The Australian Society for Medical Research

July 12th 2005

Gene Technology Ministerial Council Secretariat
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

By email: gtreview.secretariat@health.gov.au

Re: Review of Gene Technology Act 2000

Please find following comments regarding the Review of the Gene Technology Act submitted on behalf of the Australian Society for Medical Research (ASMR). The ASMR represents a broad spectrum of Australians involved in the health and medical research sector. ASMR has over a thousand individual scientific members and through 47 affiliated specialist societies, medical colleges and patient groups represents a further 140,000 Australians involved, or having a direct interest in, health and medical research.

The health and medical research sector is directly and substantially affected by the Gene Technology Act and welcomes the opportunity to provide input into the Review. The ASMR is willing and well positioned to participate in further discussions regarding our submission and the Review in general. Should further input or clarification of our submission be required, please do not hesitate to contact myself, our Chief Executive Officer, Ms Catherine West, or the ASMR Director concerned with OGTR issues, A/Prof Mike McGuckin.

Yours sincerely,

A/Prof Bronwyn Kingwell
ASMR President

Scope of Act

1. *Review the scope of the Act to determine whether the policy objectives remain valid; and consider other issues, technologies or organisms that may be included in the scope of the Act, including:*

a. *consideration of economic, marketing and trade, cultural and social impacts, and re-examine how ethical issues are considered*

b. *the definitions in the Act, including of the environment, and the need for the definition of other terms, including health*

c. *consideration of the technologies and organisms covered by the Act*

d. *consideration of a trait based or novel organism based regulatory scope*

The overarching plea from the health research sector is that the level of compliance inforced by the Act is balanced with the actual risks posed by the individual activities. The health research sector is primarily involved in dealings with GMO's that do not pose significant risks of release or adverse health consequences for the researchers. Substantial regulatory hurdles that have been introduced as a consequence of the current Act are having adverse influences on administration of research by individual researchers and their institutions, and ultimately on research productivity.

It was an unfortunate consequence of the introduction of the Act, that there was an unwarranted raising of the regulatory hurdle, at a time when GMAC would in fact have been about to further reduce the thresholds for certain dealings. This combined with a regressive view by the Regulator, and the absence of using the discretionary powers available in Act has made this Review particularly important and timely.

What is clear is that technology changes rapidly, and the Regulator needs the capacity to be able to clearly and transparently be able to capture new types of experimental work within appropriate guidelines. Similarly, as experience is gained with a particular type of dealing, it is important for the Regulator to be able to reduce the compliance burden commensurate with the demonstrated safety for humans and the environment.

Specifically, while the broad scope of the Act remains relevant and appropriate, the Act is failing to deliver to the full extent possible in the economic and health aspects due to excessive regulation of dealings that demonstrably do not pose a risk to health or the environment. To this end, by impeding the progress of health and medical research through an increased burden of regulatory compliance reduces the capacity for improvements in health and improvements in wealth of the nation. As such, the Act is failing to adhere to the scope of the National Biotechnology Strategy.

In making these broad comments, these are not to be seen as an argument for the changing the broad definitions of technologies and organisms covered by the Act, rather highlighting current and foreseen inefficiencies that can be addressed by making the Act more flexible in its interpretation and implementation.

On the question of whether the Act should be trait or novel organism based, the ASMR suggests that it should stay with the former, as this leads to an equality of review for all dealings, rather than selected changes based on selected organisms.

Act achieving objects

2. Investigate whether the object of the Act is being achieved and whether the regulatory framework stipulated in section 4 of the Act is still appropriate.

In the broadest terms, the Act is achieving its objectives of providing a regulatory framework for the introduction of gene technology taking due reference of health and environmental implications.

Operation of the Act

3. Examine the structure and effectiveness of the OGTR.

In terms of the gene technology which is undertaken by the health and medical research sector, the OGTR has created an administrative structure which has substantially increased the cost of compliance with no increase in the health or environmental well being of the nation.

