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Regulating Hybridity: Policing Pollution in Tissue Engineering and Transpecies Transplantation

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Introduction

Conventional boundaries of the material and social worlds are increasingly challenged in late modern society. Human and animal matters have been globally mobilised in a worldwide traffic of scientific, medical and commercial transactions. Whilst human implant technologies have a long history, contemporary technoscience has thrown up an ever-wider range of boundary-crossing possibilities for both the body politic and corporeal (Franklin and Lock, 2003; Brown and Webster, 2004). Medicine is now at the heart of an array of combinatorial human, animal and mechanical materials. Whilst the troubled nature of transplantation has been relatively well documented, (e.g. Fox and Swazey, 1978; 1992), less well understood are new forms of innovation that cut across machines, humans and animals raising regulatory concerns about material and cultural risk (Brown and Michael, 2004; Faulkner et al., 2004). At the same time, such hybrids are powerful sources of hope – new treatments for large populations throughout the aging societies, and new sources of wealth for countries seeking a place in the emerging tissue economies.

Hybridity takes many forms and contemporary developments in the manipulation of tissues have extended these profoundly. Hybrids signal the breach of various socio-material categories, indicating inconsistencies that disorder routines and accepted mores. It is no accident that concepts of pollution and contamination have had an increasingly important place in sociological and anthropological accounts of the life sciences lately. These disruptions are frequently framed around questions of new standards for the purity of cell lines, the cleanliness of animal tissues, new rules to secure safety and avoid hazard.

Often falling outside existing frames of institutional and disciplinary understanding, hybrids are messy/disorderly creatures. They are 'matters in

wrong places' (Douglas, 1966) and for regulation they have consequently become 'matters of concern' (Latour, 2004). This chapter compares the regulatory ordering of human tissue engineering (TE) and xenotransplantation (XT), areas of innovation which regulators have sought to govern separately and in isolation from one another. Contrasting definitional boundaries and regulatory mechanisms partition them socially and institutionally. But despite these attempts at purification, TE and XT have proven increasingly difficult to tell apart in practical and material terms. Human and animal matters, cell cultures and tissue products have much greater corporeal connection than has been institutionally recognised.

This chapter tells the story of how the messy worlds of TE and XT have leaked into one another, calling into question the abilities of regulation to adequately control hybrid innovations. Clinical XT has been subject to forceful regulatory prohibition over recent years with the relatively stable consensus that risks outweigh benefits, particularly in respect to transpecies disease. But recently the regulatory grip on XT has been called into question as various areas of TE have come to regulatory attention. This has resulted in significant attempts to 'clean up' the definition of XT, broadening its regulatory identity. 'Tissue engineering' on the other hand signifies a far more diverse set of practices whose identity in regulation has been more plastic than that of XT. As such, regulators have sought to draw a clean distinction between different aspects of implant innovation, steering TE clear of potential contamination by more problematic hybrids like XT and stem cell therapy. The chapter asks whether such distinctions can be sustained.

First the chapter sets out its conceptual terrain then discusses xenotransplantation and human tissue engineering drawing on data from two social science research projects. To conclude we consider the implications of these comparisons for understanding the variability of governance in human implant technologies.

Theorising regulatory hybridity

Novel natures – like TE and XT – are enmeshed in the production of equally novel/hybrid regulatory orders and institutions, processes whereby nature and the social are made available to each other in what Rabinow describes as 'biosociality' (Rabinow, 1992). Here we are interested in various forms of 'institutional biosociality' (Brown and Michael, 2004) through which scientific and regulatory actors – in TE and XT – configure one another materially, culturally and institutionally. In other words, regulatory bodies form particular representations of corporeal bodies and in turn subject corporeality to the innovativeness of regulation.

Hybrids present regulation with the need to alter the boundaries between existing institutional arrangements. Stem cells traverse the borders between regulated reproduction and transplantation (Waldby, 2002; Franklin, 2001).

Pharmacogenomics newly combines the regulation of genetic diagnostics and medicines (Hedgecoe and Martin, 2003). TE and XT are similarly hybrid falling into a 'regulatory vacuum' (Faulkner et al., 2003) between drugs, devices, human implants and animal research. Hybrid regulatory capacities are therefore 'risky creatures' (Brown and Michael, 2004).

Innovation occurs at the limits of conventional organisational arrangements (Gibbons et al., 1994; Nowotny et al., 2001) challenging the taken for granted and presenting novel risks. New regulatory bodies can be seen as institutional interpretations of the composition and materiality of these novel risks. Various regulatory elements are assembled together in such a way that they reflect, often imperfectly, new regulatory objects, producing intricate connections between 'natural' and 'institutional' hybrids, or as Martin puts it 'how governance arrangements are being challenged and transformed cannot be detached from these other sociotechnical changes' (2001: 158). More radically, regulatory work may also be seen as a powerful force in the very conception and conceptualisation of innovative technology (Bud, 1995: 297).

