

Project Officer- Xenotransplantation Health Ethics Section NHMRC (MDP 100) GPO Box 9848 CANBERRA ACT 2601 ahec.nhmrc@nhmrc.gov.au	Gene Technology Ethics Committee Professor Don Chalmers C/o Committee Secretariat Office of the Gene Technology Regulator MDP 54 PO Box 100 WODEN ATC 2606
--	--

**2ND ROUND SUBMISSION ON THE DRAFT GUIDELINES ON
XENOTRANSPLANTATION RESEARCH**

**ANIMAL-TO-HUMAN TRANSPLANTATION RESEARCH:
HOW SHOULD AUSTRALIA PROCEED?**

GENE TECHNOLOGY ETHICS COMMITTEE

DRAFT NHMRC GUIDELINES AND DISCUSSION PAPER ON XENOTRANSPLANTATION

Introduction

The Xenotransplantation Working Party (XWP) should be thanked and commended for the work they have done to produce the Response to the 2002 public consultation on the *Draft Guidelines and Discussion Paper on Xenotransplantation*.

This submission from the Gene Technology Ethics Committee (GTEC) emphasises aspects of particular concern to GTEC in relation to xenotransplantation involving genetically modified (GM) source animals. In its comments where GM animals are involved, GTEC is applying its broad responsibilities under the *Gene Technology Act 2000* (GT Act).

GTEC does not wish to make a submission on the issue of whether or not xenotransplantation clinical trials should be allowed to proceed in Australia.

1. The role of the OGTR

Page 153, paragraph 12.48 states that the role of the Office of the Gene Technology Regulator (OGTR) in administering the GT Act would form part of any regulatory scheme, but does not provide any further information on the role of the OGTR in the regulatory process.

It would be helpful if the document could clarify the relationship between the OGTR and its advisory committees and the proposed regulatory process. We submit the XWP may wish to include the following brief summary of the role of the OGTR and its regulatory powers under the GT Act.

The Role of the Gene Technology Regulator

The GT Act represents the Australian Government's component of a national regulatory scheme to identify and manage risk to the environment and risks to human health and safety posed by, or as a result of, gene technology. Under the GT Act, dealings with genetically modified organisms (GMOs) are prohibited unless the dealing is covered by a GMO licence, is a low risk dealing, is an exempt dealing or is included on the GMO register.

The GT Act also established three gene technology advisory committees to respond to requests for advice from the Gene Technology Regulator (the Regulator) or the Gene Technology Ministerial Council (the Ministerial Council). These committees are the Gene Technology Technical Advisory Committee (GTTAC), the Gene

Technology Community Consultative Committee (GTCCC) and the Gene Technology Ethics Committee (GTEC).

The GTTAC is mandated under the GT Act to provide scientific and technical advice on gene technology, GMOs and GM product; applications made under the GT Act; and the biosafety aspects of gene technology. In addition, the GTTAC can provide advice on the need for policy principles, policy guidelines, codes of practice and technical and procedural guidelines in relation to GMOs and GM products, and the content of such principles, guidelines and codes.

The GTCCC is mandated to provide advice on matters of general concern identified by the Regulator in relation to applications made under the GT Act, and matters of general concern in relation to GMOs. In addition the GTCCC can provide advice on the need for policy principles, policy guidelines, codes of practice and technical and procedural guidelines in relation to GMOs and GM products, and the content of such principles, guidelines and codes.

The GTEC is mandated to provide advice on ethical issues relating to gene technology. GTEC also advises on the need for, and content of, codes of practice and policy principles in relation to the ethics of conducting dealings with GMOs, and in relation to dealings with GMOs that should not be conducted for ethical reasons.

The gene technology advisory committees could be requested, by the Regulator or Ministerial Council, to provide advice on issues relating to xenotransplantation dealings that fall within the scope of the GT Act.

As described on Page 130 of the Response Paper, in terms of xenotransplantation, the Regulator would only regulate the use of GM source animals. It is anticipated that the actual transplantation products, sourced from these GM animals for use in humans, would be classified as GM products under the GT Act. These GM products would not be further regulated by the Regulator, as regulation of these products would be conducted by the relevant agency (in this case the Therapeutic Goods Administration). However, the TGA is required to seek advice on GM products from the Regulator.

The Ministerial Council, in response to advice from the Gene Technology Advisory Committees can form policy principles and policy guidelines in relation to the use of GMOs. The Regulator is required to take these into consideration when assessing a GMO licence application and must not issue a licence that is inconsistent with a policy principle.

It would also be helpful if a formal mechanism of direct communication existed between the body overseeing xenotransplantation work and the OGTR to ensure that decisions are not made in isolation.

We invite the XWP to consider whether readers of the proposed Guidelines may need be reminded how preliminary research (eg into genetic modification of the donor animals or pre-clinical animal to animal research) is regulated so that it is clear how this fits in with any proposed clinical trials.

