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**SUBMISSION ON THE DRAFT GUIDELINES ON
XENOTRANSPLANTATION RESEARCH**

GENE TECHNOLOGY ETHICS COMMITTEE

DRAFT NHMRC GUIDELINES AND DISCUSSION PAPER ON XENOTRANSPLANTATION

Introduction

The Draft Guidelines and Discussion Paper were found by the Gene Technology Ethics Committee (GTEC) to be generally thorough, clearly written and accessible to a public audience.

The Working Party should be thanked and commended for the work they have done to produce the public consultation document.

These proposed guidelines demonstrate a commendably cautious approach to clinical xenotransplantation. During the 1997-2000 triennium the NHMRC began initial consideration of xenotransplantation. The Australian Health Ethics Committee (AHEC) did not draw up guidelines at this time. The AHEC decided not to proceed until reliable scientific advice had been received from the Xenotransplantation Scientific Working Party. These Draft Guidelines and the accompanying Discussion Paper continue this careful, considered and cautious approach to this issue.

The proposed Guidelines are consistent with, and should be read in conjunction with, the *National Statement on Ethical Conduct of Research Involving Humans* (National Statement). This is a sensible proposal ensuring consistency with the over-arching National Statement Principles. Specific Xenotransplant Guidelines are to be included in a separate document. This is entirely consistent with other similar complex early stage research. For example there are separate guidelines for somatic cell gene therapy and those guidelines are read in conjunction with the National Statement.

This submission from GTEC makes general comments on the Draft Guidelines and Discussion Paper, but also emphasises aspects of particular concern to GTEC in relation to xenotransplantation involving genetically modified animal donors. In its comments where genetically modified animals are involved, GTEC is applying its broad responsibilities under the *Gene Technology Act 2000* (GT Act). GTEC is working towards the development of broadly based ethical principles for application under the GT Act, that will include those that relate to protection of the environment, not just relating to protection of the health and safety of people.

Fundamentally GTEC is concerned that the 'medical model' upon which these Draft Guidelines is based is not sufficient to deal with broader environmental concerns and animal welfare issues. This is of particular concern where the donor animals are genetically modified (GM).

GTEC notes that the working party was asked to address issues arising for humans *and* for animals. Basic research not directly related to clinical practice was outside the scope of the Working Party, but GTEC is concerned about the lack of oversight of pre-clinical research and the

likelihood of inadequate information about pre-clinical research to guide decision-making in relation to clinical research.

At the very least, more needs to be said in the introduction to the summary paper about the animal-animal research and how that is currently regulated, with some greater elaboration of the role of the Office of the Gene Technology Regulator (OGTR) where GM animals are involved.

The Draft Guidelines and regulatory structure draw an artificial distinction between animal-to-animal studies and animal-to-human studies. The proposed regulatory system must be able to examine and discuss the full range of ethical and scientific issues arising from xenotransplantation research. Animal welfare concerns arise with both pre-clinical and clinical research, and these concerns are the same whether the source animal's tissue is transplanted to a human or another animal. The regulatory authority will require information on animal-to-animal studies to inform its decisions on when it is appropriate to progress to clinical studies. The same researchers will be involved and there is likely to be considerable overlap between the two study types, especially since they will be using the same source animals. It is also likely that animal-to-animal studies will be carried out in parallel to animal-to-human transplants as the science progresses.

The Discussion Paper states that there may be an "ill-defined point at which little or no further progress can be made without proceeding to a human clinical trial" (page 59, 5.6.1, last paragraph). The proposed regulatory authority should be the body making the final decision about when this point has been reached, rather than the researchers involved, however such a decision would require knowledge of the progress of current preclinical studies.

Xenotransplantation research must pass through many developmental stages before reaching a proposal for clinical trials. These stages will involve many animals, may take place over a number of separate institutions and may be examined by a number of separate institutional Animal Ethics Committees (AECs). At present there is no means of monitoring the development of xenotransplantation through animal-to-animal studies, since there is no requirement for these studies to be reported outside of the AEC. While AECs are required to weigh the scientific value of a study against the potential effects on the welfare of the animals, this is done on a case-by-case basis. With the proposed system, preclinical trials would continue to be carried out without examination of the ultimate ethical implications of such work, and with no means of comparing the quality or progress of such studies across institutions.