Initially, the OGTR was slow to develop procedures, typically unable to provide consistent guidance on interpretation of the Act or Regulations. The recent IBC Forum held in Canberra did ultimately serve the purpose of more closely aligning the goals of the OGTR and institutional IBC's. This forum and encouragement of IBC networks should help to alleviate some of the hurdles faced particularly by IBC's representing smaller institutions.

4. Review the consultation provisions of the Act including:
a. their effectiveness with respect to their costs and benefits, including the value of advice received, and the transparency and accountability they provide
b. the functions and roles of the statutory advisory committees
c. the statutory timeframes for applications under the Act
d. the stakeholders included in consultations for various applications under the Act

Much of this section deals with DIRs and therefore is outside the remit of health and medical research.

One area that is particularly relevant is human gene therapy. The interaction of OGTR and GTRAP has been poor and the process for a study sponsor seeking approval for such trials has been particularly difficult over the past 4 years. Greater harmonisation of these roles is clearly necessary.

The excessive regulation provided under the scope of the Act is starkly highlighted by the fact that gene therapy interventions on patients are not subject to the same requirements as contained laboratory dealings.

A second area which requires attention is the ability of the Regulator to rely on advice from relevant committees in exercising discretionary powers. The Regulator has considerable discretionary powers under the Act, but is naturally cautious to use them. The ASMR propose that when a matter has been assessed by GTTAC and a clear recommendation has been made to the Regulator, that the Regulator should exercise clearly articulated and well considered discretionary powers until such time as that decision is incorporated into an amendment of the Act or a revision of the Regulations or Guidelines. Moreover, the ASMR proposes that such powers be included in the current review of the Act, thus providing a means by which the Regulator can respond to newly emerging issues, or address issues that have been found not to present any risk to humans or the environment in a clear and transparent matter.

In particular, this comment is made following requests, based on clearly documented cases to have the regulator exercise discretionary powers in regard to declaring knockin single amino acid changes in mice as exempt dealings. Not only was this request denied, the Regulator appeared unwilling or unable to engage in any justification of this decision based on an evaluation of the risk assessment for this dealing.

5. *Determine whether the powers of the Act allow enforcement of compliance which is effective and appropriate to the circumstances including instances where GMOs may be detected that are present unintentionally.*

No comments.

Regulatory burden

6. *Examine whether compliance and administrative costs, including information requirements, for organisations working in gene technology are reasonable and justified compared to benefits achieved and possible alternatives to legislation.*

Compliance and administrative costs have been significant. Most organizations have had to appoint dedicated staff to service the regulatory burden created by the Act. This is highlighted by the fact that the actual safety provisions have not increased over the GMAC voluntary system, just the compliance and administrative costs.

In addition, as cost recovery has not yet been adopted, the full costs of the Act are far from obvious. If, as has been argued, health and medical research investments are seen as public good, then the costs already imposed and the potential implications of cost recovery would be seen as extremely difficult to justify in terms of the benefits achieved. The ASMR made a specific submission regarding Cost Recovery in 2004.

However, the public has a reasonable right to expect an appropriate legislative framework to protect human health and the environment. Therefore, the solution to this dilemma is to more appropriately align the regulations and guidelines with the risk assessment for each dealing. By adopting a more commonsense approach it will be possible to appropriately reduce the regulatory burden while still using the Act to provide effective regulation.

7. *Review the system of approvals and the application of regulatory requirements commensurate to the level of risk.*

As will be self evident, this is the area of the Act that is in need of the greatest attention. The Review Committee will no doubt be informed by the submission to the review of the Regulations, but the lack of implementation of change is further demonstration that the Act is failing to deliver benefits in accord with the National Biotechnology Strategy.

The overarching principle behind each of the following suggestions listed below is to ensure that the safety of people, directly and indirectly involved, and environment is ensured. However, when individuals are forced to operate under guidelines, which they consider are inappropriately restricted, this leads to lower levels of compliance because they have no fear of adverse consequences to their health and safety. Compliance will be optimised by reviewing the regulations and guidelines and to focus regulations and monitoring on situations that genuinely require care and containment and equally by exempting situations

that do not warrant such attention. Moreover, a higher level of compliance will then be directed to those dealings that may present potential risk rather than those which do not.

