

XENOME WP5

DRAFT

Report on Models of Risk: US, EU, Canada and Australia

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1. Introduction

Xenotransplantation (XT), the transplant of tissues or organs from animals to humans, is seen as a promise to solve the problem of shortage of human organs. Amongst the numerous difficulties implied in this complex biomedical technology – which still primarily deal with the technical feasibility and efficacy of XT, the controversy over the use of animals, and the individual acceptability of informed consent – safety remains the main concern. The potential risk of infections that may be transmitted from the animal source to the human recipient, and also public health threats due to the possibility that XT may transmit novel infectious agents (most likely latent viruses such as retroviruses) or known animal pathogens from the xenotransplant source to the recipients, possibly causing the emergence of a novel and potentially untreatable human infection. XT has the potential to introduce new infections (so-called xenzoonosis or xenogeneic infections) into humans by infecting recipients with agents that were not previously endemic in human populations (Chapman, Folks, Salomon 1995, 1498-1501; Chapman and Bloom 2001, 2304-2306).

In this challenging context, moving from preclinical to clinical trials, regulatory frameworks have been established as an attempt to normalize XT by creating conditions that neutralize the potential risks of infections while respecting the tenets of democratic societies. However, the existing and proposed legal frameworks dealing with this medical technology are heterogenous, and some

of them show greater concern with legitimating XT than with exploring its social feasibility.

The legal history of XT illustrates how regulation has been used to bypass discussion by the desirability of the technology for granted. Regulating a certain technology has been often used to imply and suggest that the technology *per se* is acceptable.

This report explores three different regulatory approaches to XT, namely the US (2001), the European (Council of Europe and European Commission of the EU) (2003), and the Canadian (2002) and the Australian regulations (2004) (as two variants of the same model). The aim is to analyze how science and the law interact and generate one another (Jasanoff 2004) in each case. These different legal approaches show how science and norms are co-constructed producing different regulatory schemes (Brown and Michaels 2001, 3-22; Brown and Webster 2004). Scientific and legal statements are mutually adjusted to each other to support the legitimacy of XT. Specific scientific assumptions are adopted if and when they match desirable legal outcomes, while scientific needs are used to justify legal constraints.

The factual and normative elements of these different regulatory regimes are not only interdependent and mutually adjusting, but they reveal broader and more complex imaginaries of sovereignty and legitimate government. In each case something different is at stake: in the case of the US it is the maintenance of a coherent contractual liberal vision of society. In that of the EU and COE it is the assertion of the existence of a political entity such as Europe. In the case of

Canada and Australia it is the construction of public as a community and its role. Each policy model, and its way of reinforcing State's sovereignty, fails in its own way to establish adequately the legitimacy of this new technology. Substituting normalization for legitimation risks that these policy strategies become even more of a chimera – the mythological figure made of different animals' parts – than their object.

2. Normalization through normativity: the precautionary principle

The rationale on which XT depends on the generally accepted assumptions that there is a shortage of human organs (Bach and Fishman 1998; Bach, Fineberg 1998; Beauchamp 1999; Cooper and Lanza 2000; Bach et al. 2001; McLean and Williamson 2005; Anderson 2006; Welin and Sandrin 2006; McLean and Williamson 2007). This shortage is the main argument invoked to justify heavy constraints on patients and other subjects to implement XT safely. As has already happened in other fields, ethical principles and legal rules are used more to legitimize technoscience than to critically discuss its impacts on individuals and society.

In the case of XT, the tension between the potential benefits to individuals and the potential risks to the population through the transmission of infectious agents from patients to the general public is tricky. There is no strong evidence of either safety or efficacy that counterbalances the burdens imposed on patients in order to minimize risks to the public. On the other hand, the

frightening construction and legitimization of segregated, marginalized identities is very real.¹ Moreover, there is no conclusive evidence that individual burdens effectively minimize public risks.

2.1. Scientific uncertainty, risk and precaution

Contemporary scientific knowledge has been described as increasingly characterized increasingly by uncertainty (O’Riordan and Cameron, 1994). This is due not only because both the risks and the unpredictability linked to it are increasing, but above all because of the intrinsic incompleteness and indeterminacy of scientific knowledge compared with the needs to make social choices, public policy, and legal decisions. Such uncertainty is the daily condition where science works, and it shapes the social issues, where complex collective and individual trends must be reformulated through methodological decisions and through the reductionist analytical character of scientific procedures. The expression “scientific uncertainty” has been used to refer to different forms of lack of information in science: the complexity of knowledge, the lack of data, the unpredictability of results, and the stochastic character of predictions. This means that more and more often, the experts involved in regulatory science are unable to adopt an unequivocal position, and, therefore, that science produces different or partially diverging theses.

¹ Other controversial solutions have been proposed (Robert and Baylis 2003, 1-13), such as experimenting on people in a permanent vegetative state (Ravelingien et al. 2004, 92-98), or on patients at risk of dying with no alternative treatment available (Welin 2000, 231-236).

The unending work that characterizes scientific research has already shifted to radical forms of indecisiveness. Beginning with the eighties, uncertainty in science has been widely explored after philosopher of science Ian Hacking remarked that the centrality of ignorance in contemporary science has not received attention enough as to its epistemological statute (Hacking, 1986). According to Smith and Wynne, lack of knowledge may lead to different situations: risk, uncertainty, ignorance and indeterminacy (Smith and Wynne, 1989). In decisions under conditions of risk, the main variables of a problem are known and the respective probability of different outcomes is quantified. In contrast, in decisions under conditions of uncertainty, even if we know the main variables of a system, we do not know the quantitative incidence of the relevant factors, and so we ignore the probability of an event. A different definition qualifies uncertainty as “a probability of the second order” (Bodansky, 1994). This means that, while in cases of risk we can quantify the probability of the event, in cases of uncertainty we can only quantify the probabilities relating to alternative risk assessments. Ignorance is the situation defined as that of “unknown unknowns” (European Environmental Agency, 2001), when, since the basic elements of a problem are unknown, the possible negative outcomes are also unknown, they are unpredictable unless new cognitive elements emerge. Finally indeterminacy is the concept that summarizes the basically open and conditional characteristic of all knowledge, particularly its contextual meaning and its socio-cultural determination.

Scientific uncertainty seems to challenge the reliability of decision-making process. The last few years have seen the radical subversion of the conditions that made the theoretically neutral and separate relationship between science and law tenable. Scientific activities and products subjected to the scrutiny of law have increased exponentially, and contexts have appeared in which science has at once created risks and proved largely incapable of controlling them (Raffensperger and Tickner, 1999). The technoscientific component has increasingly constituted the cognitive content of norms, but the number of situations is increasing in which law has to fill cognitive gaps, since scientific data prove uncertain, insufficient or susceptible to sharply diverging interpretations.

On the one hand, the strong presence of scientific learning in subjects of normative competence means that it is necessary to explore relationships between science and law as an intersection between scientific and legal concepts and qualifications. On the other, the indeterminate or uncertain character of much scientific knowledge poses the problem of selecting specific norms to overcome the gaps left by science.

2.1.1 The precautionary principle

The problem of the legal treatment of uncertainty is at the root of the precautionary principle. The precautionary principle (PP) was introduced internationally in 1992 – as precautionary approach – by Principle 15 of the Rio

Declaration on Environment and Development: "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damages, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation".

The Maastricht Treaty (Art.130 R, par.2, art.174 of Amsterdam EC Treaty, now European Convention, Sec. 5, Environment, Article III-129) presented the PP for the first time as distinct and autonomous from the principle of prevention. Some overlaps exist between precaution and prevention. The preventative element is certainly present in the PP, even if it is a question of the prevention of a damage only potentially hypothesized. It is more correct to speak of anticipatory aspect: i.e. the anticipation of the (political) judgment of the presence of "signs of causality" in absence of ascertained causal links.

The most interesting interpretation of precaution has developed according to this vision: the awareness that the law must intervene "even before a causal link has been established", where the anticipation does not hint at a general preventive intervention, but it hints at the critical awareness that causal and scientific evidence may be achieved too late or may be unattainable (Bodansky, 1994). Thus, law and science appear to complement each other in decision-making process under conditions of uncertainty.

With PP, law frees itself from submission to science and it works out a critical position that acknowledges a positive role to ignorance. As Bodansky has outlined, "Risk assessment, unlike the precautionary principle, generally

assumes that we can quantify and compare risks. It is information intensive and rational. Moreover, it can and often does take a neutral attitude towards uncertainty. (..) In contrast, the precautionary principle is not neutral towards uncertainty – it is biased in favor of safety” (Bodansky, 1994: 209). The passage from a two-value science to a three-value science is fulfilled: from an idea of scientific quality which confines itself to evaluating the truth/falsity (verification/not verification) of the scientific hypothesis, to a science which expressly considers and recognizes the hypothesis of uncertainty and of indecision. The need for this three-value science, as Shrader-Frechette has pointed out, depends on an essential difference between theoretical science and science applied to risks. Actually, while the former moves in the abstract perspective of true/false, the latter is connected to the real and complex question of risk acceptability or unacceptability (Shrader-Frechette, 1996).

In risk analysis, two different kinds of errors may happen in decisions under uncertainty: errors of type-I occur when one rejects a true null hypothesis (a claim of no effect); errors of type-II occur when one fails to reject a false null hypothesis. In assessing environmental impacts, in a situation of uncertainty where both types of error cannot be avoided, when we minimize type-I error, we minimize the error of rejecting a harmless development; when we minimize type-II error, we minimize the error of accepting a harmful development. The former depends on an excessive scientific optimism, the latter on an excessive prudence. The prospect inherent in the precautionary principle tends to reduce as much as possible the mistakes that produce risks for people, considering that

it is better to make a mistake harmful to the economy – a mistake that limits development not risky in itself – but not harmful to people.

In 2000, the Communication of the European Commission on the PP qualified it as a general principle of the European Union for human, animal, vegetable, and environmental health (Commission of the European Communities, 2000). The PP – the Commission says – must be considered inside a unitary process of risk analysis (communication and management) and may be used when scientific information is inadequate, inconclusive and uncertain. Once evoked, the PP may be applied by adopting different measures of information and protection, as well as deciding not to adopt any particular measure. But what the Commission makes very clear is that the PP is a political principle, namely the principle that considers certain risks as “inconsistent with the high level of protection chosen for the Community”, and “an eminently political responsibility”.

The PP is the object of great criticism by the scientific world which judges it to be a kind of obscurantism and an instrumental support of the people’s irrational fears. The philosophical and moral reflection which, at the roots of its theoretical foundation, has had a great impact on this interpretation is Hans Jonas’ perspective of the “heuristics of fear” (Jonas, 1985): according to the Author, when confronted with scientific uncertainty and in order to protect what is possibly at stake and what we must beware of, it is wiser and more responsible to accept the priority of the prophecy of doom on the predictions of hope.

