DISCUSSION PAPER

XENOTRANSPLANTATION
A REVIEW OF THE PARAMETERS, RISKS AND BENEFITS

NHMRC 2009
Preface

Xenotransplantation is the use of live cells, tissues, or organs from a non-human animal source transplanted or implanted into a human, or used for ex vivo contact with human body fluids, cells, tissues, or organs that are subsequently given to a human recipient (CDC 2001).

In early 2001, NHMRC established a Working Party on Xenotransplantation (XWP) to investigate whether clinical research into animal-to-human transplantation should be allowed in Australia. An animal issues subcommittee was also established to assist the XWP with issues of animal ethics, animal welfare and regulating the use of animals in xenotransplantation research. In September 2004, following two rounds of public consultation and a series of public meetings, the XWP provided Council with its final advice, recommendations and draft guidelines on xenotransplantation clinical research in Australia, should it be recommended that this type of research go ahead.

The XWP proposed that guided animal-to-human transplantation clinical research should be permitted under a strict regulatory system. Specifically, clinical trials involving extracorporeal devices, use of co-cultured tissue or human cells and cellular transplants such as islets could proceed under careful auspices. Among other recommendations, the XWP recommended that a broadly representative national committee be established for the oversight of research into animal cell therapies and animal external therapies. No clinical trials would be permitted unless the committee and Australia’s Therapeutic Goods Administration (TGA) were satisfied that certain conditions were met. Animal organ transplants were not to be considered for another five years.

Council considered the advice provided, and in December 2004 determined that there should be no clinical trials in Australia involving animal organ transplants, animal cell therapies or animal external therapies except procedures utilised in current clinical practice that involve the culturing of human cells on feeder layers of irradiated mouse cells. Furthermore, Council concluded the risks of transmission of animal viruses to transplant recipients and the wider community had not been adequately resolved and xenotransplantation research was at an early stage, therefore clinical trials in the foreseeable future were unlikely to be of significant benefit to research participants.

This discussion paper will examine a number of issues relevant to xenotransplantation in the Australian setting to inform Council’s review of its 2004 recommendation on xenotransplantation in Australia. In accordance with Council’s view at the time that:

- the risks of transmission of animal viruses to transplant recipients and the wider community had not been adequately resolved; and
- xenotransplantation research was at an early stage therefore clinical trials in the foreseeable future were unlikely to be of significant benefit to research participants;

these issues will be specifically addressed. Predominantly, literature published from 2004 onward has been considered, on the assumption that literature published prior to this was considered by NHMRC as part of the current recommendation.

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1 Animal cell therapies are procedures in which cells from nonhuman animal source are transplanted or implanted into a human patient to compensate for deficient functioning of the patient’s own cells.
2 Animal external therapies are procedures that occur outside of the body, in which cells or fluids from the patient are perfused through or cultured with animal cells and returned to the patient.
3 Animal organ transplants are procedures in which whole organs (eg a heart, kidney) or tissues (eg skin) from a non human animal source are transplanted or implanted into a human patient to replace a diseased organ.
1. Introduction

Transplantation between members of the same species is known as allotransplantation, and in humans this is a very successful way to treat a variety of illnesses. However, very few human tissues, cells or organs are available for transplantation and many patients who could benefit from a transplant wait in vain for a suitable donor. This is not limited to Australia but occurs worldwide, including in countries with high organ donation rates.

Xenotransplantation may provide a solution to the shortage of allogenic human organs and tissues available for the treatment of various life-threatening diseases. Transplant specialists are therefore considering animals as possible donors for human transplantation. The greatest benefit of animal-to-human transplantation would be a potentially unlimited supply of cells and tissues for use in humans.

Some animal devices, such as pig heart valves, have been used in humans for many years. These devices are treated so they contain no living cells. Xenotransplants differ from these devices in that they are alive and can perform the same functions as the organ, tissue or cells that they replace.

A major concern in xenotransplantation is that disruption of anatomical barriers combined with the routine immunosuppression of recipients, may facilitate interspecies transmission of xenogeneic infectious agents. The term ‘xenosis’ (also ‘zoonosis’ or ‘xenoozoonosis’) was generated to reflect the unique epidemiology of infection resulting from organisms carried by xenogeneic tissues.

In theory, porcine pathogens and even non-pathogenic microorganisms may adapt to the immunocompromised human recipient causing disease, or recombine with human viruses creating new pathogens. Xenotransplantation may therefore be the starting point of a threat to the health of not only the xenotransplant recipient, but those in close contact with the recipient as well, due to the possibility of infection with unknown pathogens.

Research undertaken in the last five years suggests that whole organ xenotransplantation remains distant despite significant progress in xenograft survival in primate models. Further research will be required to overcome immunological hurdles associated with whole organs xenografts. Greater progress has been made in cellular xenotransplantation involving porcine pancreatic islets. The immunological, microbiologic, and physiologic barriers are being addressed in pre-clinical models. Ultimately, these will need to be addressed in well designed clinical trials involving cell and tissue xenografts.

2. Early attempts at animal-to-human transplantation

The use of animals as cell and tissue donors for humans is not a novel idea. The first documented attempt at engrafting animal tissue was in 1667 when Jean Babtiste Deny transfused sheep blood into a human. Early attempts in solid organ xenotransplantation were made by Matheiu Joubolay, who performed two kidney xenografts in 1906. Joubolay connected a pig and a goat kidney respectively, to the circulation of two patients with renal failure. The kidneys functioned only briefly.

The lack of success was discouraging and further attempts of xenotransplantation were not made until the 1960s and 1970s when scientists gained a better understanding of the immunology associated with transplantation. Studies in humans during this time included
transplantation of baboon and chimpanzee kidneys into several patients in the United States (US). One of six patients who received a chimpanzee kidney, a 23 year old woman, survived for nine months after the transplant (cited in Boneva & Folks 2004). Her death resulted from an illness of an undetermined cause. A post mortem examination revealed the xenograft appeared normal at the time of her death. Whilst this case may have been encouraging, other attempts during this period were less successful and most patients died with minutes, hours or days after receiving the xenotransplant.

A well publicised xenotransplant was performed in the US by Dr Leonard Baily in 1984. The procedure involved the transfer of a baboon heart into 12-day-old “Baby Fae”, born prematurely and diagnosed with hypoplastic left-heart syndrome. Baby Fae died of progressive graft necrosis 20 days after receiving the xenotransplant.

In the 1990s, two further attempts of xenotransplantation were made by a team of surgeons in the US where two AIDS patients coinfected with hepatitis B received baboon liver transplants. Transplanted livers would normally be at risk of reinfection with hepatitis B and AIDS in patients where the disease manifests, however baboons are not susceptible to HIV or hepatitis B. Therefore, xenotransplantation with a baboon liver offered a potential advantage over allotransplantation. The patients survived 24 and 70 days respectively. The recipients died of complications of immunosuppression including Aspergillus infection and developed transient activation of both baboon and human cytomegalovirus.

More recently, clinical research into xenotransplantation has focussed strongly on cellular transplants, concentrating efforts on demonstrating safety and efficacy through tissue and cell xenotransplants. Organ xenotransplant research has also been active, but lags behind at the preclinical level.

3. Source Animals

Non-human primates are not suitable as source animals for organs and cells for several reasons. Due to the size of the litter, endangerment of species and logistical difficulties in creating a sufficient number of specific pathogen-free (SPF) animals the supply would not suffice. Most likely, baboons would have been considered a primary source however they carry viruses such as B virus which are known to cause lethal infections in humans. The ethical considerations associated with higher primates are unlikely to be overcome and the size of the organ is not comparable with humans; for example a non-human primate heart is inadequate to support human circulation.

Pigs are the most favoured donor animal for human transplants primarily because porcine organs are similar to humans’ in size and physiology and the supply is potentially unlimited. Other benefits include a short generation interval and high number of progeny and pigs can be manipulated genetically to enhance the quality of the tissue donor. Furthermore, maintenance under hygienic conditions is feasible allowing for SPF breeding and exclusion of bacteria and other microorganisms (gnotobiotic) (Dieckhoff et al. 2008).

4. A glimpse of recent studies in humans

4.1. Pancreatic islet transplants for type 1 diabetes.

4.1.1. Recent studies

The global experience with clinical trials involving xenotransplantation is limited and the focus has been primarily on porcine pancreatic islet cells for the treatment of type 1 diabetes.
To date, results of six clinical trials involving xenotransplantation of islets have been published in peer reviewed journals or presented at scientific congresses. These trials are summarised in Table 1.

Table 1  Summary of studies published or presented at conferences which involve the xenotransplantation of porcine islet cells into humans with type 1 diabetes.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of Patients</th>
<th>Country</th>
<th>Year(s)</th>
<th>Results</th>
<th>Principal Investigator</th>
</tr>
</thead>
</table>
| Foetal porcine islets transplanted into kidney capsule or via intraportal infusion | 10                 | Sweden         | 1979 - 1993 | • No porcine C-peptide detected in plasma  
• Urine C-peptide detected for 460 days after transplant in 1 patient  
• Kidney biopsy showed viable cells containing insulin and glucagon. | C. Groth              |
| Alginate-encapsulated neonatal porcine islets transplanted into peritoneal cavity | 2                  | New Zealand    | 1996        | • Temporary reduction in exogenous insulin requirements  
• Urinary C-peptide production detected  
• Temporary decreased glycosylated haemoglobin | R. Elliot            |
| Neonatal porcine islets injected into the hepatic artery                  | 22                 | China          | 1999-2005   | • In some patients temporary reduction in exogenous insulin requirements  
• Porcine C-peptide detected | W. Wang              |
| Neonatal and sertoli cells combined within a subcutaneous autologous collagen-covered device and transplanted into the anterior wall of the abdomen | 12                 | Mexico         | 2001-2005   | • Reduction in exogenous insulin requirements for up to 4 years in some patients  
• No detection of porcine C-peptide  
• Glucagon and insulin positive cells detected | R. Valdés-González  |

In the first trial listed in the table (Groth) a decrease in insulin requirement was not observed. However, the trial was successful in demonstrating safety and the survival of transplanted porcine cells within the human body for several months.

There have however been a handful of studies which have reported a temporary decrease in exogenous insulin requirements post xenotransplantation. For example, Elliott’s studies detailed transplanting encapsulated neonatal porcine islets into the peritoneal cavity of two patients in 1996. The clinical significance of this study was an observed decrease in exogenous insulin requirement (up to 34% reduction) and detection of urinary porcine C-peptide excretion for up to 14 months in both patients. Graft function for up to 2 years after the procedure was evident with the effects disappearing at 27 months post-transplant. Upon follow up no evidence of PERV proviral DNA or RNA was detected. Furthermore, in a 9.5 year follow up, one of the patients had capsules that were still intact containing small amounts of functional porcine islets (Elliott et al. 2007).