Regulation is innovative. Here we employ the concept of the 'regulatory order' (Faulkner et al., 2004) and 'regulatory ordering' to draw together strands of theory relevant to the innovativeness of hybrids. Firstly, we can regard corporeal and institutional hybridity in terms of cleanliness and dirtiness (Douglas, 1966). Pollution is a fundamental axis in the dynamics of everyday life. 'Dirt is essentially disorder' (1966: 12), 'matter out of place' which must be excluded if order is to be maintained, insights into boundary-work and categorisation that have proven highly influential in the analysis of medical and scientific knowledge (Bloor, 1978; Gabe, 1995; Carter, 1995; Mody, 2001). But arguably the Douglasian perspective, while bringing into view the value-laden partitioning of material and social boundaries, assumes relatively static categories – pollution as the expression of an underlying structuralist order.

By contrast we look to a second set of theoretical perspectives which are more dynamic and indeed even celebrate transgressive intermixing (Ansell Pearson, 1999). The two views might be articulated in terms of Deleuze and Guattari's (1988) conception of 'being and becoming'. Between the extremes lies a more ambivalent position that can be identified with, amongst others, Haraway (e.g. 1991a, 1991b; Prins, 1995). Myerson has unpacked this ambivalence in relation to Haraway's (1997) writing on the oncomouse, a profoundly ambiguous figure with whom 'we can acknowledge our kinship ... either as victims or as heroes' (Myerson, 2000: 73). Haraway's hybrid, the cyborg, also has political potential in terms of holding out the prospect of couplings that ultimately demolish oppressive dichotomies operating across genders, races, species and machines. And for Latour hybrids are perhaps even more ambivalent (1993). They are often dangerous, even catastrophic – the ozone hole, climate change, BSE – and are evidence of the underlying hidden connections between humans and nonhumans, and especially between

‘objective’ science and ‘subjective’ politics. Hybrids challenge representational order, disturbing the very basis of modernity’s sorting. And of course, they can be highly hazardous unless recognised as such in political process, a ‘parliament of things’ (ibid). Hybrids have agency in as much as they can undermine attempts to conceal connection.

Regulatory re-ordering, therefore, requires the important concepts of cleaning/dirtying of normative categories, pollution, purification and decontamination. Equally, it requires the sense that hybridity is much more highly unstable and volatile, constantly challenging systems of classification and the material boundaries of technology.

The jurisdictional fields of socio-technology that regulation attempts to define can be usefully conceptualised as ‘zones’ (Barry, 2001) or ‘territories’ (Sharp, 2002). It is part of the regulatory construction of such zones that the technologies that we will discuss here have come to be known conventionally as ‘tissue engineering’ and ‘xenotransplantation’. Jurisdictional structures can be difficult to establish in processes of regulatory ordering, but are ‘meant to invoke order and to demarcate boundaries’ (Hogle, 2002: 243). Processes of regulatory ordering engage with a fluid governance jigsaw – a web of interlinked laws, regulations, guidance and surveillance interacting with the negotiation of technology zones. Regulation exhibits, *par excellence*, societies’ attempts to establish links between innovative technologies and the social management of their opportunities and risks, stabilised in institutions and patrolled through standard-setting and surveillance.

As we illustrate in the two cases that follow, the ordering of the regulatable zones of bioscience is in the view of many stakeholders – though not all – severely challenged by human and animal tissue-based technologies. In this discussion we will see that both XT and TE have been subject to important contestations over their definitional, regulatory identities – that is, what is or is not to be considered inside or outside their leaky borders. We now present these two cases as examples of the workings of ‘regulatory re-ordering’.

Xenotransplantation

XT has hovered controversially on the horizons of biomedicine for decades but remains firmly locked within a whole range of presently prohibitive dangers. Nevertheless, some research has continued together with corresponding developments in regulation and public consultation. One of the foundational problems for regulation in this area has been how to define xenotransplantation separate and distinguishable from other developments in bioscience. That is, what are its limits? What is and is not XT? How might regulators ‘clean up’ the messy worlds of bioscience such that they have a precise understanding of their regulatory object?

In 2001 the US Food and Drug Administration revised its definition of xenotransplantation as it became aware of an apparently ‘unrelated’ medical

procedure which had until then not been considered relevant to xenotransplantation regulation. Since 1987 Genzyme had been marketing Epicel™ a method for culturing human skin for treating severe burns. The problem was that the production method requires base layers of irradiated mouse cells on which to culture human epidermal grafts.

