
When Venturing into Foreign Parts...

The case for public consultation prior to any animal-human transplants

October 2007

Executive Summary

- Community involvement in setting a sound regulatory regime for the transplant of animal cells to humans is a pre-requisite to any trials being undertaken in New Zealand.
- Health Minister, Pete Hodgson, is to soon decide whether to approve a proposed clinical trial involving this technique – known as xenotransplantation.
- Melbourne-based company, Living Cells Technologies Ltd (LCT) is applying to conduct Phase I/IIa clinical trials of an experimental treatment that involves introducing pig cells into people with Type 1 diabetes. The pig cells are intended to produce insulin, in the hope that the treatment will reduce the dependency on insulin injections. Earlier this year, the company began trials in Russia, and is now seeking to conduct further trials in New Zealand.
- Transplantation of animal cells and organs into humans is widely understood to carry the risk of introducing novel infectious diseases into the human population. HIV, SARS and the worldwide influenza epidemic of 1918 illustrate the scale of harm that can result from viruses that cross from animals to humans. Decisions around the use of xenotransplantation thus involve balancing the health of the wider community against the merits of experimental procedures for treating individual members of the community.
- Australia believed that too little was known about the risks to the wider community, and introduced a 5-year moratorium on xenotransplantation in response. New Zealand decided to provide a legal framework so the technology can proceed subject to a set of high-level conditions that the Minister of Health must ensure are met. Among them, the minister must be satisfied that the procedure does not pose an unacceptable risk to the public and that the risks can be appropriately managed.
- Although Government enacted this gatekeeper legislation in 2002, key components of the overall regulatory framework have yet to be determined, and there has been no public consultation on how the public health risks are to be managed.
- Significant issues that have yet to be resolved, and have not been subject to consultation with the wider community include:
 - How to ensure patients can legally be monitored on a life-long basis for infectious diseases;
 - How and when independent facilities will be established for: a national register, biological sample archive, and monitoring;
 - Who bears liability for the costs associated with any novel disease outbreak; and
 - Ensuring consent to the risks involved is also obtained from the public.
- Government agencies such as the Health and Disability Commissioner have argued strongly that individual consent is not sufficient given the risks the technology poses. Instead collective consent, by means of further public consultation is required to resolve key policy issues before Government considers allowing xenotransplantation to proceed.
- Few clinical trials of xenotransplantation have yet been conducted anywhere in the world due to safety and efficacy concerns. With the current application, New Zealand would be placed at the

forefront, not only of conducting clinical trials, but also in having to devise ways to protect against and respond to the potential emergence of novel infectious diseases.

- There is no need to rush decisions about the regulatory framework as there are no timeframes under which the Minister is required to respond to the current application. The baseline requirements that must be agreed upon first have been well flagged in government documents for a number of years so there are no grounds for short-cutting due public process.

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1. New Zealand Considers Xenotransplantation Application

Melbourne-based company, Living Cells Technologies Ltd (LCT) is applying to conduct Phase I/IIa clinical trials in New Zealand of an experimental treatment (called “Diabecell”) that involves introducing pig pancreatic islet into Type 1 diabetics. The pig cells are intended to produce insulin, in the hope that the treatment will reduce the dependency of people with Type 1 diabetes on insulin-injections. Earlier this year, the company began trials in Russia, and is now seeking to commence further trials in New Zealand.

Under the Medicines Act, clinical trials involving xenotransplantation procedures must be signed off by the Minister of Health in addition to obtaining Medsafe and regional ethics committee approval.

Thus far, the Medsafe committee responsible for assessing applications for clinical trials involving xenotransplantation procedures has recommended that the trial be approved. This clearance was not originally expected. Updating the Minister of Health in October 2006, Ministry of Health officials predicted:

It is likely that the opinion provided by GTAC will be to defer Living Cell Technology Ltd’s application (or decline it on the grounds that the safety of the product has not been demonstrated or that the risks of the study are otherwise unacceptable.)¹

The regional ethics committee has also apparently cleared the application. The final decision now lies before the Minister, who can approve the application only if satisfied that:

- (a) the conduct of the procedure or class of procedure does not pose an unacceptable risk to the health or safety of the public:
- (b) any risks posed by the conduct of the procedure or class of procedure will be appropriately managed:
- (c) any ethical issues have been adequately addressed:
- (d) any cultural issues have been adequately addressed:
- (e) any spiritual issues have been adequately addressed.

(Medicines Act 1981, s96E(1))

The pending decision by the Minister – the first under the legislation – is a test case as to whether the conditions in s96E(1) provide sufficient safeguards for public health, particularly in view of the qualifiers “unacceptable risk” and “appropriately managed”, which implicitly set standards and will inform the nature of the tradeoff between individual benefits and public risk. This decision is also a test of the readiness of the regulatory regime for managing any risks, should an approval be forthcoming.

¹ Ministry of Health (27 October 2006) *Application for approval of xenotransplantation clinical trial*. Briefing to the Minister obtained under the Official Information Act.

2. Public Health Risks Associated with Xenotransplantation

Xenotransplantation is proposed as a possible means of treating human illness, by providing an additional source of transplant tissue (such as cells, organs) and/or providing new and potentially improved treatments. It is one of a range of experimental approaches, including stem cell research and gene therapy, currently being explored around the world.

Xenotransplantation procedures are associated with a number of risks. Some (such as the risk that the foreign tissue will be rejected) are restricted to the transplant recipients. Other health risks extend well beyond those who elect to receive the treatment. As the Ministry of Health has noted, “xenotransplantation is unlike other medical treatments as the risks posed are borne by both the transplant recipient and the community at large.”²

In particular, it is widely accepted that the transplantation of animal tissue into humans for therapeutic purposes carries with it the risk of introducing novel diseases to the human population.³ Xenotransplantation, the FDA explains, “provides a unique environment for adaptation and cross-species transmission of infectious agents”.⁴

A range of different types of infection may be transmitted from animals to humans. Many of these are known, and there are well-established methods for their detection. Others are not well understood and/or may not be detectable or known at the time.

In recent years, rare events with far-reaching consequences have occurred outside the limits of medical understanding. These include cross-species infections. It is believed that new variant Creutzfeldt Jacob disease is a human form related to the “mad cow disease” that broke out in the United Kingdom in the 1990s. The triggers and processes for the transmission are not yet well understood. However, as a result of the Mad Cow/vCJD link, the New Zealand Blood Service does not accept blood from individuals who have lived in certain countries where there is a risk of acquiring vCJD, including people who received blood transfusions in the United Kingdom from 1980 onwards. The Blood Service explains that “we simply do not know enough about these conditions and how they spread” and there are currently “no tests available to detect these conditions in blood donations.”⁵

One source of animal-human potential viral infection is a group of viruses called ‘endogenous retroviruses’ or ERVs. They are among those viruses that, due to their composition and position in the genome, may be transmitted undetected to transplant

² Ministry of Health (2001) “Application from Diatranz Ltd to conduct a clinical trial involving xenotransplantation”. Internal memo to the Director General of Health, July 11 2001.