It is interesting to observe that Jonas has provided the PP with a “psychological” foundation – the feeling of fear – instead of an epistemic one. In Jonas’ philosophical vision, there is no room for a cognitive dimension outside the objectivity and certainty of science. Lack of full knowledge is also lacking an epistemic statute and ignorance is more a psychological position than a cognitive one. Accordingly, fear appears as a substitute for cognitive dimensions towards the unknown, and an adequate mechanism for a prudent behavior. But uncertainty is not just a synonym for non-rationality or irrationality. According to Hacking, we should reflect on the “statute of lack of knowledge” in its cognitive aspect and determine our actions accordingly. This means a behavior of active scientific wisdom combined with the awareness of the value-laden dimensions of science, and strengthened by the use of procedures aimed at making choices more legitimate, objective and shared. But this position does not reflect the reality of the PP.

Although the PP is considered the most characteristic feature of an emerging European epistemological identity in science policy (Tallacchini, 2002a), it is hard to see it as an innovative principle in the political decision-making process. Even though some legally binding European documents, such as the Directive 2001/18/EU on the deliberate release of Genetically Modified Organisms (GMOs) or the Directive 2004/40/EC of 29 April 2004 on the minimum health and safety requirements regarding the exposure of workers to the risks arising from electromagnetic fields, make the consultation with the public mandatory, these procedures do not unequivocally reflect a more

democratic attitude towards science-based policy, but may be aimed mainly at obtaining consensus. In fact, according with the Communication on the PP, the principle can be institutionally evoked only by the European Commission and no legal power is granted to citizens about it.

It is important here to observe that both the positivist view of science – denying the existence of uncertainty – and the “psychological” foundation of the PP (Jonas, 1985) – denying the cognitive side of ignorance – are similar in their easily leading to authoritarian political results. The former is associated with a technocratic perspective where the scientific community informs the content of legal and political decisions. The latter, even when linked to public consultation, can in any case have authoritarian results, relying exclusively on a political will, divorced from a cognitive rationale and supported by public fear. Actually, both the perspectives agree on a “certainty-or-irrationality” alternative, the model according to which, outside scientific certainty, only opinions or merely felt preferences exist. But theoretical reflections on the relations among science, policy and the law have gone beyond this alternative, which actually is an absence of alternatives.

2.1.2 Beyond the Precautionary principle? Democratising science, expertising democracy

Jerry Ravetz (Ravetz, 1999) and Silvio Funtowicz (Funtowicz, 2001), referring to the normative challenges set by life sciences, have coined the expression “post-

normal Science” to indicate the situations where “typically facts are uncertain, values in dispute, stakes high, and decisions urgent”. But the present situation concerning the social impact of technoscience nearly always represents post-normal science: in other words, post-normal science usually represents the “normal” situation in most of scientific social choices.

From this point of view, the PP, so as it has been defined by Principle 15 of the Rio Declaration on Environment and Development, seems to be conceptually superseded. Principle 15 actually describes a “lack of full scientific certainty” thus implicitly assuming that the normal condition of science is certainty, and that uncertainty is always circumstantial and temporally limited. Again, it concerns an incremental model of science where sooner or later the truth is reached. According to Jean-Pierre Dupuy, in the PP, the very notion of uncertainty is missed: “The key notion here is that of informational incompressibility, which is a form of essential unpredictability. In keeping with von Neumann’s intuitions on complexity, a complex process is defined today as one for which the simplest model is the process itself. The only way to determine the future of the system is to run it: there are no shortcuts. This is a radical uncertainty” (Dupuy, 2004: 80).

In Dupuy’s view, the introduction of subjective probabilities in statistics has allowed the reduction of uncertainty to the concept of quantifiable risk, because subjective probabilities no longer correspond to any sort of regularity found in nature, but simply to the coherence displayed by a given agent’s choices. “A risk can in principle be quantified in terms of objective probabilities based on

observable frequencies; when such quantification is not possible, one enters the realm of uncertainty. It is easy to see that the introduction of subjective probabilities erases the distinction between uncertainty and risk, between risk and the risk of risk, between precaution and prevention. No difference remains compared to the case where objective probabilities are available from the outset. Uncertainty owing to lack of knowledge is brought down to the same plane as intrinsic uncertainty due to the random nature of the event under consideration. [. . .] In truth, one observes that applications of the “precautionary principle” generally boil down to little more than a glorified version of ‘cost-benefit’ analysis” (Dupuy, 2004: 78–79).

More advanced perspectives on science policy are overcoming the PP. They are beyond the idea of an emergency principle about science, and they are supporting a more general democratization of scientific expertise and public participation in scientific decisions for public policy. The appearance of risks and uncertainties linked to the social implementation of science has revealed a double need: in the first place, the need to widen consultation with scientists where the divisions of opinions arise about the possible occurrence of potentially harmful events; in the second place, the opportunity to involve citizens more in science-based decisions that directly concern the civil society (Irwin and Wynne, 1996; Nowotny, 2003).

The European Commission White Paper on Governance (Commission of the European Communities, 2001, 2004) goes in this direction. It expresses the need for deepening democracy in Europe, and it includes the topic of science

governance. The European context has been shaken by emergencies linked to inadequate and inefficient regulating measures in scientific fields. But the European reflection about science governance is not only a pragmatic answer to the political need to re-establish citizens' trust in the institutions facing scientific challenges. It also reflects a theoretical effort to work out a European way to regulate policy-related science.

The changes in the relation between science and society are deeply modifying the institutional structures and all the rights that are linked to the notion of a social contract and particularly to the idea of a constitutional state (Fuller, 2000). The political rights granted to citizens in the *lato sensu* liberal democratic governments have been mostly the ones that help people to determine their political orientation using their vote. The need to make more visible and transparent the decisional procedures inside the institutions has more recently formed a new kind of participation in government action (at least potentially) through what is more and more recognized to be the citizens' right to know.

The store of warranties which define the very idea of a constitutional state has not adequately affected the relationship among science, individuals and institutions. The appointment of experts, the setting up and running of scientific and technical boards, and the same scientific knowledge considered the expression of an objective and certain method, have not been considered a problematic topic from the point of view of the protection that the state offers to its citizens (De Schutter et al., 2001). The need to introduce specific warranties and rights as well as to promote greater democratic participation of the civil

society today specifically concerns science regulation, a field where up to now citizens' absence has been nearly complete.

This vision of the relationship between science and society does not refuse to acknowledge the privileged character of scientific language. Science may speak particularly reliable words, but it does not have the power to utter the exclusive or final word about social choices. We must establish the conditions of public acceptance of the different kinds of knowledge; we must determine the forms of public control of such knowledge, the different methodological and axiological assumptions, that suggest their operation; no form of knowledge may be asserted only on the basis of a predefined validity or truth.

In this sense, the governance of science is a problem of democracy: here, the word democracy does not refer to the predominance of a majority, but to the open and unauthoritative characteristic of any language (including scientific ones). Every social decision must be screened in different places and through a plurality of knowledge, comparisons and transactions. Moreover, law becomes the place where different knowledge and languages are discussed and guaranteed through the participation of different subjects.

It would be reductionist to interpret such a position as an antiscientific one. It does not consist of a limitation on science and scientists' freedom—if such freedom is ethically qualified and it is not seen as a merely arbitrary explication. On the contrary, it is a question of favoring a deeper comprehension of the complex links between science and society, determining more adequate ways and procedures in scientific and technological choices, at the root of social and

civil transformations. In a recent publication devoted to democratizing scientific expertise and to expertizing democratic procedures, Angela Liberatore and Silvio Funtowicz clarify their use of such challenging terms: "If democracy is only seen as majority voting, and expertise as a self-referential system in which only peers can recognize and judge each other, then clearly democratizing expertise, is a contradiction in terms. When such premises are challenged however, the contradiction disappears, while different issues still need to be addressed" (Liberatore and Funtowicz, 2003: 147). This is the wider context of science policy where the PP has to be placed, having had the pioneering merit to indicate that the times were ripe to reflect on our criteria for democracy and rationality. "Science (seen as that activity performed by technicians and experts) is considered as a part of the relevant knowledge_ and it is included only as a part of the probative evidence of a process. The ideal of rigorous scientific demonstration is thus replaced by an ideal of open public dialogue. Inside the knowledge production process, citizens become both critics and creators. Their contribution has not to be identified as 'local', 'practical', 'ethical', or 'spiritual' knowledge, but it has to be considered and accepted as a plurality of rightful and coordinated perspectives with their own meanings and value structures. The strength and the importance of scientific evidence may be then the object of the citizens' analysis, every scientific aspect may be the object of a dialogue in order to be enriched in its content. Otherwise, it may turn out to be fictitious and imperfect. Through this co-production of knowledge, the existence of a

wide community of experts and revisers may be the source of a kind of ‘experience democracy’ ” (Liberatore and Funtowicz, 2003: 147).

2.2 The precautionary principle and XT

The history of the precautionary principle (PP) in the field of XT is part of the history of the PP itself, even though in XT, as it will become clearer later in this chapter, it has been *de facto* lead to self-contradiction in order to reduce uncertainty to controllable risk.

The PP is described as an “alternative method of risk analysis” that implies either that “the burden of proof should lie with those developing the technology” or that “the development of some technologies simply should not be pursued”.² In the debate (WHO 1996; IOM 1996; OECD 1999) following the release of the 1996 US draft guideline (FDA, DHHS, PHS 1996), the Nuffield Council on Bioethics (Nuffield Council on Bioethics 1996, 74-75) raised the idea of extending the PP from environmental issues (the field where the PP was firstly applied) to environmental health issues like XT. The voice of the Nuffield Council remained isolated, but in 1997 the Committee of Ministers of the

² Nuffield Council on Bioethics 1996, 74-75: “The principle of precaution offers an alternative method of risk analysis and assessment. This has been developed within the field of environmental policy and applied to the control of pollution and the release of genetically modified organisms. The principle of precaution requires that action should be taken to avoid risks in advance of certainty about their nature. This challenges the view that, until there is evidence that a new technology is harmful, it is acceptable to proceed with its development. It suggests that the burden of proof should lie with those developing the technology to demonstrate that it will not cause serious harm. An implication of the principle of precaution is that the development of some technologies simply should not be pursued. The Working Party concluded that the risks associated with possible transmission of infectious diseases as a consequence of XT have not been adequately dealt with. It would not be ethical, therefore to begin clinical trials of XT involving human beings”.

Council of Europe, in a recommendation to Member States, raised questions about the safety of XT. In 1998, prominent US scientists advocated the moratorium in the scientific community (Bach et al. 1998, 141-144), and other international documents expressed concern about XT. In 1999 the Council of Europe called for a moratorium.

The idea of a moratorium was quickly dismissed in the following discussion at the COE level, however, and the PP was reinterpreted as cautious risk management. In the US the moratorium was never considered and 'precautionary measures' merely referred to safety requirements for XT (DHHS-FDA-CBER 1999).

Working on the central notion of burden of the proof, the EU and the COE went further in customizing the PP by substituting prevention with progress. In fact the idea that it should be up to "those developing the technology to demonstrate that it will not cause serious harm" was shifted from the technology itself to the subjects (patients) physically carrying the technology. By making the 'XT product' (the engineered tissue or organ) almost indistinguishable from the 'XT product recipient' (the patient), the regulation implies that the real threat is not XT *per se*, but xenotransplanted patients: otherwise neutral and harmless becomes dangerous only when it is mixed with human agency.