GTEC considers that the solution to this problem is to expand the terms of reference of the proposed regulatory models to include (preclinical) animal-to-animal trials.

Alternatively, if the current scope of the Draft Guidelines is to remain in the final version, the title of the document and guidelines should make it clearer that they refer only to clinical xenotransplantation.

Although the content of the Discussion Paper is comprehensive, some important points tended to be over simplified or lost in the distillation in the Summary Paper, and some additional matters dealt with in the Discussion Paper should be included/highlighted in the guidelines themselves.

Draft guidelines

The draft guidelines do not make any direct reference to the need to ensure high standards of animal welfare. Guideline 1 (Efficacy) refers only to the need for animal-to-animal studies to be “conducted in accordance with the NHMRC *Code of Practice for the Use of Animals in Medical Research*” which is already a legal requirement. It is suggested that the sentence “conducted in accordance with the NHMRC *Code of Practice for the Use of Animals in Medical Research*” is removed from Guideline 1, and a new guideline inserted:

“Guideline (Animal welfare)

All xenotransplantation studies involving animals must be conducted with due regard for high standards of animal welfare and in accordance with the *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* and any relevant associated guidelines or policies. The use of non-human primates as source animals for xenotransplantation is considered to be ethically unacceptable.”

Include a guideline that refers to the National Statement to set the fundamental standards for this research.

Include a guideline that refers to compliance with the standards and requirements of all relevant pieces of legislation, such as the GT Act, *Therapeutic Goods Act 1989* (TG Act) etc.

At Guideline 2 include the need to assess the potential socioeconomic impact of this work (mention is made of some relevant points on page 23 of the Discussion Paper). Also include the need for follow-up studies of efficacy and safety in the protocols, not just assessment of immediate safety issues or establishment of vague ‘surveillance’.

There is no specific guideline on the "common good". A guideline to the effect that; "any proposed xenotransplantation trial should demonstrate that there

are both public and individual benefits and that there are no suitable alternative procedures available" should be included.

Guideline 2, dealing with the critical concerns about risk, should also reflect the general standard in the National Statement of the acceptable balance between risks and benefits. Again there seems to be some discordance between the very brief Guideline 2 and the detailed safety risk analysis in section C of the Advice regarding the application of the proposed guidelines. Perhaps Guideline 2 could include some reference to the completion of a detailed risk assessment analysis before consideration of approval of the proposed trial.

Guideline 4 could perhaps make clear that the surveillance may include both data linkage studies and further monitoring and contact. The research protocol must indicate appropriate information giving and consent for both types of surveillance.

Guidelines 5 or 6(b) may be where information about proposed linkage as well as contact studies is set out.

Guideline 6 (a) should include reference to this information including identifying information.

Advice

The common good (**Advice: A**): should include some mention of the risk to the public and the environment (eg where GM animals are involved). There also should be a requirement for the design of the study to include a good protocol for follow-up of efficacy.

Efficacy assessment: (**Advice B**): should include some advice on the route to approval if a GM animal is involved (or would this fit better in C or E?).

Reference should be made to the requirement for surveillance to be carried out in well-designed studies. The proposal design should include a protocol for assessment of the short and long term risks. It seems that while a great deal is made of the need for careful assessment of the safety of the proposals and the need for ongoing 'surveillance' of the proposals is discussed, little is made of how this 'surveillance' will be carried out. Surely this is a vital part of any proposal. More attention needs to be given to the setting of guidelines and advice re the design of good follow-up studies that should be part of every proposal. Although likely not to have many specific requirements relating to xenotransplantation, it should be clear that well designed follow-up is an integral part of these studies. Assessment of the proposals should include assessment of the follow-up proposed.

Information and consent (**Advice D**): Must include that ID information will be kept and that this may be used for linkage studies, with or without consent, but with HREC approval.