³ US Food and Drug Administration (2003) *Guidance for Industry. Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans*, p. 2; World Health Organisation (2004) Fifty Seventh World Health Assembly, Resolution WHA57.18

⁴ US FDA (2002) *Guidance for Industry. Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts*. Draft Guidance, p. 3.

⁵ New Zealand Blood Service (2002) *Blood Safety. Why it all starts with the donor. Important information for all deferred donors*.

recipients, and potentially form new pathogens, that may in turn be transmitted to the wider community. As the Minister of Health noted in 2002:

Evidence indicates that xenotransplantation may be associated with an increased risk of transmission of a wide range of viral, bacterial, and other infections known to occur in the sourced animals. There is a theoretical risk that xenotransplantation could increase the risk of new infections jumping the species barrier from animals to humans.⁶

The recognition that ERVs carried by pigs (porcine endogenous retroviruses or PERVs) could be transmitted through xenografts first emerged in the 1990s. Evidence that PERV can infect human cells was demonstrated *in vitro*.⁷ That discovery was made when xenotransplantation clinical trials had begun and came as a surprise for some xenotransplant developers.⁸

It is generally thought that an ERV passing from transplanted pig tissues to create a novel infectious disease in humans would be a rare event. However, the consequences of such an eventuality are potentially severe:

If [...] an infected xenotransplant recipient spreads the infection to human contacts, society could be placed at risk of an epidemic from an unidentified pathogen, particularly if the clinical manifestations of the infection have a long latent period, as is the case for HIV-1.⁹

“[D]etermining the risk from endogenous retroviruses remains a daunting task”, the US Department of Health reports.¹⁰ Further, as the Health and Disability Commissioner cautioned in a submission to the Bioethics Council, one should not assume that because the likelihood of PERV-transmission to humans is low, the overall level of risk is low:

In my view, it is inappropriate to rely solely on the probability of the risk [...] This is extremely pertinent in the case of xenotransplantation, where although the risk of infection may be low, the consequences of infection would be significant. The probability of the risk eventuating must be weighed against the magnitude of the potential harm and the availability of other options.¹¹

Unknown unknowns

There is still a considerable lack of knowledge and understanding about the processes and conditions that lead to the activation of endogenous retroviruses. Among the

⁶ Minister of Health (2005) *First Reading of the Medicines (Specified Biotechnical Procedures) Amendment Bill*, April 12 2005.

⁷ US Department of Health and Human Services (2001) *PHS Guideline on Infectious Disease Issues in Xenotransplantation*, p. 6.

⁸ Interview with LCT chief scientist on Radio New Zealand *Nine to Noon*, August 30 2007.

⁹ Sykes M, d’Apice A and M Sandrin (2004) “Position Paper of the Ethics Committee of the International Xenotransplantation Association”. In: *Transplantation* 78 (8), pp. 1102-3.

¹⁰ *Ibid.*, p. 18.

¹¹ Health and Disability Commissioner (2005) Submission on the Bioethics Council discussion document, *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal-to-human Transplantation*, p. 4.

issues that remain unresolved include the existence and potential pathogenicity to humans of as yet undetected forms of ERV or other viral agents present in the pig genome. In addition, methods of detection may not be able to assist in identifying potential disease-causing agents.

The US Department of Health and Human Services notes that while there are diagnostic tests capable of reducing the risk of transfer of some infectious agents, other surprises in the form of as yet unknown viral agents capable of causing disease in humans may be present:

there is no doubt about the future emergence of unknown exogenous and endogenous infectious agents, for which no means of detection currently exist. [...]. As yet undiscovered, novel transmissible agents constitute a potential risk to the transplant recipients themselves, their intimate contacts, health care workers, and the population at large.¹²

Relying on existing knowledge to determine potential pathogens is not sufficient as xenotransplantation procedures create novel pathways of exposure:

it is difficult to predict the infectious agents that may cause disease in a recipient of a xenotransplantation product solely on the basis of naturally occurring zoonoses because there are major differences between normal contact of humans with animals and contact of a recipient with a xenotransplantation product.¹³

Examples of recent outbreaks of previously unidentified animal-human diseases include of severe acute respiratory syndrome (SARS) and Nipah and Hendra viruses.¹⁴

It is also conceivable that there could be a considerable time lag before clinical disease develops from a novel viral infection in humans. This could allow the infection to be spread widely before detection, as was the case with HIV/AIDS:

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 was recognised.¹⁵

Thus, the potential for a rare cross-species infection event to generate severe consequences is heightened by the risk of hitherto unknown viral agents to become the source of infection.

For such reasons, the Director-General of Health in 2001 declined an application to trial an earlier version of the treatment that LTC now seeks to trial:

¹² US Department of Health and Human Services, Secretary's Advisory Committee on Xenotransplantation (2004) *Draft Report on the State of the Science in Xenotransplantation*, p. 17.

¹³ US Food and Drug Administration (2003) *Guidance for Industry. Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans*, p. 2.

¹⁴ US Department of Health and Human Services, Secretary's Advisory Committee on Xenotransplantation (2004) *Draft Report on the State of the Science in Xenotransplantation*, p. 17.

¹⁵ US Department of Health and Human Services (2001) *PHS Guideline on Infectious Disease Issues in Xenotransplantation*, p. 16.

Given the uncertainty about the risk of transmission of infection with xenotransplantation, my advisors have advocated use of the precautionary principle, which requires that the regulator give the balance of doubt to protecting the community should there be uncertainty about the evidence of risk or benefit, when considering your application¹⁶

Progress in understanding

Understanding of ERVs and the risk of other porcine viral agents infecting humans is still emerging. It is now believed that there is potential to reduce the risk of infection of *some known* viral agents that could infect humans by breeding and containment strategies. PERV, however, are considered to be “embedded in the pig genome” and while there are theories that some forms of PERV have resulted from domestication and breeding¹⁷, it is not considered possible to breed these out of source animals using surveillance and screening programmes.¹⁸

Feral pig populations, it is believed, may be free of *known* viral agents. The source of cells that LCT is proposing to use in clinical trials is a feral pig herd from the Auckland Islands – one believed to have lived in isolation for around 200 years.¹⁹ The company states that while PERV is present in its source herd, the PERVs that have been found to be present are not transmissible.²⁰ However, the full set of conditions under which such hypotheses about the infectiousness of PERV might hold are not known.

