ABSTRACT

The debate over the acceptability of clinical trials for xenotransplantation has focussed primarily on analyses of: 1) the medical benefits that might accrue to individual patients in need of organ replacement therapy; 2) the risk of introducing new infectious disease(s) into the population; and 3) the ability of public safety measures to minimize that risk. It is now generally accepted that if we are to proceed with xenobiotechnology, sufficient public safety measures must first be adopted. Despite the growing consensus as to the indispensability of scientific safeguards, few authors have questioned the ability of current or novel legal frameworks to sustain and enforce such safeguards. A legal analysis of the public health concerns must be incorporated into the debate if we are to ensure a thorough and responsible decision-making process.

ABRÉGÉ

Le débat sur l'acceptabilité des essais cliniques pour les xénotransplantations a essentiellement porté sur les analyses : 1) des bienfaits médicaux dont pourraient bénéficier les patients nécessitant une thérapie de remplacement d'organes; 2) des risques d'introduction d'une ou de plusieurs nouvelles maladies infectieuses au sein de la population; et 3) des capacités qu'ont les mesures de sécurité publique de minimiser ce risque. Tout le monde reconnaît aujourd'hui que si nous devons aller de l'avant avec la xénobiotechnologie, il faut tout d'abord mettre en place des mesures suffisantes pour protéger la sécurité publique. En dépit du consensus croissant pour reconnaître qu'il est indispensable de disposer de mesures de protection scientifiques, rares sont les auteurs qui doutent que les cadres juridiques actuels et nouveaux ne puissent pas faire appliquer pareilles mesures de protection. Il importe donc d'intégrer au débat une analyse juridique des préoccupations relatives à la santé du public si l'on veut s'assurer de suivre un processus de prise de décisions qui soit complet et fasse preuve de responsabilité.

Xenotransplantation and Public Health: Identifying the Legal Issues

Patrik S. Florencio, BSc, BCL 2,¹ Timothy Caulfield, BSc, LL.M.²

The seductive sirens of scientific progress are reverberating once again. Scientific and technological advances in xenotransplantation – the transplantation of cells, tissues, or organs from non-humans to humans – have fuelled a scientific debate over the potential risks and benefits of introducing this new biotechnology into clinical practice. Although xenobiotechnology promises tremendous medical benefits, it also carries with it an array of ethical and policy issues including: the monitoring and control of clinical trials, concern for animal welfare, the cost of the technology to the health care system, and, perhaps most importantly, the serious risk of introducing and spreading new infectious diseases into the population.¹⁻³ From the perspective of this paper, it is important to highlight that this latter issue – that is, the potential public health threat associated with xenobiotechnology – raises legal problems not normally encountered with most new medical technologies. It is essential that scientists and policy makers alike be aware that, in order to ensure the effective implementation of public safety measures, there are a number of legal concerns that need to be addressed prior to a decision to proceed with xenobiotechnology.

Xenotransplantation is a technology which would fall under the *Food and Drug Act* and, as such, its clinical application can certainly be regulated by Health Canada.⁴ While there are currently no regulations specifically

designed for xenotransplantation, Health Canada has been considering the issue.⁴ To date, however, there has been little discussion, particularly in Canada, about how the unique consent and public health law issues will be addressed. This article seeks to highlight these novel legal dilemmas in the hope of focussing future policy development.

Risks and benefits

Given the already extensive literature on the risks and benefits associated with animal-to-human organ transplantation,⁵⁻⁸ we provide only a brief synopsis here. The most commonly cited advantage to xenotransplantation is that, by offering an almost unlimited supply of organs for transplantation,⁹ it may provide a solution to the ongoing organ shortage. Apart from being an organ replacement therapy, xenobiotechnology also has the potential to assist patients suffering from many other illnesses such as hemophilia, AIDS, diabetes, Alzheimer's and Parkinson's diseases.¹⁰ For example, neural cells from pig fetuses could be transplanted into the brains of patients suffering from Parkinson's disease to replace degenerated tissue.¹¹

Although xenobiotechnology may offer substantial benefits to individual patients, it may also pose a significant threat to public health. Fear over the possible introduction of new infectious diseases intensified last year when scientists discovered a porcine endogenous retrovirus capable of replicating in human cells.¹²⁻¹³ This finding raises the question as to the number of as of yet unidentified infectious agents existing in pigs (and other animals) that could infect and cause disease in human cells. The potential of these retroviruses to cause human disease *in vivo* remains unknown. Nevertheless, it would be irresponsible to proceed with