Wang reported a pilot trial of neonatal porcine islets in humans in China from 1999 to 2005. The trial involved 22 type 1 diabetic patients who were injected with porcine islets into their hepatic artery. It was reported that exogenous insulin requirements were temporarily reduced
by 33-62% for up to 1 year post-transplant. One patient became insulin independent for a few days following the procedure. Porcine c-peptide was also detected. Again, no evidence of PERV infection was found in any of the participants (Wang 2007).

In Mexico, Valdes-Gonzalez and colleagues reported a trial in which 12 non-immunosuppressed adolescent diabetic patients received subcutaneous transplantation of collagen coated devices containing neonatal porcine islets and Sertoli cells. Upon follow-up, 6 of the patients demonstrated a 50% or greater decrease in insulin requirements, with the other half showing only a slight reduction. Two patients became insulin independent temporarily. Surprisingly, porcine C-peptide was not detected in the urine of any patient and PERV infection was not evident (Valdes-Gonzalez et al. 2005).

The Valdes-Gonzalez trial met with significant criticism. Following publication of the study, several journal articles criticising ethical aspects of the trial were also published (Sykes & Cozzi 2006; IXA Council & Ethics Committee 2006).

4.1.2. Current studies

Living Cell Technologies (LCT) is a publicly listed company incorporated in Australia and listed on the Australian Securities Exchange.

The company commenced a Phase I/IIa clinical trial involving the transplantation of DIABECCELL®, a product comprising encapsulated porcine islets for type 1 diabetes in Russia in June 2007. It is intended that the porcine cells will produce insulin, reducing the need for daily insulin injections in diabetic patients. In a press release dated 5 May 2009, LCT reported insulin independence in two of the seven patients who received DIABECCELL® as part of the trial. No adverse effects have been reported. At present, the trial is ongoing therefore results have not yet been published in a peer-reviewed journal. The safety of the islets preparations has not been established by external investigators.

In 2008 the then New Zealand Health Minister, the Honourable David Cunliffe, approved an application from LCT to conduct a Phase I/IIa clinical trial of DIABECCELL® in New Zealand. The Minister of Health’s approval was subject to conditions, including completion of an international peer review to determine the adequacy of LCT’s application, risk management and safety procedures in safeguarding the health and safety of the trial’s participants. Subsequent to the peer review, the New Zealand’s current Minister of Health, the Honourable Tony Ryall authorised commencement of LCT’s trial. The trial, which is limited to patients with poorly controlled diabetes commenced on 23 July 2009. A total of eight patients will participate in the trial conducted by Dr John Baker, Clinical Director and Diabetes Physician at Middlemore Hospital, Auckland.

DIABECCELL® is supplied by LCT’s manufacturing unit which is Good Manufacturing Practice (GMP) certified by the New Zealand government regulator Medsafe. The trials described above are conducted without the use of immunosuppressants, achievable because the porcine islets are encapsulated and thus not recognised as foreign material when transplanted into the patient. Furthermore, LCT has lessened the risk associated with viral transmission by sourcing a unique breed of pigs (originating from Auckland Island) which are thought not to secrete PERVs and are not genetically modified. The pigs meet the definition of ‘null’ pigs and consequently the US Food and Drug Administration (FDA) requirements for pigs suitable as a source of tissue for human therapeutics. These safety parameters have not been confirmed by other investigators. It is also unknown whether the
‘null’ status for porcine retroviral viral transmission is a permanent characteristic in tissues from these or other swine herds. (Martin et al. 2006).

4.2. Extracorporeal liver system for acute liver failure

In 2000, Levy et al. published results of two successful cases of extracorporeal perfusion of a transgenic pig liver in patients awaiting allotransplantation for fulminant hepatic liver failure. The pig livers were transgenic for two human genes specifically, therefore reducing or eliminating the rejection which is inherent in pig-to-primate xenotransplants.

The two patients were successfully bridged to allotransplant by porcine livers perfused via an extracorporeal circuit for 6.5 hours and 10 hours respectively.

No circulating PERVs have been detected in either patient. Surveillance of both patients continues.

The published results of the study are provided at Attachment A.

In a separate study, US based Cedars-Sinai Medical Center (CSMC) conducted a 3 year Phase II/III prospective, randomised, controlled trial to examine the effects of an extracorporeal bioartificial liver treatment on survival in patients with acute liver failure. The bioartificial liver system, named ‘HepatAssist’ was developed by a group at CSMC. It comprised of porcine hepatocytes housed within a hollow-fibre bioreactor. In the trial, blood was drawn from patients and filtered through the HepatAssist. The blood was cleaned and nourished within the various components of the bioreactor and once detoxified, the blood was returned to the patient. This occurred at the same rate as blood was being drawn out.

The study included 147 patients who suffered from fulminant or subfulminant hepatic failure and 24 patients whose livers had failed post transplantation. Patients were enrolled in the trial at 20 different centres across Europe and the US from 2001 to 2004. Of the 174 patients in total, 85 received HepatAssist liver treatment while 86 received standard supportive care.

For the entire patient population, survival at 30 days was 71% among the HepatAssist group, compared with 62% for those receiving traditional care. Analysis of results amongst only the 147 patients with fulminant or subfulminant hepatic failure revealed that the HepatAssist provided a 44% reduction in mortality.

The published results of the study are provided at Attachment B.

4.3. Foetal Porcine cells in Parkinson’s disease and Huntington’s disease

In 2000, Fink et al. reported the outcomes of an open label Phase I clinical trial where porcine foetal neural cells were grafted into Parkinson’s disease and Huntington’s disease patients in an attempt to deliver healthy neurons to the central nervous system. The trial was intended to establish safety and efficacy in xenotransplantation of porcine foetal neural cells into humans.

Twelve patients with idiopathic Parkinson’s disease and twelve patients with Huntington’s disease underwent unilateral implantation of foetal porcine ventral mesencephalon (NeuroCell-PD) and striatal tissue (NeuroCell-HD), respectively.
At twelve months post transplantation, a clinical improvement of 19% was observed in the total UPDRS (Unified Parkinson’s Disease Rating Scale) score in the off state (more than 12 hours since last medication) in ten of the Parkinson’s disease patients. Three patients improved more than 30%. One patient died as a result of a pulmonary embolism 7.5 months after the transplant. An autopsy revealed porcine foetal ventral mesencephalon cells, some of which were dopaminergic (related to dopamine cells) at the graft site in the putamen.

All twelve Huntington’s disease patients transplanted with NeuroCell-HD showed a favourable safety profile, however there was no change in functional capacity score twelve months after the xenotransplant. Furthermore, the mean motor subscore of the UHDRS (Unified Huntington’s Disease Rating Scale) increased (worsened) by 36%.

There was no evidence of PERV DNA in patient samples taken from six to twelve months after the xenotransplantation. The published results of this study are provided at Attachment C.

A Phase II clinical trial of NeuroCell-PD followed. Eighteen patients with severe Parkinson’s disease were enrolled in this double-blind, randomised, placebo-controlled trial across three medical centres in the US. Ten patients received NeuroCell-PD transplants and eight patients received placebo surgery.

Both the NeuroCell-PD patient group and the control patient group, on average, showed improvement after eighteen months. However there was no difference between the treatment and control groups. Furthermore, four out of ten patients who received NeuroCell-PD transplants experienced serious adverse events as did five of the eight patients in the control group. Analysis of the results showed there was a higher incidence of adverse events associated with immuno-suppressants among the patients treated with NeuroCell-PD. All patients tested negative for PERVs and there were no reports of other treatment-related infections. No serious adverse events that involved disabling dyskinesia were reported.

4.4. Foetal porcine cells for basal ganglia infarcts.

The results of a safety and feasibility study of xenotransplanted foetal porcine cells into patients with basal ganglia infarcts were published in 2005.

The study was an open label trial of patients with ischaemic stroke and stable neurological deficits. The study was initially planned to enrol twelve patients. However, only five patients underwent treatment before the US Federal Drug Administration terminated the study following the occurrence of adverse events in two of the patients.

Patients were implanted with lateral ganglionic eminence (LGE) cells derived from primordial porcine striatum which had been modified prior to transplantation to prevent tissue rejection (an anti-MHC class I F(ab’)2 fragment which lacks the Fc region). Consequently, patients in this trial did not receive immuno-suppressive agents.

The first three patients had no adverse effects. The fourth patient had temporary worsening of motor deficits three weeks post transplantation, and the fifth patient developed seizures one week after transplantation. MRI in both the patients that experienced adverse effects demonstrated areas of enhancement remote from the transplant site which later resolved. Two of the five patients showed improvement in speech, language and/or motor impairment over several months and persisted at 4 years. No evidence of pig-to-human transmission of microorganisms, such as porcine endogenous retroviruses was found.
The published results of this study are provided at Attachment D.

5. Activity in Australia

In Australia, xenotransplantation is used in current clinical practice for the treatment of severe burns. The procedure involves taking a skin sample from a patient and culturing the cells using animal feeder layers. The cultured cells are then harvested and grafted onto the patient’s wound to assist in healing. This procedure is exempt from the NHMRC Council’s 2004 recommendation.

NHMRC has actively engaged in activities to inform the review of its current position. On 8 August 2008, NHMRC held a workshop to discuss the risks and benefits associated with xenotransplantation in Australia. In the context of the review of NHMRC’s position, the workshop considered:

- the types of xenotransplantation procedures which are most likely to progress to clinical trial, and the consideration of timeframes for when these could be expected to occur;
- the current risks and benefits of xenotransplantation technologies; and
- the current status of international regulation of xenotransplantation, and considerations for any additional regulatory frameworks required in Australia.

Workshop participants (Attachment E) agreed that the understanding of the safety and efficacy of xenotransplantation technologies has progressed significantly over the past four years and advised that the potential risks to individuals and the community were not sufficient to justify a continuing ban on clinical trials in Australia. Furthermore, maintaining the ban effectively prevents development of necessary regulatory and infrastructure frameworks which are required to facilitate pre-clinical research in xenotransplantation. Participants agreed that reversing the NHMRC’s Council current position on xenotransplantation would allow appropriate regulatory and surveillance frameworks to be developed in anticipation of these technologies reaching clinical applicability.

In December 2008, Council noted the outcomes of the workshop and recommended that NHMRC continue to examine issues pertinent to xenotransplantation in Australia, prior to consideration of its current position in the second half of 2009.

5.1. Consequences resultant to Council’s 2004 recommendation

Council’s 2004 recommendation was not intended to inhibit preclinical xenotransplantation research. Rather, the intention was to allow time for more preclinical research to be done to provide further information about the likely efficacy and safety of clinical application of xenotransplantation. However, researchers have raised their concern (with NHMRC) that the recommendation has not only prevented clinical trials for 5 years, but has inhibited progress toward clinical trials in Australia by at least a further 5 years.