Despite advances in piecing together a picture of ERV (and other infectious agents) that might cause harm in xenotransplantation, the state of knowledge is still fragmentary and emergent.

Lack of infection does not prove lack of risk

Some developers claim that theories about the risk of cross-species ERV infection have now been laid to rest as a result of testing of xenograft recipients:

Considerable recent evidence and monitoring now suggests that the concerns over PERV were unjustified.²¹

¹⁶ Letter from the Director-General of Health to Diatrantz Ltd, 11 07 01)

¹⁷ Elliott R B (2006?) “The uniquely useful biology of pigs abandoned on the Auckland Islands”. Presentation to the Royal Society of New Zealand, Auckland Islands Bicentennial. <http://www.rsnz.org/events/akl-isl/symposium/Elliott.pdf>

¹⁸ US FDA (2002) *Guidance for Industry. Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts*. Draft Guidance, p. 3.

¹⁹ Elliott R B (2006?) “The uniquely useful biology of pigs abandoned on the Auckland Islands”. Presentation to the Royal Society of New Zealand, Auckland Islands Bicentennial.

²⁰ Elliott R B (2006?) “The uniquely useful biology of pigs abandoned on the Auckland Islands”. Presentation to the Royal Society of New Zealand, Auckland Islands Bicentennial.

²¹ Living Cell Technologies (2006) “LCT reports positive meetings with FDA and MedSafe - preparing for cell therapy trials”. Company press statement, 16 February.

It is the case that since the potential for ERV infection was first postulated, testing for the transmission of ERVs to humans that have thus far received xenografts from pigs has not detected cross-species infection. However, **the absence of detected ERV transmission is transplant recipients to date does not constitute evidence of the absence of risk.** This is supported by the US Department of Health, which notes that the lack of detected PERV transmission may result from the fact that the relevant studies were “limited in the types of samples that could be evaluated”.²² Similarly, the International Association for Xenotransplantation also notes that such results “must be interpreted with caution owing to limitations in the transmissibility of PERV to nonhuman primates and because human data have not involved recipients with chronic immunosuppression or long-term survival of large amounts of porcine tissue.”²³

²² US Department of Health and Human Services, Secretary’s Advisory Committee on Xenotransplantation (2004) *Draft Report on the State of the Science in Xenotransplantation*, p. 20.

²³ Sykes M, Pierson III R N, O’Connell P, D’Apice A, Cowan P, Cozzi E, Dorling A, Hering B, Leventhal J and J P Soilillou (2007) “Reply to ‘Critics slam Russian trial to test pig pancreas for diabetes’”. In: *Nature Medicine* 13(6), p. 662. See also US Department of Health and Human Services: “Some viral infections [...], can remain in a latent state within the source animal, and potentially, in transplant recipients for prolonged periods, even decades. These persistent or chronic infections are of concern because they may not be recognized during the post-transplant recovery period.” (US Department of Health and Human Services, Secretary’s Advisory Committee on Xenotransplantation (2004) *Draft Report on the State of the Science in Xenotransplantation*, p. 19).

3. International Community Responds Differently to Xeno

Countries have responded differently to the concerns about the introduction of novel infectious diseases to the human population through xenotransplantation, and about the ability to prevent or manage such cross-species infections. Some have concluded that the risks are currently not manageable. In 2004, following public consultation, Australia introduced a federal-level moratorium on the clinical trialling of xenotransplantation procedures. According to the Australian National Health and Medical Research Council, such an approach is warranted as:

the risks of transmission of animal viruses to transplant recipients and the wider community have not as yet been adequately resolved.

Further,

xenotransplantation research is at an early stage and clinical trials in the foreseeable future are unlikely to be of significant benefit to the research participants.²⁴

The moratorium currently extends until 2009.

Other countries – including the US, Canada and the UK – have introduced specialist legislation that allow for case-by-case assessment of clinical trials involving xenotransplantation.

However, the mobility of people across borders means that the health implications of a national-level decision to proceed with xenotransplantation are not restricted to the citizens of that country alone. As the US Department of Health and Human Services notes, “because of the potential for secondary transmission of infectious agents, the public health risks posed by xenotransplantation transcend national boundaries”²⁵.

For this reason, regional and intergovernmental bodies have underscored the necessity for cooperation between countries to manage the risks of xenotransplantation. Resolution WHA57.18 under the World Health Organisation urges countries “to allow xenogeneic transplantation **only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place**” (our emphasis); to harmonize guidelines; and collaborate in “the prevention and surveillance of infections resulting from xenogeneic transplantation”.²⁶

Similarly, the Council of Europe has stated that: “no clinical xenotransplantation research should take place **unless sufficient efficacy and safety is demonstrated through pre-clinical research**” and acknowledged that while this might “considerably limit the number of xenotransplantations in the coming years”, such standards would “allow[] for an appropriate risk assessment”.²⁷

²⁴ Australian Government National Health and Medical Research Council (2005) Statement on Animal-to-Human Transplantation (Xenotransplantation) Research.

²⁵ US Department of Health and Human Services (2001) *PHS Guideline on Infectious Disease Issues in Xenotransplantation*, p. 3.

²⁶ World Health Organisation (2004) Fifty Seventh World Health Assembly, Resolution WHA57.18. Also see WHO (2001) *OECD/WHO Consultation on Xenotransplantation Surveillance: Summary*, pp. 35-6.

²⁷ Council of Europe (2003) Recommendation Rec (2003)10 of the Committee of Ministers to member states on xenotransplantation. Adopted June 19 2003.

4. The LCT Application: Test Case for Regulatory Regime

The New Zealand Government chose to adopt a framework that provided a route for xenotransplantation clinical trialling to proceed, subject to special gatekeeping legislation that requires sign-off from the Minister of Health and establishes certain hurdles. Legislation providing for this was enacted in 2002.

The application now before the Minister raises the prospect that New Zealand will become one of the very few countries in the world trialling xenotransplantation procedures. Entities such as NZBio believe that “New Zealand is well placed to lead such advancement”.²⁸ However, taking the lead would also place the New Zealand population in an experiment at the frontier of scientific understanding with little experience in managing the uncertainties and risks that xenotransplantation poses.

In addition to ensuring that the proposed research will be of benefit to the target community and that sufficient pre-clinical research has been undertaken to warrant the move to clinical trials, Government must be sure that public health will be protected. As the Health and Disabilities Commissioner noted, the latter is paramount:

the overwhelming principle should be that the potential and possible risks to public welfare should take priority over individual interests.²⁹

Specifically, Government must be convinced that:

- (a) the conduct of the procedure or class of procedure does not pose an unacceptable risk to the health or safety of the public;
- (b) any risks posed by the conduct of the procedure or class of procedure will be appropriately managed. (Medicines Act 1981, s96E(1))

The ability to manage the risks to the wider community from xenotransplantation clinical trials rests upon the strength of the New Zealand regulatory regime, and in particular:

- the ability to properly identify the risks; and
- the existence of appropriate infrastructure and legal arrangements to ensure the necessary monitoring and surveillance of trial participants.