1. From the Faculty of Law, McGill University, Montreal, QC, Canada.

2. From the Health Law Institute, Faculty of Law, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB

Correspondence: Timothy Caulfield, Health Law Institute, Law Centre, University of Alberta, Edmonton, AB, T6G 2H5, Tel: 403-493-8343, Fax: 403-492-9575, E-mail: tcaulfld@law.ualberta.ca

xenotransplantation until at least those dangers we have evidence for have been scientifically verified to be negligible.

There clearly exists sufficient evidence to suggest that a cautious approach should be adopted. Animals have frequently served as reservoirs for infectious agents capable of causing widespread devastation when transmitted to human populations.¹⁴⁻¹⁵ To give but one example, the deadly influenza epidemic of 1918, which is estimated to have killed between 20 to 40 million people in less than a year,¹⁶ is thought to have been caused by a porcine virus that was transmitted to humans from pigs.¹⁷ Xenotransplantation could expose patients to a host of new animal agents which could, in turn, be transmitted to the general public. As was recently pointed out, the inherent difficulty with xenotransplantation is that "the worst-case scenario (a major new epidemic) is extremely grave, and its likelihood is difficult if not impossible to quantify".¹⁸

The need for novel consent mechanisms and public safety measures

Consent

Unlike most medical interventions, where the advantages and disadvantages are confined to a given patient, xenobiotechnology may put the health or lives of third parties at risk. Because of the societal nature of these risks, extensive consent mechanisms and public safety measures must be a prerequisite to clinical trials. Indeed, as noted by a number of commentators, the tremendous potential risks associated with xenotransplantation arguably necessitate some form of "societal consent" or a "public mechanism for determining the acceptability of, and method of consent to, the risk."⁸⁻⁹ Meeting this requirement will not be easy. Because the traditional model of individualized informed consent would obviously not be practical on a societal level, an acceptable method of obtaining public consent is greatly needed. There are, however, numerous factors which will make obtaining this goal extremely difficult, including the scientific complexity of the topic, the context-dependent nature of the issues, and the inherent difficulty of designing a process or mechanism which can obtain an accurate picture of an entire community's opinion.

If, in fact, the societal consent hurdle can be passed, novel public safety measures will

be required to monitor for the potential spread of new infectious diseases. For example, there is an emerging consensus that both national and local xenotransplant registries will be necessary for the screening, discovery and detection of new infectious agents.^{3,5,19} For effective epidemiological surveillance, tissue sample duplicates should be obtained from xenotransplant candidates and should be archived at both national and local centres. These centres would also be responsible for the lifetime monitoring of patients and their close contacts. For example, in the United States, the Food and Drug Administration will require that "all future xenotransplant recipients [be monitored] for infectious diseases over their entire lifetime" and will prohibit recipients "and their close contacts from donating blood".¹⁹

The lifelong obligations associated with the recommended surveillance programs will create unique informed consent issues.¹⁹⁻²¹ Not only will patients need to understand the complexity and inherent risks of the procedure, they must appreciate the extent to which the necessary public safety measures will intrude upon their lives.⁹ Indeed, patients need to be informed that proceeding with a xenotransplant operation may involve future obligations such as possible quarantine and autopsy upon death. It must also be understood that the proposed public safety measures are essential as a lack of compliance would virtually eliminate our ability to detect and isolate new infectious agents. Surveillance is "the foundation for control of infectious diseases,"²² permitting "early detection and rapid response to epidemics."²³ As such, patients should be made aware that a lack of cooperation may even result in the use of coercive public health mechanisms (e.g., the invocation of public health legislation).

It is also important to note that these long-term obligations will make it impossible for patients to exercise their well-established legal right to withdraw consent for a health care procedure or participation in a medical experiment.²⁴ In fact, some commentators have gone so far as to suggest that xenotransplantation will "transform the nature of informed consent into a binding contractual agreement."¹⁹ While it is probably legally inaccurate to view any informed consent mechanism as creating a binding contract,

the required public health provisions will, on a practical level, have that effect. This would be a unique development in the area of consent law – particularly because the erosion of the patient's right to withdraw would be justified on the basis of third party interests.