Researchers have noted that the recommendation has effectively delayed development of infrastructure necessary to support research in Australia prior to the commencement of clinical trials, as the need is ambiguous whilst the recommendation is in place. Potentially, this could include development of a national regulatory framework; guidelines for the maintenance and qualification of donor animals and for containment facilities; and building containment facilities for source pigs.
6. Regulation of xenotransplantation in Australia

The *Therapeutic Goods Act, 1989* (The Act) and associated Regulations establishes a uniform, national system of regulatory controls to ensure the quality, safety, efficacy and timely availability of therapeutic goods for human use. Responsibility for the regulatory controls lies with the Therapeutic Goods Administration (TGA). Clinical trials of unapproved therapeutic goods in Australia are regulated by the TGA, and require endorsement by a Human Research Ethics Committee.

There are two schemes under which clinical trials involving therapeutic goods may be conducted in Australia: the Clinical Trial Exemption (CTX) Scheme and the Clinical Trial Notification (CTN) Scheme. Xenotransplantation is one of a number of biological therapies that carry potential risk. Therefore, it is proposed that xenotransplantation trials should be subject to the more stringent CTX route which requires TGA assessment and approval of the safety and quality of the trial product and proposed trial structure prior to commencement of the clinical trial. This is in contrast to the CTN route, where safety is overseen by an institutional Human Research Ethics Committee.

The Act and associated Regulations for clinical trials currently do not specify xenotransplantation, and TGA is investigating options for including it within the definition of biologicals under its proposed new regulatory framework for Human Cellular and Tissue Therapies (HCT). Under this framework, due for implementation in mid 2010, xenotransplantation would most likely fall into the Class 4 (highest risk) category of the HCT classification. TGA is currently in the process of drafting novel legislation to ensure that all clinical trials using Class 4 HCTs undergo assessment via the CTX route. The legislation is to be an adjunct to the new HCT regulatory framework.

In the interim, there is no provision to force clinical trials using Class 4 therapeutic products/preparations through the CTX scheme (TGA 2004). TGA may consider implementing a regulatory change for the interim period so that clinical trials using xenotransplantation technology are forced to go via the CTX scheme. The decision to apply this type of regulatory change lies with the Office of Prescription Medicines (OPM) at the TGA.

A summary of classes of therapies and clinical trial schemes is at Attachment F.

It is important that regulatory and surveillance frameworks are developed to ensure Australia is equipped to manage the progression of xenotransplantation. It is not feasible to wait for efficacy data to be adequate for specific technologies before developing an appropriate framework; rather it is necessary to anticipate the regulatory processes which would be required. Development and management of surveillance strategies and ongoing patient monitoring has not traditionally been a responsibility of the TGA. Consequently, it is important to determine who should take carriage of these important issues and how surveillance will be coordinated.

7. International activity

The World Health Organization (WHO) has established a Global Knowledge Base on Transplantation (GKT), with the aim of bringing together in one database information on organ, tissue and cell donation and transplantation from around the world. The GKT will be a source of information for all involved from the lay public to health professionals and health authorities responsible for cell, tissue and organ transplantation. The GKT is based on four
pillars: GKT1: Activity and Practices; GKT2 Legal framework and organisational structure; GKT3 Vigilance, Threats and Responses; and GKT4 Xenotransplantation.

In relation to GKT4, xenotransplantation trials utilising various animal tissues and organs are listed on a database created by the University Hospital, Geneva and the International Xenotransplantation Association (IXA), in collaboration with WHO that aims to inventory all human-related xenotransplantation practices that have taken place worldwide. Participating countries include New Zealand, USA, Mexico, Russia, Germany, Switzerland, Malaysia, Ukraine, Sweden, France, Italy and China. There are currently 30 trials listed on the register, and it is highly likely that others have taken place around the world.

A joint meeting of the IXA and International Pancreas and Islet Transplant Association (IPITA) was held in Venice in October 2009. International regulation of xenotransplantation, a report on consensus statements, the WHO position on regulation, and ethical issues were addressed at two joint IXA/IPITA plenary sessions on 14 and 15 October.

7.1. Individual Countries and Regions

With the exception of the USA, United Kingdom and European Union, there is little information in the public domain on the status of xenotransplantation and/or its regulation in different countries. Some information on regulatory developments in xenotransplantation has been synthesised by the Organisation for Economic Co-operation and Development (OECD), however as the website does not appear to have been updated since 2001, the currency of information relating to the status by country is questionable. More comprehensive information has been synthesised by WHO although this has not been updated since 2005. A summary of activities taking place within specific countries and region is provided at Attachment G.

7.2. International cooperation on xenotransplantation

The WHO has been active in the field of xenotransplantation for several years, and has facilitated efforts to develop an internationally agreed oversight framework for xenotransplantation activity, including conducting clinical trials. A number of different departments within WHO are involved in xenotransplantation policy; for example the Department of Essential Health Technologies Clinical Procedures Unit, which is responsible for transplantation (including xenotransplantation) is cooperating with Departments that are responsible for communicable disease surveillance and response (WHO 2005).

7.2.1. Activity leading to WHA Resolution 57.18 (2000-2004)

Global discussions on the challenges of conducting and monitoring xenotransplantation are not new. In October 2000, delegates at OECD/WHO meeting said that the issue required a “new paradigm”, at the very least with a loose international network of specialists to provide a response to any worrying adverse events (Nature 2007, 407:666-667). In 2001, the Epidemic and Pandemic Alert and response Unit of WHO released a series of guidance documents relating to xenotransplantation, including a strategy for international cooperation and coordination on xenogeneic infection / disease surveillance and response (WHO 2001).

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4 http://www.humanxenotransplant.org
5 http://www.oecd.org/countrylist/0,3349,en_2649_34537_1783767_1_1_1_1,00.html
In May 2004, 192 countries at the World Health Assembly (WHA) adopted Resolution 57.18. This resolution urges Member States to allow xenotransplantation “only when effective national regulatory control and surveillance overseen by national health authorities are in place”, and to “cooperate in the formulation of recommendations and guidelines to harmonise global practices”; in effect putting the responsibility for control of xenotransplantation on Member States and their National Health Authorities (NHAs), but also requiring WHO to assist Member States (WHA 2005).

The adoption of Resolution 57.18 was regarded as a major step toward minimising infectious risks associated with xenotransplantation, and a commitment of the 192 countries to the development of adequate, harmonised regulatory procedures (Sykes 2005). The definition of xenotransplantation—“transplantation into human of living xenogeneic cells, tissues or organs, or human bodily fluids, cells, tissues or organs that have had ex vivo contact with these living xenogeneic materials”—adopted by the WHA in Resolution 57.18, and therefore supported by 192 countries, is consistent with those adopted by the USA and the Council of Europe (WHO 2005).

Xenotransplantation was subsequently discussed at the WHO Xenotransplantation Advisory Consultation (WHO 2005), at which it was noted that one aspect that has received little attention is the risk to the animal population of novel or modified animal diseases, particularly arising from the genetic modification of animals. Highly contagious diseases could spread rapidly to the animal population unless there is adequate containment.

7.2.2. The Changsha Communiqué (2004-2008)

In November 2008, the WHO, in collaboration with the Chinese Ministry of Health and the International Xenotransplantation Association conducted a global consultation on clinical trials in xenotransplantation. This consultation was intended to examine the current situation and draw up recommendations to the Member States and researchers regarding progressing clinical trials, thereby updating the WHO guidance adopted as Resolution 57.18 in 2004.

Over 50 participants discussed the present scientific status of xenotransplantation research; a review of the current status of research and / or clinical activity in represented countries; identification of essential safety requirements; aspects of clinical trials; and aspects of trials at the global level. The consultation produced a communiqué (known as the Changsha Communiqué, at Attachment H) which listed a set of principles relating to xenotransplantation, followed by recommendations to WHO; Member States of the WHA; and investigators and supporters of xenotransplant procedures and trials. The basic conclusions of the consultation are:

- Countries that do not have a comprehensive and effective national regulatory authority to oversee such clinical trials should not agree for clinical trials to be undertaken; and
- Countries with such a regulatory authority should ensure that it can provide adequate expertise to oversee a clinical trial in all its aspects.

The principles are intended to provide guidance that, if followed, will enable safe and efficient clinical trials to be carried out (WHO 2008; Cooper 2009).
8. Analysis and reduction of the risks involved in xenotransplantation

There have been three significant hurdles to clinical application. The first is transfer of zoonotic agents from the graft to the recipient and potentially to other members of society. The second hurdle is physiological incompatibility between the xenograft and the recipient, and the third hurdle is the host’s immune response against the graft.

As highlighted earlier in this document, Council, in 2004 concluded the risks of transmission of animal viruses to transplant recipients and the wider community had not been adequately resolved. Furthermore, Council considered xenotransplantation research to be at an early stage, therefore clinical trials in the foreseeable future were unlikely to be of significant benefit to research participants.

The following sections examine the current viral risks associated with xenotransplantation and discuss the progress with regards to the development and application of the therapy.

8.1. Xenosis

A major concern in xenotransplantation is that disruption of anatomical barriers combined with the routine immunosuppression of recipients may facilitate interspecies transmission of xenogeneic infectious agents. In xenotransplantation, porcine pathogens and even non-pathogenic microorganisms may adapt to the immunocompromised human recipient and cause disease or recombine with human viruses to create new pathogens. The risk of xenosis may be decreased by a careful characterisation of the zoonotic agent and by appropriate prevention actions (Fishman et al. 2004; Sachs et al. 2008).

Transmission of known viral, parasitic, bacterial and fungal infections can be avoided through selective breeding and screening of donor animals. It is also important to avoid to the degree possible the development of antibiotic-resistant pathogens in donor animals through the judicious use of antimicrobial agents in such herds ((e.g., meticillin-resistant Staphylococcus aureus, or vancomycin-resistant Enterooccoci). It should be noted that human organ donors are not free of significant pathogens for human recipients. Transplantation into immunosuppressed recipients will be associated with infection in recipients regardless of the source species (Fishman 2007).

Source animals which are free from designated pathogens and are required to be bred and maintained in biosecure facilities where they are protected from outside contaminants. These animals undergo regular screening to maximise safety.

Risks posed by four virus families which are of potential risk in the xenotransplantation setting are examined in greater detail in this discussion paper. As these viruses have been shown in vitro (i.e., in tissue culture but not in clinical trials) to be zoonotic or possess infectious potential in xenotransplantation, it is important to apply well researched methods to minimise risk.

In addition to recognised potential risks discussed in the paragraphs that follow, there is a potential risk of unknown pathogens being transmitted to humans via the xenograft. As these pathogens are yet to be identified, it is not possible to apply strategies to minimise this potential risk.
8.1.1. Retroviruses

Retroviruses are enveloped RNA viruses that replicate in a host cell to produce DNA from its RNA genome. The DNA becomes incorporated into the host's genome and thereafter replicates as part of the host cell's DNA.

