to the problem of maintaining regulatory oversight are viable. The legal approach focuses on legitimacy and strategies for law-making. A tension between uncertainties and legitimacy underpins the need for institutionalizing expert-stakeholders. Scientific expert involvement can help to try to ensure that knowledge gaps are bridged, and thus, legitimacy in terms of neutrality and accountability are strengthened. A gap of knowledge, being 'different', or accepted commensurable similarity of regulated bio-objects, as well as different legal cultures and legal systems are of influence on the strategy that is followed. To that extent, regulatory knowledge has to be a broad and rich concept, encompassing more domains than scientific and technical knowledge.

We can conclude that regulatory knowledge, being relevant knowledge for deciding about appropriate new assessments and measurements of emerging biotechnologies, contains, besides scientific knowledge, also knowledge about the perceived moral desirability of a new technology, knowledge about the broader policy setting, procedural knowledge about political processes and cultures, knowledge of the economy and industrial sectors, and relevant social values. The alignment of these varying dimensions of knowledge is rarely easy. Either a lack of knowledge or knowledge-informed views that a technology essentially differs from other technologies or developments, can be incentives for new regulations. Scientific facts and their open-endedness must of course be understood in the contexts of societies and economies; knowledge about societal values and industry trends can shape the direction of scientific knowledge and practices. Furthermore, knowledge about the legal context and legal process itself is relevant to determining which strategy for maintaining regulation compatible with its objects – commensurating, breaking, or a combination - will be favoured.

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