3. Regulating uncertainties in XT

Each of the regulatory models examined below presents characteristic features. The US guideline elaborates the individualistic model of rights and responsibilities of the human subject research field, and a contractual vision strongly influenced by the US history of experimentation. The ordering power of this model is so strong that certain scientific assumptions are considered sound not because they are scientifically validated, but because they 'validate' this contractual model.

The Council of Europe, which worked out its position in collaboration with the EU Commission, started by extending the idea of informed consent to include third parties (family and close contacts), but it ended by authoritatively requiring patients and their contacts to waive some fundamental rights. This extended systemic regulation, which intentionally introduces a threat to public health and then uses it as an argument to delete individual warranties, shows how European institutions use technoscience as a means to construct and implement their own idea of citizenship while constructing European society itself. [cf. Dratwa, this volume]

Finally, the Canadian and the Australian approaches seem to accept the radical challenge that scientific uncertainty poses in a renewed democratic order. However, though they apply new deliberative procedures and reflect on their strengths and weaknesses, they maintain ambiguity in re-proposing

communitarian approaches that limit individual freedoms through internal control.

3.1 The US model: reality and fiction of individual rights

On January 19, 2001, five years after the first draft had been proposed, the Public Health Services (PHS) released the Guideline on safety aspects of XT (PHS 2001). The document is presented as a technical instrument that defines the practices required in clinical trials in order to prevent and control potential infectious diseases associated with XT.³ The Guideline's technical nature also implies that the document is intended to highlight technical measures to address safety issues, and that 'does not create or confer any rights for or on any person'.

Consideration of the full range of complex normative issues raised by XT was the task of the Secretary Advisory Committee on XT (SACX), a relative novelty in US regulatory science. This reflected the recognition of the deep social implications of XT, whose normalization and management require the separation and distillation of scientific and policy issues. Similarly, deep social concerns led to formation of the Recombinant DNA Advisory Committee (RAC) which was established in the 1970s to confront the supposedly unprecedented threats posed by genetic engineering.

³ PHS 2001, 12: "This guideline was developed (...) to identify general principles of prevention and control of infectious diseases associated with XT that may pose a hazard to public health. It does not create or confer any rights for or on any person."

Presaging a special opening up to the social aspects of science, the PHS guideline dedicates a lengthy comment to the public and to the SACX's role of mediator between science and society (DHHS-SACX 2004). At the same time, the attempt to separate and purify facts and values in XT regulation recapitulates a characteristic feature of US science policy, namely the supposed separation of technical and legal-political aspects. The same technique of purification and separation is also evident in the framing of risks and precautionary measures. In fact, the approach to risks through the "measures that can be used to minimize the risk of human disease" (PHS 2001, Section 1.5) suggests that, by identifying and listing single risks, the complexities of XT can be broken down and managed. It is a structural feature of the guideline to reduce unpredictable events to well-defined facts and individual behaviors. The intention is to provide credibility to the contractual, privately sponsored, individualistic model that informs both the idea of a liberal society and the classic vision of science and society (Ezrahi 1990).

The measures meant to minimize the number of infections range from the (revised)⁴ definition of XT to the numerous provisions regarding the subjects involved in the procedure, the safety of the animal source, the traceability and recording of all practices and events, and the primary responsibility of the sponsor in designing and conducting the clinical trials.

⁴ (FDA, DHHS, PHS 1996), 49919: " For the purposes of this draft guideline, the term "XT" refers to any procedure that involves the use of live cells, tissues and organs from a non-human animal source, transplanted or implanted into a human or used for ex vivo perfusion."

Two parties dominate the scene and are considered responsible if any problem should appear: the sponsor carrying out the experimentation (including the medical and health personnel), and the patient. The potentially significant impacts on the public are virtually ignored. No attempt is made to actively involve the public beyond generally phrased requirements of information and transparency. Even though the “role of the public” is repeatedly mentioned, it is not made clear what this role should be. The idea of “public awareness and understanding,” the necessity for a “public discourse” on XT, and especially the concrete conditions for people to exert their participatory right are kept vague. The SACX meetings between 2001 and 2005 (when the Committee was discontinued), were officially opened to the public, but they have been oriented more towards experts and stakeholders than to the public. In some sense the SACX itself, due to its composition (scientists, social scientists, philosophers, stakeholders and also one XT recipient) and its role as interface between the scientific and the normative languages, has been considered to represent society-at-large –even though it is apparent that the public can remain unaware of privately funded clinical trials .

While the US policy on XT recognizes that “public discourse on XT research is critical and necessary” and “public awareness and understanding of XT is vital because the potential infectious disease risks posed by XT extend beyond the individual patient to the public at large” (PHS 2001, 9-10), it does not really go

beyond a very abstract concept of the public,⁵ thought of as adequately and rationally subsumed by the advice of expert committees.

Most of the precautionary measures meant to avoid threats to public health address the patient, who remains the key element of the guideline. The general principle underlying the technical provisions is the concept of individual autonomy, which presumes that adult individuals in full possession of their faculties give their informed consent and are, as exclusive subjects of potential risks and benefits, exclusively responsible for the outcomes of experimentation. Where capacity for autonomy is presumed to exist, there is no need to formally involve third parties (family and close contacts).

The most prominent feature of the US guideline, made explicit in the informed consent provisions, is that it applies to XT the same legal requirements that inform the rules on human experimentation.⁶ The document suggests that regulation of XT is essentially a question of limits on human subjects research, integrated with provisions on risks of contagious diseases (Vanderpool 2003, 45-60).

The weakness of this assumption becomes apparent when we look at the context and the content of informed consent. First of all, the definition of XT itself is a warning about the borderline identity and condition of the XT patient, technically referred to as 'XT product recipient'. In fact, the revised notion of XT

⁵ On January 18, 2001, the FDA published a proposed rule in the Federal Register that would make available for public disclosure "information necessary to ensure a continued mechanism for public education and input" about XT and gene therapy. *Federal Register* Vol. 66, No. 12, January 18, 2001, 4688-4706.

⁶ As codified in Title 45 Code of Federal Regulations Part 46; Title 21 Code of Federal Regulations, Parts 50 and 56.

includes not only the “use of living cells, tissues and organs from a non-human animal, transplanted or implanted in a human being, or used in ex vivo perfusion,” but also “human fluids, cells, tissues and organs which have been in ex vivo contact with living non-human cells, tissues, organs” (PHS 2001).

The relationship between the XT product and the XT product recipient is analogous to the part and the whole, or to the single components of the body and the body as an integrated entity. A metaphysical vision comes into play here in order to separate the ontologies of what is human and what is not, and to detect where the product ends and the recipient begins (and vice versa).

The definition of XT is just the premise for the content of informed consent. The extensive article outlining the requirements for patient education and consent describes the long list of constraints with which the recipient must comply in terms of ‘necessities’ and ‘importance’. These indispensable requirements for patient behavior accurately draw the compliant or tamed identity of the ‘educated recipient.’ The patient’s awareness about “the potential for infection with zoonotic agents” and “the potential for transmission to the recipient of unknown xenogeneic infectious agents” is a prelude to his/her consent to the “potential need for isolation procedures during any hospitalization” (PHS 2001, 2.5.5.), and for the “importance of complying with long-term or life-long surveillance” (PHS 2001, 2.5.7).

In order to fulfill the individualistic regulatory approach and to maximize the possibility that consent will be given, the guideline makes the patient responsible for the control of family members and close contacts. During the

informed consent process the patient is informed of his/her responsibility to educate close contacts about the possibility of xenogeneic infections (PHS 2001, 2.5.4) and about the “behavioral modifications” -i.e., limitations on behavior— that entering the clinical trial will involve also for them (e.g., duties to report any significant unexplained illness, limits on unprotected sex, breast-feeding, and any activity that might involve exchange of blood or body fluids).

The unnatural extension of patient obligations to the control of third parties, which depend on the imperfect analogy between XT and the general principles for human experimentation, makes the limits of the US model evident. Potential risks of infectious diseases can hardly be confined and conveyed, much less controlled, through the structure of individual informed consent. Informed consent is intended to authorize personal risks and constraints ; it is not meant to affect and bind other people, and it is not adequate for doing so.

After the draft guideline (CBER 1997) was published, it was proposed to introduce informed consent for close contacts - though problems of diminishing patient’s autonomy were recognized. The initial internal FDA debate made it clear that this new form of informed consent for close contacts was not a proxy consent but, rather, notice of what they would be expected to do and what they might be required to do. Nevertheless, the strong tradition of individual consent was never challenged.

Informed consent can be effective only when the patient accepts lifelong surveillance. Risks can be effectively isolated in patients only if they accept all containment measures, and agree to be isolated from the rest of the world.

Moreover, informed consent is conceived of as a process of education of the patient. In the context of XT the act of consenting is just one aspect of a complex screening procedure: the patient's choice to undertake the trial is preceded by and subordinated to investigators' choice of the patient. Only reliable and compliant patients are allowed to 'choose' to undergo the experimentation.

Years ago, when the draft PHS guideline was first published, a discussion on the safety measures to be adopted by FDA made it clear that the patient cannot be really free to choose.

Dr. Siegel: Let me clarify a specific question. In the report from one of the subgroups there was a comment about not discriminating socially, such as based on past history of substance abuse, but there are, especially as we are talking about liver support, potential patient populations who are actively involved in intravenous or alcoholic substance abuse. You could have a chronic cirrhotic who is still drinking and goes into acute alcoholic hepatitis deterioration. In particular, since those people are not generally considered suitable recipients of human organs, they are potentially a very desirable population. Nevertheless, this committee and others experts have told us these transplants should go into people that you can count on for the rest of their lives, who will tell all of their contacts, will come in for their annual checkups and screening, give all the specimens, and should we be making the determinations whether or not there are populations that we really can't count on to do the things necessary to protect the public health? (CBER 1997, 296-297)

"Transplantation," it is reported in the same transcript, "is not for everyone; XT is not for everyone either, and there will be times when the consent process

becomes so convoluted that you say this is not an appropriate therapy for you, and that is okay" (CBER 1997, 294).

Finally, the overall credibility of the individually-based XT policy is provided by the science that supports the guideline. The science of XT is not framed independently from the liberal model of rules that the guideline proposes, but in accordance with it. The behavioral measures are made to cohere with the potential risk of XT. The construction of risk as individual rests on the tacit assumption that potential xenogeneic pathogens will be compatible with a social order where individual choices and responsibilities may prevent and avoid major infections and epidemics. Although potential infections from XT may not be known, they are assumed to be largely controllable through the good will of individuals.

The main analogy that the guideline draws in dealing with risks of transmissible diseases is a scientifically known, socially organized and accepted epidemic, namely AIDS. The guidelines mention AIDS to illustrate the danger that clinical trials in XT should avoid. The analogy serves to tame the unknown risks by reducing them to a scary but already familiar situation. AIDS is a disease that the world has more or less accepted, an issue that has evolved as a community-endorsed one and a case for human rights protection. Most of all, AIDS represents an infection that can be adequately controlled through responsible behavior. In fact, not only is the AIDS virus communicated through intimate contacts, but these contacts are generally under the control of individuals' will.