In xenotransplantation, concern relates to the potential for ‘silent’ transmission to recipients where an unapparent infection is capable of altering gene regulation or causing oncogenesis or recombination with other viral nucleic acids. Activation of a latent virus and the development of clinical manifestations (which may be subtle) could be delayed for over a decade. Porcine endogenous retrovirus (PERV) is present in all pig strains. It is the only retrovirus identified that possesses infectious potential for human cells in vitro in xenotransplantation. PERV has never been associated with any form of human disease or with malignant transformation or recombination in human cells or tissues in vivo or in vitro.

Three PERV subgroups have been identified: PERV-A; PERV-B and PERV-C. Each of the three PERVs binds different cellular receptors to enter and infect certain human and porcine cells. PERV-A and PERV-B are capable of infecting both porcine and human cells (polytropic) whereas PERV-C is capable only of infection and replication in cells from the original host species (ecotropic) (Louz et al. 2008). However, recombinant PERV-AC uses the envelope and receptor binding activity of PERV A with the viral substrate of PERV C. PERV AC can infect human cells in vitro with greater efficiency than PERV A (Denner 2008). PERV AC has been demonstrated in the genomes of pig tissues (Martin et al. 2006).

Published studies of humans exposed to swine cells and tissues have produced no clinical or laboratory evidence of PERV infection to date, suggesting the risk of pig to human infection is very low. Pooled together, the studies examine over 200 patients (Paradis et al. 1999; Louz et al. 2008; Thanos & Elliot 2009). Although there is no evidence of the transfer of PERV infection, long lasting porcine cell microchimerism has been found in some patients indicating the possibility that PERV infection can’t be ignored (Boneva & Folks 2004). Furthermore, the possibility of PERV transmission and infection or combination with human endogenous retroviruses to give rise to novel viruses with unknown pathogenic potential also remains.

8.1.2. Herpesviruses

Herpesviruses are a large family of DNA viruses (Herpesviridae) that cause diseases in animals, including humans. They can cause latent or lytic infections and are well known for their ability to establish lifelong infections.

Research suggests that reciprocal molecular interactions between human and porcine herpesviruses exists and several viruses which are of significance in the xenotransplantation setting have been identified; porcine cytomegalovirus (PCMV), porcine lymphotropic virus-1 and-2 (PLHV-1, PLHV-2) and hepatitis E virus (HEV).

PCMV is regarded as a ubiquitous virus, having a significant incidence in pig populations. No clinical evidence of PCMV infection of human cells under experimental conditions exists however activation of baboon CMV and PCMV in a pig-to primate model has been demonstrated. PCMV has been removed from some breeding herds by early weaning of piglets or hysterectomy derivation (Mueller et al. 2002; Gollackner et al. 2003).
Direct effects resulting from a PCMV infection are characteristic of organ dysfunction and include pneumonia, neutropenia and hepatitis. Indirect effects include immunological effects which may be predisposing to opportunistic secondary infections including bacterial or fungal infections, or cause consumptive coagulopathy, allograft rejection or lymphoma (Mueller et al. 2004; Fishman & Patience 2004). Therefore, by preventing transmission of PCMV, survival of the xenografts may be prolonged thus increasing safety by eliminating yet another viral risk. Research has demonstrated that it is possible to successfully exclude PCMV from donor animals through early weaning of piglets.

Little is known about the infectivity, long term consequences and basic properties of PLHV. What is known is that PLHV-1 and -2 are comparable with human viruses; PLHV-1 is homologous to Epstein-Barr virus (EBV) which is associated with post transplantation lymphoproliferative diseases in allotransplants and PLHV-2 is homologous to human herpesvirus 8 (HHV8) which is associated with Kaposi’s sarcoma (KS) (Santoni et al. 2006).

PLHV is an endemic virus, present in high-health status and commercial herds. Breeders have attempted to remove PLHV from commercial herds using techniques such as early weaning, hysterectomy derivation and barrier rearing with little success (Fishman & Patience 2004; Mueller & Fishman 2004). One particular breed of pig however, the feral Auckland Island pigs, have tested negative to PLHV (Garkavenko et al. 2004) in addition to a number of other important viruses.

Recent data suggest the possibility of infection of porcine tissues by human cytomegalovirus and herpes simplex viruses.

HEV is a major cause of viral hepatitis in the developing world and is also endemic in industrialised countries. It has been detected in pigs in several countries including Australia and New Zealand (Fishman & Patience 2004; Garkavenko et al. 2004). There is growing evidence that swine HEV may be zoonotic.

8.1.3. **Circoviruses**

Circoviruses are small non-enveloped circular viruses with a single stranded circular DNA genome. The members of this family of virus are animal viruses, most of which affect birds although type 1 and type 2 PCV (PCV-1 and PCV-2) affect pigs and wild boars. Circoviruses are the smallest pathogenic DNA viruses that have been identified and characterized in animals.

All circoviruses known at present, except PCV-1 are associated with immunodepressive diseases (Faurez et al. 2009). PVC-1 is non-pathogenic to pigs and PCV-2 is believed to be the causative agent of an infectious disease called post weaning multisystemic wasting syndrome which is characterised by progressive weight loss, jaundice and respiratory distress.

PCV-2 is known to be capable of infecting human cells in vitro. Antibodies to PCV-1 have been detected in humans, however neither virus nor viral genome has been detected in any mammalian species other than swine (Garkavenko et al. 2004).
8.1.4. Picornaviruses

Picornaviruses are amongst the oldest and most diverse viruses. They are small, nonenveloped viruses containing a single positive strand RNA. Picornaviruses commonly produce subclinical infections; acute diseases range from minor illness to paralytic disease.

Encephalomyocarditis virus (EMCV) is a widely distributed picornavirus capable of infecting many animal species including pigs and humans. Research suggests that the virus can cause interspecies infections, making it an important zoonotic agent (cited in Brewer et al. 2001). The few documented cases of EMCV in humans have been associated with fever, neck stiffness, lethargy, delirium, headaches and vomiting, however there is also evidence that EMCV causes acute fatal myocarditis and reproductive failure (Denis et al. 2006). In Australia, cases of human EMCV infection have been reported in areas where there is high incidence of the disease amongst pigs (Brewer et al. 2001).

At present there is no treatment for EMCV, however, there is an inactivated vaccine available in the United States which is used prophylactically to protect pigs and research has demonstrated replication of porcine EMCV can be inhibited using short interference RNAs (Jia et al. 2008).

8.1.5. Influenza viruses

Human epidemics of viral influenza have originated from animal strains (largely birds and swine) that have then become adapted to human hosts, heightening concern for transmission from animals to humans via xenotransplantation.

Influenza A viruses circulate amongst many animal hosts that may serve as a reservoir for human disease. In most of these cases, the virus is not adapted for human infection and therefore cannot cause disease in humans. Pigs may also serve as the host for adaptation of avian viruses to human hosts. Therefore, human, porcine and avian viruses (e.g. H1N1) may undergo genetic reassortment in pigs to produce novel pathogens with pandemic potential.

8.1.6. Reducing the risk

Data generated over the last ten years suggest the risk of infection resulting from xenotransplantation is manageable and the risk to those in close contact with xenotransplant recipients is low.

Although there is a lack of evidence (in the 200+ patients), the risk of transferring viruses from animals to humans via xenotransplantation cannot be eliminated completely and is one of the major concerns in the developing area of xenotransplantation. All risks must be managed appropriately. Exclusion lists can ensure screening encompasses all pathogens relevant to the donor species. However, there appears to be a lack of consensus internationally with regards to testing for various pathogens. The WHO has developed a guidance document to assist in preparing a xenotransplantation infectious agent exclusion list (Attachment I). An approach similar to that which is applied to allograft transplantations may also be employed.

Specific pathogen-free (SPF) breeds that have tested negative to many of the viruses discussed above have been identified. One of these is the New Zealand Auckland Island (AI) pig (Garkavenko et al. 2004). Analysis of the breed in 2003 indicated that AI pigs are free from PCMV, PLHV, EMCV, PCV-2, HEV and PERVs. Furthermore, antiviral agents that
have efficacy against PERV \textit{in vitro} are available (Wilhelm \textit{et al.} 2002). Therefore, by applying breeding strategies and critical selection of donor animals that do not express or secrete potential pathogens such as the AI breed, capacity exists to minimise the risk of xenosis in the xenotransplant setting (Denner \textit{et al.} 2009).

8.2. Avoidance of immune responses

One of the main obstacles in achieving successful xenotransplantation has been overcoming immunological hurdles. The immune response to xenotransplantation differs depending on whether the graft consists of isolated cells or a vascularised organ. Vascularised organ xenografts are subject to four types of xenotransplantation rejection: hyperacute rejection; acute vascular rejection; acute cellular rejection; and chronic rejection (Boneva & Folks 2004).

The initial and major response is hyperacute vascular rejection and can destroy the transplanted organ within minutes or hours of a vascularised xenograft perfusing with human blood. Humans produce natural antibodies against epitopes expressed on the surface of porcine vascular endothelial cells. Hyperacute graft rejection occurs when these antibodies recognise their counterpart antigen in the xenograft and bind, activating (usually the classical pathway of) complement.

Free tissue or cell xenotransplants on the other hand, are subject to failure caused by primary non-function, failure of neovascularisation or failure of the microenvironment to support survival and function of the xenograft. If the tissue or cells succeed at engraftment, they are still susceptible to cellular or humoral rejection.

Immunosuppression, together with a number of other approaches such as depletion of natural antibodies or genetic manipulation of the donor animal demonstrates that the immunological hurdles can be overcome. However, genetic manipulation may facilitate transmission of viruses to humans and by depleting natural antibodies, the immunological defence against human infection by retroviruses, parasites and other organisms is lessened and may facilitate transmission of porcine viruses (Louz \textit{et al.} 2008; Boneva & Folks 2004).

The long term complications associated with the use of immunosuppressants remains unclear, consequently there is obvious potential to apply other technologies to manipulate the immune system. One such technology developed to overcome immunological rejection is ‘encapsulation’. Cells encapsulated with non-degradable devices and macrocapsules may provide a permeable selective membrane which protects the cells from the host’s immune system while simultaneously allowing diffusion of substances (e.g. nutrients and hormones) into and out of the cell. Each such encapsulated graft must be tested to determine whether infectious agents diffuse from the tissues to the host.

8.3. Physiological incompatibility

Physiological incompatibility between organs, cells, tissues and the xenogeneic environment is another challenge to successful xenotransplantation. Xenografts may have basic physiological functions compatible with the host provided the graft survives, however it is possible that the xenograft will not function in a physiologically compatible manner and may interfere with the function of metabolic processes in the host. For example, while porcine insulin differs from human insulin by a single amino acid and it is able to provide excellent control of glucose metabolism, pig and human albumin have an amino acid agreement of less than 65%, erythropoietin less than 82%, and complement less than 70%. This disparity can
potentially induce the alternative complement pathway in the human recipient, and result in unknown side effects (Beschorner 2006).