Below are a list of specific suggested changes to the system of approvals and application of regulatory requirements which are commensurate with the level of risk. In particular, detailed comments about the specific regulations are made.

Regulation: **Schedule 2 Part 1 Item 1**
Issue: **Transgenic Animals**
Dealings involving transgenic (and knock in) mice and other laboratory animals (including mice, rats, fish, insects, worms, etc) should be declared exempt.

The decision to regulate the area is one based on history and the precautionary principal. The original high profile transgenic mice studies reported by Palmiter et al (1982) expressed growth hormone and resulted in transgenic mice that were oversized. From a regulatory point of view, this led to concerns about possible escape. The only basis of concern for these dealings and the sole reason for their NLRD status is due to the possibility of escape. There are no other health or safety concerns. Containment is fully covered by the use of either PC1 or PC2 facilities both of which require identical escape proof housing. By defining transgenic mice as exempt (in the same manner as knock out mice) would eliminate the anomaly of being able to clone and express a gene in approved host vector systems, and to create knockout mice under exempt classification but having to have NLRD approval to create the transgenic mice. There are over 20 years of practical experience with transgenic mice with no reported adverse effects that could impact the health and safety of people or the environment.

Although this position has been argued from the perspective of transgenic mice, the most commonly manipulated transgenic organism, so long as these are contained dealings, other species of laboratory animals should also be made exempt. This would include Drosophila, *C. elegans*, zebrafish, rats, and all other routine laboratory organisms.

Ref: Palmiter RD, Brinster RL, et al. (1982) Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes. Nature 300:611-615.

Suggested Amendment:
Replace the definition of Item 1 of Schedule 2 Part 1 with "Any dealing with genetically modified laboratory animals (including mice, rats, fish, insects, worms, etc) if no advantage is conferred on the adult animal and the animal is incapable of giving rise to infectious agents" or similar.

Regulation: **Schedule 2 Part 2**
Issue: **Transgenic Animals**
Dealings involving transgenic (and knock in) mice and other laboratory animals (including mice, rats, fish, insects, worms, etc) should be declared an approved host vector system.

The decision to regulate the area is one based on history and the precautionary principal. The original high profile transgenic mice studies reported by Palmiter et al (1982) expressed growth hormone and resulted in transgenic mice that were oversized. From a regulatory point of view, this led to concerns about possible

escape. The only basis of concern for these dealings and the sole reason for their NLRD status is due to the possibility of escape. There are no other health or safety concerns. Containment is fully covered by the use of either PC1 or PC2 facilities both of which require identical escape proof housing. By defining transgenic mice as exempt (in the same manner as knock out mice) would eliminate the anomaly of being able to clone and express a gene in approved host vector systems, and to create knockout mice under exempt classification but having to have NLRD approval to create the transgenic mice. There are over 20 years of practical experience with transgenic mice with no reported adverse effects that could impact the health and safety of people or the environment.

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Ref: Palmiter RD, Brinster RL, et al. (1982) Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes. Nature 300:611-615.

Suggested Amendment:
Make laboratory animals (including mice, rats, fish, insects, worms, etc) approved host vector systems. This would mirror the status of somatic delivery of naked DNA to animals which is currently exempt (Item 2).

Regulation: **Schedule 3 Part 1 Section 1.1 (a)**
Issue: **Transgenic Animals**
Dealings involving transgenic (and knock in) mice and other laboratory animals (including mice, rats, fish, insects, worms, etc) should be declared exempt.

The decision to regulate the area is one based on history and the precautionary principal. The original high profile transgenic mice studies reported by Palmiter et al (1982) expressed growth hormone and resulted in transgenic mice that were oversized. From a regulatory point of view, this led to concerns about possible escape. The only basis of concern for these dealings and the sole reason for their NLRD status is due to the possibility of escape. There are no other health or safety concerns. Containment is fully covered by the use of either PC1 or PC2 facilities both of which require identical escape proof housing. By defining transgenic mice as exempt (in the same manner as knock out mice) would eliminate the anomaly of being able to clone and express a gene in approved host vector systems, and to create knockout mice under exempt classification but having to have NLRD approval to create the transgenic mice. There are over 20 years of practical experience with transgenic mice with no reported adverse effects that could impact the health and safety of people or the environment.