Since the discussion of infectious diseases began after the draft guideline was published, and even though other diseases are occasionally mentioned, HIV has become the paradigm for potential risks in XT (CBER 1997, 291-292). And AIDS is still the paradigmatic example of what could be expected in the 2001 Guideline.⁷

There are plenty of reasons to think of AIDS as a possible model to shape the regulatory aspects of XT. AIDS is the major epidemic of the second half of the twentieth century. Its presumed causes are at least partly found in laboratory experiments (Elswood and Stricker 1994, 347-354; Martin 1998, 175-179; Hahn et al. 2000, 607-614; Martin 2003, 253-256). Its spread has lagged behind the initial infections in Africa by many years. It took time for scientists to become aware of it, and to alert, organize and control the more exposed communities. All this knowledge about the spread of AIDS can be very useful and might be the most important learning experience about infectious diseases. But, at the same time, AIDS also demonstrated that epidemics can be managed through educating people and raising their awareness (Epstein 1995, 408-437), adopting a very familiar frame of rights and responsibility.

The AIDS model would not be applicable if the basis for thinking of regulation were an epidemic like SARS, Ebola or Avian Flu, which are much less susceptible to control, and whose containment can be achieved only through

⁷ PHS 2001, 15: "Emerging infectious agents may not be readily identifiable with current techniques. This was the case with the several year delay in identifying HIV-1 as the etiologic agent for AIDS. ...As the HIV/AIDS pandemic demonstrates, persistent latent infections may result in person-to-person transmission for many years before clinical disease develops in the index case, thereby allowing an emerging infectious agent to become established in the susceptible population before it is recognized."

containment and isolation. It is unknown whether XT will follow the former or the latter course.

This is not just a matter of speculation about potential unknowns, but a very real and daily situation when dealing with immunosuppressed xenotransplanted patients: in fact, in these patients' assays of antibody response may not detect infections reliably. As the Guideline recognizes, "culture systems, genomic detection methodologies and other techniques may detect infections for which serologic testing is inadequate" (PHS 2001, 4.2.2.1).

The regulatory science of XT has been shaped according to a comfortable model of epidemics, one that is compatible with the premises of a liberal state. Moreover, AIDS or SARS, in a sense, simply happened; they were not directly part of implementing a technology. But a complex biomedical technology, which was introduced to solve the organ shortage, but that instead turns out to require compulsory safety measures against risks of epidemics, makes apparent the hidden and unruly aspects of technological progress.

The Guideline occasionally mentions other potential transmissible diseases that openly require the adoption of compulsory safety measures. These less controllable infections that require "the most restrictive level of isolation" are listed separately, as requirements for infection control.⁸ They are not mentioned in the context of informed consent, as if consent is not relevant to

⁸ PHS 2001, 38: "Additional infection control or isolation precautions (e.g., Airborne, Droplet, Contact) should be employed as indicated in the judgment of the hospital epidemiologist and the XT team infectious disease specialist. (...) The most restrictive level of isolation should be used when patients exhibit respiratory symptoms because airborne transmission of infectious agents is most concerning".

these unpredictable events: in fact it is not, since the measures are compulsory, and not to be consented to.

The fear of epidemics led to the introduction of an 'indirect' strategy to expand the sphere of safety. In 2004 a rule concerning the eligibility of human cell and tissue donors excluded close contacts of xenotransplanted patients, labelling them as "intimate contact of a xenotransplantation product recipient." The circle of connections through definitions grows. By employing a chain of words that in turn implies a chain of relations - from the XT-product to the XT-product-recipient, to the XT-product-recipients'-intimate contacts - categories at risk are constructed and identified. This suggests that the boundaries are completely blurred among species and among people directly, or potentially, involved.⁹

3.2 The European model: waiving rights in the name of technology

On 30 September 1997, the Committee of Ministers of the Council of Europe (COE) adopted Recommendation No R (97) 15 on XT,¹⁰ asking Member States to establish a mechanism for the registration and regulation of certain aspects of XT. However, after the need for a moratorium was raised within the scientific community in 1998, in 1999 the Parliamentary Assembly of the COE unanimously adopted, in the name of the precautionary principle,

⁹ DHHS, 21 CFR Parts 210, 211, 820, and 1271 *Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products*; Final Rule and Notice, Federal Register, Vol. 69, No. 101, May 25, 2004, 29786-29834.

¹⁰ Council of Europe, *Recommendation 15/1997 of the Committee of Ministers on Xenotransplantation*. (Adopted by the Committee of Ministers on 30 September 1997).

Recommendation 1399(1999) on XT,¹¹ which called for a legally binding moratorium on all clinical trials. As a response, while some European countries adhered to the moratorium, the Committee of Ministers of the COE set up, under the joint responsibility of the Steering Committee on Bioethics (CDBI) and the European Health Committee (CDSP), a multidisciplinary Working Party on XT (WPx), composed of specialists in ethics, law, medical research, clinical practice, epidemiology, immunology and animal protection. The WPx was established to prepare a Report on the State of the Art in the field of XT, taking into account the COE Convention on Human Rights and Biomedicine.¹² In 2000 a first report was published (COE 2000), in order to allow the preparation of a new Recommendation.

A willingness to maintain the connections between the technical and the normative aspects of XT characterized this early European approach to XT (Tallacchini 2001, 154-156), whose epistemic interest for values has been largely divulged as a prominent feature of science policy in Europe (notably about risks) (Tallacchini 2002, 60-66). Solidarity was presented as a distinctive element of the European vision of bioethics that was capable, unlike the individualistic US approach, of more organically connecting individuals and the society-at-large.

¹¹ Council of Europe, *Recommendation 1399/1999 of the Committee of Ministers pleading for a moratorium on all clinical Xenotransplantation*. (Adopted by the Assembly on 29 January 1999).

¹² *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine)*, adopted by the Ministers Committee the 19th of November 1996 and open to signature in Oviedo the 4th of April 1997.

While the explicitly ethical language in matters of science would have sounded improper from the perspective of a US agency, the European WPx was at ease in mixing descriptive and normative terminology, raising ethical questions, for instance, about microchimerism, the co-existence of human and porcine stem cells (COE 2000, at 4.3.5).

This holistic approach is evident in the close link established between individual consent, family consent, and societal acceptance. Each step was perceived as problematic due to restrictions on individual freedom, the risks placed on health workers and family members, and the creation of new societal risks. Therefore, only the network of safeguards and social cohesion resulting from the participation of all parties involved could make clinical experimentation acceptable.

Informed consent from relatives was not discussed as a challenge or potential 'veto' on patient consent. Instead, it was considered an element of a broad negotiation of the acceptance of a high-risk procedure.

Inspiring the entire European document was the conviction that high impact technologies such as XT need the approval of society. For a new biotechnology to be legitimate, citizens have to show that they are ready to accept certain risks while institutions actively contribute to creating and safeguarding initiatives of public importance.

When the final report (COE 2003) was completed and a new Recommendation (Recommendation 10(2003))¹³ on XT was approved in 2003, deep changes had occurred in terms of risk perception in the three years since the first report.

The WPx report of 2003 gives greater attention to public health than the report of 2000. The 2003 report observes that several national and international surveys have shown that XT posed more problems than expected; and it recalls how several health emergencies in Europe (namely BSE, Creutzfeldt-Jakob disease, and the anxiety over GM food) “have created an atmosphere of distrust of science and scientists in the public mind,” so that “no one is really ‘in control’ or ‘knows what will happen’ “ (COE 2003, 53).

Although neither the earlier nor the later report support the precautionary principle, which is interpreted as anti-progress because it mandates that “all those involved in deciding about XT must be satisfied that the risk to the individual recipient, their families, the medical and nursing teams, and the general public are minimal and controllable,” (COE 2003, 70), this awareness [which?] is not used to justify a more stringent evaluation of the feasibility of xenotransplants. On the contrary, they conclude that more restrictive precautionary rules must be applied to patients and their relatives. The result is that the PP, initially applied (by Rec 1399(1999)) to XT as the source of potential risk, has been redirected (by Rec 10(2003)) to apply to the patient as the most

¹³ Council of Europe, *Recommendation Rec(2003)10 of the Committee of Ministers to member states on Xenotransplantation* (Adopted by the Committee of Ministers on 19 June 2003 at the 844th meeting of the Ministers’ Deputies).

real, and most controllable, source of risk. Precaution against xenotransplants is transformed into precaution against xenotransplanted patients.

Unlike the US Guideline, which stretches the potentiality of informed consent and assumes AIDS as the default hypothetical infection in order to justify and maintain its liberal approach, the COE, when faced with the increased risks posed by XT, does not reduce the potential unknowns of xenotransplants to tamed risks.

Instead, the COE regards the risks associated with XT as so unpredictable that an authoritarian State can step in and require that fundamental rights be waived.¹⁴ The European Union has completely endorsed this compulsory implementation of XT. The European Commission Scientific Committee on Medical Products and Medical Devices, commenting on the COE report, asserted without hesitation that in order to proceed with xenotransplants, some fundamental human rights – for the patient and ‘others’ !– may be ‘suspended.’

Some of the measures that may need to be taken in a surveillance system may have legal implications as they could be in violation of the Declaration of Helsinki and other guidelines for research on human subjects. In the recent EC directive for conduct of clinical trials, the right of a subject to withdraw from a clinical trial is explicitly stated (EC 20/2001), and this could be a problem for prolonged surveillance in xenotransplantation clinical trials. As XT has implications

¹⁴ Explanatory Memorandum to Rec (10)2003, 69-70: “It is hard to see how the normal pattern of a freedom to withdraw can be allowed in the case of XT. (...) The risks of XT are considered potentially so significant that informed consent should be obtained from relatives and family. It is hard to see how such people are able freely to give consent, but it is important that those in close personal relationships with the recipient are as fully informed and educated as possible.”

for public health, it may be that certain rights may have to be modified in such a way that surveillance can be continued. Patients (and others?) could therefore have to agree to waive some of their human rights. (European Commission 2001, 11)

Although its stated goal is “to protect all persons involved in XT (...) as well as public health” (Art.1), Rec 10(2003) has de facto reversed the priority of individuals over the State in biomedical matters, endorsing public health protection first (Article 7) and mentioning informed consent in this context (at Articles 13 and 16).

In this perspective, as in the U.S. Guideline, patients do not choose, but are chosen, and the choice will naturally exclude all unreliable people. The overwhelming power exercised by the medical staffs is also stated very bluntly. According to the report, “(T)hose engaged in transplant work stress that the recipients will be well known and therefore it will be easy to assess how willing they will be to conform. Transplant patients are historically conformist” (COE 2000, at 6.5.2).

Chapter IV, dedicated to “Protection of patients and close personal contacts,” accurately describes what will happen to non-compliant patients:

“If, after the XT has been carried out, the recipient or his or her close personal contacts refuse to comply with the constraints associated with XT, public authorities should intervene and take appropriate measures, where public health protection so requires, in conformity with principles of necessity and proportionality. Depending on the circumstances and in accordance with the

procedures provided for by national law, such measures might include registration, compulsory medical follow-up and sampling” (Rec10(2003), Art.21).