9. Ethical, legal & social challenges in safeguarding public health

Decisions as to whether clinical trials should be conducted require balancing the science-based risk assessment with the many interests in society, which can include patient preferences, industry interests, ethical and cultural considerations, and economic, social and public health costs and benefits (Einseidel et al. 2004). While xenotransplantation offers promising solutions to shortages of human transplant organs and tissues, the potential risk of transmission of contagious diseases from animal tissues to human recipients is one of the major reasons why xenotransplantation clinical trials are not permitted in some countries.

Uncertainty over potential public health risks has led to some countries (such as the Netherlands and India) actively opposing clinical xenotransplantation trials (WHO 2005). It has also led to recommendations for the establishment of national oversight agencies and for a global regulatory approach in which clinical trials and procedures will be conducted within internationally agreed frameworks to protect the global community, including ethical and monitoring guidelines (Sykes, Sandrin & Cozzi 2004). Countries in which human-related xenotransplantation clinical trials are currently permitted include New Zealand, USA, Mexico, Russia, Germany, Switzerland, Malaysia, Ukraine, Sweden, France, Italy and China. It is highly likely trials in countries in addition to these are taking place around the world.

9.1. International oversights and national sovereignty

While international agencies like WHO can produce principles and guidance on conducting clinical trials and scientific research, governmental regulatory bodies have the sovereign power to interpret them. Guidelines and other national regulatory tools are unlikely to be consistent between regulatory and legal systems, enforcement of fundamental human rights, and procedures (and resources) for addressing health issues and spread of disease. Similarly, sovereign nations that have endorsed international agreements may have limited resources to develop and oversee their own regulations in accordance with these agreements. The role of WHO and other international agencies may therefore not be sufficiently strong to make a difference in terms of compliance with desirable legal standards or with regard to adequate protection for individual and collective rights.

International cooperation on xenotransplantation that is effective will need to consider ways of combining legally binding measures with statements of principle, at local, national and international level (Tallacchini 2008).

9.2. Xenotravel

The issue of “xenotravel” or “xenotourism”—where people travel abroad for procedures that are not available in their country of residence—has raised important questions for both monitoring of individual patients and mechanisms to safeguard public health. It has been argued (Bucher et al. 2005) that as the public health risks of xenotransplantation have the potential to transcend sovereign borders, countries such as Australia, in which clinical trials are not currently taking place, have no mechanism for monitoring and surveillance of people who may have been involved in trials abroad. It is highly likely that patients returning from treatments abroad would at the very least inform their GP; however there may not be any requirement (or mechanism) that the GP in turn informs local or national authorities, even when the GP considers that the patient may be considered a public health risk.
Similarly, there is no mechanism for monitoring patients who have had xenotransplantation procedures and are temporarily visiting Australia. Surveillance for the purpose of safeguarding public health will necessarily involve agencies outside the health sector, to ensure that health authorities are aware of patients returning home after treatment abroad, and of non-residents who have had xenografts entering Australia. Cooke et al. (2004) suggest that a process similar to that adopted by the USA, where under the Immigration and Nationality Act foreign visitors are required to declare any communicable diseases of public health significance, may be appropriate. Such a process would avoid unwarranted quarantine for the xenograft recipient while protecting the host nation. International cooperation will also be necessary if tracking the movement of people between jurisdictions is deemed appropriate (Tallacchini 2008).

The issue of xenotravel has been raised by Yang and Sykes (2005) as an example of the need for worldwide harmonisation of regulatory oversight of xenotransplantation in relation to patients travelling to a country without regulatory oversight and have a xenograft and return to their home country where public health authorities lack awareness of the procedure. However, public health authorities may be equally as likely to be unaware of the procedure if it takes place in countries with oversight.

As with any notifiable health issue, NHAs would be required to report any adverse event associated with xenotransplantation to WHO.

### 9.3. Patients’ rights

#### 9.3.1. Monitoring and surveillance of patients

The potential risk of transmission of contagious diseases from animal tissues to human recipients has given rise to suggestions that, in the interests of protecting public health, people who have participated in xenotransplantation clinical trials (or have received treatments) require lifelong monitoring and ongoing surveillance (e.g. Sykes, Sandrin & Cozzi 2004; Cooke et al. 2004; Sykes, D’Apice & Sandrin 2004). Effective monitoring and surveillance will require cooperation at local, national and international level—for example, monitoring of patients and trial participants will require that patients and clinical teams are aware of the importance of reporting any problems to local authorities. At national level, health authorities will be responsible for implementing a surveillance system as part of their own regulatory framework, possibly including a patient register. Whether existing frameworks for monitoring disease spread would be effective, or whether laws specific to xenotransplantation are required, needs to be debated. Public education and public dialogue will also be important to monitoring procedures working well.

Some professional societies for allotransplantation have voluntary registries with 100% capture of information (e.g. ANZDATA which relates to outcomes of those with end stage renal failure). At the NHMRC workshop, the feasibility of establishing a central registry of xenotransplantation patients (perhaps with Medicare, or TGA) was discussed. Currently, participants in Australian clinical trials are placed on a patient register. However, there is no central register and patients are listed on registries specific to the type of procedure, or that are held within institutions such as hospitals. Long term monitoring of patients therefore rests with the institution, rather than a central agency.

Calls for lifelong surveillance and monitoring of patients who have undergone a xenotransplant procedure have led to concern that this equates to patients having to waive fundamental rights and freedoms (movement within and across jurisdictions, privacy, and
freedom to withdraw from the trial). However, this potential is not unique to xenotransplantation, as states have the power to limit personal freedoms and rights when public health or security is at stake. Article 24 of the Declaration of Helsinki—adopted by the World Medical Association (WMA) as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data regarding patient consent and individual choice—includes that “the potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal” (WMA 2008). The proposed lifelong surveillance of xenotransplantation patients is often cited as being contrary to the Declaration.

9.3.2. Consent

Potential risks to public health and society (Yang & Sykes 2007) have implications for many aspects of clinical research in xenotransplantation, including the informed consent process, the right to privacy and the right of the research subject to remove him or herself from a research study in which long-term infectious monitoring is mandated as a protective measure for other members of society.

Contention that trials are being conducted in countries where regulatory frameworks are weak or not enforced (Sykes, Sandrin & Cozzi 2004) has led to calls for development of an effective regulatory framework that is committed to strong (preclinical) evidence for safety and efficacy before clinical trials are undertaken. This may help to prevent loosely regulated trials from being conducted, and vulnerable people consenting to participation in trials without fully understanding the implications, and/or being coerced into participating (Tallacchini 2008).

While it may be possible to obtain global agreement on preclinical evidence, appropriate legal, ethical and regulatory frameworks for clinical xenotransplantation will have to be resolved on a country-by-country basis in accordance with health care funding arrangements and in relation to cultural notions of death and informed consent (and lack of choice among patients who are gravely ill).

9.4. Balancing risk with benefit

Concerns regarding the potential infectious risks of xenotransplantation often do not take into account the potential benefits of this technology in comparison with allotransplantation. Potential advantages of xenotransplantation include (Fishman & Patience 2004; Boneva & Folks 2004):

- a virtually unlimited source of grafts;
- the possibility of better timing of the procedures (patients can receive xenotransplants at the time of greatest clinical need);
- reduced duration of pre-transplant hospitalisation and exposure to nosocomial pathogens;
- the resistance of some animal species to certain infections (resistance of the xenogeneic tissue to infection by human pathogens such as HIV);
- careful microbiological screening of the xenogeneic tissue (compared with the allotransplantation setting where pre-transplantation screening of human tissues is time-limited, xenotransplant donor animals will be screened in advance,
extensively, and multiple times. In this respect, xenografts may be safer than allografts;

- limited duration of exogenous immune suppression is a component of many proposed protocols for xenotransplantation (this could potentially reduce the risk for opportunistic infections); and

- possibility of no immunosuppression (some recipients of encapsulated xenografts may not need immunosuppression at all and therefore could potentially be less vulnerable to infections).

Infection is a major challenge in immunosuppressed human allotransplantation recipients. Infection takes the form of a primary diagnosis underlying organ failure (e.g., hepatitis B or C, recurrent pneumonias in cystic fibrosis), in recurrent disease post-transplantation, and in opportunistic infections (cytomegalovirus, varicella zoster virus) in immunosuppressed recipients. Infection may be transmitted from organ donors to recipients or complicate management prior to (sepsis) or following transplantation. Clinical xenotransplantation may alleviate some of these limitations.

Xenogeneic tissues also appear to be relatively resistant to infection by some of the human pathogens commonly complicating allotransplantation including HIV and the hepatitis viruses. Such species’ specificity may reflect the absence of receptors or of host cellular machinery needed to support for viral replication in human cells.

It has been suggested that internationally agreed prerequisites for conducting clinical trials would help protect the rights and wellbeing of patients, particularly in trials conducted in countries with minimal or no regulatory oversight (Sykes, Sandrin & Cozzi 2004). In 2004, the Ethics Committee of the International Xenotransplantation Association \(^6\) (IXA) summarised the principle based actions that it considered must be followed in the conduct of clinical trials, including regulation, approval, use of source animals, prerequisites in terms of preclinical data, and consideration of the risks to the patient and society (Sykes, D’Apice & Sandrin 2004). Further, Cozzi \textit{et al.} (2007) suggest that “only convincing efficacy data generated in relevant preclinical primate models and the reasonable expectation of a favourable risk/benefit ratio will indicate that the time has come for the initiation of carefully designed and monitored clinical trials in man”. Therefore, if NHMRC were to recommend that clinical trials involving xenotransplantation be permitted to take place in Australia, consideration should be given to the development of a suite of guidance documents to provide a scaffold for researchers. The following activities may contribute to developing a robust standard of regulation, oversight and monitoring. It is currently unclear which agency would take on these responsibilities if it is decided they are necessary.

- \textit{Regulation of clinical trials involving xenotransplantation -} Inclusion of xenotransplantation into the TGA’s forthcoming regulatory framework for Human Cellular and Tissue Therapies if Council advise that clinical trials involving animal-to-human transplantation be permissible in Australia.

- \textit{Establish an adequate National Surveillance System -} If deemed appropriate, effective monitoring and surveillance will require cooperation at local, national and international level, for example, monitoring of patients and trial participants

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\(^6\) IXA was established at the Montreal’98 Congress of The Transplantation Society, with the aim of providing a forum for those with a special interest in Xenotransplantation, and with the mission to promote xenotransplantation as a safe, ethical, and effective therapeutic modality.
will require that patients and clinical teams are aware of the importance of reporting any problems to local authorities.