Xenotransplantation regulators saw in this the very same dangers that concerned them about transpecies transplants, particularly human/nonhuman disease transmission through viruses embedded deep within the DNA of a species, that, when introduced into an unrelated species can become highly infective and harmful.

Years earlier, Epicel™ had been originally regulated as a 'medical device', though its connection to the risks associated with XT were not foreseen at the time, nor included in the definition of XT that emerged during the early and mid 1990s. But with a now increased regulatory focus on transpecies disease the status of Epicel™ as a 'device' began to collapse, as did the existing definition of XT. The previous definition used by the FDA and the British regulatory body for XT (the United Kingdom Xenotransplantation Interim Regulatory Authority) did not account for production methods whereby human and animal tissues may be subject to 'ex-vivo contact' as is the case with Epicel™. Whilst they foresaw that there would be the need to regulate clinical practices involving ex-vivo 'perfusion' (pig livers used temporarily outside of the body to support a patient in hepatic failure), ex-vivo contact remained outwith the duties of responsibilities of regulators. The amended FDA definition now reads:

... any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs. (FDA, 2001)

This realisation in the late 1990s and the FDA's redefinition, undermined the adequacy of existing regulation and also the belief held by many authorities that they had produced a precautionary regulatory process. Regulators had been fundamentally committed to the principle that recipients of xenografts should be registered within a programme of life-long surveillance, monitoring potential cross-species infection. But in testimony to the FDA, representatives of Genzyme acknowledged that whilst many thousands of patients had been treated internationally with Epicel™, there was no registry of recipients and no means of checking for cross-infection. Awareness of Epicel™ and other products suggested that the xeno-horse had indeed already long since bolted.

So these questions of definition and what is or is not the object of regulatory action, and by which regulatory institution, are therefore far from trivial. And in this case there are issues about whether a new clinical practice

is a device/appliance or a medicine, or more crucially whether it is alive or dead, inert or animate, benign or dangerous. As one respondent from the UK Department of Health commented:

... the mice who provided the cells were long dead. Years and years ago, so it's an established cell line that's being used, really without people thinking about it as being particularly mousy. (DoH member 1 – June 2001a)

Questions of species were crucial here – a device's 'mousiness' or not! Initially, the 'radar' of regulation was focused on the species that looked most likely to be the primary donor source, pigs. Therefore, characterising the pig and its potential donor-host relationship to recipient humans occupied most of the regulatory workload. Non-human primates too were at the centre of sustained discussion, particularly in respect to their welfare as proxy humans in preclinical trials. Plus the focus was initially skewed towards large organ transplants and perfusion techniques from pigs rather than cellular applications involving mice, and perhaps other slightly more mundane technologies including Epicel™.

In all, cells and mice were arguably peripheral in the regulatory consciousness:

first it was all about ... whole organs ... concern as a committee tended to shift more towards the use of animal tissues ... Infusion devices, transplanting foetal cells, this kind of thing ... this arose out of an American experience where their definition included any tissues which had been in contact with animal body fluids, and this then became relevant in certain things ... notably the growth of tissue cells, using at one stage mouse cells as a base, and that this was not xenotransplantation according to our definition because no cells or vital animal tissues were transplanted. But human cells have been in contact with mouse cells. And this created quite a difficult problem ... because there was a possibility that we might have inadvertently created a lot of xenotransplant patients simply by changing the definition. (UKXIRA member 2, Oct 2001)

As these definitions shift so too does the ground on which regulators understand transpecies risk. As one of our respondents put it, there are differing degrees of risk between whole organs which are transplanted and irradiated mouse cells which are not. In this case there is the difficulty of balancing the fact that there are now many more various forms of xenotransplantation and differing degrees of contact, but 'contact' nonetheless. An expert witness from Genzyme at an FDA committee hearing acknowledged that contact may be sufficient cause for regulatory concern:

I think the assumption that one takes using any mouse cell line is that there is the potential for expression of a xenotropic retrovirus from that

line. The fact that these tests are negative is comforting at the post-production level, and the fact that they're radiated prior to their use as a feeder cell line is comforting to some extent in that they're not actively replicating. But there is always a potential with any mouse line the assumption being that there is potentially endogenous retrovirus there. (D. Moore, Genzyme, FDA hearing, April, 2000)

This account shows how the once 'black boxed' (Latour, 1987) definition of xenotransplantation was opened up to controversy, how the 'zoning' of XT has expanded, and evolved in relation to institutional assumptions about species difference, and about whether something is an inert device or an active biological agent. The focus on pigs distracted the regulatory gaze from other xenogeneic hybrids including the living cells of long dead mice and the many thousands of human skins cultured on them. The broader point is that the *disjunction* between the apparent hybridity of a body like UKXIRA and its actual (species) rigidity generates apparently new risks.