Managing the risks is not simply a duty to New Zealanders, as any risks the New Zealand Government decides to take will be imposed on the international community.

4.1 An Incomplete Regulatory Regime

The current legislation covering xenotransplantation was enacted in 2002. It provides an overall framework for decision-making, but is only one element of the regulatory regime needed to manage the risks.

²⁸ NZBio (2005) Submission on Xenotransplantation, p. 9.

²⁹ Health and Disability Commissioner (2005) Submission on the Bioethics Council discussion document, *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal-to-human Transplantation*, p. 3.

In 2005, the Health and Disability Commissioner stated that

significant work [would] need to be undertaken to ensure that the risks are adequately managed and to reconcile the impact any such policy may have on any current areas of law.³⁰

The Commissioner expressed that view in a submission to the Bioethics Council, when it ran a public consultation process directed to addressing the cultural, spiritual and ethical issues that xenotransplantation raises. The Council explicitly excluded consideration of the safety and efficacy of the technology.³¹ Thus, it did not assess the desirability of proceeding with xenotransplantation; nor did it address New Zealand's capacity to manage the risks of allowing experimental procedures involving xenotransplantation to be trialled in the community.

Those questions have not subsequently been worked through in consultation with the public.

The following has been undertaken prior to consideration of the current application:

- **Review of GTAC guidelines for assessing applications:** GTAC has revised the guidelines for assessing applications for xenotransplantation clinical trials in the last year. These guidelines, which draw from the US FDA model, were not open for public consultation.³²
- **Advice sought from GTAC on the sufficiency of current law:** In 2006, the Minister of Health sought advice from GTAC on whether the law provided sufficient controls to manage the risks, and if additional controls were necessary, what these should be, and whether such controls should be in place before a clinical trial is approved.

Officials are now working through the detail in response to the LCT application but we are not aware of any public response from Government setting out the detail of a proposed regulatory regime for xenotransplantation. In the absence of such policy, the following identifies key components of a public health protection plan (as endorsed by the US, the WHO and OECD), and discusses how far these have progressed.

³⁰ Health and Disability Commissioner (2005) Submission on the Bioethics Council discussion document, *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal-to-human Transplantation*, p. 7.

³¹ "We are not directly concerned with assessing the safe and effectiveness of xenotransplantation, the extent of the public health risk it causes, the best ways of dealing with the risk [...]." Bioethics Council (2005) *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal to Human Transplantation. Discussion Document*, p. 10.

³² HRC Gene Technology Advisory Committee (2007) *Guidelines for Preparation of Applications Involving Clinical Trials of Xenotransplantation in New Zealand*.

4.2 National Registry and Biological Sample Archive

The WHO, the EU and health authorities in developed countries concur that certain facilities and provisions are key to protecting public health from the risks of novel infections. A national register and biological sample archive are among them, as they provide the basis for traceability in the event that a novel infection is detected. As such, they are essential not only to protect New Zealand citizens; they allow New Zealand to fulfill its responsibility to the international community in the event that it decides to take risks that affect other countries, many that are not yet prepared to take such risks and are considered by regional and international bodies as a prerequisite for any country contemplating allowing xenotransplantation clinical trials.³³

The importance of a register and sample archive has also been underscored by New Zealand advisory bodies. GTAC advised the Minister of Health last year that a centralised national registry and sample archive were “additional controls that must be in place before GTAC would approve any xenotransplantation clinical trial in New Zealand”³⁴. GTAC has insisted on the baseline importance of these facilities to managing the public health risk of xenotransplantation procedures. In recommending that an application by Diatrantz (the predecessor company to LCT) be declined, GTAC stated:

Even should the risk of transmission of retrovirus be deemed acceptable, the absence of the infrastructure of independent centralised data collection and analysis, and tissue storage facilities required by the international guidelines means that New Zealand could not adequately manage the risks of xenotransplantation at this point in time.³⁵

Further advice to Government has underscored that any such register and sample archive should be independent of developers, although clearing requiring their cooperation. In 2001 GTAC emphasised that the archive should be “independent”, while its advice five years later affirms that there should be a “centralised national” register and archive and that:

Ideally responsibility for the biological sample archive would lie with government to ensure its sustainability³⁶

GTAC further advised that “Government would need to consider the financial implications”³⁷ of maintaining such facilities.

³³ World Health Organisation (2004) Fifty Seventh World Health Assembly, Resolution WHA57.18; Council of Europe (2003) Recommendation Rec (2003)10 of the Committee of Ministers to member states on xenotransplantation; WHO (2001) *OECD/WHO Consultation on Xenotransplantation Surveillance: Summary*, pp. 35-6.

³⁴ GTAC (2006) “Advice of the Gene Technology Advisory Committee to the Minister of Health, Pete Hodgson”.

³⁵ Ministry of Health (2001) “Application from Diatrantz Ltd to conduct a clinical trial involving xenotransplantation”. Internal memo to the Director General of Health, July 11 2001.

³⁶ GTAC (2006) “Advice of the Gene Technology Advisory Committee to the Minister of Health, Pete Hodgson”.

³⁷ GTAC (2006) “Advice of the Gene Technology Advisory Committee to the Minister of Health, Pete Hodgson”.

Despite not addressing the science and safety issues surrounding xenotransplantation, the Bioethics Council also stressed that a register be “kept by the Ministry of Health”.³⁸

Such facilities have yet to be costed by officials, but we understand an indication of the expected cost is likely to feature in the advice to the Minister.

The proposed compromise: a company-run register

With such consistent advice, it is therefore surprising that GTAC has now recommended proceeding with the trial, and indicated that it would support the applicant undertaking those functions until such time as government-run facilities are set up. In a letter to LCT, the Interim Manager of Medsafe, Stewart Jessamine, advised that creating national facilities “would take some time and resource” and that as the study involved a small number of study participants, Medsafe would therefore support:

as an interim measure the Ministry of Health, with support from GTAC, seek assurance and written commitment from LCT that it will hold the patient information and tissue collected as set out in the study protocol and provide them on request of the Ministry of Health to an appropriate government administered register and tissue archive when they are established.³⁹

The company has indicated that on the recommendation of the ethics committee, it is now working with Medsafe and the Ministry of Health on the database for a register of transplant recipients and an archive for biological samples.⁴⁰

The importance of independence

This apparent, albeit interim, concession made by GTAC raises several concerns with respect to the level of public health protections that would accompany this trial. Discussing the importance of independence, Jessamine points to experiences in the US, which led health authorities there to conclude that full reliance upon industry reporting is unwise because xenotransplantation companies (particularly those funded by venture capital), were:

unwilling to publish negative findings or reports of serious adverse or unexpected outcomes of their research than the pharmaceutical industry, as such findings negatively effect the ability of a venture capital funded company to attract new investment.⁴¹

³⁸ Bioethics Council (2005) *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal to Human Transplantation. A Report on Xenotransplantation*, p. 34.

