THE UNIVERSITY OF
NEWCASTLE
AUSTRALIA

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RE: 2011 Review of the Gene Technology Act 2000 (GT Act)

The University of Newcastle welcomes the opportunity provided by the Department of Health and Ageing to participate in the independent review of the GT Act. To assist in this review please see consolidated responses within the terms of reference below that have been provided by members of the University of Newcastle research community:

1. Exemption of low-risk recombinant rodents

a) emerging trends and international developments in biotechnology and its regulation

Although there have been improvements since the Act was first introduced, there continues to be relatively stringent requirements for the research use of low-risk transgenic mice and other rodents.

In contrast, as of January 2011, most dealings with low-risk genetically modified (GM) rodents (including knock-out as well as other transgenic rodents), including transfer and cross-breeding experiments, are now exempt from the United States National Institutes of Health (NIH) Guidelines administered by the Office of Biotechnology Activities. This includes breeding of low-risk GM rodents as a result of amendment of Section III–E–3 of the NIH Guidelines and addition of a new appendix section Appendix C–VII. The new exemption applies to most rodents which can be appropriately maintained under biosafety level BL1 conditions, comparable to Australian physical containment level PC1.

The rationale for the changes to the US guidelines is that cross-breeding of transgenic rodents that can be housed under BL1 conditions (i.e. low risk) results in progeny that can also be housed under BL1 conditions and such breeding experiments do not pose an appreciable risk to human health or to the environment. (Rare exceptions involving rodents containing large amounts of viral sequence are specified in the amended guidelines.)

b) The regulatory burden and whether compliance costs for organisations working in gene technology are reasonable and justified compared to benefits achieved and if the regulatory requirements for classes of approval under the Act are commensurate with the level of risk

It was noted by the US Office of Biotechnology Activities that the total number of registrations required represents a significant collective administrative burden on IBCs and researchers that is not commensurate with the very low biosafety risk.

c) *Opportunities for improvement in efficiency.*

It is recommended that low-risk recombinant rodents, currently classified as NLRD (PC1) under the Act, be re-classified as Exempt, allowing regulation to be managed through routine IBC procedures and therefore reduce unwarranted administrative burdens for IBCs, researchers and the OGTR.

2. Anthropomorphocentricity

Opportunities for improvement in effectiveness

The proposed changes to the Australian Act are highly anthropomorphocentric in places (e.g. Part 2. 1 i-m; Part 3.1 d, e, j) compared to, for example, the existing Act or US NIH Guidelines, which appear to take more account of potential inappropriate risks to animal health. It is not clear that all proposed changes adequately cover unanticipated consequences for other organisms. This is particularly important in view of the preponderance of agricultural applications in higher risk GMO dealings.

3. Quality of evidence and arguments used for risk evaluation

Opportunities for improvement in effectiveness

The quality of evidence and arguments used for risk evaluation in applying the Act is sometimes concerningly weak. Conclusions are based on one or two studies, often by researchers with potential conflicts of interest and frequently involving small sample sizes, without apparent regard to statistical issues such as power or individual differences in genotype or other factors.

One example is DIR 097, in which 35 healthy children at various Australian hospitals were infected with a genetically modified replication competent virus. Infected persons shed infectious viral particles and there is little known about and long-term consequences of infection with the genetically modified virus remaining unstudied but potentially including asthma. Assessment of the possibility of consequences of viral shedding was based primarily on a single study in which 10 children were exposed to infected children in a play group.

As often observed, lack of evidence (due to relevant studies not yet having been conducted) is not evidence of lack of effect.

It also appears to be frequently assumed in reviewing applications that pathogenicity is not going to be a serious problem unless some pathogenic factor is added to an organism yet this assumption may be dangerously flawed. For example, paradoxically, for reasons that are not yet fully understood, one of the few consistent differences between anthrax (B. anthracis) and less virulent related organisms is the absence of a pathogenicity factor in anthrax-causing variants, and this can arise due to a single point mutation.