In this sense then, hybrid corporealities are in profound tension with hybrid institutional bodies – what we described earlier as a form of 'institutional biosociality'. That is, institutions – like other areas of specialisation within the biosciences such as professions, disciplines, royal societies, etc. – have a certain species identity or emphasis. In this way they may be aptly described as 'institutional animals', each resonating with particular elements in nature.

In the UK, two regulatory bodies in particular emerged as crucial to the management of human and nonhuman risk in XT: UKXIRA, but also the Home Office's Animals Procedures Committee (APC). UKXIRA is an interesting illustration of a hybrid or transpecies institutional capacity. Its terms of reference include oversight of applications to undertake clinical trials in humans and also consideration of the welfare of source animals from which tissues and organs might be derived. Its remit, its routes of consultation and even its membership criss-cross various 'relevant' regulatory capacities that feed into its role as an intermediary focus in the UK regulatory system for XT:

The authority's role as a focal point for xenotransplantation issues is important given the number of interests which xenotransplantation brings together – animal and human welfare and ethics, industry, public health, and the other regulatory systems which exists for medicines and medical devices ... (UKXIRA, 2003: 5)

The important point here is that it is, we might say, a predominantly human-medical regulatory animal. On the other hand, we also have the Home Office's APC, responsible for preclinical experimental procedures on animals, a nonhuman-welfare regulatory animal.

Whilst both of these committees are crucial regulatory bodies for XT they have been entrenched in institutional arrangements that inhibit good joint

responsibility for 'interspecies' regulatory problems. A crucial issue here is that the APC is bound by clause 24 of the Animal (Scientific Procedures) Act 1986 making it a criminal offence for members of the APC to disclose information to third parties, 'otherwise than for the purpose of discharging his functions under the Act'. This also applies to the disclosure of information to other regulatory authorities, even when their terms of reference may directly apply. One of our respondents sat on both of these committees and found themselves at the centre of critical institutional tensions.

The APC ... is all tied up with confidentiality ... when somebody applies to the APC to do a project on xenotransplantation involving primates, the logical thing to do would be to refer back to the body that regulates xenotransplantation [UKXIRA] ... but you can't do that because UKXIRA cannot have sight of the project licence application ... (UKXIRA/APC member 1, April 2002)

Another respondent was a member of UKXIRA but not the APC. They expressed their frustration at being consulted by the APC about licence applications, the contents of which they were forbidden from seeing:

... the APC ... doesn't allow the dissemination of information to anybody outside the committee. I mean the sort of issues which arise are whether a series of experiments on a group of primates would be of sufficient importance ... to justify the suffering ... And we would get a question about the health of the animals from the Home Office but we couldn't get details of the experiments, and we couldn't get details of previous experiments to put them in context ... (UKXIRA member 2, Oct 2001)

There is then a legal firewall here in the governance of humans and animals, reflected in the structure of government departments and regulatory bodies. These species divisions represent potential weaknesses in the risk management of innovations like this that cut across institutions and natures. So despite its hybrid character, UKXIRA clearly has a species identity. Its institutional location reflects a stronger alignment with networks of human-medical-governance than it does with those of animal-welfare governance. Increasingly, clause 24 has come under greater scrutiny but is likely to remain in place until legal process has taken its long and circuitous institutional course through processes of consultation, lobbying and parliamentary timetabling. In the mean time, hybrid bodies like UKXIRA remain pragmatic and rely on a variety of strategies with which to extend their hybridity and to better meet their terms of reference (UKXIRA, 2003: 9).

This story illustrates the limits to institutional hybridity, that the capacity of regulatory bodies to move smoothly across long established institutional structures is limited. More importantly, this reflects institutional representations of

boundaries that are seen to exist in nature, and of course those boundaries traversed or innovated in biotechnology. Xenografts, as with other biotechnological innovations, often belie both 'natural' and 'institutional' classification, as we could see in the debates about the definition of XT, challenging the way in which routes of responsibility are organised. But as we will see next in our discussion of tissue engineering, these problems of 'making a mess' and 'cleaning up' are endemic as novel natures are generated and the definitional and institutional alignments of regulation become unsettled.

Tissue engineering

The discussion of XT highlights a number of key features of regulatory re-ordering that are important to consideration of human tissues and TE including the purification of the regulatory object, a strong alignment of regulatory institutions with one rather than another substantive field of governance, and the dynamic tension between institutional hybrids and novel natures. We now draw upon recent research – principally in the UK and Europe – elaborating TE as a regulatable zone and in relation to XT.

