The University of Melbourne

SUBMISSION TO THE 2017 REVIEW OF THE GENE TECHNOLOGY SCHEME

Summary

The University of Melbourne's Institutional Biosafety Committee (IBC) welcomes the opportunity to provide input to the review of the Gene Technology Scheme. Previous reviews have resulted in a number of positive changes to assist with research involving dealings with regulated materials. In conjunction with the technical review currently being undertaken by the Gene Technology Regulator (the Regulator) the timing of this Scheme review enables further discussion and consideration of options proposed by the Regulator, as well as issues that were outside the scope of the technical review of the Gene Technology Regulations (the Regulations).

The regulatory Scheme that has been in place for the past 16 years has clearly met its objectives of protecting the health and safety of people and the environment from the risks posed by gene technology. Indeed, the IBC is unaware of any incidents in Australia involving gene technology that have adversely affected the health and safety of people and the environment. One notable although underappreciated outcome of the Scheme has been a better understanding of the risks associated with the different forms of gene technology and how the use of these techniques can change the risks inherent with work with certain classes of organisms. Our submission will therefore advocate a revision of Schedules 1 and 1A, to expand the list of techniques and organisms that are not regulated under the Scheme, as well as a review of Schedule 2 to increase the range of dealings that are considered of such low risk that formal notification is not required. These recommendations are entirely consistent with the intention of developing a regulatory Scheme that is robust, agile and effective.

The consultation process and relationships developed between stakeholders and the Office of the Gene Technology Regulator (OGTR) is an important factor to the success of the Scheme. Nevertheless, some areas remain problematic. For example, as a large, research-intensive university with numerous certifications the 90-working day period for facility certifications can significantly impact university business. Whilst we appreciate the incredible efforts of the OGTR to work with stakeholders where possible to minimise delays, research endeavours and the completion of major building projects are jeopardised with the current timeframes.

Specific comments and recommendations in relation to the Terms of Reference for the 2017 Review of the Scheme are made below.

1. Current developments and techniques, as well as extensions and advancements in gene technology to ensure the Scheme can accommodate continued development.

The University of Melbourne's Institutional Biosafety Committee (IBC) fully supports and endorses a Scheme that continues to be based on scientific evidence and where gene technology activities are regulated commensurate with the risk posed by the genetically modified organism (GMO) to the health and safety of people or the environment. To continue meeting the object the Gene Technology Act (the Act), a robust nationally consistent regulatory Scheme that is able to accommodate new technologies or trends without introducing ambiguity, or increasing regulatory burden where there is clear scientific evidence that risks to people or the environment is low or negligible, is key.

In the University's submission to the Regulator for the 2016-2017 technical review of the Regulations regarding the appropriate way to deal with new technologies such as the site-directed nuclease (SDN) techniques, we indicated Option 4 (to exclude from regulation) was the most sensible option and should be the ultimate goal. However, the University's IBC thought it difficult to see how this could be implemented without a corresponding

review of the Scheme and without potentially increasing the burden for IBCs. It was for this reason the University's submission supported option 2 (to include SDNs in the Regulations) at the time.

Recommendation 1

The University of Melbourne's IBC recommends a review of the definitions in the Act and the Regulations to ensure the Scheme can accommodate current developments and techniques or advancements. The intent of the current definitions was to ensure the Act had the capacity to capture new technologies, but current advancements in gene technology have highlighted how the broadness of the definitions can, and is, causing ambiguity. The review requires robust discussion as to whether the current definitions for a genetically modified organism and gene technology remains relevant and continues to serve the purpose intended when the Scheme was introduced; managing risks posed by or as a result of gene technology through regulating certain dealings with GMOs.

The current definition for a GMO is directly linked to the use of gene technology with no consideration as to the outcome of the modification. Focusing on the use of gene technology to determine whether an organism is a GMO has the potential to include low and negligible risk organisms within the regulatory Scheme. Where use of gene technology can result in modifications indistinguishable from naturally occurring mutations, and where the naturally mutated organism is not regulated by another regulatory Scheme, and scientific knowledge provides evidence the technology does not pose a risk to the health and safety of people or the environment, these GMOs or techniques should be excluded from the regulatory Scheme. Regulation of any gene technology, not only new technologies, needs to be commensurate with the risks posed by the use of the technology and/or the product resulting from the use of the technology.

Recommendation 2

The University of Melbourne's IBC recommends wording in the Regulations is reviewed to improve clarity, particularly for dealings with GMOs where no foreign DNA has been introduced but gene technology has been used to modify, insert or delete genes and the resulting organism potentially poses a risk to people or the environment.