Public Health Legislation

Current public health laws could be interpreted as applying to xenotransplant recipients who have an infectious disease which has the risk of becoming an epidemic. That is, public health laws could be used, in extreme cases, to detain and quarantine an infected patient.²⁵ However, existing legislation would require modification in order to compel the continued surveillance of asymptomatic individuals. In general, Canadian public health laws are designed to allow a response when an individual has a known infectious disease. There are no "monitoring" provisions. For example, sections 49 and 50 of Alberta's *Public Health Act* permit the apprehension of possibly contagious recalcitrant patients in order to "mitigate the disease or limit its spread to others."²⁵ In order to give legal backing to the proposed public safety mechanisms a similar provision would be needed to allow (in extreme cases) the monitoring of uncooperative xenotransplant recipients. Given our society's justifiable reverence for individual autonomy,^{24,26-28} there is no doubt that the proposed public safety measures could, in law, be construed as harsh. Nevertheless, policy makers must be made aware that proceeding with xenotransplantation, even at the stage of clinical trials, in the absence of legally robust public safety measures may be analogous to proceeding in the absence of any public safety measures at all. Therefore, before implementing this technology, we must be confident that the public safety measures we adopt are not only scientifically sound, but can be enforced through an applicable legal framework.

The limits of public safety measures

Even if appropriate public health regulations were developed, many of the risks associated with xenotransplantation would undoubtedly remain. First, surveillance is not the same as prevention. New infectious agents may spread and cause disease among human populations before surveillance

techniques have permitted their detection and isolation. Further, detection and isolation of infectious agents does not equate to the containment of their propagation at the human level. For example, "it has been virtually impossible to stem the spread of HIV among the general population in spite of the wealth of knowledge about HIV's transmission."³

Second, non-compliance with surveillance policies could become a common phenomenon. Indeed, patients may even seek to challenge the legality of the relevant public health provisions. Although xenotransplant candidates would have to agree to participate in all public health measures to be eligible for the transplant procedure, once the procedure has taken place and their health has improved, patients may feel that the restrictions on their rights are too onerous. The monitoring requirements will likely involve a curtailment of previously enjoyed rights and privileges. For example, the need to monitor close contacts infringes upon the right to confidentiality of one's medical records. The need for lifetime close monitoring and follow-up infringes upon mobility and liberty rights. The need for autopsy upon death may infringe upon freedom of religion. Would such restrictive public health laws survive a challenge based on the *Canadian Charter of Rights*?²⁹ There is no doubt that the needed regulations would give the state unprecedented power to monitor the health of individuals. Though Canadian courts have shown a willingness to carefully balance the mitigation of public health risks against individual rights (e.g., upholding legislation which requires blood donors and public health authorities to be notified of the donors' HIV positive status),³⁰ it is difficult to predict how a court would react to the extreme measures necessitated by xenotransplantation.

Third, as already noted, "modifying human behaviour has proven to be a daunting task, and a largely undesirable one, so the problem becomes enforcing the surveillance requirements if compliance is not provided voluntarily."³¹ On a practical level, implementing public safety measures may prove to be extremely difficult (e.g.,

people travel or move). Moreover, those legal remedies currently available, such as detainment or monetary fines, will not improve the quality of epidemiological data. Effective implementation of public safety measures necessitates that guidelines be complied with to the letter. Incomplete and unreliable data will greatly reduce our power to detect and contain outbreaks of infectious disease. In the end, we need to determine whether available, or even novel, monitoring techniques will be able to provide sufficient protection.

CONCLUSION

Everyone is in favour of medical progress that has the potential to save lives. However, where progress carries significant risks to public health, our first priority must be to those individuals who partake in the risk yet receive no direct advantages. Caution, prevention and responsible decision-making must serve as our guiding principles. By imparting a sense of urgency, the seductive sirens of scientific progress have "the power easily to tip the balance of careful public policy considerations."³² Prior to a decision to proceed with xenotransplantation, it is essential that we first scientifically determine what public health mechanisms are necessary in order to safely reap the benefits of this technology. Next, we must determine whether available or novel legal frameworks will enable the effective implementation of those mechanisms. Finally, we must consider the probable limitations of even the most carefully designed public health policy and whether we, as a society, are still willing to accept the residual risks.

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