- **Development of a National Patient Register** - Currently, participants in Australian clinical trials are placed on a patient register specific to the type of procedure, or that are held within institutions such as hospitals. There is no central register, and long term monitoring of patients therefore rests with the institution, rather than a central agency.

- **Appoint a Xenotransplantation Advisory Committee** – Human Research Ethics Committees (HRECs) responsible for the approval of clinical trials may lack the specific expertise required to assess new techniques or evaluate risks and benefits associated with research proposals involving animal-to-human transplantation. Through the appointment of several key experts in areas such as xenotransplantation and virology, the committee would be able to provide medical and technical advice to HRECs and the TGA and position itself at the forefront of research involving xenotransplantation.

- **Development of animal-to-human transplantation guidelines** – The development of guidelines would provide a cautious framework within which unsafe or unsuitable research is effectively prevented, while potentially safe and beneficial research may be allowed to process under strictly monitored conditions. The document could advise on how to process research proposals and under what conditions the research may or may not be permitted. It may also advise on animal husbandry practices. The XWP developed draft guidelines in 2004 to support researchers involved in animal-to-human studies in xenotransplantation. If Council were to advise that research of this sort be permitted in Australia, these guidelines could be developed further.

- **National Statement on Ethical Conduct in Human Research** – A supplementary discussion on the ethical issues relating to xenotransplantation could be added to the NHMRC document.

- **Australian code of practice for the care and use of animals for scientific purposes** – A supplementary discussion on animals used as source animals in xenotransplantation could be added to the NHMRC document.

### 10. The way forward

NHMRC Council’s recommendation that trials not be conducted in Australia was made on the basis that risks of transmission of animal viruses to transplant recipients and the wider community had not been adequately resolved, and that xenotransplantation research was at an early stage and clinical trials in the foreseeable future were unlikely to be of significant benefit to research participants. The recommendation was made to protect Australians.

NHMRC’s current recommendation is due to lapse in December 2009. Xenotransplantation research has progressed significantly in the last five years. Researchers now have a more comprehensive understanding of the risk of transmitting animal viruses via xenografts, and significant achievements—such as demonstrated efficacy in pre-clinical and clinical trials with particular success in relation to porcine islet xenotransplantation—have been demonstrated such that researchers consider that the reasons for supporting the recommendation are no longer relevant. Overall, the consensus is that the risk posed by animal viruses is low and can be managed via herd selection and screening strategies provided there is a regulatory mechanism to obligate compliance. In reality, the risks of novel infection is more likely to be greater with allotransplantation compared with...
xenotransplantation as human donors are not screened or held in specialised containment facilities.

Consideration needs to be given as to Australia’s capacity to implement novel strategies to support this new and emerging therapy while also safeguarding the public’s health.
Attachments

A: Abstract - Liver allotransplantation after extracorporeal hepatic support with transgenic (hCD55/hCD59) porcine livers: Clinical results and lack of pig-to-human transmission of the porcine endogenous retrovirus 1

B: Abstract - Prospective, Randomised, Multicentre, Controlled Trial of a Bioartificial Liver in Treating Acute Liver Failure

C: Abstract - Porcine Xenografts in Parkinson’s Disease and Huntington’s Disease Patients: Preliminary Results

D: Abstract - Neurotransplantation of Fetal Porcine Cells in Patients with Basal Ganglia Infarcts: A Preliminary Safety and Feasibility Study

E: NHMRC 2008 Xenotransplantation Workshop – List of participants

F: TGA Human Cell and Tissue Therapies Framework - Therapy classification

G: Xenotransplantation – a summary of what’s happening around the world

H: Changsha Communiqué

I: WHO criteria for developing a xenotransplantation exclusion list
References


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Liver allotransplantation after extracorporeal hepatic support with transgenic (hCD55/hCD59) porcine livers: clinical results and lack of pig-to-human transmission of the porcine endogenous retrovirus.


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BACKGROUND: Whole organ extracorporeal perfusion of a genetically modified humanized (transgenic) pig liver has been proposed as a technology that may sustain patients with severe liver failure while awaiting human liver transplantation. METHODS: We report on two cases of successful extracorporeal perfusion of a transgenic pig liver in patients awaiting transplantation for fulminant hepatic failure. The pig livers used were transgenic for human CD55 (decay-accelerating factor) and human CD59. These transgenic modifications are designed to reduce or eliminate the hyperacute rejection inherent in pig-to-primate xenotransplants. We also report on the results of serial surveillance testing for presence of the porcine endogenous retrovirus (PoERV) in these two patients. RESULTS: Extracorporeal perfusion in two patients was performed for 6.5 and 10 hr, respectively, followed by the successful transplantation of a human liver and resultant healthy patients (18 and 5 months later as of this writing). The porcine livers showed evidence of synthetic and secretory function (decreasing protime and bilirubin, bile production). Serial polymerase chain reaction analysis of these patients' peripheral blood mononuclear cells has failed to show presence of PoERV DNA sequences. CONCLUSIONS: The CD55/CD59 transgenic porcine liver appears capable of safely "bridging" a patient to liver transplantation. Human PoERV infection from these livers has yet to be demonstrated.

**Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure.**


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OBJECTIVE: The HepatAssist liver support system is an extracorporeal porcine hepatocyte-based bioartificial liver (BAL). The safety and efficacy of the BAL were evaluated in a prospective, randomized, controlled, multicenter trial in patients with severe acute liver failure. SUMMARY BACKGROUND DATA: In experimental animals with acute liver failure, we demonstrated beneficial effects of the BAL. Similarly, Phase I trials of the BAL in acute liver failure patients yielded promising results. METHODS: A total of 171 patients (86 control and 85 BAL) were enrolled. Patients with fulminant/subfulminant hepatic failure and primary nonfunction following liver transplantation were included. Data were analyzed with and without accounting for the following confounding factors: liver transplantation, time to transplant, disease etiology, disease severity, and treatment site. RESULTS: For the entire patient population, survival at 30 days was 71% for BAL versus 62% for control (P = 0.26). After exclusion of primary nonfunction patients, survival was 73% for BAL versus 59% for control (n = 147; P = 0.12). When survival was analyzed accounting for confounding factors, in the entire patient population, there was no difference between the 2 groups (risk ratio = 0.67; P = 0.13). However, survival in fulminant/subfulminant hepatic failure patients was significantly higher in the BAL compared with the control group (risk ratio = 0.56; P = 0.048). CONCLUSIONS: This is the first prospective, randomized, controlled trial of an extracorporeal liver support system, demonstrating safety and improved survival in patients with fulminant/subfulminant hepatic failure.
Porcine xenografts in Parkinson's disease and Huntington's disease patients: preliminary results.


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The observation that fetal neurons are able to survive and function when transplanted into the adult brain fostered the development of cellular therapy as a promising approach to achieve neuronal replacement for treatment of diseases of the adult central nervous system. This approach has been demonstrated to be efficacious in patients with Parkinson's disease after transplantation of human fetal neurons. The use of human fetal tissue is limited by ethical, infectious, regulatory, and practical concerns. Other mammalian fetal neural tissue could serve as an alternative cell source. Pigs are a reasonable source of fetal neuronal tissue because of their brain size, large litters, and the extensive experience in rearing them in captivity under controlled conditions. In Phase I studies porcine fetal neural cells grafted unilaterally into Parkinson's disease (PD) and Huntington's disease (HD) patients are being evaluated for safety and efficacy. Clinical improvement of 19% has been observed in the Unified Parkinson's Disease Rating Scale "off" state scores in 10 PD patients assessed 12 months after unilateral striatal transplantation of 12 million fetal porcine ventral mesencephalic (VM) cells. Several patients have improved more than 30%. In a single autopsied PD patient some porcine fetal VM cells were observed to survive 7 months after transplantation. Twelve HD patients have shown a favorable safety profile and no change in total functional capacity score 1 year after unilateral striatal placement of up to 24 million fetal porcine striatal cells. Xenotransplantation of fetal porcine neurons is a promising approach to delivery of healthy neurons to the CNS. The major challenges to the successful use of xenogeneic fetal neuronal cells in neurodegenerative diseases appear to be minimizing immune-mediated rejection, management of the risk of xenotic (cross-species) infections, and the accurate assessment of clinical outcome of diseases that are slowly progressive.
Neurotransplantation of fetal porcine cells in patients with basal ganglia infarcts: a preliminary safety and feasibility study.


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BACKGROUND: Cell transplantation is safe in animal models and enhances recovery from stroke in rats. METHODS: We studied the safety and feasibility of fetal porcine transplantation in 5 patients with basal ganglia infarcts and stable neurological deficits. To prevent rejection, cells were pretreated with an anti-MHC1 antibody and no immunosuppressive drugs were given to the patients. RESULTS: The first 3 patients had no adverse cell, procedure, or imaging-defined effects. The fourth patient had temporary worsening of motor deficits 3 weeks after transplantation, and the fifth patient developed seizures 1 week after transplantation. MRI in both patients demonstrated areas of enhancement remote from the transplant site, which resolved on subsequent imaging. Two patients showed improvement in speech, language, and/or motor impairments over several months and persisted at 4 years. The study was terminated by the FDA after the inclusion of 5 patients. CONCLUSION: This is the first report on the transplantation of nontumor cells in ischemic stroke patients.
# NHMRC 2008 Workshop on the Risks and Benefits of Xenotransplantation in Australia

## Participants

**Chair:**
Dr Ian Alexander – Chair NHMRC CTAC

**CTAC Members:**
A/Prof Philip O’Connell – Westmead Hospital  
Dr Paul Verma – Monash Institute of Medical Research

**International Experts:**
Prof Megan Sykes – Harvard Medical School, USA  
Dr Emanuele Cozzi – University of Padua, Italy  
Dr Richard (Robin) Pierson – University of Maryland, USA  
Dr Keith Wonnacott – US Food and Drug Administration (FDA)  
Dr Luc Noel – World Health Organization (WHO)

**Australian Experts:**
A/Prof Mark Nottle – University of Adelaide  
A/Prof Peter Cowan – St Vincent’s Hospital, University of Melbourne  
Prof Tony d’Apice – St Vincent’s Hospital, University of Melbourne  
Prof William Rawlinson – Prince of Wales Hospital, University of NSW  
Prof Chris Moran – University of Sydney

**Invited Observers:**
Prof Kathy Crosier – Gene Technology Advisory Committee (GTAC), NZ  
Ms Megan Willmott – Health Research Council (HRC), NZ  
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The Australian Health Ministers’ Conference (AHMC) agreed to the regulatory framework for Human Cell and Tissue Therapies proposed to it in November 2006 by the Therapeutic Goods Administration. However, it recommended that organs and un-manipulated reproductive tissues (for Assisted Reproductive Technology) be subject to further detailed analysis and deliberations before making a decision regarding their inclusion in Class 1 of the framework. In July 2008 AHMC agreed that there was no requirement for further regulation of un-manipulated reproductive tissues and that possible regulatory arrangements for solid organs be referred to the new national organ donation and transplantation authority.