³⁹ Medsafe (2007) Letter to Living Cell Technologies, April 10 2007.

⁴⁰ Living Cell Technologies (2007) “LCT Receives Approval for Diabecell Clinical Trial in NZ”. Company announcement, September 12 2007.

⁴¹ Thompson L Human gene therapy: harsh lessons, high hopes. FDA Consumer magazine Sept/Oct 2000. Cited in Jessamine S S (2002) *Certain Peril? A Risk Evaluation of Xenotransplantation in New Zealand*, p. 118.

An additional risk is that the security of the data held privately cannot be guaranteed as the longevity of companies competing in high-risk fields is not certain.

“It is obvious”, Jessamine concludes, “that creating a system that is totally dependant on the study sponsor maintaining and reporting the results of research and tests of samples **cannot adequately protect the public health**”⁴² (our emphasis).

The acceptability of an interim measure turns on:

- the protocols developed between Medsafe and the applicant; and
- the timeframe Government has committed to for the establishment of Government-run registry.

The first of these have not been made known although, as indicated above, the applicant has announced that the protocols are being drawn up with Medsafe and the Ministry of Health.

4.3 Monitoring of Xenograft Recipients: Complex Legal Issues

Monitoring of experimental xenograft recipients is considered to be essential to public health protection. Life-long monitoring is considered appropriate⁴³, given novel infectious diseases may only emerge in the long-term. FDA guidelines outline minimum frequency of tissue-collection and testing of xenograft recipients, and the length of time (half a century) that samples must be maintained.⁴⁴

However, life-long monitoring of recipients raises some difficult legal issues in respect of the rights of the individual, on the one hand, and the rights of the community to health protection, on the other. This tension was clearly set out by the Health and Disability Commissioner in 2005. The conundrum is that the requirement for life-long monitoring could “potentially transform informed consent into a ‘binding contractual agreement’”. That, however, would breach the rights of the individual to withdraw consent to treatment, enshrined in the Code of Health and Disability Services Consumers’ Rights and the Bill of Rights Act 1990.⁴⁵

Conversely, if a binding commitment to life-long monitoring can not be obtained from research participants, an appropriate level of protection for the wider community cannot be secured. For example, it is conceivable that while at the time of approval, research participants are fully prepared to submit to routine testing, some might later grow to see this requirement as an unnecessary imposition and withdraw. Thus, relying upon the goodwill of research participants would not allow Government to require samples to be taken. As the Health and Disability Commissioner noted:

⁴² Ibid

⁴³ US Department of Health and Human Services (2001) *PHS Guideline on Infectious Disease Issues in Xenotransplantation*, p. 37.

⁴⁴ US Food and Drug Administration (2003) *Guidance for Industry. Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans*.

⁴⁵ Ibid

The problem [...] is how could we be sure that a recipient would honour any such restrictions, after many months or even years?⁴⁶

Of course, in the event that a research participant who has withdrawn from monitoring presents to a GP or hospital with an infection, reference to their medical records will then allow action to be taken. However, by the time that the person presents the novel disease may already have infected others in the community.⁴⁷

The above indicates the importance of working from worst case scenarios to ensure appropriate protection for the wider community. Relying upon voluntary participation in a life-long monitoring programme is simply not a sufficient response to such scenarios. It will not accord the community the protection it deserves. Further, New Zealand will not be able to assure the international community that it can provide the information that is required should a novel disease be transmitted beyond New Zealand's borders.

The Health and Disability Commissioner indicated that the apparent tensions between the rights of the individual and those of the wider community was an issue that needed to be resolved, and that, in his view, "legislation is the preferred method to regulate xenotransplantation, and specific xenotransplantation legislation is desirable."

GTAC's newly released guidelines indicate life-long monitoring⁴⁸, but Government has not yet indicated how it intends to legally resolve this issue. However it is a significant public policy issue that public law specialists, health professionals and patient interest groups among others would rightly seek to participate in determining.

4.4 Behavioural Requirements for Xenotransplant Recipients

Further provisions that also raise human rights and related legal issues are behavioural requirements of xenotransplant recipients that the WHO and some developed countries have determined may reduce the risk of novel disease transmission and allow for traceability should this occur.

Behavioural requirements specify what research participants should be told and what they must tell close contacts. For example, the US FDA informed consent guidelines recommend that recipients and, in some cases, their intimate contacts should be prevented indefinitely from donating whole blood and blood components.⁴⁹

⁴⁶ Health and Disability Commissioner (2005) Submission on the Bioethics Council discussion document, *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal-to-human Transplantation*, p. 7. Provisions under the Health Act 1953 (Part 3 Infectious and Notifiable Diseases) allow a medical officer to require a person to submit themselves for medical testing and to isolate them for the purpose of preventing the outbreak or spread of any infectious disease. However, these provisions are not likely to be appropriate to apply to routine monitoring of xenograft recipients.

⁴⁷ See for example, US FDA (2002) *Guidance for Industry. Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts*. Draft Guidance, p. 3; US Department of Health and Human Services (2001) *PHS Guideline on Infectious Disease Issues in Xenotransplantation*, p. 16.

⁴⁸ HRC Gene Technology Advisory Committee (2007) *Guidelines for Preparation of Applications Involving Clinical Trials of Xenotransplantation in New Zealand*, 7.2.

⁴⁹ For close contacts, there are some case-by-case decisions made in respect of certain tissues. US Food and Drug Administration (2003) *Guidance for Industry. Source Animal, Product, Preclinical*

Further surveillance measures that assist in identifying potential sources of risk and in the cooperation between countries include proposed border entry requirements under which xenograft recipients declare the treatment they have received.⁵⁰

Whether New Zealanders believe that the level of protection targeted by the FDA guidelines is sufficient remains to be seen.⁵¹ Government has chosen at this time to withhold the conditions that GTAC and the regional ethics committee have recommended be placed on the proposed trials, so these are not yet known.

Of note, however, is that in advice to the Minister last year, GTAC did not support compulsory border notification by xenotransplant recipients. Agreeing on the importance of traceability, it nevertheless reasoned that “this approach was likely to be limited by non-compliance”.⁵² This is a flawed logic for rejection of the measure. All laws are limited by non-compliance, but most would agree that this is not a reason to dispense with law. More surprisingly, GTAC did not urge the Minister to pursue other solutions to ensure that New Zealanders would be afforded some protection in the event that a visiting xenograft recipient developed a novel infectious disease. In the advice to the Minister, it appears, ‘that was that’.