Having subordinated individual welfare to public welfare, the Recommendation replaces the concept of ‘patient’s individual rights’ with that of ‘patient protection’. The patient, formerly a subject of rights, now becomes an object of protection, subject to compulsory protective treatments.

Although the European legal construction of XT clearly violates the European Convention on Human Rights, the representatives of the European Court of Human Rights (ECHR), when asked to give their opinion (possibly to prevent a conflict with the judicial power), have reassured the COE about the legitimacy of the constraints.¹⁵ In clarifying the reasons for this legal feasibility, the members of the Court go even further than the terminology of the Recommendation, making it clear that the expression ‘compulsory constraints’ –or ‘interferences’ !– refers to ‘detention,’ a ‘lawful’ detention. “(T)he Convention in Article 5(1)(d) permitted the lawful detention of persons to limit the spreading of infectious diseases. With regard to Article 8 of the Convention, which guarantees respect for, *inter alia*, private and family life, it was explained that interferences could be justified, provided they were necessary in a democratic society. Moreover, in certain circumstances it might be assumed that

¹⁵ Council of Europe, *Explanatory memorandum to Recommendation Rec(2003)10 of the Committee of Ministers to member states on Xenotransplantation*. (5 June 2003).

an individual, by giving consent to a particular interference, had thereby already waived his or her rights".¹⁶

Although the representatives of ECHR acknowledged the novelty of XT legal issues, they failed to take into account that XT is not some sort of unpredictable 'natural' event, but a new technology associated with several predictable 'unknowns'.

The representatives' clarifying statement reinforces the position of COE: "The surveillance procedures associated with XT can only be effective if they are complied with to the letter. (...) Many of the rights in the Convention [on Human Rights] were subject to permissible restrictions and involved establishing a proper balance between competing interests' " (COE Explanatory Memorandum 2003, Art.7, at 22).

Some deeper meaning can be found behind the inverted order of importance of individuals and the public, introduced by Rec 10(2003). The role that Rec 10(2003) emphatically ascribed to the public could be mistakenly understood as willingness to make the debate on XT more democratic. The opposite is the case: public opinion is completely subsumed by the activities of the regulatory bodies, advisory groups and working parties, "who provide the framework within which proper informed debate may take place" (COE 2003, 72).

¹⁶ Ivi, Appendix: "In determining whether a restriction or "interference" is in conformity with the requirements of the Convention, the Court examines whether it has a proper legal basis, and in particular whether the law is accessible and the effect of its application is foreseeable, and whether the interference can be regarded as justified in a democratic society in pursuit of one of the legitimate aims specified in the Convention."

By its reference to the public dimension Rec 10(2003) shows the primary relevance that public health has acquired in Europe. That relevance causes individuals' rights to fade away when confronted with the epidemiological perspective. In the context of health, 'public' refers to a power that belongs to, and is managed by, the State.

This concern for public health is more than the State's responsibility for its citizens. Public health issues that have endangered the credibility of European science policy and have urged the adoption of a declared policy-related vision of science (Funtowicz et al 2000, 327-336), also represent a powerful opportunity for Europe to construct and project its image as a political entity; even though this image is mainly defined on the scary landscape of risks.

In legal theory the concept of survival of humankind has been considered a 'minimum content of natural law' – according to the formula used by Herbert Hart (1961) – meaning that it is a basic aim for all legal systems. Safety has become a sort of substitute for the basic value of survival in the sense that it provides legitimacy to legal constraints in the name of a 'naturalized' content of the law: "something presupposed by the terms of the discussion" (Hart 1961, 188). From this point of view, the appeal to safety is a way to reinforce State sovereignty and Europe is making abundant use of these issues to legitimize its supposedly collective identity.¹⁷

¹⁷ This strategy of using safety as a way to create a European public supposedly integrated by adherence to common values has been employed in the regulation of other technoscientific issues such as the donation of human cells and tissues (Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation,

3.3 The Canadian and Australian models: expert-citizens and dog-watching communities

In contrast to the US and European (EU and COE) approaches, which aim at reinforcing their respective traditional visions of government (Allspaw 2004, 417-428), Canada and Australia have used XT as a case to experiment not only with science, but also with participatory democracy, which these countries have explored through involving professional and social communities, interest groups, and individual citizens, and through using heterogeneous techniques to generate information and decisions.

The theoretical framework lying behind the involvement of citizens in the decision-making process on XT is neither explicit nor unequivocal. In exploring new ways to deal with complex policies, these models at times fall back on traditional strategies of seeking consensus or relying on old-fashioned communitarian models.

3.3.1 Canada

In 1999, the Canadian government launched an extensive public programme on XT (Health Canada 2000). The report *Animal-to-human transplantation: Should Canada proceed? A public consultation on XT* (CPHA 2001), summarized the

storage and distribution of human tissues and cells). In that context solidarity, endorsed as the European philosophy of donation and imposed to citizens, is described as “a factor which may contribute to high safety standards for tissues and cells and therefore to the protection of human health” (Whereas 19).

essential points of the project and clarified the reasons for wide public involvement (Health Canada 1999): the government was not merely seeking public approval of high-impact technologies, but also wanted to strengthen democracy in health policies and assess people's willingness to share responsibilities for risks (Tallacchini 2002b, 371-373).

The newest element consisted in introducing the new identity of the expert-citizen. The Canadian initiatives aimed at presenting and shaping the public as composed of 'lay-experts' and 'citizen-scientists', as people who acquire specific skills and knowledge about scientific issues in order to participate in decision-making (Michael and Brown 2005, 39-57). While only a small fraction of the population was actively involved, the experiment initiated a long learning process.

The final document produced through the consultation proposed a 'made-in Canada' (CPHA 2001, 11) approach to XT; it focused largely on how information had shaped the decisions and on how the learning process had transformed peoples' identities. Special emphasis was placed on describing the metamorphosis of 'uninformed Canadians' into 'informed Canadians:' "When generally uninformed Canadians were asked if Canada should proceed with XT, the majority said yes. However, as they became more informed, a shift occurred and the majority of informed Canadians said no, Canada should not proceed" (CPHA 2001, 10).

The conclusion that these 'new Canadians' reached through the participatory process -"Canada should not proceed" - is framed as a special knowledge in

which science merges with social wisdom (Allspaw 2004). Self-reflecting on knowledge acquired through the learning process, representatives of the Canadian public asked for more education both on science and on solidarity, healthy lifestyles, and fair allocation of resources. The precautionary principle was invoked once more, as a democratic call for a moratorium: informed Canadians were not opposed to XT, but thought that those who wished to proceed with XT (scientific community and industry) had to determine the risks, and demonstrate that the benefits would outweigh them. Finally, the public asked for continued public debate on XT.

The scientific community took note of the negative outcome of public consultation in Canada. Intervening in two main journals in the field, a Canadian physician, James R. Wright (Wright 2002, 40-42; Wright 2003, 475-476; Wright 2004, 1112-1113), was disappointed with the results of public consultation, and he re-wrote the final outcome of Canadian report, providing a personal interpretation of it. Wright re-calculated the numbers in order to dismiss the official negative results, argued that actual attitudes of Canadians were misrepresented and urged that the Canadian report not be taken literally,. He invented a new public: if 'informed Canadians' refused XT, the (recalculated) reliable citizens supporting XT are 'meaningfully informed Canadians'.

... public consultation is crucial. Therefore, I am not opposed to meaningful public consultation.... However, ...[t]he lay public cannot be educated in one weekend to the point of

being able to decide whether it is time to proceed with XT clinical trials. However, when presented (albeit unevenly) with the best available information on potential risks, benefits, and alternatives, as well as on the legal, social, and ethical implications of XT, 35% of citizen panelists voted “never proceed” to clinical trials, while 65% voted either “qualified yes” or “qualified no” (defined as “not yet”). As the difference between “qualified yes” and “not yet” is vague and probably highly dependent upon the group dynamics at each of the regional fora, I believe that these should be interpreted as essentially the same. This suggests that approximately two-thirds of “meaningfully” informed Canadians support XT” (Wright 2003, 476)

If the scientific community remained skeptical and disappointed, the Canadian government adopted an ambiguous position. While acknowledging the importance of Canadians’ point of view, Health Canada established a Working Group to further analyze XT before adopting a policy decision. Having launched the innovative, mainly qualitative initiative, the Canadian government remained puzzled about its official political meaning. Eventually it came to endorse the concept of ‘meaningful public consultation’. In 2002 the Public Advisory Committee (PAC), a forum providing advice from the consumer/public perspective, was established to supply Canada with ‘new ‘risk communication products’ (!) (Health Canada 2003). The easiest way for the Canadian government to show its commitment to democratic procedures was to appoint another Committee. ¹⁸

¹⁸ http://www.hc-sc.gc.ca/ahc-asc/public-consult/index_e.html (accessed March 2008).

3.3.2 Australia

In 2001 the Australian National Health and Medical Research Council (NHMRC) established the XT Working Party to provide advice on the scientific and normative aspects of XT, to produce guidelines for clinical trials, and to consult with the community. In July 2002, the XT Working Party released a Discussion Paper (NHMRC 2002) to promote an informed community discussion, that took place through two rounds of consultation (NHMRC 2003 a; NHMRC 2003b). In constructing a public, the Australian government introduced the two interdependent identities of the 'socially responsible scientist' and the 'responsible citizen,' who were jointly responsible for addressing 'social risks,' i.e., risks linked to the social implementations of technology. Because in XT this risk is seen to come mainly from the non-compliant patient whose behavior may create unanticipated situations, 'responsibility' came to mean accountability for patients' behavior both in hospitals and society.

In the US and the EU approaches, the constraints listed in the informed consent represent the attempt to control these risks by placing the burden entirely on patients. Neither the US guideline nor the European Recommendation deal with science as a socially embedded activity in terms of sharing and negotiating the social burdens that new technology brings with it. In order to proceed with XT, both the US and EU regulatory models ask for scientific requirements to be

established – namely safety and efficacy – but neither engages in the social dimension of XT except with respect to surveillance and containment measures. The Australian report, on the other hand, considers it unacceptable to impose the entire burden on patients. Scientific experimentation whose safety requires patients’ constraints is unfair; science that is premised on the violation of fundamental human rights is not sound science.

“It has been suggested that XT trial participants should be asked to consent to compulsory monitoring for the rest of their lives and to movement restrictions if an infection emerges. Such measures would mean waiving the currently accepted right of research participants to withdraw from a trial at any time, may not be practical to apply and should not be relied on as an infection control measure. (...) The working party concluded that investigators should provide sufficient evidence of safety to show that there is no undue risk to the community if some participants choose to leave the trial” (NHMRC 2003a, 79).

It is not prudent, the Australian document explains, to assume that sick and vulnerable people will keep their word. Nor is it ethical to require them to make such promises in the first place. Finally, it violates principles of sound science (mostly for scientific rather than ethical reasons) to rely on a promise¹⁹ as an infection control measure. Because patient compliance cannot substitute for scientific evidence of safety, responsible investigators need to provide evidence

¹⁹ The example given to illustrate this point is significant: “eg women who are asked to agree not to become pregnant during a trial do become pregnant.” (!) (NHMRC 2003a, 83).

of the safety of the proposed procedure in order to make restrictive monitoring or quarantine unnecessary.