More heterogeneous than XT, TE includes cultured cell implants for cartilage repair, bone substitutes and 'living' skin tissues (like Epicel discussed above). Future developments are expected to include vascular prostheses, organ-assist devices (liver, kidney), whole organs, structures (heart valves, joints), neurological tissues and stem cell therapies. One influential definition describes TE as the 'regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules' (SCMPMD, 2001a). They are often conceived of in regulatory policy communities themselves as 'borderline' or 'hybrid' products – occupying a 'regulatory vacuum' at the borders of existing regulatory frameworks. The notion of a regulatory vacuum has been the starting-point for much of the recent development of regulatory policy for human tissues, and the boundaries between pharmaceuticals, medical devices and TE are crucial areas of negotiation in re-ordering regulation. Some TE products have already been regulated as pharmaceuticals whilst some parts of combination products (e.g. using synthetic scaffolds) need to gain approval as medical devices. In the face of this complexity there has been a widely, though not unanimously, perceived need for 'new regulation' for human tissues and TE.

TE embraces two closely related regulatory fields whose boundaries are themselves unclear and overlapping. On the one hand, 'human tissues and cells' (HTCs) are defined and covered in Europe by the Tissue and Cells Directive (TCD) on the sourcing, storage, processing (e.g. cleaning) and distribution of a wide range of human materials (excluding, as we shall see, matters like blood and blood products and whole organs). On the other hand, the proposed 'human tissue engineering regulation' (TER) refers to

manufacturing and market approval, excluding the accreditation of safety and quality of sourcing and storage covered by the TCD, and distinguishes between autologous (donor is also patient) and allogeneic (multiple recipient) applications. These two jurisdictions were already separated in the United Kingdom, whose regulatory work in the early 2000s included a tightening of standards and accountability through a code of practice for tissue banking (Department of Health, 2001b), and then a code of practice for 'human-derived therapeutic products', voluntary guidance for manufacturers in the TE field (MDA, 2002).

Importantly, the European directive concerned with sourcing and storage is nevertheless framed, as discussed below, in terms of transplantation and therapeutic application. A TE manufacturer or tissue establishment engaged in significant tissue manipulation would have to meet requirements of both fields. These ambiguities are characteristic of the hybrid aspects of tissue-based therapies, pointing to a distinction between the traditional tissue banking for transplantation and the emerging activity of engineering tissues in implants. This is an increasingly troubled distinction as tissue banks engage in manipulation, and industry engages in tissue 'banking'.

It has been important for both commercial and regulatory interests that a clearly delineated zone of activity can be identified. European Commission Directorate-General Sanco negotiated the TCD in seeking to fulfil its requirements to protect public health, prefacing this directive that 'The transplantation of human tissues and cells is a strongly expanding field of medicine offering great opportunities for the treatment of as yet incurable diseases' and 'As tissue and cell therapy is a field in which an intensive worldwide exchange is taking place, it is desirable to have worldwide standards.' Note here the inclusion of 'cell therapy' in their definition.

Biomedical zones are matters of negotiation, with national and sectoral interests playing an important role. Unlike XT it is not the case with TE and HTC that an initially stabilised definition has been changed by a later revision, but that a range of definitions have been proposed and continue to be negotiated, taking the form of partitioning and cleaning with attempts to distinguish TE and HTCs from xenografts. In what follows we also illustrate further attempts to cleanse TE, variously including or excluding embryonic stem cells, whole organs and blood products.

We saw how the definition of XT had been formed in isolation from regulated 'devices', and how, given the production method used (irradiated cultures of nonhuman cells) that zone began to collapse, overwhelmed by the hybrid linkages. Now, whilst XT regulators have been slowly expanding the definition of XT, just the opposite has been taking place in human TE. Regulatory efforts have been directed, with mixed success, at distancing TE and human tissues/cells from the allied worlds of XT. One respondent spoke of how regulators sought to maintain a firm distinction

between TE/HTCs and XT:

Q: What about the use of animal or ... ?

A: Animal? for me it's a separate area ... xenografting ... we should have a centralised authorisation system for that.

Q: if you look at Apligraf [TE wound treatment] ... it makes use of bovine serum during the culturing process.

A: Oh, we have a problem of definition here again because for us a xenograft is the use of the animal part in the body or in the perfusion extra-corporeal. But it's a direct use. We have a specific category of products we call Produits Thérapeutiques Annexes which means additives you could say. And we have a specific authorisation for additives.

Q: Including?