Summary Paper

With regard to the **Ethical issues**...p xxxvii...the top paragraph is odd, referring to 'a proper relationship between the giver and the receiver' when the giver is an animal. Need to redraft this to reflect what is said in the Discussion Paper, so this not just a phrase lifted from human donor situations!

Discussion Paper

Chapter 1.

Page 3. The danger of cross species infection as indicated at the bottom of the page ought to be spelled out more clearly and appropriate caution expressed.

Page 5. 1.3.3. It says that the OGTR is part of the 'target audience'. That is possibly an insult to the regulatory body that should have been involved in the development of the Discussion Paper.

Page 7. 1.5. Response to the Discussion Paper is limited to the questions they raise.

Chapter 2.

Definitions and key issues

The definition of xenotransplantation (eg excluding inert animal tissues) was considered by GTEC to be appropriate and it was agreed that any animal-to-human xenotransplantation must be for therapeutic research only.

From a community viewpoint however, the use of heart valves from a pig, while technically different from living cells, still raises a negative reaction. From the animal welfare point of view, the use of live and inert tissues both involve the killing of animals, however inert tissues may be derived from animals killed for other purposes (such as human consumption). It is the steps involved in the production of these animals that determines the impact on their welfare and these should be taken into account in the ethical decision making process.

Page 13. 2.2.

Essentially the argument justifying the use of xenotransplantation is based on the growing demand for organ transplantation and the possible effectiveness of transplant of cells etc for the treatment of a variety of diseases (diabetes etc). There is a detailed discussion of all the alternative possibilities such as artificial organs, but the conclusion reached is that xenotransplantation is the most likely source in the future.

The onus should be on researchers to demonstrate that other medical solutions are unavailable.

Page 20 Key Issues.

'Serving the common good': There is no attempt to define the ethical values that are acceptable to the community. On the other hand there is recognition of the negative public opinion about xenotransplantation. One would imagine that this is part of the overall distrust about gene technology and therefore community education on gene technology is vital.

Need also to reflect briefly that concern for the environment is a responsibility where GM animals are involved (GT Act).

Chapter 3

Is xenotransplantation acceptable?

GTEC agrees that, in principle, the procedure is justifiable. However, GTEC notes that there are serious impediments to its implementation, particularly arising from concerns about risk. GTEC considers it would not be ethical to do what is unsafe.

Are there other important ethical issues that need to be considered.....?

GTEC also considers that there are other important ethical issues that need to be considered in this debate, particularly where GM animal donors are involved.

In considering the basis of ethical consideration of xenotransplantation (page 24) the Discussion Paper separates personal values from public policy. There is reference to the importance of justice in the allocation of resources, but there is no mention of the impact on the ecology as a whole. What gene technology has done, however, is to demonstrate that the dividing line between individual values and ecological values is no longer distinct.

The Discussion Paper suggests it is acceptable to use animals for xenotransplantation so long as protocols are humane to animals and respect the essential characteristics and welfare of their species (page 23). This is an over-simplistic approach. The Discussion Paper says simply that the genetic modification of animals raises ethical issues that will need to be considered on a case by case basis. That begs the broader question of the place of animals in the ecosystem.

In addition, the Draft Guidelines and Discussion Paper are based on a medical model. This is understandable since they are directed towards clinical research. The ethical guidelines proposed by the Discussion Paper are strictly in accord with those already in place for medical research and the interpretation of the last of them ('public health risks') is likely to be similarly limited. However the model needs to be far more holistic – for example, the involvement of gene technology research requires the inclusion of ecological issues and social justice issues.

As set out below, GTEC has identified a tentative list of seven principles that are designed to provide a framework for ethical reflection on issues pertaining to gene technology. When these principles are applied to xenotransplantation it is apparent that, in principle, the procedure is justifiable although as noted above, there are still serious impediments to its implementation.

The issues involved with the Draft Guidelines and Discussion Paper are complex but can, for the sake of simplicity, be divided into two categories:

- The first involves *the pragmatics of the proper ethical conduct of the processes involved*. That is, for the process to proceed it has to be demonstrably safe with minimal risk. Under normal conditions it is not ethical to do what is unsafe. Similarly, appropriate consents are required and all work must involve adequate safeguards for the well-being of animals involved.
- The second category involves *matters of basic principle*. That is, it involves a consideration of whether the procedure ought to take place at all and whether there are any fundamental ethical principles that would prohibit such activity.