Here the duo of the socially responsible scientist and citizen comes into play. The former has to ensure that there will be no undue risk to the community, the latter is contrasted with the few citizens-patients not compliant with safety measures and not responsible towards the community. [not completely clear] “While it is expected that, under these circumstances, most patients will adhere to the request for lifelong monitoring, individual recipients may withdraw their consent” (NHMRC 2003a, 82-83).

The noncompliant patient is simultaneously legally protected and socially alienated. Having recognized that the patient is as free to withdraw consent as in any other trial, the document assumes that this situation will be rare, as Australian citizens are inherently reliable, and even more so because the social community will ostracize noncompliant patients. This communitarian vision of science and society leaves little room for individual freedom. The relationship between scientists and the public is depicted as a well-disciplined cooperative community where social control is often stronger than legal sanctions.

The guidelines strongly rely on patient’s ‘ethical’ behavior, observing that “having entered the trial, xenotransplant recipients also have an ethical and social responsibility to comply with such provisions.” The languages of ethics and social relationships should sound more flexible than a legally binding rule, but in a communitarian context the practical result could be the opposite. And the communitarian perspective that pervades the Australian approach is made

clear by the title of the report on XT: *Guide for the community*. A strong and watchful community can enforce compliance even better than legal measures.²⁰ In September 2004, the NHMRC adopted a five-year moratorium on any clinical research on animal-to-human whole organ transplants in Australia (Pettigrew 2004). It is hard to say how this decision reflects the participatory process: legally enabling a self-monitoring community may have appeared a scarier prospect than the potential risks of XT.

The actual outcome of this globalized challenge – the overcoming of regulatory gaps v. the emergence of new places for xenotourism – is that xenotransplantation has now become an unavoidable issue. Globalizing the risks of XT transforms these risks from obstacles to be overcome into the final word that is pushing this technology forward.

²⁰ The most recent Australian publication has provided a more strict regulation of patient's behavior. Here the patient still has the right to withdraw the consent but is not allowed "to withdraw from the monitoring and follow-up associated with infectious diseases." ((NHMRC 2003a, 14).

4. Further steps: Regulating xenocells. The different approaches of the United States and the European Union

Cell-based therapies and tissue-engineering products have been developed separately from xenotransplants both from the scientific and regulatory points of view (EMEA 2003; Wonnacott 2005; Farrugia 2006). However, recent developments in pancreatic islets have given rise to closer connections between the two domains and called for joint attention from the respective scientific experts and regulatory authorities (Sanzenbacher et al. 2007). Several cell therapies and tissue-engineered products use cells of human, as well as of animal, origins, which makes the regulatory issues between the two fields necessarily overlapping and intertwining. However, there are differences between the United States and European Union regulatory strategies towards cell-based products. In the United States, the FDA Center for Biologics Evaluation and Research (CBER) and, specifically, the Office of Cellular, Tissue and Gene Therapies (OCTGT) oversees cellular products and tissues that meet the regulatory criteria for biologic products, which have been regulated since the 1990s. Allogeneic pancreatic islets are regulated as biological products subject to licensing under Section 351 of the Public Health Service Act (PHS Act), 42 USC 262. They also meet the definition of 'drug' in the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 USC 321(g), and are thus subject to certain requirements of the FD&C Act (Wonnacott 2005). FDA considers somatic cell therapy in the United States to be 'experimental', rather than a

standard medical practice. Therefore, cellular products cannot be used clinically without an Investigational New Drug (IND) application or an approved Biologics License Application (BLA) issued to licensed products.

Regarding xenogeneic pancreatic islets, although OCGT is competent for both allogeneic and xenogeneic cells, these products are regulated by different provisions. In fact, as has been again recently reaffirmed in a 2008 FDA Guidance (FDA 2008), whenever a product contains cells of animal origin (also if a feeder cell line of animal origin is used to propagate human cells), the final product falls within the definition of a xenotransplantation product, and the Guidance for Industry of 2003 (FDA 2003) and the PHS Guideline of 2001 will, therefore, apply (Bloom 2007).

In the European Union, at the end of 2007, Regulation 1394/07 was approved on so-called advanced therapy medicinal products (ATMP), namely gene therapy, somatic cells therapy and tissue-engineered products.

This regulation established provisions for placing viable cell-based and tissue-based products for human use in the market. Somatic cell therapy and tissue-engineered products may contain cells of human and/or animal origin, whereas, in tissue-engineered products, allogeneic and xenogeneic cells are associated with medical devices *ex vivo* or *in vivo* (e.g. microcapsules, intrinsic matrix scaffolds, biodegradable or not). The main rationale for the legal document (that entered into force on December 30, 2008) is the establishment of a centralized authorization procedure for all AMTP through an interdisciplinary expert committee, the Committee for Advanced Therapies

(CAT), within the European Medicines Agency (EMA), as the main accountable body in defining and evaluating advanced therapies. Due to the special safety and quality precautions, the regulation authorizes stricter requirements on risk management, including the complete traceability of donors, recipients, tissues and products in order to prevent potentially negative public health events.

Therefore, in the United States two distinct regulatory provisions apply to human and to animal-based products. In contrast, in the European Union, Regulation 1394/07 covers all ATMP products. A single template for the Revised Clinical Trial Application (CTA) form for ATMP, which sets the standards for clinical trials with allogeneic and xenogeneic cells investigational medicinal products, is under preparation within the European Commission (European Commission 2007). In 2003, EMA established the points to consider for xenogeneic cell therapy medicinal products (EMA 2003), which should be revised and updated by the end of 2008 when Regulation 1394/07 enters into force in all European Union Member States (EMA 2007).

5. National and international regulatory frameworks

When we take the global dimension of XT into account, it becomes clear that the different legal models described above still leave room for regulatory gaps. The recently invoked threats of 'xenotourism' and 'xeno-bioterrorism' project XT onto a worldwide landscape (Kobayashi and Yamanouchi 2006, 10-11). "The

world is my patient” recites an Editorial on *Xenotransplantation* (Ravelingien 2005, 88-90),²¹ metaphorically suggesting a globalized world that is also medicalized. Frightening scenarios of XT recipients travelling through the world without control (xenotourism), attracted by unscrupulous ‘entrepreneurial xenotransplanters’ [sic!] (Sykes et al 2003, 194-203) and of bioterrorists taking advantage of these situations (Fishman 2003, 909) have been presented (WHO 2004; WHA 2004) as reasons to regulate XT more effectively and to strengthen surveillance by immigration authorities.

Not only do the majority of countries around the world still lack adequate regulation, both for xenotransplants and cell-based and tissue-based products, but also the regulatory gaps among different legal systems as to public health protection and the uneven enforcement of fundamental human rights between developed and developing countries, leave the worldwide normative landscape looking quite inadequate to cope safely with the new therapies (Cozzi, Sykes 2007).

There has been a call for worldwide regulation (Sykes and Cozzi 2006). Such regulation, though necessary – since it has been shown that regulation only on the local level may be dangerous (McLean and Williamson 2007)²² –, can be still

²¹ A global “geoethical” approach has been suggested. It would consist of obliging all the countries in the world to consent to and to participate in the detection, treatment and follow-up of xenozoonosis. The poor countries not directly benefiting from xenotransplants should be granted basic health care support (basically at industry expense) in exchange for consenting to randomized blood sampling and public health control (Rothblatt 2004).

²² The authors illustrate the flaws and risks connected to the weakening of the regulatory system in the UK after the demise in 2006 of the UK Xenotransplantation Regulatory Authority.

ineffective due to the power of sovereign States to freely interpret most of international agreements (Tallacchini 2007; Tallacchini 2008).

Although the health issues and threats originating from globalization, primarily the potential spread of infections, are complex and largely unaddressed, an increasing number of clinical trials with animal cells therapies are submitted to health authorities in various countries (Valdez-Gonzalez et al. 2005). Recently, the problems connected to private and commercial funding in xenotransplantation trials have become more extreme as the lack of regulatory measures may attract research teams and industries willing to conduct experimental procedures that would hardly be accepted in countries with stronger regulation (Sykes 2007). In Malaysia, the case of a cell-factory – whose activities have been recently stopped by the government – advertised human and animal stem cell transplants as ‘worldwide available treatments for incurable and untreatable diseases’. This case is just one striking example of this challenging situation (Editorial 2007).

The WHO has been very active since the late nineties (Noël 2007) in exploring the problematic issues associated with xenotransplants and in raising Member States’ awareness of both the potential benefits and risks involved in it through the publication of several reports [WHO 1998, 2001.1, 2001.2) and the launch of a public consultation. In 2004, WHO emphasized the role of national regulatory authorities, urging Member States ‘to allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place’ (WHA 2004).

However, despite the WHO warning, in 2006 one major national regulatory body in the United Kingdom, UKXIRA (the United Kingdom Xenotransplantation Regulatory Authority) was discontinued, whereas other nation states have only established local or regional authorities. The case of UKXIRA, established in 1997 to advise the US Secretary of State on specific issues such as safety, shows how the risk of inadequate regulation may also be found in countries that have addressed xenotransplantation scientific and normative issues since the very beginning of research. The flaws of local systems of control may consist in 'a return to the cyclic performance of experimental xenotransplants' (Maclean, Williamson 2007) and, in general, in unsafe conditions in public health, with the potential challenge of pandemics. A regulation at the national level – and possibly at the international one – is the appropriate and necessary response.

In 2007 and 2008, several initiatives have been undertaken at the international level to stop organ trafficking and transplants tourism (Budiani-Saberi, Delmonico 2008, Transplantation Society and International Society of Nephrology 2008). The risks involved in xenotourism may result in even wider public health threats. The discovery of a new arenavirus in allotransplanted patients (Palacios et al. 2008) and the renewed concern in xenotransplants about the potential adaptation of PERVs to humans (Denner 2008a; Luz et al. 2008) – which in a worst-case scenario, might result in the emergence of a new viral disease – should be a constant reminder of safety aspects, even though other studies have shown more reassuring results (Garkavenko et al. 2008). In an interesting

analysis that highlights the growing global burden caused by emerging infectious diseases (EIDs) between 1940 and 2004, it has been shown (Jones et al. 2008) that EID events are dominated by zoonoses (60.3%) (Denner 2008b), the majority of which (71.8%) originates in wild animals (for example, severe acute respiratory virus and Ebola virus), and are increasing significantly over time.

Both the need for safety and the promising applications of xenotransplants have revived WHO's attention regarding the need for guidelines for clinical trials, and appropriate controlling mechanisms for such trials. In November 2008, a Global Consultation on Regulatory Requirements for Xenotransplantation was held in Changsha (China), co-organized by WHO, the Chinese Ministry of Health, the University of central-south China, and the International Xenotransplantation Association (WHO 2008). Among WHO's interests in strengthening its attention and normative role in xenotransplantation is the need for a global system overseeing xenotransplant regulation, the need for national competent authorities, the exchange of information, the prevention of unregulated 'xenotourism', and the granting of support for states and the coordination of xenotransplantation vigilance, surveillance and response to suspected infections.