Although this position has been argued from the perspective of transgenic mice, the most commonly manipulated transgenic organism, so long as these are contained dealings, other species of laboratory animals should also be made exempt. This would include Drosophila, *C. elegans*, zebrafish, rats, and all other routine laboratory organisms.

Ref: Palmiter RD, Brinster RL, et al. (1982) Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes. Nature 300:611-615.

Suggested Amendment:
Delete Item 1.1 (a) from Schedule 3 Part 1

Regulation: **Schedule 2 Part 1 Item 4 (a ii)**
Issue: **Dealings involving oncogenes should be declared exempt.**

The reason for making this change is based on history and the precautionary principal. The original discovery of virally encoded DNA oncogenes was made by Harold Varmus and J Michael Bishop and resulted in the award of the 1989 Nobel Prize in Physiology or Medicine "for their discovery of the cellular origin of retroviral oncogenes". This work built on the earlier 1966 Nobel Prize in Physiology or Medicine awarded to Peyton Rous "for his discovery of tumour-inducing viruses". While original concerns were that such oncogenes could be overtly dangerous, this has not been borne out by over 20 years of practical experience with oncogenes. The ASMR is not aware of any reported adverse effects that could impact the health and safety of people or the environment.

Suggested Amendment:
Delete Schedule 2 Part 1 Item 4 (a ii)

A gene is not inherently dangerous just because it can cause tumour formation. It is well recognised that routine manipulation of an oncogene in approved host vector systems does not result in any increased risk to people or to the environment.

Regulation: **Schedule 2 Part 3**
Issue: **The term oncogenes should be clearly defined.**

The reason for requesting this change is that the definition of oncogene has become so blurred that many groups and IBCs are making, in my view, inappropriate decisions as to which genes are included and excluded under the undefined term oncogene. This arises because there is not a relevant definition of oncogene in the Act or regulations. For example, the ASMR understands that some IBCs are taking the view that normal genes such as transcription factors could be oncogenes and, as such, work which is manifestly exempt is being pushed inappropriately to PC2 levels.

Suggested Amendment:
Provide a definition of oncogene in Schedule 2 Part 3.

One common definition of an oncogene is any gene that can cause foci formation in cells in culture eg NIH3T3 cells. However, the ASMR considers that this interpretation is too generalised and that cellular foci are not pathogenic tumours and do not present a risk to humans. Moreover, many normal cellular genes (as originally demonstrated with the mas gene, which is a normally occurring unmodified human gene) will be inappropriately included as

oncogenes under such a definition. The ASMR understands that the term oncogene is not meant to include normal cellular genes.

A suitable definition would be that an oncogene causes tumour formation in a test animal. The ASMR considers that this would be an appropriate definition as it actually relates to the cancerous processes in which oncogenes are involved.

Regulation: **Schedule 3 Part 2.1 (d)**
Issue: **Terms should be clearly defined.**

The reason for requesting this change is that the definition of "product known to play a role in the regulation of cellular growth" and "toxic to mammalian cells" be defined. These terms have become so blurred that many groups and IBCs are perhaps making inappropriate decisions as to which genes are included and excluded under the undefined terms. For example, does this include expression of genes involved in gluconeogenesis or the cellular cytoskeleton? Or does it refer to properly defined (see above) oncogenes? Similarly does toxic means toxins as fully defined (ie LD50 <100ug/kg) or could it include overexpression of endogenous cellular gene products?

Suggested Amendment:
Provide a definition of "product known to play a role in the regulation of cellular growth" and "toxic to mammalian cells" in Schedule 3 Part 2.