A: ... bovine serum in many culture processes. ... And our regulation of xenograft existed since '96 ... that only the Health Minister can authorise a xenograft trial ... You can see that it's been placed at the most important level. (A-EU4, 2003)

Essentially, however, the respondent is describing a national regulatory boundary TE and XT that no longer exists in the US and will cease to exist in those regulatory arenas that take their lead, like the UK. The distinction of two regulatory jurisdictions will no longer be tenable, with both defined as XT. This clearly signifies the increasing reach of cleansing policies, with 'problems of definition' potentially jeopardising both the political and material cleanliness of TE and HTCs. Critical clinical commentary also recognises this:

In ex-vivo corneal stem cell expansion ... there is a need for accreditation of laboratories conducting such work. The use of ... of co-culture system must be in consultation [with regulators]. Without such stringency, there will be a risk of cross-animal contamination such as the one we witness [*sic*] recently in outbreaks of SARS. (Kong Y. Then, 2003)

This writer recognises the extension of XT and the role of the TCD in providing a framework for international accreditation. These processes of cleaning and re-organising are as much material as they are institutional and regulatory, calling to mind what Rheinberger describes as the 'intracellular representation of extracellular projects' (2000: 19). The quotation further illustrates the ambiguous boundaries around HTCs and TE, where adult stem cell therapy *may* be regarded as a form of TE.

In what follows, a respondent in the academic-commercial TE sector talks about their attempt to materially re-engineer the methods used to culture

skin cells, seeking to replace the use of animal ‘feeder layers’ with human equivalents, reflecting similar attempts across the TE industries.

We are very keen to develop a methodology that doesn’t use any bovine materials. Personally I’m more concerned about using bovine than mouse cells as a feeder layer. ... [XT regulators in the UK] are very concerned with our groups using mouse fibroblasts, but when I ask them ‘aren’t you concerned about bovine material?’, they say that’s not part of our remit because the cells are not alive. At which point you put your head in your hands and cry. We are working very hard to ... [develop] a methodology for using the patients’ own fibroblasts to substitute for bovine serum. ... (S5, 2003)

The statement highlights a further classificatory distinction in TE regulation, that of viability/non-viability. Here we see a hybrid ‘consumer’ of regulation troubled by the codified distinction between XT and medical device, and the regulatory vacuum for human TE products. (European medical *device* directives cover the use of *nonviable* animal materials in medical device manufacture). Industry has sought to maintain the limited relevance to final TE products of ‘ancillary’ *viable* XT in production processes, as we will see below. The following statement from the European parliamentary debate on the draft TCD concedes some serious ambivalence about the exclusion of XT in the new legislation for HTC:

Organs, tissues and cells of animal origin for human therapy are still in the research phase, but nevertheless pose different regulatory problems that will need to be addressed in due course (from the Explanatory memorandum to the proposal for a directive on quality and safety of human tissues and cells (EU Commission/DG Sanco (2003))

Animal tissues and cells were in fact excluded from the final Directive. The EC here is thus acting to preserve the integrity of HTCs as a regulatable zone uncontaminated by animal matters.

The EC’s DG Enterprise found in its consultations on TER – the TE-specific regulation in 2002 and 2004 – that most stakeholders favoured a separate regulatory framework for XT *products*. However, some attempt to address the question about contact with animal materials during production was suggested. Responding, industry associations proposed the following text:

hTEPs containing not intentionally small quantities or traces of material of animal origin (used during the manufacturing process) which do not perform any function *in the finished product* are not, for the purpose of this regulation, regarded as xenogenic products. (EuropaBio et al., 2004; author italics)

Thus they attempt to preserve TE production processes *against* the incursion of the extended definition of XT as discussed above in the case of the US and UK. Such *products* should be regarded as TE products in spite of viable XT elements in the production process.

The UK has a dedicated XT regulatory body but the European Union does not. The UK's code of practice for human derived therapeutic products (MDA, 2002) is the basis of interim guidance for manufacturers of TE technologies while the EU TER is being formulated. The UK code states that 'Where cell culturing techniques use cell lines that are not of human origin, for example, murine fibroblasts used for co-culture, guidance should be sought from UKXIRA.' The code specifies appropriate measures to avoid material contamination and to provide for regulatory accountability:

Documentation shall be obtained that demonstrates the application of appropriate quality assurance measures by suppliers of biological material, including origins and veterinary certificates for the animals used in the preparation of the material (e.g. bovine serum albumin).

and:

Culture media, reagents and processing materials derived from animals shall be evaluated for the risk of contamination with micro-organisms, particularly viruses and agents of transmissible spongiform encephalopathies ...

Thus it is clear the UK TE policy group assumed that the UK system, including UKXIRA, should and will adopt the extended definition of XT, and allows for a linkage between regulatory zones with parallels to that seen above between medical and animal welfare domains.

