the **Australian Society** *for* **Medical Research**

ACN 000 599 235 - ABN 18 000 599 235
145 Macquarie Street. Sydney, 2000
Ph: (02) 9256 5450, Fax (02) 9252 0294
Email: asmr@world.net,
Website: www.asmr.org.au
Snr. Executive Officer: Catherine West

September 16th 2003

Dr Sue Meek
Gene Technology Regulator
PO Box 100
Woden ACT 2606
Dr Sue Meek<ogtr@health.gov.au>

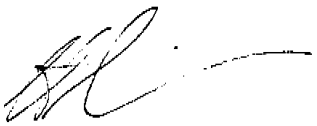
Dear Dr Meek,

Re: **Suggested amendments to the *Gene Technology Regulations 2001***

I write on behalf of the Australian Society for Medical Research (ASMR) the peak body representing health and medical researchers. In addition to direct membership, ASMR represents the sector through 42 affiliated professional societies and Medical Colleges, representing some 15,000 people actively involved in health and medical research in Australia. In addition, corporate and disease related foundation memberships bring a further 85,000 Australians with an interest in health and medical research into association with ASMR. ASMR's mission is "to foster excellence in Australian health and medical research, and to promote community understanding and support for health and medical research in Australia". ASMR achieves these goals through public, political and scientific advocacy

Thank you for providing this opportunity to highlight current deficiencies in the Gene Technology Regulations. The overarching principle behind each of the following recommendations 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 projects that may present potential risk rather than those which do not.

Yours sincerely,



Professor Peter R Schofield (PhD DSc)
Immediate Past-President, ASMR

Attch. 1

Suggested amendments to the *Gene Technology Regulations 2001*

Regulation to be amended	**Description of issue/ difficulty encounted etc**	**Suggested amendment and associated comment**
Schedule 2 Part 1 Item 1	*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.	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.

	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.	
Schedule 2 Part 2	*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	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).

	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.	
Schedule 3 Part 1 Section 1.1 (a)	*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	Delete Item 1.1 (a) from Schedule 3 Part 1

	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.	
Schedule 2 Part 1 Item 4 (a ii)	*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	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.

	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. We are not aware of any reported adverse effects that could impact the health and safety of people or the environment.	
Schedule 2 Part 3	*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 our 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, we understand 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.	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, we consider 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 proto-oncogene, which is a normally occurring unmodified human gene) will be inappropriately included as oncogenes under such a definition. We understand 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. We consider that this would be an appropriate definition as it actually relates to the cancerous processes in which oncogenes are involved.
Schedule 3 Part 2.1 (d)	*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 making, in our view, inappropriate decisions as to which genes are	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.

	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?	
Schedule 3 Part 1 Item 1.1 (e iii)	*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. We are not aware of any reported adverse effects which could impact the health and safety of people or the environment.	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.
Schedule 2 Part 2 Item 4	*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	Thus we suggest 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, <u>AND</u> also contain genes that could have

	(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.	adverse effects. Thus, we would consider that a replication defective viral vector that can infect human cells and is expressing a toxin should be a NLRD and require PC2 containment.
Schedule 2 Part 2	***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.	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.
Schedule 3 Part 2.1 (d)	*Viral Vectors* We consider 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.	Clarification of current terminology
Regulation 29 Part 4 Division 3 Item (2)	*GTTAC advise to the Regulator* The Regulator has considerable discretionary powers under the Act, but is naturally cautious to use them. We 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, we propose that such powers be included in the current review of the Regulations, thus providing a means by which the	The Regulator act on the Resolutions of GTTAC for the purpose of exercising discretionary powers.

	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.	