4.5 Response in the Event of an Outbreak of a Novel Disease

GTAC advised the Minister last year that a public health protection plan should be in place “before xenotransplantation clinical trials commence”⁵³ and that the *National Health Emergency Plan: Infectious Diseases* could serve as a basis for developing a response. The committee also recommended that the Minister should still seek advice on whether additional measures would be necessary should a novel disease be detected in a xenotransplant recipient.

The plan should also, GTAC advised, be developed with a recognition of the international context of the risk (as xenograft recipients traveling to other countries could assist in the wider broadcasting of any disease). Planning should involve cooperation with the WHO, among other agencies.

The details of any such plan, should it exist, have yet to be released. Among the issues this raises, is who is to bear the costs of a response.

and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans, p. 53; and FDA (2002) *Guidance for Industry. Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts*. Draft Guidance, pp. 5-6;

⁵⁰ The Bioethics Council also recommended that such notification be required. Bioethics Council (2005) *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal to Human Transplantation. A Report on Xenotransplantation*, p. 36.

⁵¹ As noted earlier, GTAC has just released its revised guidelines, which are modeled on the FDA’s. HRC Gene Technology Advisory Committee (2007) *Guidelines for Preparation of Applications Involving Clinical Trials of Xenotransplantation in New Zealand*.

⁵² GTAC (2006) “Advice of the Gene Technology Advisory Committee to the Minister of Health, Pete Hodgson”.

⁵³ Ibid

4.6 Cost-benefit Analysis

This document does not develop a cost-benefit assessment for xenotransplantation or for the application currently before the Minister. However, such an analysis is crucial to developing credible public policy on xenotransplantation.

In 2005, the Health and Disability Commissioner indicated the scope of work that would be required to make such an assessment:

Whether xenotransplantation is justifiable on a cost-benefit analysis turns on whether the benefit of xenotransplantation outweighs the potential (even if slight) risk to the wider community from the spread of cross-species infections. Because of the potential global risks of xenotransplantation, the risk-benefit analysis has to extend beyond the national sphere of New Zealand.⁵⁴

In 2001, GTAC also indicated that assessing the harm should extend beyond the potential impacts to community health. It noted that should a novel disease emerge from xenotransplantation activities, such an event could also impact New Zealand's agricultural export economy. It also noted that in such an event, heavy demands would be placed on public health services:

Costs and Liabilities. Should transmission of PERV become a reality the potential economic effects on the economy of a country could be significant. Government services would be responsible for treatment of infected persons, which will have an impact on available health resources. Emergence of a new infection that was pathogenic in either native species, or our primary export market could also have a devastating effect on the New Zealand economy.⁵⁵

The potential impacts on agriculture identified above relate to the risk of so-called "reverse zoonoses": reinfection of the source species or other animals from a virus originating in the source species and undergoing modification in the human body. As a Ministry of Health official noted two years ago, this potential raises issues for New Zealand that are particularly sharp given our reliance on agriculture:

While the risk of reverse zoonosis⁵⁶ may be acceptable to an urban New Yorker, it may be totally unacceptable to a pastoral trading nation such as New Zealand.⁵⁷

We are not aware of any comprehensive policy analysis or modeling to assess the overall costs and benefits, and how these are distributed.

⁵⁴ Health and Disability Commissioner (2005) Submission on the Bioethics Council discussion document, *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal-to-human Transplantation*, pp. 2-3.

⁵⁵ Ministry of Health (2001) "Application from Diatrnz Ltd to conduct a clinical trial involving xenotransplantation". Internal memo to the Director General of Health, July 11 2001.

⁵⁶ A zoonosis is a disease communicable from animals to humans under natural conditions.

⁵⁷ New Zealand Herald (2005) "Raiding the piggy bank", February 1 2005.

4.7 Allocation of Potential Liabilities

The extent of the harm that could arise from the creation of a new disease in the human population raises questions about the sufficiency of current liability arrangements in respect of xenotransplantation.

According to Jessamine, current policy around clinical research “allows the sponsor company to take the gains if the transplant is successful [...] while the patient and health service provider take the physical and financial risks.”⁵⁸ This raises the question of whether the “pharmaceutical model of reimbursement of medical services to trial patients” is adequate given that this would not cover the risks in the event of a novel disease outbreak.

The need for a review of whether standard liability arrangements are sufficient for xenotransplantation clinical research was also identified by the Bioethics Council, which recommended that Government seek advice from the Law Commission. However, to our knowledge, there is no evidence on the public record that this recommendation was acted upon.⁵⁹

4.8 Guidelines for Assessing Clinical Trial Applications

One advance has been the revision of the guidelines by which GTAC assesses application to conduct xenotransplantation clinical trials. According to GTAC, these guidelines are modeled on those of the FDA, and were used, in draft form, to assess the LCT application.

Apparently, the guidelines were reviewed by the FDA, international experts and commercial parties involved in xenotransplantation. Surprisingly, however, they were not open for public consultation.

4.9 Regulatory Oversight and Community Participation

A common recommendation to Government has been that a special regulatory committee be established not only to assess applications to conduct clinical trials, but also to oversee the monitoring and reporting of these trials.⁶⁰

GTAC’s own advice to the Minister in 2006 was that no further bodies were required.

However, there are at least two significant limitations in continuing to rely upon GTAC.

⁵⁸ Jessamine S S (2002) *Certain Peril? A Risk Evaluation of Xenotransplantation in New Zealand*, p. 122.

⁵⁹ Bioethics Council (2005) *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal to Human Transplantation. A Report on Xenotransplantation*, p. 34.

⁶⁰ The Bioethics Council, for example, recommended that “The Government puts in place a monitoring body to oversee the development of the regulatory and decision-making framework, and developments in xenotransplantation technology.” Bioethics Council (2005) *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal to Human Transplantation. A Report on Xenotransplantation*, p. 31.

First, under current provisions, GTAC is responsible for assessing applications, but has no regulatory powers for monitoring the development of xenotransplantation in New Zealand and other countries.

A further limitation of GTAC that is evident in respect of the current application is that it “operate[s] in a closed fashion without either consumer representation or an ability to involve the public in their decision-making process.”⁶¹ Lack of provision for involving the public on individual applications could well become a source of ongoing tension, and undermine trust in decisions that are made by remote committees.