The construction of a stronger regulatory framework committed to both safety and efficacy – and not just to safety – for clinical trials may prevent the performance of loosely regulated trials, the exploitation of vulnerable populations, and the improvement of safety and security. The need to connect local, national and supranational regulatory bodies and to strengthen the

effectiveness of the international normative level should be an essential part of this regulatory framework (Tallacchini 2008). Although high profile international institutions such as WHO may appear to be more relevant as soft law regulators, the connection between xenotransplants and the need to prevent epidemics around the world may lead to a strengthening of the role of WHO in this field.

The International Health Regulations (IHR) were initially adopted by the Health Assembly in 1969 with the limited aim of covering six 'quarantinable diseases', but through time they underwent substantial changes due to the need to cope with the emergence or reemergence of international disease threats and other public health risks. The present purpose of IHR (IHR 2005) is 'to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade'. The successful implementation of the WHO International Health Regulations (IHR), which is binding for all the countries who committed to meeting the new requirements of the regulations, may contribute significantly to enhancing national, regional and global public health security. A possible harmonization of current national policies against infectious diseases does not depend only on the availability of scientific expertise and economic resources for public health, but it is also a function of heterogeneous 'public health cultures' - namely of approaches to

communicable disease control that are more community oriented or more liberal and rights based (Gainotti et al. 2008).

References

- Allspaw, M. Kathleen. "Engaging the public in the regulation of xenotransplantation: would the Canadian model of public consultation be effective in the US ?" *Public Understanding of Science* 13 (2004): 417-428.
- Anderson, M. "Xenotransplantation: a bioethical evaluation." *Journal of Medical Ethics* 32 (2006): 205-208.
- Bach, Fritz H., Jay A. Fishman, N. Daniels et al. "Uncertainty in XT: Individual benefit versus collective risk." *Nature Medicine* 4 (1998): 141-144.
- Bach, Fritz H., H.V. Fineberg. "Call for moratorium on xenotransplants." *Nature* 391 (1998): 326.
- Bach, Fritz H., Adrian J. Ivanson and The Honorable Christopher Weeramantry, "Ethical and Legal Issues in Technology: Xenotransplantation." *American Journal of Law & Medicine* 27, 2 & 3 (2001): 283-300.
- Beauchamp, Gilles. "Ethics and Xenotransplantation." *Canadian Journal of Surgery* 42, 1 (1999): 5-6.
- Bloom, Eda T., "National policies for xenotransplantation in the USA", *Xenotransplantation* 2007; 14:345-346.
- Bodansky, Dan, *The precautionary principle in US environmental law*. In: O'Riordan, T., Cameron, J. (Eds.), *Interpreting the Precautionary Principle*. Earthscan, London 1994, pp. 203- 228.
- Boneva, Roumiana S., Thomas M. Folks, and Louisa Chapman. "Infectious Disease Issues in Xenotransplantation." *Clinical Microbiology Reviews* 14, 1 (2001): 1-14.
- Brown, Nik and Mike Michaels. "Switching between Science and Culture in Transpecies Transplantation." *Science, Technology & Human Values* 26, 1 (2001): 3-22.
- Brown, Nik and Andrew Webster. *New Medical Technology and Society. Reordering Life*. Cambridge UK and Malden MA: Polity Press, 2004.
- Budiani-Saberi DA, Delmonico FL., "Organ trafficking and transplant tourism. A commentary on the global realities", *Am J Transplant* 2008; 8:925-929.
- CBER (Center for Biologics Evaluation and Research). Xenotransplantation Subcommittee, Biological Response Modifiers Advisory Committee. *FDA meeting (December 17, 1997), Transcript*, <http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3365t1.pdf>
- Chapman, Louisa E., and Eda T. Bloom. "Clinical Xenotransplantation." *Journal of the American Medical Association* 285, 18, May 9 (2001): 2304-2306

Chapman, Louisa E., Thomas M. Folks, Daniel R. Salomon, et al. "Xenotransplantation and xenogeneic infections." *New England Journal of Medicine* 333 (1995): 1498-1501.

COE (Council of Europe), Working Party on Xenotransplantation. *State-of-the-art report on Xenotransplantation*. Strasbourg (7 July 2000); and *Interim Report on the State of the Art in the Field of XT*. Strasbourg (25 October 2000).

COE (Council of Europe), Working Party on Xenotransplantation. *Report on the the State of the Art in the Field of Xenotransplantation*. Strasbourg (21 February 2003).

Commission of the European Communities, Communication from the Commission on the Precautionary Principle, Brussels 2.2.2000, COM(2000)1.

Commission of the European Communities, Health & Consumer Protection Directorate General, , *Opinion on the State-of-the-art concerning Xenotransplantation*. Adopted by the Scientific Committee on Medicinal Products and Medical Devices on 1st October 2001, http://europa.eu.int/comm/food/fs/sc/scmp/out38_en.pdf

Commission of the European Communities, *European governance. A White Paper*. Brussels, 25.7.2001, COM(2001) 428 final, http://europa.eu.int/eur-lex/en/com/cnc/2001/com2001_0428en01.pdf

Commission of the European Communities, *Report on European Governance (2003–2004)*. Brussels, 22.09.2004, SEC(2004) 1153 http://europa.eu.int/comm/governance/docs/rapport_gouvernance_2003-2004_en.pdf.

Commission of the European Communities, Enterprise and Industry Directorate General, Draft Amendments to the Clinical Trial Application Form as regards Advanced Therapy Medicinal Products, Regulation (EC) No 1394/2007, http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/advanced_keydoc.htm.

CPHA (Canadian Public Health Association). *Animal-to-human transplantation: Should Canada proceed? A public consultation on Xenotransplantation*. (December 2001), http://www.xeno.cpha.ca/english/index_e.htm

Cooper, David K.C., and Robert P. Lanza. *Xeno. The promise of Transplanting Animal Organs into Humans*. Oxford-New York: Oxford University Press, 2000.

Cozzi, Emanuele, Sykes Megan, "Xenotransplantation: current standards for clinical trials", *Xenotransplantation* 2007; 14:347.

Denner J., "Recombinant porcine endogenous retroviruses (PERV-A/C): a new risk for xenotransplantation?", *Arch Virol* 2008a; 153:1421-1426.

Denner J., "Emerging infectious diseases and xenotransplantation", *Xenotransplantation* 2008; 15:305-1305.

De Schutter, O., Lebessis, N., Paterson, J. (Eds.), *Governance in the European Union*. Office for Official Publications of the European Communities, Luxembourg (http://europa.eu.int/comm/cdp/cahiers/resume/gouvernance_en.pdf)

DHHS-FDA-CBER (Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research). *Draft Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from XT Product Recipients and Their Contacts*. (12/23/99), <http://www.fda.gov/cber/gdlns/zooxeno.pdf>.

DHHS-SACX (Department of Health and Human Services, Secretary's Advisory Committee on Xenotransplantation). *Informed Consent in Clinical research Involving Xenotransplantation*. Draft, June 2004.

Dupuy, Jean-Pierre, *Complexity and Uncertainty a Prudential Approach to Nanotechnology*. European Commission, A Preliminary Risk Analysis on the Basis of a Workshop Organized by the Health and Consumer Protection Directorate General of the European Commission, in Brussels 1 - 2 March 2004, http://europa.eu.int/comm/health/ph_risk/documents/ev_20040301_en.pdf

Editorial. Malaysia to be stem cell producer's global hub, *New Straits Times* 2007, <http://www.nst.com.my/>.

Elswood, B.F. and R.B. Stricker, "Polio Vaccines and the Origin of AIDS". *Medical Hypotheses* 42 (1994): 347-354.

European Medicines Agency (EMA), *Points to consider on xenogeneic cell therapy medicinal products (EMA/CPMP/1199/02)*, London, 17 December 2003.

European Medicines Agency (EMA), Committee for Human Medicinal Products (CHMP), *Concept Paper on the Revision of the Points to Consider on Xenogeneic Cell Therapy Medicinal Products (EMA/CHMP/165085/2007)*, London 2007.

Epstein, Steven. "The Construction of Lay Expertise: AIDS Activism and the Forging of Credibility in the Reform of Clinical Trials." *Science, Technology, & Human Values* 20, 4 (1995): 408-437.

European Environmental Agency, *Late Lessons from Early Warnings: The Precautionary Principle 1896- 2000*, Copenhagen 2001, <http://www.eea.eu.int>.

Ezrahi, Yaron. *The Descent of Icarus*. Cambridge MA: Harvard University Press, 1990.

Farrugia, Anthony, "When do tissues and cells become products? Regulatory oversight of emerging biological therapies", *Cell Tissue Bank* 2006; 7:325-335.

FDA, DHHS, PHS (Food and Drug Administration, Department of Health and Human Services, Public Health Services). *Draft Public Health Service Guidelines for*

Xenotransplantation. Federal Register Volume 61, Number 185 (Sept.23, 1996): 49919-49932.

FDA, Guidance for industry: source animal, product, preclinical and clinical issues concerning the use of xenotransplantation products in humans, April 2003,

<http://www.fda.gov/cber/gdlns/clinxeno.htm>.

FDA, Guidance for FDA reviewers and sponsors: content and review of chemistry, manufacturing, and control (CMC) information for human somatic cell therapy investigational new drug applications (INDs) - 4/9/2008

<http://www.fda.gov/cber/gdlns/cmcsomcell.htm>.

Fishman, Jay A. "SARS, Xenotransplantation and Bioterrorism: Preventing the Next Epidemic." *American Journal of Transplantation* 3, 8 (2003): 909.

Fishman, Jay A., and Clive Patience. "Xentransplantation: Infectious Risk Revisited." *American Journal of Xenotransplantation* 4 (2004): 1383-1390.

Fuller, Steven, *The Governance of Science*. Open Univ. Press, Buckingham 2000.

Funtowicz, Silvio O., Ian Shepherd, David Wilkinson, and Jerry Ravetz, "Science and Governance in the European Union: a contribution to the debate." *Science and Public Policy* 27, 5 (2000): 327-336.

Funtowicz, Silvio O., "Post-normal science. Science and governance under conditions of complexity". In: Tallacchini, M., Doubleday, R. (Eds.), *Science Policy and the Law: Relationships Among Institutions, Experts, and The Public*, *Notizie di Politeia* (2001), vol. XVII, 62, pp. 77- 85.

Funtowicz, Silvio O. "Models of Science & Policy: From Expert Demonstration to Post Normal Science." International Symposium: Uncertainty and Precaution in Environmental Management. Copenhagen (June 2004), <http://upem.er.dtu.dk/files/Funtowicz.pdf>.

Gainotti S, Moran N, Petrini C, Shickle D., "Ethical models underpinning responses to threats to public health: a comparison of approaches to communicable disease control in Europe", *Bioethics* 2008; 22:466-476.

Garkavenko O, Dieckhoff B, Wynyard S, et al. Absence of transmission of potentially xenotic viruses in a prospective pig to primate islet xenotransplantation study", *J Med Virol* 2008; 80:2046-2052.

Hacking, Ian, *Culpable ignorance of interference effects*. In: MacLean, D. (Ed.), *Values at Risk*. Rowman & Allanheld, Totowa, NJ 1986, pp. 136-154.