Recommendation 3

The University of Melbourne's IBC recommends the provisions of the Act enable the Regulator to issue technical and procedural guidelines in relation to GMOs in a timelier manner to avoid prolonged uncertainty relating to advances in gene technology. Although the current definitions of a GMO and gene technology permit the Regulations to exclude specific GMOs or gene technologies, amending the exclusion lists is a complicated and timely process.

2. Existing and potential mechanisms to facilitate an agile and effective Scheme, which will ensure continued protection of health and safety of people and the environment.

IBCs play a key role in the effective and efficient operation of the regulatory Scheme and are integral to the regulatory system. Organisations rely heavily on the assistance of IBCs and for many organisations IBC membership consists of volunteers from within the organisation with specialised expertise who donate considerable time and energy to fulfilling IBC responsibilities under the Act. Delegation to IBCs to assess and authorise low risk work enables research to commence in a timely manner. However, the inability to grant extensions to assessed and authorised NLRDs after the five-year approval period lapses is an increased regulatory burden that does not mitigate risk. Furthermore, the inability to vary assessed and authorised NLRDs adds to this burden and generates additional administrative work for both IBCs and the OGTR. To facilitate an agile and effective Scheme, regulatory body guidelines need to be standardised where the documents are common to the regulatory bodies. This is particularly important with respect to physical and engineering controls required for containment facilities.

Recommendation 4

The University of Melbourne's IBC recommends the role IBCs have in the certification process of containment facilities be extended to inspecting and conditionally approving certifications for physical containment level 1 (PC1) and level 2 (PC2) facilities. Conditional approval would enable research to commence while the Regulator officially accepts the application.

The delegation of PC1 and PC2 facility applications to IBCs could include restrictions to ensure facilities requiring specific exemptions, or where the facility is a large grazing or large scale facility, are still assessed by the OGTR. IBCs currently inspect facilities for compliance against the OGTR guidelines, and the relevant Australian and New Zealand standards. The OGTR's decision to grant a facility certification is dependent on the IBC's inspection for PC1 and most PC2 facilities. Enabling IBCs to assess and grant conditional approval for new certifications, to manage variations, and suspensions, is an extension of a current mechanism that facilitates an agile and effective Scheme, and would address a problematic issue for many stakeholders.

Recommendation 5

In relation to facility guidelines issued by the Regulator, the University of Melbourne's IBC recommends the adoption of the Australian/New Zealand Standards as the benchmark for certifying facilities. This will avoid the current partial duplication, which currently with the existence of separate guidelines and standards is problematic for stakeholders. There is further room to improve the harmonisation of arrangements and requirements with other regulatory agencies, to provide clarity to stakeholders and improve the efficiency and effectiveness of the Scheme.

Recommendation 6

The University of Melbourne's IBC recommends Division 2 of the Regulations be reviewed to permit IBCs to extend and vary assessed and authorised NLRDs. The requirement to complete a new assessment does not mitigate risk but amendments to Division 2 of the Regulations have the potential to streamline or eliminate administrative burden for both IBCs and the OGTR without compromising the object of the Act.

Recommendation 7

The University of Melbourne's IBC recommends further clarity is provided for the viral vector criteria in the Regulations, as this will assist IBCs with the assessment process.

Recommendation 8

The University of Melbourne's IBC recommends the classification of certain dealings be reviewed for downgrading or exclusion (see below).

8(a) In addition to low risk GMOs such as *Drosophila melanogaster*, a review of GM laboratory mice, rats, rabbits and guinea pigs currently able to meet the NLRD PC1 (a) criteria and GM plants where a long history of presenting no risk to the health and safety of people and the environment, should be considered.

As outlined in the University's submission to the Regulator for the 2016-2017 technical review of the Regulations we recommend *Drosophila melanogaster* be downgraded from meeting the NLRD PC2 criteria to NLRDs suitable for containment in PC1 facilities as is the current situation for GM laboratory mice, rats, rabbits and guinea pigs when the modification does not confer an advantage or the modification does not enable the modified animal to secrete an infectious agent. The following information was provided with the University's submission for the Technical Review in 2016 to support the recommendation and is provided again now with this submission.

We propose an amendment to the requirement to contain all genetically modified *Drosophila melanogaster* in at least a PC2 Invertebrate facility. The proposal is to lower the requirement so that dealings with GM *Drosophila melanogaster*, where the modification does not confer an advantage on the fly or, the fly is not capable of secreting or producing an infectious agent as a result of the modification, be suitable for containment in at least a Physical Containment Level 1 facility. The rationale for the proposal is that the containment requirements are not commensurate with the risk and nor with standard requirements by collaborators internationally, and we do acknowledge that this would require a corresponding amendment to the Guidelines for Certification of Physical Containment Level 1 Facility.