(a) Subject matter of regulation

The agreed definition for the Human Cell and Tissue (HCT) Framework covers

- “all articles containing or consisting of, or derived from, human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient”;
- and
- the definition of HCTs:
  - excludes blood, blood components and blood products; and
  - excludes secreted or excreted human product, such as hormones, human breast milk or urine; and
  - may exclude other articles that may be declared from time to time in a Therapeutic Goods Order (an Order)

(b) Classification of HCTs

- The HCT regulatory framework comprises four classes of HCTs with varying levels of regulation applying, based on a risk benefit analysis of the types of HCTs;
- the four classes be defined as follows:

  **Class 1**

  An HCT is Class 1 if:
  
  (a) it is not banked (that is, stored for future use); or
  
  (b) it is not processed (that is, manufactured by a process other than minimal primary separation\(^1\)); or
  
  (c) it is declared by an Order to be a Class 1 HCT.

  **Class 2**

  A human tissue or cell that is stored, maintained or preserved for future use and:
  
  (a) is not in any respect a Class 3 or 4 HCT; and
  
  (b) is not for direct transfer from donor to recipient; and
  
  (c) is not a Class 1 HCT.

\(^1\) ‘minimal primary separation’ means a process involving any of the following actions: centrifugation, freezing, storage, trimming, flushing, washing, any similarly simple action; and not involving, for example: freeze-drying, separation by monoclonal antibody affinity chromatography or cultivation of cells
**Class 3**
A cell or tissue

(a) processed in a manner that may alter the structure and properties of the cell or tissue but does not purposefully alter the biological activity; or

(b) declared by an Order to be a Class 3 HCT.

**Class 4**
A cell or tissue

(a) processed so that the biological properties are deliberately manipulated; or

(b) processed for a purpose for which the cell or tissue is intended to be used is not its usual biological function; or

(c) declared by an Order to be a Class 4 HCT.

**c) Level of regulation to be applied to each class**

The level of regulation applied to HCTs will be as follows:

- **Class 1: Declaration of compliance with relevant Standards**
  
  An applicant will be required to attest to compliance with relevant mandatory Standards, through the submission to the TGA of a Declaration. The Standards will be based on existing industry Standards.

- **Class 2: Compliance with Standards and Manufacturing Principles**
  
  Applicants for a Class 2 HCT cell or tissue type will be required to:
  
  (a) demonstrate compliance with Manufacturing Principles. Compliance will be evidenced by the TGA issuing a Manufacturing Licence in respect of the relevant activities at the facility in which the tissue will be banked; and

  (b) demonstrate compliance with relevant Standards for each tissue type.

  If both of these requirements are met, the TGA will enter the approved tissue(s) on the ARTG.

- **Class 3: Compliance with Standards (and demonstration of safety, quality efficacy) and Manufacturing Principles**
  
  Applicants for a Class 3 HCT product will be required to:
  
  (a) demonstrate compliance with Manufacturing Principles – as evidenced by the TGA issuing a Manufacturing Licence in respect of the relevant activities at the facility in which the cells or tissue will be manufactured; and

  (b) demonstrate that the particular HCT is safe, efficacious and of high quality. This will require the applicant to submit a Dossier to the TGA.

  If the applicant meets both of these requirements the TGA will enter the approved Class 3 cell or tissue on the ARTG.

- **Class 4 – As for Class 3 except more detailed data required**
  
  As for Class 3 except that the Dossier will also need to contain relevant clinical data and analysis.
(d) Exemptions and exceptions

The legislation will include exemptions from the regulatory requirements described above for:

- single medical procedures. In addition to the special exemption provisions, for example, experimental use and special access, the following medical procedures will be exempt from TGA regulation:
  - single surgical procedures performed on one patient (autologous transplant) such as bone grafts and vein transplants;
  - single surgical procedures involving two patients (non-autologous or allotransplant) such as a haematopoietic progenitor cell or tissue donation from a live donor within the same facility as the transplant recipient.

- exceptional release/acceptance. It is proposed that the TGA will set standards that must be complied with by organisations proposing exceptional release/acceptance of HCTs (for example, cells that show evidence of a transmittable disease and when no alternative tissue or cells are available for the treatment of a life-threatening condition).

(e) Adverse events reporting

It is proposed that adverse event reporting for HCTs will rely on existing processes established within the TGA. Specific guidance will be developed in relation to HCTs to define what will need to be reported to the TGA (with advice on a voluntary or mandatory basis) and the timeframes for reporting.

(f) Implementation

During the agreed transition period of three years it is proposed that there will be a staged implementation of the new framework for currently supplied HCTs. Classes 1 and 4 will be implemented over the three year period. Submissions for Classes 2 and 3 products, establishing compliance with relevant standards or quality, safety and efficacy (as applicable) should be lodged with the TGA between 12 and 18 months following establishment of the framework with the expectation of full compliance by the end of the three year transition period.

The documents that will underpin the regulatory framework (including the Standards and the Manufacturing Principles) are continuing to be developed in consultation with stakeholders and with the advice of the Therapeutic Goods Committee and other relevant committees.

(g) General Provisions

The general regulatory provisions relating to sponsors, manufacturers, products, import-export, supply, record keeping and so on will also be applicable in the regulation of HCTs.
**XENOTRANSPLANTATION**

**A SUMMARY OF WHAT’S HAPPENING AROUND THE WORLD**

**United States of America**

The United States Food and Drug Administration (FDA) is responsible for evaluating the risks and the scientific and potential clinical merit of xenotransplantation clinical trials and determining whether clinical trials may proceed. Xenotransplantation products are regulated under the *Public Health Service Act* (1944) and the *Federal Food, Drug and Cosmetic Act* (1938), and trial applications are made under the FDA’s Investigational New Drug (IND) program.\(^7\)

In addition to these regulations, the FDA has published several guidance documents that address clinical trial, manufacturing, preclinical, and various safety issues raised by xenotransplantation, which include\(^8\):

- Guidance for Industry: Public health Issues Posed by the Use of Non-Human Primate Xenografts in Humans (4/99);
- Draft 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 (12/99, 2/02);
- Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (4/2003);
- PHS Guideline on Infectious Disease Issues in Xenotransplantation (1/2001)

The FDA endeavours to meet the challenge of regulating xenotransplantation to allow its development while safeguarding public health, using the existing FDA framework, publishing guidance documents, public engagement, interagency collaboration, and collaborating with international bodies (Bloom, 2007). In 2005, development started on a National Xenotransplantation Database, which was to have seven categories of information (WHO, 2005).

**European Union**

Xenotransplantation clinical trials are taking place in several different Member States of the European Union.

Council of Europe Recommendation Rec(2003)10 of the Committee of Ministers to members states on xenotransplantation was adopted by the Committee of Ministers on 19 June 2003, at the 844th meeting of the Ministers’ Deputies, and covers all xenotransplantation activities involving human beings as recipients. Article 4 of the Recommendation states no xenotransplantation should be carried out in a member state that does not provide regulation for xenotransplantation activities in conformity with the provisions of this recommendation.

In November 2006, the EU officially approved the funding of the XENOME consortium, a European Commission-funded multidisciplinary effort through which the EU will be present.

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\(^7\) [http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm](http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm)

\(^8\) [http://www.fda.gov/BiologicsBloodVaccines/Xenotransplantation/default.htm](http://www.fda.gov/BiologicsBloodVaccines/Xenotransplantation/default.htm)
in this scientific field for the next 5 years. The XENOME project has the mission of bringing xenotransplantation closer to its clinical application, and includes 22 academic/private institutions across 11 countries. XENOME contributes to critical research in life sciences and biotechnology that may contribute significantly to the Lisbon Objective of the EU, that is, for Europe to become the most competitive knowledge-based economy in the world by 2010 (Cozzi, Gianello, Soulillou, 2007).


United Kingdom

The UK Department of Health published new guidance on xenotransplantation in December 2006. The guidance (United Kingdom Department of Health 2006) recommends that all xenotransplant procedures are carried out in a research context with appropriate approval from research ethics committees, and aims to put a framework in place to help clarify requirements and allow research to continue to develop with open discussion and debate. Although the guidance provides a framework for assessment of clinical trials involving xenotransplantation, currently there are no xenotransplant trials running in the UK, and have been no pig transplants, or any animal organ transplant into humans, at any time in the past.

The release of the guidance coincides with the cessation of the United Kingdom Xenotransplantation Interim Regulatory Authority’s term of appointment.

Mexico

Xenotransplantation commenced in Mexico in 2000, in response to a very high prevalence of diabetes (12.8% of the population, 10% of which are Type 1). Findings of xenotransplantation research carried out by the Laboratorio de Xenotransplantes in Mexico have been appearing in journals since at least 2002. The same laboratory also provides treatment to patients with diabetes. Mexican Health Law contains a transplantation regulation that specifically encompasses xenotransplantation, which is supervised by the “highest health authorities in Mexico” (Valdes-Gonzalez, 2006). There is indication that trials in Mexico are approved by the National Transplant Center and the National Bioethics Committee, conducted according to relevant articles of the Declaration of Helsinki, and that the Laboratorio de Xenotransplantes intends to monitor patients indefinitely.

Canada

In 2005, there was a moratorium on xenotransplantation in Canada, which has since been lifted (WHO, 2005). Xenografts are considered therapeutic products and are subject to the requirements of the Food and Drugs Act, and the Food and Drug Regulations or the Medical Devices Regulations. Guidance Document on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Animal Tissue or their Derivative(s) outlines the regulatory safety requirements for Class IV medical devices that

9 http://www.xenome.eu/introduction.aspx
are manufactured from or contain animal tissue, in compliance with the licensing provisions in section 32(4)(j) of the Medical Devices Regulations¹¹.

Clinical trials of xenotransplantation cannot proceed without the approval of Health Canada¹².

**New Zealand**

A moratorium on conducting of xenotransplantation clinical trials was in place until 31 December 2006. In October 2008, the New Zealand Health Minister approved an application from an Australian company (Living Cell Technologies; LCT) to conduct a Phase I/IIa clinical trial of an encapsulated porcine pancreatic islet cell (DIABECELL®) in New Zealand.

The trial will be carried out on eight patients at Middlemore Hospital in Auckland. On 19 June 2009, LCT reported that it had accepted a condition requested by the New Zealand Minister of Health, the Hon Tony Ryall, that “would require (LCT) to amend the inclusion criteria of (LCT’s) study to limit participation in the study to patients with brittle diabetes who suffer from significant metabolic instability is essential to ensure that the study complies with international guidelines, which require that participants obtain maximum benefit possible from their participation in the study” (Living Cell Technologies, 2009). The trial commenced on 23 July 2009.