In the absence of sound evidence that inappropriate transmission cannot occur, there is a clear and reasonable possibility that other children will be exposed without parental consent to a GMO of unknown long-term effect with recognised immunosuppressive capacity and potential to cause asthma or other respiratory conditions. Yet no requirement for any kind of quarantine during the infectious period was imposed nor any requirement to monitor people coming into contact with infected children.

A justification often used by the OGTR to dismiss risks involved in DIRs is that encoded proteins and their products occur naturally in the environment and are therefore unlikely to be toxic or allergic to people or toxic to other organisms. This is not a sound argument. Many substances which occur

naturally in the environment are toxic or allergenic. Furthermore some naturally occurring substances which are not usually health risks are allergenic or toxic if expressed artificially within the body.

Many of the dealings in question are very worthwhile endeavours but as evidenced by early gene therapy deaths in the US, inadequate monitoring and regulation can influence public opinion, damage the credibility and reputation of regulatory bodies and institutions and create long-standing barriers for research and development.

If extreme caution is to be used for any dealings it should be directed towards DIRs rather than lower-risk research dealings.

4. Genomic subtypes

international developments in biotechnology and its regulation and opportunities for improvement in effectiveness

The effect of individual factors such as genotype on disease risks and responses are widely recognised yet this does not appear to be taken into consideration adequately, if at all, for DIRs and so is also likely to be overlooked in other dealings. For example again in DIR 097 the possibility that children or other people with genotypes affecting key immune responses may have different risks was not considered.

5. Specification of factor affecting cell proliferation

opportunities for improvement in effectiveness in relation to P43 (k) (ii) (b) – ..."a growth factor or signal transduction pathway component that if expressed may lead to cell proliferation in humans" ...

If the aim is to capture all factors that may result in disregulated/inappropriate cellular growth and proliferation then a more general statement is probably required since proteins involved in apoptosis, DNA repair etc can also lead to disregulated proliferation. Better wording may be: "a factor such as a growth factor or signal transduction pathway component that if expressed may lead to cell proliferation in humans".

6. Individual vs IBC responsibilities

opportunities for improvement in efficiency

The attempt to separate individual and IBC responsibilities lacks clarity and increases rather than reduces potential for confusion and inefficiencies in how institutions monitor and regulate researcher compliance. The use of financial year rather than end of year reporting deadlines is another potential complicating factor for IBCs.

7. Re-assessment of NLRDs and information updating

opportunities for improvement in efficiency

While NLRDs of unlimited longevity are not appropriate, a full new NLRD application at 5 years appears unwarranted in view of the additional burden on all stakeholders. It would appear to be more efficient to implement a simple extension form process for investigators wishing to extend NLRDs e.g. to confirm that there is no new relevant information from the literature or relating to the project that has not already been notified to the OGTR.

Pertaining to this, US guidelines have ongoing requirements relating to notification of any relevant new information which may arise in the course of dealings that have implications for harm to organisms or the environment. It is recommended that there be a clearer requirements for this in the Act - this is not covered by re-assessment at 5 years per se. While particularly important for licensed dealings it is also important should anything arise that may affect the status of an NLRD or exempt dealing, for example. Both individuals and IBCs may be considered to have responsibilities in this regard.

8. General Clarity

opportunities for improvement in efficiency and effectiveness

It is recommend that some part of the proposed amendments to the Act be reviewed and amended to improve clarity and reduce the potential difficultly of interpretation as the current draft is likely to create considerable problems downstream for the OGTR, IBC and researchers.

For example 13. Requirements In Relation To Undertaking Notifiable Low Risk Dealings, 13 (3) (a) "paragraph 13 (1) (d) does not prevent the transportation, storage or disposal on or after the day before which the dealing is to be undertaken..."

Another example is in Notifiable low risk dealings in relation to a GMO. Part 1 Notifiable low risk dealings suitable for physical containment level 1. (page 40) 1.1 Kinds of dealings...
Contains (a) and (c) but no (b). It is unclear if (c) should be (b) or if a third point has been erroneously omitted.