These comments relate only to this latter area and the tentative list of seven principles that may provide a framework and a foundation for discussion is suggested. The seven principles for gene technology ethics are expressed as values that ought to be preserved. These principles have not been produced with xenotransplantation in mind, but if they are genuinely applicable to the whole area of gene technology they should have something to say on this particular issue. So xenotransplantation becomes an opportunity to test these principles.

The seven basic principles suggested for gene technology ethics are:

1. Maintaining biological diversity
2. Preserving organismal integrity
3. Recognizing ecological holism
4. Producing social benefit
5. Respecting intrinsic value
6. Valuing human uniqueness
7. Minimising future liability

Social significance...Should there be a more extensive discussion of resource allocation.....?

The question of social significance is a difficult one. Xenotransplantation research and any clinical application will be expensive and one could always argue that there are better ways to allocate scarce health care resources. The cost will be high and therefore equity of access issues will need to be faced once the treatment becomes a reality. Discussions of resource allocation for xenotransplantation research and clinical trials should be embarked on now. By the time it is clear that xenotransplantation is likely to become a reality it will be too late to wind it back or change its trajectory.

Once it is a reality, access should be based on need, not on one's ability to pay.

The one alternative not presented is 'the best way to cure a disease is to prevent it' and as far as some diseases are concerned including heart, life style is probably the most common cause. Ethically therefore this should be said at some stage.

Chapter 4.

Is the central role of genetic modification of source animals in the research clearly described....?

This question is addressed at various points in the submission as GTEC does not consider this aspect to be sufficiently well addressed.

Chapter 5.

Is it possible to define a reasonable criterion for success in animal-animal studies...?

The question of efficacy needs further consideration. At present there has been only limited success of xenotransplantation of vascularised organs and marginally greater success with tissues and cells. There is obviously a long way to go before animal-to-human trials are likely to result in success rates of several months survival. If the fundamental criterion for such trials is that they must be therapeutic, then there should be a reasonable expectation that the xenotransplantation recipient is likely to benefit. Therefore, there needs to be some defined criterion for success in animal-to-animal studies on which progression to phase I clinical animal-to-human trials can be based. For example, a survival time of months rather than days or weeks. However, this would be a matter for experts, but it underlines the need for the inclusion of animal-to-animal studies in the regulatory model.

Chapter 6

Is xenotransplantation safe?

It appears to GTEC that there is a need for more careful consideration of any particular risks that may arise where the source animal is genetically modified.

The Discussion Paper does appear to suggest that there is a potential for additional risks in these cases, although in the risk analysis section of the document (chapter 6) there is only brief mention of risk analysis for xenotransplantation from genetically modified sources (page 71, para 2 & p 73, 6.5 para 2). While it is possible that the general risk analysis framework captures these risks adequately, the Discussion Paper could highlight more obviously how any special infection risks from xenotransplantation involving

genetically modified source animals (identified in 4.5, 4.5.1 and 4.5.2) are adequately addressed within the risk analysis framework.

GTEC also considers that the risk analysis framework should cover not only the scientific basis of risk analysis, but also the ethics of risk, which is an evolving aspect of GTEC's work.

More needs to be made of the need for inclusion of well-designed follow-up studies in the original protocols. Some attention in these studies needs to be given to the possibility that linkage studies may be involved in long-term follow-up and the differing consent issues for these and studies that involve contact and perhaps further intervention. The information giving and consent should prepare for the differing types of follow-up, and appropriate contact information and consent need to be obtained. However, participants should also be aware that linkage studies may be approvable by an HREC without their specific consent. Patients / close contacts should also be informed that they may be contacted if there is later public health concern or need for research and this raises a different aspect of consent to follow-up.

Chapter 7

Should close contacts be regarded as research participants?

This issue of risk is inextricably linked to questions of informed consent. Ordinarily it is the individuals who receive the treatment (and any benefits) who are asked to consent to the procedure because they will bear the burdens and risks. However, in xenotransplantation, close contacts of the recipient are also exposed to the risk of infection – yet they do not receive the treatment or benefits.