Regulation: **Schedule 3 Part 1 Item 1.1 (e iii)**
Issue: **Amend NLRD definitions to exclude the term "oncogene".**

The reason for making this change is based on history and the precautionary principal. The original discovery of virally encoded DNA oncogenes was made by Harold Varmus and J Michael Bishop and resulted in the award of the 1989 Nobel Prize in Physiology or Medicine "for their discovery of the cellular origin of retroviral oncogenes". This work built on the earlier1966 Nobel Prize in Physiology or Medicine awarded to Peyton Rous "for his discovery of tumour-inducing viruses". While original concerns were that such oncogenes could be overtly dangerous, this has not been borne out by over 20 years of practical experience with oncogenes. The ASMR is not aware of any reported adverse effects which could impact the health and safety of people or the environment.

Suggested Amendment:
Delete Schedule 3 Part 1 Item 1.1 (e iii)

A gene is not inherently dangerous just because it can cause tumour formation. It is well recognised that routine manipulation of an oncogene in approved host vector systems does not result in any increased risk to people or to the environment.

Regulation: **Schedule 2 Part 2 Item 4**
Issue: **Amphotropic viral vectors**

Amend the Exempt dealings approved host vector systems under item 4. This currently reads:
Class Tissue culture
Host Mammalian (including human) cells and cells of aquatic organisms
Vector Non-viral vectors or defective viral vectors
(including retrovirus or retroviral-helper combinations that cannot infect human cells)

The wording should be changed to make it clear that all host-vector systems using replication defective viral vectors can be used in tissue culture work (including human cells). In other words, the use of replication defective vectors provides sufficient safety that even virus that can infect human cells does not propose a significant risk when handled under PC1 containment.

Suggested Amendment:
Thus the ASMR suggests the following revised definition for Vector in Item 4:

Vector Non-viral vectors or defective viral vectors

However, an assessment of the possible risks that could involve people leads to the suggestion of the following caveat. Namely, that replication defective viral vectors should be excluded from these exempt dealings when they have the capacity to infect human cells, AND also contain genes that could have adverse effects. Thus, the ASMR considers that a replication defective viral vector that can infect human cells and is expressing a toxin should be a NLRD and require PC2 containment.

Regulation: **Schedule 2 Part 2**
Issue: **Gene delivery to laboratory animals (including mice, rats, fish, insects, worms, etc) by replication defective viral vectors should be an approved host vector system**

Given that dealings with genes in replication defective viral vectors are already classified as exempt and that somatic DNA transfer to animals is also exempt, the delivery of genes to rodents using replication defective viral vectors should also be an approved host vector system.

Suggested Amendment:
The delivery of genes to laboratory animals using replication defective viral vectors should be an approved host vector system. This would involve laboratory animals (including mice, rats, fish, insects, worms, etc) being listed as an approved host vector system in Schedule 2 Part 2.

Regulation: **Schedule 3 Part 2.1 (d)**
Issue: **Viral Vectors**

The ASMR considers that the use of the term viral vectors in the list (Schedule 3 Part 2.1d) of dealings that are not NLRDs is correct and that this does not include replication defective viral vectors.

Suggested Amendment:
Clarification of current terminology

Regulation: **Regulation 29 Part 4 Division 3 Item (2)**
Issue: **GTTAC advise to the Regulator**

The Regulator has considerable discretionary powers under the Act, but is naturally cautious to use them. The ASMR proposes that when a matter has been assessed by GTTAC and a clear recommendation has been made to the Regulator, that the Regulator should exercise clearly articulated and well considered discretionary powers until such time as that decision is incorporated into an amendment of the Act or a revision of the Regulations or Guidelines. Moreover, the ASMR proposes that such powers be included in the current review of the Act, thus providing a means by which the Regulator can respond to newly emerging issues, or address issues that have been found not to present any risk to humans or the environment in a clear and transparent matter.

Suggested Amendment:
The Regulator act on the Resolutions of GTTAC for the purpose of exercising discretionary powers.