This proposal is based on an improved understanding of the very low risks associated with most GM *Drosophila melanogaster* strains. During the past 35 years, and in particular the 15 years since the regulatory Scheme came into effect in Australia, to the best of our knowledge there have been no reports of incidents with adverse effects on human health or the environment associated with the use of common genetic modifications in *D. melanogaster*. This is in spite of the fact that Drosophila research has burgeoned in recent years (currently there are approximately 4000 papers per year on *Drosophila* species) with thousands of scientists around the world routinely using GM *D. melanogaster*. The physical containment level 2 requirements in Australia no longer align with other modern countries conducting research with GM *D. melanogaster* (such as the US, UK and Spain). Internationally work involving GM *D. melanogaster* can be undertaken within physical containment level 1 facilities or equivalent, but when the modification has an inherent higher risk a higher level of containment is still required.

D. melanogaster, also known as the fruit fly, vinegar fly or pomace fly, is an experimental species that has been used for genetic research since 1909, when it was first utilized in the laboratory of T.H. Morgan. There is a very low level of inherent risk to the environment, crops, and human health with this species for the following reasons:

- It is already an established species in Australia; it evolved in central Africa but is now a cosmopolitan species found associated with human populations throughout the world,
- It is not a disease vector like mosquitoes or tse-tse,
- It does not bite or sting, and
- It is not a crop pest.

Although *D. melanogaster* is often referred to as the common fruit fly it is not a true fruit fly such as the family Tephritidae, which is indeed a pest. It should also be distinguished from the spotted winged Drosophila species, *Drosophila suzukii*, which is also a fruit pest species. The genetic modifications commonly used in GM Drosophila research do not pose risks to the health and safety of people, or the environment. The vast majority of transgenic Drosophila stocks involve innocuous genetic elements commonly found in non-pathogenic species. These include:

- FLP, GAL4, GAL80 found in common baker's yeast,
- GFP and other fluorescent proteins found in jellyfish, coral and a variety of marine species, or
- lacZ found in common bacteria (*E. coli*).

These sorts of genes pose no risk to humans, the genes are not pathogenic or toxic, nor do the genes pose a risk to the environment. These modifications do not confer a selective advantage and would not result in a genetic modification to wild type populations in the event the GM Drosophila were unintentionally released. There will of

course always be cases in which the genetic elements are inherently at a higher risk, and in these cases a higher level of containment, such as PC2 or higher, would remain appropriate.

Studies have shown that when wild Drosophila are brought into the laboratory and cultured under standard laboratory conditions they rapidly adapt to laboratory life. A study performed by Hoffmann, Hallas, Sinclair & Partridge (Evolution, 55(2): 436-438), showed that within three years of laboratory culture (approximately 55 generations), the descendants of wild flies rapidly lost their ability to tolerate environmental stresses of the type normally encountered in the wild (for example, heat, cold or desiccation). This study, as well as those described by Sgro & Partridge (Laboratory adaptation of life history in *Drosophila*, American Naturalist. 158(6): 657-658) suggest that Drosophila grown under standard laboratory conditions for prolonged periods no longer display the traits required to survive and successfully reproduce in the wild. Our researchers may work with Drosophila that have been bred in laboratory conditions for over 70 years (over 1000 generations), consequently, genetic manipulation of this species poses minimal risk to the environment in the unlikely event that the GM *D. melanogaster* were to escape containment.

In May 2001, a report on the use of genetically modified animals was prepared by The Royal Society, London (https://royalsociety.org/~/media/Royal_Society_Content/policy/publications/2001/10026.pdf). Within the report, a section on *D. melanogaster* (page 11) states "methods for reproducibly creating stable, heritable GM insects were developed almost 20 years ago, using the well-known genetic model insect Drosophila melanogaster. It is generally considered harmless as it is neither a significant agricultural pest nor a disease vector and no adverse consequences to human health or the environment of this large-scale genetic engineering have been reported. Many thousands of different GM strains of *Drosophila* have subsequently been produced in laboratories around the world, and there are far more GM strains of *Drosophila* than there are of all other GM insects combined. It has become the paramount model organism for studying animal development and genetics…..Modern *Drosophila* research is completely depended on the use of genetic modifications for the generation and analysis of mutants, and for the insertion of expression of genes either from *Drosophila* or from other sources."