The Discussion Paper notes that to include close contacts as research participants would require the development of a new set of ethical principles, particularly in relation to the right to withdraw and long-term follow up. The Discussion Paper suggests that the inclusion of close contacts as research participants is not practical because it is difficult to rely on their long-term involvement. Making them research participants may encourage their long-term involvement and follow up. Since they are also the conduit for infection to the wider community it is important to impress upon them the importance of long term follow up. Xenotransplantation trials are not like other trials such as cancer trials, because with xenotransplantation the treatment can harm others. Therefore, the pressures that come to bear on a seriously ill person providing their voluntary and informed consent to the trial take on another dimension because the consequences may not just affect the recipient alone. In the case of xenotransplantation the proposed procedure may carry significant risks for all research participants (recipient and close contacts), which need to be matched by a real prospect of benefit and voluntary and informed consent.

GTEC considers that close contacts should be considered research participants and give their informed consent. This is in keeping with the

National Statement quoted on p80 of the Discussion Paper. Carefully developed criteria will be required however, to establish who should be considered a 'close contact'.

Are trials that require lifelong monitoring and follow-up....acceptable?

Whether or not participants should waive their right of withdrawal from the trial and agree to being followed up for the rest of their lives is also an extremely difficult issue. Perhaps in this case, because of the risks to the wider community, this unusual request may be prudent, even though it may not be prudent to rely upon it as an infection control measure.

However, it may be also imprudent to rely only upon the evidence provided by the investigators for the safety of the procedure. A number of infection control measures will need to be put in place. Xenotransplantation trials, at least in the initial period, should require life-long monitoring and follow up for emerging infectious diseases in both the recipients and their close contacts.

The comments on page xli of the Summary Paper re consent to monitoring and whether or not this should be compulsory are however quite sound, with the proposal being that organ recipients should be allowed to withdraw from the ongoing surveillance. If this is to be the prevailing position, more should be made of the sort of evidence that the investigators could provide to show that there is no undue risk should some participants withdraw from the trial. This would need also to be summarised better in Guidelines.

As noted above, some reference should be included to the different ways in which monitoring and follow-up may be carried out and the different issues associated with each. For example, monitoring carried out through linkage studies would not involve any further patient contact and may obtain HREC approval without patient consent.

Finally, the Discussion Paper does not mention what action could be taken if an outbreak of a virus such as PERV was to occur. This is an important issue that needs further consideration. Otherwise it is not clear how Guideline 2 (Safety) that "the public health risks of any proposed animal-to-human xenotransplantation trial must be minimal and must be acceptable to the community' can be reasonably satisfied.

Separation of the assessment of risk and ethics of genetically modifying animals *per se*, from the assessment of risks and ethics of the clinical application of GM materials in xenotransplantation may not be appropriate.

Chapter 8

GTEC considers that the Discussion Paper does not adequately deal with key issues for animal welfare.

The paper suggests that inherent ethical objections can be satisfactorily answered, but the writers have limited these objections to those that arise from the medical model. They do talk at the end of the page about 'practical animal ethics' (particularly with respect to animal welfare). This is added as a rider just as it is in the Declaration of Helsinki.

The Discussion Paper delineates between animal-to-animal studies, which are described as 'preclinical' and animal-to-human studies, which are described as 'clinical' (Page 18). It then goes on to say that at the moment research is confined to animal-to-animal studies in which attempts are being made to achieve genetic modification, so that immunological factors can be suppressed in subsequent animal-to-human studies. It says that all research involving animals must conform to the Australian Code of Practice for the care and use of animals (NHMRC). Again this is based on the 'medical model'.

Further information could be provided in Section 8.2 on the role of AECs, such as promoting the principles of replacement, reduction and refinement, and other aspects of their terms of reference, rather than relegating these to Appendix 4. It is also important to make the point here that AECs work in isolation from each other, and no central register of animal-to-animal xenotransplantation work is available under this system. AECs do not communicate with each other, nor are the nature of the proposals they see in the public domain.