Returning to the clean ordering of HTC's, whole organs were also excluded from the Tissues & Cells Directive, in the face of strong dissension. As one commissioner noted:

... I remain convinced that it is not appropriate to include organs in the scope of this directive. The problems to solve in this area are quite different ... requiring a different policy approach ... As organ transplantation is a highly specialised subject in its own right, the Commission is currently conducting a scientific evaluation of the available options ... Following the example of the blood directive and this proposal on tissues and cells, *we would like to get the science right first, before tabling a legal instrument in this sensitive area.* (Byrne, EC, 2003) (author italics)

We see here 'getting the science right' as a rhetorical device with the effect of proliferating separate though linked regulatory jurisdictions – blood, organs, and human tissues. These distinctions between biosocial matters are

artefacts of regulatory political process. But paradoxically purifications aimed at defining discrete fields at the same time increase the overall complexity. On the exclusion of organs again:

We should not include organs in this measure on cells and tissues. Organs are for another day. Equally, this is not the time to permit cloned human embryos or hybrid human–animal embryos ... this is a very young area of science ... leaving aside the ethical issues, one that should not be permitted now. (MEP Bowis, 2003).

This remark nicely points to the complexity of the human tissue terrain and the inevitable difficulties of policing its fragile borders. It is worth remembering here the way the regulation of XT had ‘mistakenly’ focused on whole organs, for years neglecting cell-based ‘xeno-like’ practices in tissue engineering. There is then a curious patterning in the regulation of tissues, human and xenogeneic. Whilst HTC regulators would like not to have to embrace whole organs, XT regulators would rather not have had to embrace TE. The fact that cells (particularly *ex vivo* contact) are now more central in the regulation of XT poses yet more problems for HTCs and TE legislation. It is possible that the exclusion of whole organs raises similar questions about the longer-term tenability of the TCD Directive’s boundaries.

Thus the leakiness of distinctions between types of human tissue and their methods of ‘production’ means that the isolation or segregation of particular zones of a regulatory order is difficult to achieve. Hybrids have the potential to overwhelm purification because rhetorical and material connections constantly reference new associations.

Turning to consider *institutional* hybridity accompanying the contestation of biomedical boundaries, we note that in the United Kingdom the current regulatory authority the Medicines and Healthcare products Regulatory Agency (MHRA) was formed from a merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA) avowedly as a response to the increase in materially hybrid or combination products. Products deemed ‘tissue-engineered’ are assessed in the MHRA on a case-by-case basis in the absence of TE-specific regulation. In a subsequent recent development the UK has established a dedicated Human Tissue Authority which will shortly assume responsibility for oversight of all tissue establishments and their sourcing and related activities.

Various models for an institutional regulatory agency have been proposed in Europe, to satisfy conflicting interests in the TE zone. The high status Scientific Committee for Medicinal Products and Medical Devices (SCMPMD, 2001a) proposed a separate TE Regulatory Authority. Opinion then appeared to favour founding a structure located within Europe’s existing Agency for the Evaluation of Medicinal Products (EMA). This drew criticism from those stakeholders who preferred to see TE products as ‘more

devicey' (as one informant put it) than pharmaceutical. The hybridity of the technology was further highlighted by apparent territorial disputes within the EC's DG Enterprise between the medicines and medical devices jurisdictions, which in a further twist resulted in a proposal to re-classify TE within the 'biotechnology' division of EMEA – neither pharmaceutical nor device! Following a Europe-wide guidance document (CPMP, 2001) in 2003 the EC Medicinal Product Directive (MPD) was augmented by an Annex on 'advanced therapy medicinal products' (EU Commission, 2003) which in effect extended the definition of the regulatory field of medicines (as opposed to devices, or biologics, or TE) to include somatic cell therapy products, human and xenogeneic.

The overlap of a future European TE legislation with the MPD definition of cell therapy medicinal products, and the possibility that some products would be *both* TE and medicinal, had been criticised in responses to the EU DG Enterprise consultation on the need for TE-specific regulation (2002). And it is at this point that we can return to a consideration of the chequered regulatory history and ambiguous regulatory identity of Epicel, currently described by its manufacturer Genzyme as an 'autologous cell therapy product' that is 'co-cultured with mouse cells to form cultured epidermal autografts', and uses 'a cell culture medium containing bovine serum'. Thus were Epicel and allied products to be submitted for authorisation in Europe now their regulatory status may be unclear, in spite of meeting the main criteria of TE, and even though in the case of Epicel it is regulated as a device in the US.

To summarise, the links between HTCs, TE products and the institutional hybridity of regulatory authorities in the UK and Europe are highly complex. Like XT, we see attempts to construct and align pure regulatable fields across the hybrid materiality of human tissue-derived therapies in order to control various politico-material risks. Also like XT, we see these attempts at partitioning undermined by changes in the sociotechnical definition of regulatable therapeutic materials. The XT/device divide could not be sustained, nor could the cell therapy/medicines divide, nor could the TE/medicines/devices divides as overarching distinctions. In an admission of the difficulty of assigning stable classifications to capture novel TE therapies, EC proposals for TE Regulation allow for a *lex specialis* function to adjudicate on products that are not clearly either TE or medicinal or medical device, 'to minimise the risk of grey areas for borderline products' (EC DG Enterprise, 2004). So we also see tensions between different organisational and indeed ontological claims at the very heart of the social constitution of human therapeutic materials.