2. Ethical issues raised by xenotransplantation

The Committee felt that while ethical issues were discussed in Section 4 of the Response Paper, ethics were not adequately addressed in the Guidelines themselves. This related to both the issues arising from xenotransplantation per se, and also from those specific to the creation and use of genetically modified animals.

Pages 27-28 of the Response Paper discuss some of the ethical issues raised by the genetic modification of animals to make them more suitable as a source of human tissue. Paragraph 4.31 expresses how difficult some of these issues are to resolve and that it is outside the scope of the XWP. GTEC is currently working towards the development of broadly based ethical guidelines for application under the GT Act that should include the main issues raised in this section relating to the use of genetically modified organisms.

Pages 58-60 of the Response Paper discuss the animal welfare issues raised by the genetic modification of animals.

These are summarised as:

- the nature and extent of the genetic modification;
- the potential adverse effects of the genetic modification;
- the unpredictability of adverse effects associated with genetic modification; and
- the wastage of animals.

The last three points are issues that can be dealt with, to some extent, by the current system of institutional Animal Ethics Committees (provided they receive some guidance as proposed in 5.17). However, the first point is more of an ethical issue than a purely animal welfare issue and should also be considered by the wider community.

The genetic modification of animals for the purpose of making them more suitable as sources of human tissue raises particular ethical questions in terms of how far such modification should be allowed to go. The Response Paper covers this to some extent in Chapter 4, but it is not specifically addressed in the guidelines. There is a reference to ethical issues under the "Advice regarding the application of the proposed guidelines". This advice follows the general format of the guidelines but includes as a first section "A. The common good", under which it states: "Are the ethical issues associated with the procedure acceptable to the general public?".

Suggested change to the Guidelines:

GTEC suggests that the statement referring to ethical issues (and those associated with it) under 'The common good' on p160 should be added to the previous section to form an additional Guideline, eg.

Guideline X (Ethical issues and the common good)

*Research protocols must include a discussion of the ethical issues raised by the proposed trial in terms of the benefits and risks of the procedure to the individual and the public.**

* The XWP should consider including discussion of the potential risks to other animals or the environment here.

An additional question should then be added to the section 'Advice regarding the application of the proposed guidelines' in Box A (the common good) as follows:

What ethical concerns are there about the use of this procedure?

GTEC also suggests that a review of the proposed Guidelines be built-in to the process. This review should take place no more than three years after their implementation. GTEC would like to be involved in the review process.

3. Environmental issues

The GTEC invites the XWP to consider including some comments on environmental issues. GTEC noted that there is a lack of reference to the potential environmental impacts of xenotransplantation. Animal-to-human transplants may have the potential to impact on the environment (for example, if novel or evolving disease agents were to emerge and be released as described on **page 104**). This potential impact should be recognised in order to ensure that the risk can be assessed and monitored.

Under the GT Act, the Regulator is responsible for the protection of human health and safety and the environment from risks posed by or as a result of gene technology. Dealings involving a risk to the environment posed by gene technology are only allowed to proceed if the Regulator has determined the risks to be manageable and in most cases these dealings, such as the production of GM source animals for xenotransplantation, are also required to be licenced by the Regulator. The Regulator can impose stringent licence conditions to protect the environment from the risks posed by gene technology. The TGA would be responsible for organ/tissues (GM products) used for xenotransplantation. The TGA is required to seek advice on GM products from the Regulator.

4. Control over clinical trials

There is also a concern over the assumption inherent in the document that xenotransplantation studies will be able to be controlled with the same level of clinical control as ordinary clinical drug trials. The reason for the enactment of the GT Act was that gene technology, both in research and application, requires special regulatory processes, not the least of which is the ethical component. For example, the Response Paper proposes that institutional Human Research Ethics Committees (HRECs) will continue to exercise a 'front line' role in approving or disapproving proposals for xenotransplantation research. There is a concern that the current 'mutual acceptance' approach adopted by some institutions for projects that involve more than one institution (ie. where one HREC goes through the approval process and the others 'rubber stamp' the approval), will make it very hard for independent decision making to be achieved.

5. Proposed regulatory process

GTEC supports the proposed framework that requires researchers to submit their application for a clinical trial to the National Committee (expanded GTRAP) for consideration prior to its submission to the institutional HREC or AEC. However, the Committee did not find it acceptable that researchers/sponsors could apply to a different institution if their proposal was rejected by the HREC or AEC.

GTEC suggests that there should be a requirement for the disclosure of any previous rejections by HRECs or AECs when making submissions to ethics committees. Where an application that has been rejected by one committee is revised and then presented to a different committee (or re-presented to the original committee), the applicants should be required to provide information on:

- (a) how the application has been changed, and
- (b) how the new application addresses the issues raised by the AEC/HREC, or
- (c) why the application has not addressed these issues.