**Russia**

Regulation N 4180-1¹³ covers the transplantation of human organs and/or tissues; however there is scant (online) information on xenotransplantation and its regulation in Russia. Nevertheless, both clinical trials and xenotransplantation treatments are underway in Russia. In May 2009, the Australian company Living Cell Technologies (LCT) reported preliminary data showing sustained long term clinical benefit in patients treated with the DIABECELL® implant with no remarkable adverse events, with two of seven patients reported to no longer require insulin injections. The trial is taking place at the Sklifosovsky Institute in Moscow, under the guidance of Professor Nikolay Skaletsky.

Xenotransplantation treatments are also available in Russia. For example, the Shumakov Institute of Transplantation Science and Artificial Organs, affiliated with the Russian Ministry of Health and Social Protection, states that it has conducted more than 2000 transplants of pancreatic islet cells from newborn rabbits in the treatment of Type 1 diabetes in the past 30 years¹⁴.

Concern has been expressed (Grose, 2007) that Russia does not have rules governing xenotransplantation, and that Russia may have been chosen as the location for the LCT studies because its national health authorities do not appear to have such standards for oversight and monitoring of xenotransplantation trials.

**Japan**

Regulation of xenotransplantation in Japan is not based on a law, but on Public Health Guidelines published in 2002 (WHO 2005). The Guidelines include a system for reviewing

¹³ Ведомости Съезда народных депутатов Российской Федерации и Верховного Совета Российской Федерации, 1993, N 2 “О трансплантации органов и (или) тканей человека”
xenotransplantation protocols, how to obtain informed consent, quality controls for donor animals, the records and samples to be kept for donor animals and recipients, lifelong recipient surveillance, and a reporting system. The definition of xenotransplantation in the Guidelines is consistent with that adopted by the WHA in Resolution 57.18. At 2005, no clinical xenotransplantation trials had been planned, and aside from treatment of skin cultured using 3T3 feeder cells, no xenotransplantation activities were taking place in Japan.

Korea

The Korean government has funded xenotransplantation research that includes overcoming problems of tissue rejection and function. At 2005, there were no provisions to regulate xenotransplantation specifically but some aspects could be controlled through the Bioethics and Biosafety Act, and draft ethical guidelines for xenotransplantation were in preparation and likely to be translated into law (WHO 2005).

China

At 2005, there was no regulation of xenotransplantation in China however the Ministry of health was drafting regulations. Some treatments, including use of chemically treated pig skin to treat burns, and use of bovine jugular vein for the repair or heart defects had been reported (WHO 2005).

India

In India, transplantation is regulated by the Transplantation of Human Organs Act (1994), and, at 2005, there was a moratorium on xenotransplantation. Country specific concerns include the risk of development of xenotourism, difficulty in enforcing regulation, difficulty of testing for known and unknown pathogens, and ensuring prolonged recipient follow-up. Reports of xenotransplantation using goat hepatocyte cells are unsubstantiated (WHO 2005).
First WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials
Changsha, China, 19-21 November 2008
The Changsha Communiqué
Changsha Principles

1. Successful xenotransplantation has the potential to treat a wide range of serious diseases like diabetes, heart and kidney disease. Successful xenotransplantation could provide transplants for people who currently will not get a transplant.

2. Animals, particularly pigs, could potentially provide a plentiful, readily available, high quality source of cells, tissues and organs for transplantation. Genetic modification of source animals may overcome graft rejection and may improve function. In addition the risk of transmission of infections can be greatly reduced by excluding known infectious agents. These objectives must be achieved while strictly abiding by animal welfare rules.

3. However, xenotransplantation is a complex process which carries risks, including graft rejection, inadequate graft function and transmission of infections to the recipient. There is the theoretical risk of developing serious or novel infections which could infect not just the transplant recipient, but also close contacts or the wider human or animal populations.

4. Because of these wider community risks, xenotransplantation clinical trials and procedures need to be effectively regulated. There should be no xenotransplantation in the absence of effective regulation by the government of the country. Regulation should have a legal basis with powers to ban unregulated procedures and enforce compliance with regulatory requirements. The regulatory system should be transparent, must include scientific and ethical assessment and should involve the public.

5. Because of the community risk, in proposed clinical trials of xenotransplantation there should be a high expectation of benefit to balance the risk. The level of this expectation should be in proportion to the level of the risk. The level of safety and efficacy should conform to accepted international standards and requires pre-clinical studies usually in non-human primates. Proposers of trials must provide all the information required by the regulatory authority to assess the risks and determine how the risks can be minimised.

6. Proposers of clinical trials must be able to clearly justify doing a particular trial on a specific patient population. Patient selection should be on the basis of informed consent from well-motivated patients willing to accept special conditions that may be required by the trial. Patients, and possibly their close contacts, should be effectively educated about their treatment to encourage compliance.

7. Trial participation will usually require the storage of pre- and post-treatment specimens and life-long follow-up of recipients and possibly their close contacts. There must be rigorous analysis of trial outcomes and all recipients must be registered in an appropriate database while their privacy must be protected. If anything happens to prevent the proposers continuing the trial, there must be an adequate provision for all records, data and archived samples to be taken over by the regulatory authority or other state organisation.
8. Medical teams must have appropriate expertise and understand the risks to the patients, themselves and the community. Because of the potential for community infectious risk, there must be a system in place for xenotransplant vigilance and surveillance with contingency plans to identify, contain and combat any outbreak of infection in a timely manner.

9. There needs to be a global system for overseeing xenotransplant regulation, exchanging information, preventing unregulated “xenotourism”, providing support for states and coordinating xenotransplantation vigilance, surveillance and response to suspected infections.

10. Because of the potential benefits of successful xenotransplantation, consideration should be given from the beginning to future equitable access to this therapy and the public sector should be encouraged to support xenotransplantation research and development.

The Changsha Key Recommendations

To WHO

1. WHO should have a dedicated resource to develop and support a plan for global action for xenotransplantation.

2. WHO should inform Member States of the need to assess xenotransplantation practices in their territory.

3. WHO should encourage and, if requested, support Member States in assessing their capacity to regulate xenotransplantation and identifying xenotransplantation practices in their territory.

4. WHO should promote public awareness of the potential benefits of successful xenotransplantation and of the potential dangers of unregulated xenotransplantation including xenotourism.

5. WHO should have in place a system for the identification, combat and control of any xenotransplantation infectious disease outbreak in a timely manner.

6. WHO should support the inventory of worldwide xenotransplantation practices.

7. WHO should maintain a register of xenotransplantation trials and a list of experts who can advise Member States on aspects of xenotransplantation and of specialised laboratories able to test for xenotransplant-related pathogens.

8. WHO should promote future equitable access to successful xenotransplant procedures.

To Member States

1. Member States should take immediate steps to identify any xenotransplantation practices in their territory and ban those that are unregulated. They should promote public awareness of these practices and their risks.

2. Member States should ensure that public health officials are aware of the infection risks of xenotransplantation, including those associated with xenotourism activities occurring
outside their territory, and have plans in place to timely identify, combat and control any such infection.

3. Member States should review their laws to determine whether they have adequate powers to regulate xenotransplantation, ban unregulated xenotransplantation and penalize failure to comply.

4. Member States should assess whether they have the resources and capacity to regulate xenotransplantation effectively. If not, they should ban xenotransplantation in their territory.

5. If a Member State has the capacity to regulate xenotransplantation and believes xenotransplantation should be carried out, it should ensure there is an effective regulatory process in place.

To investigators and proposers of xenotransplantation procedures and trials

1. Investigators must ensure that source animals are as safe as possible, using a closed colony of consistently known specific pathogen-free animals.

2. Investigators must provide clear justification for the trial, including adequate pre-clinical data on safety and efficacy, usually from non-human primate testing.

3. Investigators should select trial participants for whom there is no effective alternative therapy and who understand the risks and consequences of the procedure, including the need for compliance with life-long follow-up and who are motivated to modify their behaviour accordingly.

4. Investigators must provide appropriately trained and experienced personnel to provide the transplant material and conduct the clinical trial and surveillance.

5. Investigators must have a comprehensive plan for effective communication with public health authorities overseeing the trial.

6. Investigators must have a comprehensive plan for post-transplant long-term patient follow-up, timely identification and management of possible xenotransplant-related infection episodes.

7. Investigators must ensure storage of appropriate pre- and post-procedure specimens and maintain both the specimens and records for 30 to 50 years, in accordance with national regulatory guidelines.
WHO CRITERIA FOR DEVELOPING A XENOTRANSPLANTATION INFECTIOUS AGENT EXCLUSION LIST

1. Source animals should be physically and physiologically healthy and free from signs of clinical disease.

2. Source animals should be free of recognized zoonotic agents transmissible to man outside the xenotransplant environment. For example: rabies virus, monkey pox virus, *Brucella suis*, *Mycobacterium* spp., etc.

3. Source animals should be free of zoonotic agents with transmission potential that is enhanced by the xenotransplantation application. For example *Trypanosoma cruzi*, *Ascaris* spp. larvae, *Toxoplasma gondii*, EMCV, etc.
   a. agent transmission facilitated by direct tissue exposure.
   b. agent transmission facilitated by recipient immune suppression.
   c. agent transmission facilitated by other altered internal environments in the recipient, i.e. chimerism or other manipulation.

4. Source animals should be free of recognized human-origin infectious agents. For example: measles virus, Rubella virus, etc.

5. Source animals should be free of infectious agents not normally considered zoonotic but whose transmission is achieved by the xenotransplantation procedure. For example: *Hepatocystis kochi*, etc.
   d. agent transmission facilitated by direct tissue exposure.
   e. agent transmission facilitated by recipient immune suppression.
   f. agent transmission facilitated by other altered internal environments in the recipient, i.e. chimerism or other manipulation.

6. Source animals should be free of infectious agents possessing high mutation or recombination potential which could lead to pathogenicity in the new human host. For example: influenza viruses, rota viruses, parvo viruses etc.

7. Source animals should be free of infectious agents known to be resistant, non-amenable or refractory to therapeutic treatment, and be free of agents for which no effective therapeutic intervention has been defined. For example: antibiotic resistant bacteria, drug resistant parasites, etc.

8. Source animals should be free of infectious agents of geographic relevance, both domestic and exotic. For example: *Trypanosoma cruzi*, African Swine Fever, Swine Vesicular Disease virus, etc.
   g. agents endemic to the geographic origin of source animals.
   h. agents considered exotic to an area, but which have importation potential.

9. Source animals should be free, as far as technically possible, from newly recognized agents before their pathogenicity and transmission potentials are defined, and before it is determined that they do not present an unacceptable* risk to public health.

* unacceptable must be defined within the context of developed agent lists, and should reflect a consensus of both scientific understanding and reasoned public opinion. Its definition must be dependent on sound professional judgement. Unacceptable may equate to a high potential for disease transmission, pathogenic capability, and/or likelihood of exposure. It might, however, equate to moderate or low potentials combined with low public tolerance for a transmission event.