4.10 Requirements by Medsafe and Ethics Committee Unknown

It is possible that some of the above considerations have been addressed by GTAC and the regional ethics committee, and that mending these gaps will be a condition of approval. Further, the company has also reported that the proposed trial follows US FDA guidelines⁶² and that it has achieved a world first with its virology facilities.⁶³

These may be positive developments in themselves, yet it is of concern that an application is being considered before significant aspects of the xenotransplantation regulatory framework are in place. And, as noted above, there are indications that sub-optimal arrangements are considered sufficient by officials and advisory bodies when there is not an adequate basis for relaxing the best practice provisions to protect public health.

The fundamentals of a public health protection plan and broader policy on xenotransplantation should be subject to wider comment and finalised *before* any decision on any application is made.

⁶¹ Jessamine S S (2002) Certain Peril? A Risk Evaluation of Xenotransplantation in New Zealand, p. 117.

⁶² Living Cell Technologies (2007) “LCT Receives Approval for Diabecell Clinical Trial in NZ”. Company announcement, September 12 2007.

⁶³ Ibid

5. Due Process: No Transplantation Without Representation

Due to the parallel processing of the LCT application and the public policy issues, a central consideration must be one of how the Minister of Health is to take the decision.

The provisions regulating xenotransplantation clinical trials under the Medicines Act allow the minister to make a decision based exclusively on the Medsafe and the regional ethics committee assessments. Yet the minister can also deem that wider consultation would ensure that the necessary conditions set out in s96E have been satisfied. Section 96F allows the minister to establish a committee or seek the advice of an existing entity to address information gaps. At that point, wider consultation is required.

Opening this decision to wider consultation is desirable for several reasons. It is well established that risk management is not simply a technical exercise, but has social dimensions, particularly when proposed activities carry risks that extend beyond the individuals or groups who elect to participate. Expert bodies – such as Medsafe and the regional ethics committee – are clearly critical to risk management, but risk management is not their exclusive domain. That is, they are necessary, but not sufficient. The social dimension of risk management concerns both process and outcomes. It seeks to:

1. Involve those at risk in determining whether or how activities are to be approved;
2. Achieve broad social acceptance of the outcomes of decision-making; and
3. Secure trust in the regulatory system that carries to subsequent decisions.

5.1 Collective Consent: Those who bear the risks should be involved

As the community is the ultimate risk-bearer, public participation is warranted in determining the level of risk that the community is prepared to assume in order to gain access to the potential benefits of new technologies. This principle has added force when the risks associated with the procedures for treating individuals have implications not just for the health of the present community as a whole, but potentially also for future generations in worst case scenarios.

This was implicitly recognised by Ministry of Health officials when outlining the grounds for declining an earlier application to trial ‘Diabecell’:

The nature of these risks [of xenotransplantation] raises questions about the validity of seeking informed consent only from the transplant recipient when in fact the entire community may be at some risk.⁶⁴

The Health and Disability Commissioner echoed this view four years later.

⁶⁴ Ministry of Health (2001) “Application from Diatranz Ltd to conduct a clinical trial involving xenotransplantation”. Internal memo to the Director General of Health, July 11 2001.

The risk of xenotransplantation potentially include the whole community and, **as such, individual consent to xenotransplantation research and treatment is insufficient.** [...] There is an argument that if it is unethical to subject individual patients to procedures which they have not consented, then it is also unethical to subject the public to risks associated with xenotransplantation without having obtained **collective consent.**⁶⁵ (Our emphasis)

The Commissioner has emphasised that wide consultation with the public is required before xenotransplantation proceeds:

More public discussion is required to ensure that the public are informed and willing to take that risk before xenotransplantation proceeds.

And

Further consideration and debate needs to take place, and any development of xenotransplantation therapy in New Zealand should be put on hold until we can be more certain of its safety and efficacy [...]⁶⁶

In a discussion document from 2004, the Ministry of Health also recommended that the risks, efficacy and ethics of xenotransplantation must be publicly debated. Until that time, the ministry recommended prohibiting the use of xenotransplantation procedures:

Until these types of issues have been debated publicly, the Ministry considers that xenotransplantation should be placed in the proposed new section of the legislative framework that prevents new activities taking place until the implications of the technology have been fully considered.⁶⁷

The public response, as the ministry reports, supported prohibiting xenotransplantation *until* more was known about the safety of the technology and the regulatory regime put in place:

The majority of individuals and organisations who addressed this issue in their submission supported the addition of xenotransplantation to a proposed new list of prohibited activities in legislation **pending further work on its public acceptability, safety and also the development of any special requirements that may be needed if it is to be undertaken in New Zealand.**⁶⁸ (Our emphasis)

For the removal of any doubt, the Bioethics Council consultation cannot be considered to have dispatched Government's duty to consult, as the science, efficacy and safety of xenotransplantation were explicitly excluded from the scope of its considerations. (Noting this, the chair of the Bioethics Council working group is reported to have acknowledged that "the debate can't be had without discussing safety

⁶⁵ Health and Disability Commissioner (2005) Submission on the Bioethics Council discussion document, *The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal-to-human Transplantation*, p. 5.

⁶⁶ Ibid, pp. 3 and 7 respectively.

⁶⁷ Ministry of Health (2004) *Review of the Regulation of Human Tissue and Tissue-based Therapies. Discussion document*, p. 93.

⁶⁸ Ministry of Health (2004) *Review of the Regulation of Human Tissue and Tissue-based Therapies. Submissions Summary*, p. 114.

issues and without having some view about how effective xenotransplants are likely to be”⁶⁹.)

The current application

In the case of the current application, no provision has yet been made to allow the wider community to decide whether or on what terms the proposed experiment might be allowed to proceed.

Neither the GTAC nor the regional ethics committee assessments have been open to the public or allowed for input beyond that solicited by the committees. This, despite the operating principles of the Health and Disability ethics committees that assess applications for clinical trials, which state that “[a]s part of the accountability to the public they protect, it is desirable for the meetings of Ethics Committees to be open to the public”, their guidelines state.⁷⁰ (Our emphasis)

We understand that at least in respect of the ethics committee, this is due to the presence of commercially sensitive information in the application. There are obvious reasons for protecting commercially sensitive information; yet this should not be achieved at the expense of due process such that the wider community is excluded from decisions of this nature. Issues dependent on confidential information can, if necessary, be considered separately in closed session.

The ability of the public to participate meaningfully in complex issues

It might be argued that the issues around xenotransplantation are too complex and require a level of expert knowledge that effectively precludes the public from meaningfully participating in regulatory development. Under such reasoning, consultation becomes a costly, superficial public relations exercise delaying efficient policy development.