Interface with other systems

8. Examine the nationally consistent scheme for gene technology regulation in Australia and identify any need for, and ways to achieve, improvements in its consistency, efficiency and coordination.

No comments.

9. Examine the interface between the Act and other Acts and schemes (either Australian Government or State and Territory) that regulate gene technology and gene technology products. Identify any discrepancies, including regulatory gaps and areas needing consistency and harmonisation of provisions.

As highlighted above, there is a significant operational gap in the area of human somatic gene therapy clinical trials with regulation via OGTR, TGA and NHMRC (GTTRAP and AHEC). This needs to be more clearly addressed.

Changing circumstances

10. Examine emerging trends and international developments in biotechnology and its regulation and whether the regulatory system stipulated by the Act is flexible enough to accommodate changing circumstances.

The greater ability to use and apply transparent discretionary powers, as detailed above, would allow the Regulator to respond appropriately to emerging trends and developments.

Changes to the legislation

11. Recommend amendments to the Act (including consideration of those recommendations made by State or Territory Parliamentary Committees), or alternatives to legislation, which improve the effectiveness, efficiency, fairness, timeliness and accessibility of the regulatory system.

Regulation: Schedule 2 Part 1 Item 1
Issue: Transgenic Animals
Suggested Amendment:
Replace the definition of Item 1 of Schedule 2 Part 1 with "Any dealing with genetically modified laboratory animals (including mice, rats, fish, insects, worms, etc) if no advantage is conferred on the adult animal and the animal is incapable of giving rise to infectious agents" or similar.

Regulation: Schedule 2 Part 2
Issue: Transgenic Animals
Suggested Amendment:
Make laboratory animals (including mice, rats, fish, insects, worms, etc) approved host vector systems. This would mirror the status of somatic delivery of naked DNA to animals which is currently exempt (Item 2).

Regulation: Schedule 3 Part 1 Section 1.1 (a)
Issue: Transgenic Animals
Suggested Amendment:
Delete Item 1.1 (a) from Schedule 3 Part 1

Regulation: Schedule 2 Part 1 Item 4 (a ii)
Issue: Dealings involving oncogenes should be declared exempt.
Suggested Amendment:
Delete Schedule 2 Part 1 Item 4 (a ii)

Regulation: Schedule 2 Part 3
Issue: The term oncogenes should be clearly defined.
Suggested Amendment:
Provide a definition of oncogene in Schedule 2 Part 3.
A suitable definition would be that an oncogene causes tumour formation in a test animal.

Regulation: **Schedule 3 Part 2.1 (d)**
Issue: **Terms should be clearly defined.**
Suggested Amendment:
Provide a definition of "product known to play a role in the regulation of cellular growth" and "toxic to mammalian cells" in Schedule 3 Part 2.

Regulation: **Schedule 3 Part 1 Item 1.1 (e iii)**
Issue: **Amend NLRD definitions to exclude the term "oncogene".**
Suggested Amendment:
Delete Schedule 3 Part 1 Item 1.1 (e iii)

Regulation: **Schedule 2 Part 2 Item 4**
Issue: **Amphotropic viral vectors**
Suggested Amendment:
Revise the definition for Vector in Item 4:
Vector Non-viral vectors or defective viral vectors

Regulation: **Schedule 2 Part 2**
Issue: **Gene delivery to laboratory animals (including mice, rats, fish, insects, worms, etc) by replication defective viral vectors should be an approved host vector system**
Suggested Amendment:
Laboratory animals (including mice, rats, fish, insects, worms, etc) be listed as an approved host vector system in Schedule 2 Part 2.

Regulation: **Schedule 3 Part 2.1 (d)**
Issue: **Viral Vectors**
Suggested Amendment:
Clarification of current terminology

Regulation: **Regulation 29 Part 4 Division 3 Item (2)**
Issue: **GTTAC advise to the Regulator**
The Regulator act on the Resolutions of GTTAC for the purpose of exercising discretionary powers.

IGA achieving its aims

12. Investigate whether the Intergovernmental Agreement on Gene Technology is achieving the aims listed in its Recitals.

No comments.