Hart, Herbert L.A. *The Concept of Law*. Oxford: Oxford University Press, 1961.

Hahn, Beatrice H., George M. Shaw, Kevin M. De Cock, Paul M. Sharp. "AIDS as a zoonosis: Scientific and public health implications." *Science* 287, 5453, Jan 28 (2000): 607-614.

Health Canada, Therapeutic Products Programme. *Survey on human organ donation and XT*. (December 17, 1999).

Health Canada, Therapeutic Products Programme. *Report from the Planning Workshop: Public Involvement on XT. Draft Proceedings*. Government Conference Centre, April 10 - 11, 2000, Ottawa, Ontario.

Health Canada. *Revised Fact Sheet on Xenotransplantation*. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/xeno_fact-fait_e.pdf

IHR, International Health Regulations (2005), Geneva, World Health Organization 2008. <http://www.who.int/csr/ihr>.

IOM (Institute of Medicine), Committee on Xenograft. *Transplantation: Ethical Issues and Public Policy*. Washington: National Academy Press, 1996.

Irwin, Alan, and Brian Wynne (eds.). *Misunderstanding science? The public reconstruction of science and technology*. Cambridge: Cambridge University Press, 1996.

Ivinson J. Adrian and Fritz Bach. "The xenotransplantation question: public consultation is an important part of the answer" *Canadian Medical Association Journal* 167 (2002), July 9, (1): 42-43.

Jasanoff, Sheila (ed.). *States of Knowledge: The Co-Production of Science and Social Order*. London-New York: Routledge, 2004.

Jonas, Hans, *The Imperative of Responsibility. Search of an Ethics for the Technological Age*. University of Chicago Press, Chicago 1985 (Frankfurt a.M. 1979).

Jones KE, Patel NG, Levy MA, et al., "Global trends in emerging infectious diseases", *Nature* 2008; 451:990-993.

Kobayashi, Takaaki, and Kazuya Yamanouchi. "Commentary: The Cartagena Protocol on Biosafety: implications for xenotransplantation." *Xenotransplantation* 13 (2006): 10-11.

Liberatore, Angela, and Silvio O. Funtowicz (Guest Editors). "Special issue on democratising expertise, expertising democracy." *Science and Public Policy* 3, 30 (2003).

Louz D, Bergmans HE, Loos BP, Hoeben RC., "Reappraisal of biosafety risks posed by PERVs in xenotransplantation", *Rev Med Virol* 2008; 18:53-65.

Martin, Brian. "Political refutation of a scientific theory: the case of polio vaccines and the origin of AIDS." *Health Care Analysis* 6 (1998): 175-179.

Martin, Martin. "Investigating the origin of AIDS: some ethical dimensions." *Journal of Medical Ethics* 29 (2003): 253-256.

McLean, A.M. Sheila, and Laura Williamson. *Xenotransplantation. Law and Ethics*. Aldershot UK, and Burlington VT: Ashgate Publishing, 2005.

McLean, A.M. Sheila, and Laura Williamson. "The demise of UKXIRA and the regulation of solid organ xenotransplantation in the UK." *Journal of Medical Ethics* 33 (2007):373-375.

NHMRC (National Health and Medical Research Council), Xenotransplantation Working Party. *Draft Guidelines and Discussion Paper on Xenotransplantation, Public Consultation 2002*, Commonwealth of Australia (2002).

NHMRC (National Health and Medical Research Council), Xenotransplantation Working Party. *Animal-to-human transplantation research: How should Australia proceed? Response to the 2002 public consultation on Draft Guidelines and Discussion Paper on XT*. Commonwealth of Australia (2003a), <http://www.nhmrc.gov.au/publications/pdf/e55.pdf>

NHMRC (National Health and Medical Research Council), Xenotransplantation Working Party. *Animal-to-human transplantation research: A guide for the community. Public consultation on XT 2003/04*, Commonwealth of Australia (2003b), <http://www.nhmrc.gov.au/publications/pdf/e54.pdf>

Noël, Luc, "The proactive role of the WHO", *Xenotransplantation* 2007; 14:348-349.

Nowotny, Helga, "Democratising expertise and socially robust science". In: Liberatore, A., Funtowicz, S.O. (Eds.), Special Issue on Democratising Expertise, Expertising Democracy, *Science and Public Policy* (2003), pp. 151-156.

Nuffield Council on Bioethics, *Animal-to-Human Transplants: the Ethics of Xenotransplantation*. London 1996.

OECD (Organisation for Economic Co-operation and Development). *Xenotransplantation: international policy issues*. Paris: OCDE Publications, 1999.

OECD/WHO, *Consultation on xenotransplantation surveillance: summary*, World Health Organization Department of Communicable Disease Surveillance and Response, WHO/CDS/CSR/EPH/2001.1.

O'Riordan, Timothy, Cameron, James (Eds.), *Interpreting the Precautionary Principle*. Earthscan, London 1994.

Palacios G, Druce J, Du L, et al., "A new arenavirus in a cluster of fatal transplant-associated diseases", *N Engl J Med* 2008; 358:991-998.

Pettigrew, Alan (Chief Executive Officer). Update on the National Health and Medical Research Council's Consideration of Animal-to-Human Transplantation (Xenotransplantation), Oct 1, 2004,

<http://www.nhmrc.gov.au/media/rel2004/xenocom.htm>

PHS (Public Health Services). *Guideline on Infectious Disease Issues in Xenotransplantation*. January 19 (2001), <http://www.fda.gov/cber/gdlns/xenophs0101.pdf>

Raffensperger, C., Tickner, Joel (Eds.), *Protecting Public Health and the Environment. Implementing the Precautionary Principle*. Island Press, Washington, DC. 1999.

Ravelingien, An. "The world is my patient." *Xenotransplantation* 12 (2005): 88-90.

Ravetz, Jerry R. (Ed.), Special Issue: Post-Normal Science, *Futures*, 1999, vol. 31.

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.

Robert J.S., and F. Baylis. "Crossing Species Boundaries." *American Journal of Bioethics* 3 (2003): 1-13.

Rothblatt, Martine. *Your Life or Mine. How Geoethics Can Resolve the Conflict Between Public and Private Interests in Xenotransplantation*. Aldershot UK, and Burlington VT: Ashgate Publishing, 2004.

Sanzenbacher R, Dwenger A, Schuessler-Lenz M, et al., "European regulation tackles tissue engineering". Letter to the editor. *Nat Biotech* 2007; 25:1089-1091.

Shrader-Frechette, K.S., *Methodological rules for four classes of scientific uncertainty*. In: Lemons, J. (Ed.), *Scientific Uncertainty and Environmental Problem Solving*. Blackwell, Oxford 1996, pp. 12- 39.

Smith, Roger, Wynne, Brian (Eds.), *Expert Evidence: Interpreting Science in the Law*. Routledge, London 1989.

Sykes, Megan, Anthony d'Apice, Mauro Sandrin. "Position paper of the Ethics Committee of the International XT Association." *Xenotransplantation* 10 (2003): 194-203.

Sykes, Megan, and Emanuele Cozzi. "Letter to the Editor: Xenotransplantation of pig islets into Mexican children: Were the fundamental ethical requirements to proceed with such a study really met?" *European Journal of Endocrinology* 154 (2006): 1-3.

Sykes, Megan, "2007 IXA Presidential Address. Progress toward an ideal source animal: opportunities and challenges in a changing world", *Xenotransplantation* 2008; 15:7-13.

Tallacchini, Mariachiara. "Commentary: Council of Europe Working Party on Xenotransplantation: state-of-the-art report on xenotransplantation (2000)." *Xenotransplantation* 8 (2001): 154-156.

Tallacchini, Mariachiara. "Epistemology of the European Identity." *The Journal of Biolaw & Business*, Supplement Series Bioethix (2002a): 60-66.

Tallacchini, Mariachiara. "Commentary: Regulatory issues in Europe and Canada." *Xenotransplantation* 9 (2002b): 371-373.

Tallacchini, Mariachiara. "Community and public participation in the risk assessment of experimental clinical trials." *Xenotransplantation* 14 (2007):356-358.

Tallacchini, Mariachiara. "Defining an appropriate ethical, social and regulatory framework for clinical xenotransplantation." *Current Opinions in Organ Transplantation* 13 (2008):159-164.

Transplantation Society and International Society of Nephrology, *The Declaration of Istanbul on Organ Trafficking and Transplant Tourism*, International Summit on Transplant Tourism and Organ Trafficking, Istanbul, Turkey, April 30-May 2, 2008. *Transplantation* 2008; 86:1013-1018.

Valdez-Gonzalez A. Rafael, Dorantes L.M., Garibay G.N., Bracho-Blanchet E., Mendez A.J., Davila-Perez R., Elliott Robert B., Teran L & White D.J.G. "Xenotransplantation of porcine neonatal islets of Langerhans and Sertoli cells: a 4-year study." *European Journal of Endocrinology* 153 (2005): 419-427.

Vanderpool, Harold Y. "The Regulation of Clinical XT in the United States." in *Trapianti e xenotrapianti. Aspetti etici e giuridici*, Edited by Domenico Palombo, Adriano Ramello, Paolo Tappero, Torino: Selcom Editoria, 2003.

Welin, Stellan and Mauro Sandrin. Symposium on Ethical Aspects of Xenotransplantation. *Xenotransplantation* 13 (2006): 500-501

WHA (World Health Assembly), *Organ and Tissue Transplantation*, Fifty-Seventh WHA57.18, 22 May 2004.

WHO (World Health Organization). *Xenotransplantation and Infectious Disease Prevention*, Geneva 1996.

WHO, *Xenotransplantation: guidance on infectious disease prevention and management*, World Health Organization: emerging and other communicable diseases, surveillance and control, WHO/EMC/ZOO/98.1.

WHO, *Guidance on xenogeneic infection/disease, surveillance and response: a strategy for international cooperation and coordination*, World Health Organization, Department of Communicable Disease Surveillance and Response, WHO/CDS/CSR/EPH/2001.2.

WHO (World Health Organization). *Ethics, access and safety in tissue and organ transplantation : Issues of global concern*, Madrid, Spain, 6-9 October 2003, Geneva 2004.

WHO, Global Consultation on Regulatory Requirements for Xenotransplantation -

Changsha, China. Co-organized with the Chinese Ministry of Health, the University of central-south China, and the International Xenotransplantation Association. <http://www.who.int/transplantation/events/en/index.html>.

Wonnacott, Keith, "Update on regulatory issues in pancreatic islet transplantation", *Am J Transplant* 2005; 12:600.

Wright, R. James Jr. "Alternative interpretations of the same data: flaws in the process of consulting the Canadian public about xenotransplantation issues" *Canadian Medical Association Journal* 167,1 (2002): 40-42.

Wright, R. James Jr. "Letters to the Editor." *Xenotransplantation* 10(2003): 475-476.

Wright, R. James Jr. "Public consultation on xenotransplantation." *Transplantation* 78 (2004): 1112-1113.

Wynne, Brian et al. Taking European knowledge society seriously. Brussels, Belgium: European Commission; 2007. http://ec.europa.eu/research/science-society/document_library/pdf_06/european-knowledgesociety_en.pdf. [Accessed 5 February].