Conclusion – boundaries redrawn

Unmistakable connections cut across the regulatory and material practice of life science innovation generally, particularly evident in the context of the two innovative areas discussed here. That is, engineered human and

nonhuman tissues are inherently messy and liable to 'leakiness' (Hogle, 2002). Their edges, their boundaries, are for regulators annoyingly variegated, and a source of frustration in their attempts at definition, cleanliness and purity. TE/HTCs and XT both illustrate new capacities of isolation and mobilisation in life science innovation. Here, processes of 'purification' render matters isolatable, manipulable, and legible in laboratory-based science (Knorr-Cetina, 1999: 27). Cells, tissues and bodies, as Waldby (2002) points out, are increasingly caught up in 'biotechnical fragmentation' (239). Crucially, at stake here are regulatory processes of 'territoriality' or 'political ecology' (Sharp, 2002). That is to say, natural objects are delegated to various arms of regulatory order, institutionally enacted readings of biological risk that subsequently order cells, tissues, embryos.

There are important lessons to be learnt from hybrids and dirt. Crucially, mess is a consequence of purification and not a cause, a 'by-product' of ordering and for Latour, it is the very act of purification that proliferates the production of hybrids. Boundary-making is intended to deny connection, to foreclose the production of hybrids, and so paradoxically acts to facilitate their manufacture. And all too often, regulatory ordering systematically obscures the complex interplay of regulated matters. Risks flourish, it seems, when practices of regulatory purification continue to be applied, in ignorance and denial of evident associations between technical and social considerations.

This prompts crucial questions of regulatory activity in the areas of HTCs and TE and XT – especially the sustainability of regulating them separately when based upon political or commercially pragmatic differences. This is not to suggest that acts of purification and cleaning-up are bad, even avoidable. They are not, especially in a context where transpecies innovations depend upon strong and rigorous regulatory ordering to lessen the chances of potentially devastating population-wide risks. As Barad puts it, 'boundaries are not our enemies' and we can hardly expect to do without them, they are:

... necessary for making meanings, but this does not make them innocent. Boundaries have real material consequences ... Our goal should not be to find less false boundaries for all spacetime, but reliable, accountable, located temporary boundaries, which we should anticipate will quickly close in against us. (Barad, 1998: 187)

Biotechnological innovations are reciprocally enabled by regulatory structures that facilitate particular sorts of research regimes and interactions out of which emerge biotechnological innovation – what we describe above as a form of 'institutional biosociality'. These are highly heterogeneous interactions between multiple forms of social, biological and institutional participants who jointly constitute innovation (Callon et al., 1986; Bijker,

1995; Hughes, 1983). Indeed, it might be useful to think of this as an institutional form of 'intercorporeality' (Waldby, 2002; Weiss, 2000), the connections of identification and disidentification between bodies that are as 'inter-institutional' as they are inter-embodied. That is, various innovated corporealities (stem cells, growth media, pigs, mice, primates, plants, viruses, patients, etc.) are distributed between regulatory bodies each participating in a complex process of exchange and interaction, potentially embodied in both donors and recipients of transplantable tissues.

In summary the messy material hybridity of biomedical regulatory objects highlights societal attempts to introduce clear partitions, jurisdictions and stable regulatory orders in highly complex socio-political zones. We have illustrated how the formations of XT and TE have interacted with shifting regulatory terrains. We have seen both successful and unsuccessful attempts to maintain boundaries, particularly between XT and human tissues. In both fields we have seen the strength of biomedical and pharmaceutical 'institutional animals' in shaping the discourse in which novel technological governance is constructed. And we have seen the shifting definitions of scientific and social appraisal of public health risk being refracted through the composition of the regulatory bodies that governance activity produces. Thus in order to understand the variability of governance in different innovative technological fields, it is necessary to develop accounts of the hybridity of their material forms, to bring into view the detailed social, cultural and material shaping that produce regulatory orderings. And it is here perhaps that we can return to the link between regulatory ordering and deeper categorising of nature, the human, animal and the moral. For the messy work of regulating is also an inalienably social and moral process of seeking benefit and minimising risk in highly pluralistic, technologically inventive societies. Hybrid technologies highlight the manufactured disturbance of foundational categories and societies' attempts to manage this disruption, a partitioning and aligning process that, in turn, redistributes the productive elements for the continuing hybridisation of biomedical technologies.

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