In the United States GM *Drosophila* is not regulated (https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/permits-notifications-petitions/sa_permits/ct_permits_drosophila) and many other countries do not require PC2 invertebrate facilities for the containment of standard GM *D. melanogaster* work. In the US, almost all transgenic *Drosophila* research is undertaken within BSL1, which is equivalent to our PC1 facilities. However, when the nature of the genetic modification(s) constitutes a real risk, then a higher level of containment is required. Examples of such modifications would include flies containing pathogenic microbes or flies expressing prion sequences or flies expressing gene-drive constructs. Thus the containment should correspond with the real risks. Similarly, in the UK a risk assessment in the form of an environmental impact statement is required when working with GM *D. melanogaster*. If that risk assessment concludes that the risk to the environment is minimal then Biosafety Level 2 containment is not required (The Genetically Modified Organisms (Contained Use) Regulations 2014). The UK *SACGM Compendium of Guidance* further notes: It is a regulatory requirement to thoroughly assess the risks posed by GM animals. However, in practice, activities with GM animals are unlikely to pose a risk to human health and the main consideration will be in regards to preventing the animal escaping into the environment. Therefore, activities should be assessed in a way that is commensurate with the actual hazards posed. There is a need for an informed and pragmatic approach, rather than an overcomplicated assessment and unwarranted control measures.

Given the low risk and precedent overseas, we propose the requirement for GM *D. melanogaster* dealings to be contained in at least a PC2 invertebrate facility be reviewed and amended so that low risk dealings can be undertaken within a suitably certified PC1 facility.

8(b) *In addition to the information provided in University's submission for the 2016-2017 technical review of the Regulations we recommend GM laboratory mice, rats, guinea pigs and rabbits currently able to meet the NLRD PC1 (a) criteria because the modification does not confer an advantage or the modification does not enable the modified animal to secrete an infectious agent, be downgraded to Exempt Dealings. The downgrade could be conditional on the containment facilities meeting specific requirements such as the need for rodent barriers on all access doors and screening on vents, windows and openings or this grouping of GMOs could continue to be contained in OGTR certified PC1 facilities.*

8(c) *We further recommend GM plants currently meeting the NLRD PC2 (b) criteria, but with a long history of not presenting a risk to the health and safety of people and the environment and where there is undisputed scientific evidence to support this, be downgraded to at least NLRDs suitable for containment in a PC1 facility, with consideration given for a further downgrade to Exempt Dealings.*

The organisms listed above all fall into the 'model organism' category and have been used for many years without incident. Scope to include other model organisms such as the fungi *Aspergillus nidulans* would be desirable as well, particularly as *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* are currently included in Schedule 2 Part 2.

3. The appropriate legislative arrangements to meet the needs of the Scheme, now and into the future, including the Gene Technology Agreement.

As a leading University recognised for research excellence, our projects involve collaborations with interstate institutions and are of great interest to international colleagues. To facilitate research in Australia, to be innovative, to conduct research that involves gene technology and which has potential social or economic benefits, Australia requires a nationally consistent Scheme void of confusion or limitations due to additional laws regulating GMOs in different states or territories or delays in the adoption of changes to legislation.

Recommendation 9

The University of Melbourne's IBC recommends continued efforts to have a Scheme that is nationally consistent be pursued. Collaborative research endeavours within Australia should not be further challenged by the need to navigate varying state or territory government restrictions or varied legislations when there is a Scheme that is intended to be nationally consistent.

4. Funding arrangements to ensure sustainable funding levels and mechanisms are aligned with the level and depth of activity to support the Scheme.

Stakeholders contribute significant resources to ensure regulatory obligations are met. There are administrative costs associated with supporting the business of an IBC and ensuring institutions or organisations are compliant with regulatory requirements. Stakeholders currently cover the costs associated with increasing activity, but what has been noted by the University of Melbourne's IBC is the increased activity of stakeholders has not been aligned with the resourcing provided to the Regulator of the Scheme and the team responsible for supporting the Regulator in administering the Scheme. This disparity between activity and resourcing is particularly noticeable with facility certifications.

Recommendation 10

The University of Melbourne's IBC recommends the current arrangements continue with respect to stakeholders. Any introduction of cost recovery initiatives would further increase the financial burden on stakeholders who already invest considerably in order to meet and manage regulatory requirements. Sourcing funds from stakeholders to

ensure sustainable funding levels to support the Scheme is not the solution. We would hope that the Department of Health, having established the OGTR to support the Regulator, would ensure that it is sufficiently resourced.