In 2001, GTAC considered otherwise. In its deliberations over an application by LCT predecessor company, Diatranz, it concluded that despite the complexities, the public should be consulted:

While there were questions asked about the ability of the public to meaningfully participate on a debate of such complexity, a consensus emerged that the public should be involved in debating both the safety of xenotransplantation and whether it would support the introduction of this technology to New Zealand⁷¹

Further, government-appointed committees are rarely the sum total of the country’s expertise in their respective areas. There is a wealth of knowledge and experience in the wider community, and a wide range of non-governmental organisations that can make significant contributions in assessing the economic, scientific, public health and

⁶⁹ NZ Herald (2005) “Ethical conundrums in pig-cell transplant debate”, May 21.

⁷⁰ New Zealand Health and Disabilities Committees (2004) *Manual for Chairpersons of Health and Disability Ethics Committees*.

⁷¹ Minutes of the fourth meeting of the Gene Technology Advisory Committee (April 23 2001)

legal implications of the technology. This is evident in the submissions to the Bioethics Council, if not evident in the Council's report.

5.2 Trust in the Regulatory System

Trust in decisions made by regulators is an important component of successful risk management. Trust is stronger where there is a sense of ownership of decisions.

In 2001, when the Director-General of Health was advised to decline the application, the importance of involving the wider public in decisions involving xenotransplantation was stressed. At that time, there were no such provisions in the Medicines Act for public consultation over clinical trial applications. Officials advised that failing to consult would not serve the interests of Government or regulatory credibility:

Such an approach poses an unacceptably high risk to Government, as xenotransplantation shares a number of risk factors or triggers with genetic modification likely to increase public concern and evoke fear or outrage. The decision to manage the risks of xenotransplantation without consultation creates the type of information vacuum, which amplifies consumer perception of risk.⁷²

With this first determination under the 2002 legislation, Government will be seeking to build support for, and trust in, the decision-making procedure amongst the wider community. Following the path of open consultation on this as a minimum condition to achieving such an outcome.

5.3 Managing the Government's Position as Funder and Regulator

In the case of the current application, Government's involvement is not solely that of regulator. State-funding of around \$3.2 million was invested in the company in 2006, through the Foundation for Research Science and Technology (FRST), as well as the New Zealand Trade and Enterprise (NZTE).⁷³

In cases where Government is both funder and regulator of an activity, it must be scrupulous in its regulatory process. This is particularly the case when the proposed activities involve considerable third party risks, as with xenotransplantation.

5.4 Infrastructure and Policy not in Place

Recent media coverage may have created an impression that the Minister's decision is a purely administrative exercise.

⁷² Ministry of Health (2001) "Application from Diatrnz Ltd to conduct a clinical trial involving xenotransplantation". Internal memo to the Director General of Health, July 11 2001.

⁷³ Living Cell Technologies (2006) "Living Cell Technologies awarded NZ\$2.7m investment through the Foundation for Research, Science and Technology". Company press statement, 26 April 2006; Living Cell Technologies (2005) "LCT awarded \$480,000 grant by NZTE". Company press statement, December 15 2005.

LCT anticipates the NZ Minister of Health will accept the approvals from the regulatory bodies in the next few weeks, which will enable clinical trials of DiabeCell® in type I diabetes patients to commence in NZ in the last quarter of the 2007 calendar year.⁷⁴

While on its website, for example, the company claims:

LCT will conduct two type I diabetes clinical trials in 2007. [...] The trials will be conducted in Auckland, New Zealand and Moscow, Russia, under strict regulatory guidelines and monitoring protocols.⁷⁵

In the face of suggestions that ministerial approval is certain and imminent, the call for a public process may appear unnecessary, burdensome on the company and not sufficiently mindful of those wishing to take part in the proposed trial.

We also understand that GTAC took seven months to consider the application and sought the advice of overseas experts.⁷⁶ The final assessment recommending approval and proposed conditions for the trial are not being released to the public at this stage.

However, the application before the minister is the first under the current legislation. It is being considered at a point when key components of public health protection, both legal and infrastructural, have yet to be put in place. There are indications that interim fixes are being developed, should the trial be approved.

The current decision however is not simply a decision about the LCT application to conduct clinical trials; it also requires significant decisions about the xenotransplantation regulatory regime and the level of public health protection this will afford. Elements either still to come into place or be released include:

- National registers and biological sample archives;
- Public health protection plan in the event of the emergence of a novel infection; and
- Cost-benefit analysis, and the allocation of potential liabilities arising from the trial.

Even assuming that some of the above has been addressed but not made public, the proposed management regime should be subjected to wider consultation.

⁷⁴ Living Cell Technologies (2007) "LCT Receives Approval for DiabeCell® Clinical Trial in NZ". Company press statement, September 12.

⁷⁵ <http://www.lctglobal.com/diabecell.php>

⁷⁶ Living Cell Technologies (2007) "Regulatory review allows LCT clinical program to proceed". Company press statement, April 10 2007.

6. Requirements Going Forward

The application by LCT to conduct xenotransplantation clinical trials comes at a point when key components New Zealand's regulatory regime have not yet been resolved. Since Government introduced legislation allowing for applications to be considered, progress building the regulatory regime has been slow and piecemeal. This may be due in part to the low level of experimental xenotransplantation activity in New Zealand and the considerable demands on health policy-makers in general. Whatever the cause, it remains the case that New Zealand is on the brink of considering whether to approve a clinical trial without the necessary infrastructural and legal arrangements in place.

Many observers, including the Health and Disabilities Commissioner and other advisory bodies, have stressed the need for consultation on issues of safety, as well as cultural, ethical and spiritual concerns. Advice to Government has also emphasised that certain measures must be in place before a trial is approved. Announcing these measures at the same time as a decision to approve is a nominal fulfillment of that conditionality.

Advising the minister on the progress of the application last year, officials then predicted that GTAC would defer or even decline the application.⁷⁷ While the committee ultimately decided to recommend approval, Government should not be tempted to rush decisions about the regulatory regime. Indeed, there are no timeframes under which the minister is required to respond under Part 7A (although it is reasonable to expect that the decision be taken in a timely manner). This allows Government to open consideration of the above issues to wider consultation before a decision on the current application is taken.

The Health Minister must be satisfied that the clinical trialling of xenotransplantation procedures does not pose an unacceptable risk to the public and/or that the risks can be appropriately managed. (s96F)

As a first step, the minister will need to use the powers available under S96F to investigate whether New Zealand's regulatory regime is sufficiently prepared to manage the risks arising from xenotransplantation clinical trials, and he should allow for due public consultation on those matters, followed by development of the outstanding regulatory components.

At that point, the minister can then turn to the application before him to determine whether New Zealand is able to manage the risks that would attend the proposed trial.

⁷⁷ Ministry of Health (27 October 2006) *Application for approval of xenotransplantation clinical trial*. Briefing to the Minister obtained under the Official Information Act.