Section 8.3 assumes that the genetic modification sought for xenotransplantation studies is unlikely to alter the animal in a significant way. However, the outcomes of the insertion of human genes into the pig genome are unpredictable, particularly given the lack of control over the insertion point of those genes. There is always the possibility that altering the pig genome will have a deleterious effect on the welfare of the animals involved and this should be acknowledged.

It is also difficult, if not impossible in many cases, for an individual AEC to build upon previous experience in an emerging technology, as suggested here, since there is no opportunity for AECs to share information on proposals. The researchers themselves are the most likely ones to use their experience to refine their proposals to the AEC. Most AECs are not in a position to 'learn from early experiences' unless they have been able to track proposals from a particular researcher and follow the development of this work.

There is currently no specific advice for AECs to help them in the assessment of proposals involving xenotransplantation. A checklist along the lines of that proposed on pages xxv-xxx would help with this.

The Chapter does not provide any information on the specific requirements for housing and husbandry imposed by xenotransplantation studies, such as the level of bio-containment and associated restrictions on enrichment, socialisation, rearing practices etc. Many of the techniques involved in the breeding and rearing of source animals will have significant adverse effects on the welfare of the animals involved and should not be overlooked. Details of each of these techniques and their welfare consequences should be provided. A statement should be added on the need to ensure that any adverse effects arising from the production of qualified-pathogen-free animals are minimised. Consideration should also be given to developing guidelines on the housing and care of pigs intended for use as xenotransplant source animals similar to those produced by the UK Home Office.

Section 8.5 makes a number of statements about the proposed role of the NHMRC AWC in overseeing animal-to animal studies. The AWC is not empowered to oversee such studies and reliance on the work of the AWC is misplaced.

Does this discussion adequately cover the key issues for animal welfare in xenotransplantation research?

The Discussion Paper has a number of major inadequacies when it comes to addressing the welfare effects of xenotransplantation research. Chapter 8 glosses over the welfare of source animals (ie pigs) and of recipient animals in animal-to-animal trials (ie non-human primates), leaving the impression that there few issues of concern, and that the AWC adequately covers those issues that do arise. In fact the AWC is not empowered to fulfil this role.

Are there any other areas of expertise that may be needed by the regulatory authority responsible for xenotransplantation in order to consider the issues addressed in this chapter?

The necessary areas of expertise are well covered by the inclusion of members as described, however it is important to ensure that these categories are clearly specified in the membership of the regulatory authority, ie it may not be enough to have animal welfare concerns represented by a cross-member with the AWC, unless that member's primary interest is animal welfare. The AWC, as with many such committees, has members whose primary interest (eg biomedical research) is different from the main aim of the committee but whose role is to provide relevant advice and a balanced viewpoint.

Chapter 9

The Discussion Paper makes several misleading references to the NHMRC AWC where it assigns the AWC a role in the overseeing of animal-to-animal xenotransplantation studies. This is not an accurate reflection of the role of the AWC since the Committee is not informed of individual research proposals, nor are institutional AECs required to report to the Committee. Furthermore the AWC's influence as an advisory committee extends only to NHMRC-funded research.

Section 9.2 states that the AWC monitors compliance with the Code of Practice. The AWC cannot do this since it is not informed of individual research protocols. The AWC carries out occasional inspections of facilities and can subsequently report on breaches of the Code, but its powers of enforcement are limited to the potential to withdraw NHMRC funding. In those states where the Code is attached to relevant legislation, the responsible government agency will carry out compliance checks and take action where breaches of the Code are found.

Involvement of the OGTR and the Therapeutic Goods Administration (TGA)

The section describing the GT Act and responsibilities of the OGTR needs to be much more clearly described and set out, to make clear differing requirements for approval depending on whether or not the donor animals have been genetically modified.

The Discussion Paper, under the GT Act section (eg 9.4) states that the genetic modification of source animals falls under the OGTR. This is quite clear. However at 9.3.2 it talks about the role of the NHMRC and the Gene and Related Therapies Research Advisory Panel (GTRAP) as the provider of advice to HRECs.

P. 109. The Paper's summary of the GT Act and the role the OGTR will play in the role of the regulator of xenotransplantation research in Australia is not considered to be adequate as it does not set out clearly the complex interrelationships between OGTR, NHMRC, GTRAP and TGA, let alone all the other federal and state bodies involved. There is a particular need to clarify the regulation of xenotransplantation research involving genetically modified source animals.

The GT Act specifically states that the Gene Technology Regulator (the Regulator) administers the GT Act and has its regulatory powers. That is the starting point for any discussion. If the Regulator sees fit to delegate responsibility or seek advice, that is their prerogative, however the Regulator retains the right to control all ventures involving GM.

Chapter 11

Options for regulation

The Draft Guidelines propose that all animal-to-human xenotransplantation trials must be overseen by a single national committee. This proposal is consistent with the approval processes for gene therapy trials. Animal-to-human xenotransplantation is at a very early stage of development. Applications should not be left to an individual institution or HREC (to approve a proposed trial).

Model 1 and model 2 in practice both may involve the same bodies GTRAP, HRECs, the OGTR where necessary). The question is whether animal-to-

human clinical trials be under the surveillance of a national committee comprising a reconstituted GTRAP (model 1) or a new national Xenotransplantation Committee (model 2).

GTEC considers that the model outlined as model 1 would be the preferred model.

This would fit with changes being implemented in the TGA and the new OGTR. Xenotransplantation would be overseen by a peak body (extended GTRAP) with relevant expertise and leadership.

There are a number of reasons favouring an extension of the existing GTRAP. The committee is independent, it is established within the NHMRC structure, it now interacts well not only within the NHMRC but in relation to the TGA and the OGTR. GTRAP has already been reconstituted in response to changed somatic cell gene therapy guidelines. Many of the issues in relation to animal to human xenotransplantation trials are not substantially dissimilar to the medical, technical, public health and scientific issues addressed by GTRAP currently. In addition, there is a limited pool of independent expertise in this country. It may be difficult to identify sufficient members for Model 2's proposed Xenotransplantation Committee. The current U.K. guidelines recognize this fact and require up to six approvals of any proposed trial (noting that no clinical trials are currently in progress in the U.K.).

This model has operated effectively so far in the area of human gene therapy. It is an appropriate model for xenotransplantation.

In terms of the membership of the proposed new committee based on GTRAP, it has already been suggested that those members identified in Chapter 8 should be represented.

Close communication between GTTAC, GTEC and the NXGTC will be essential where genetically modified animals are to be developed specifically for the purpose of xenotransplantation. Cross-membership between GTEC and the new NXGTC and relevant committees under the *Gene Technology Act 2000* should be supported.

Importantly, facing the national committee within the NHMRC structure provides greater public assurance of transparency and accountability. The NHMRC is required to place annual reports before parliament and is subject to the scrutiny of the Senate Estimates Committee.

In practice the OGTR and TGA should receive reports about ongoing xenotransplantation trials to ensure that both organisations are aware of transgenic work. The OGTR must retain its right to control all ventures involving GM.

As noted in the general points at the beginning of these comments, consideration should also be given to expanding the terms of reference of this committee to include animal-to-animal studies.

GTEC agrees with the views expressed in the Discussion Paper that the TGA is not the appropriate body for the purpose of approval of xenotransplantation trials. The complexity of both scientific and ethical issues are more appropriately dealt with within the existing HREC system, subject to oversight by a single national committee.

The complex interrelationships between GTRAP, OGTR etc and the NHMRC Act, TG Act and the GT Act (where genetically modified animals are to be involved) needs to be set out more clearly. The relationships where GM animals are involved are complex. More explicit flow charts would help clarify responsibilities between the regulatory/approval bodies and the order of steps to be taken in obtaining approval. This needs to be clear for situations where the animal is and is not GM.

Again on Page 105 the Discussion Paper reiterates that the Regulator administers the GT Act and approval of GM projects.

There appears to be no opportunity for public comment on wider environmental risks as part of the risk assessment process (page 76 and Chapter 6).

Glossary:

'Environment' should be defined here as per GT Act.