Submission to the Legislative and Governance Forum on Gene Technology (LGFGT) for the 2017 Review of the National Gene Technology Scheme

The Australian National University welcomes this opportunity to respond to the Terms of Reference for the 2017 Review of the Gene Technology Scheme.

Term of Reference 1: *Current developments and techniques, as well as extensions and advancements in gene technology to ensure the Scheme can accommodate continued technological development*

In an era of synthetic biology, it is possible to modify genes in situ without the introduction of nucleic acids e.g. using TALENs, or the retention of nucleic acids e.g. using CRISPR ribonucleoprotein (RNP) complexes i.e. some gene-editing technologies can be implemented transiently rather than through the introduction of transgenes retained by the GMO. Given that these new gene-editing technologies are capable of making small, precise changes indistinguishable from changes that occur in nature, without retention of the technology used to make them, it is clear that the current gene-technology based (i.e. process-based) definition of a GMO has become outdated and is in urgent need of revision. New gene-editing techniques and "gene drive" technologies need to be regulated in terms of the outcomes they produce rather than the technology used. The extent of their regulation should be commensurate with the risks those outcomes pose.

In simple applications, gene-editing technologies can be used to make small changes such as single nucleotide deletions or substitutions at precise locations. These small changes pose risks no greater than equivalent mutations that might arise in nature or be induced by chemical or radiation mutagenesis and are not and never have been subject to regulation. In more advanced applications, gene-editing technologies can be used to introduce a series of precise mutations in a gene or to replace one gene with another e.g. an orthologous gene (allele) from the same or a closely related species or an entirely different (foreign) gene. Clarity needs to be provided about what is considered foreign in this context. A non-orthologous (non-allelic) gene or a gene from a species in a different genus could be the basis for one definition. A non-homologous gene or a homologous gene with a different function could form the basis for another. Template-driven gene-editing technology used for the purposes of allelic replacement produces an outcome equivalent to that produced by homologous recombination, but without the associated linkage drag, and therefore pose risks no greater (and arguably less) than similar recombination events that arise in nature and are not and never have been subject to regulation. In still more advanced applications, gene-editing technologies can be used to establish "gene drives", which could be selectively advantageous, neutral or deleterious. The control of pest animals is a particularly attractive application of "gene drive" technology in Australia, but is not without risks e.g. if the pest animal also happens to be a domestic animal. Regulation of gene-editing technologies should be based on the outcomes they produce and the risks associated with those outcomes, not on the methods used to produce them. Outcomes equivalent to those produced by processes

that have been shown to cause no harm and have never been subject to regulation e.g. conventional breeding, or chemical or radiation mutagenesis, should not be subject to

regulation. Other outcomes should be judged on the risks they pose and be regulated accordingly. Some "gene drives" could pose an existential threat to a species and should therefore be regulated with a high degree of caution.

The current Gene Technology Scheme is often portrayed as process based rather than outcome based. Although this perception is not entirely true, there is a strong view that regulation should shift from a process-based approach to an outcome-based approach because the current approach serves as a barrier to innovation. The ANU supports this view, but also notes that there is already ample precedent among the existing regulations for an outcome-based approach to the regulation of gene technology i.e. exclusions from certain categories of dealings and inclusions in others based, for example, on the presence or absence of a replication-defective viral vector, the introduction of a gene able to confer a selective advantage, the introduction of a gene able to confer an oncogenic modification or the introduction of a gene encoding a protein with an immunomodulatory function. Perhaps this precedent could be extended to some of the products of gene-editing technologies. Clearly, legislative change is required, but this will likely be a time-consuming process. Perhaps another solution to this problem can be provided in the short term by changes to the regulations using the provisions in the Gene Technology Act as it currently stands. Whilst the Act defines a GMO as an organism that has been modified by Gene Technology, the Act defines Gene Technology as any technique for the modification of genes or other genetic material, *but does not include any other technique specified in the regulations for the purposes of the paragraph* defining Gene Technology. The regulations could therefore, for example, specify the use of CRISPR/Cas9, TALEN or other gene-editing technologies to introduce changes that already occur in nature with less precision, such as deletions or nucleotide substitutions, in circumstances where the inciting CRISPR RNPs or TALEN proteins are no longer present or the genes encoding these components have been segregated away, as not being Gene Technology for the purposes of defining a GMO. Whether either of these solutions would be legally viable is another matter. The only long-term solution is legislative change.

The benefits that could be gained through the application of gene-editing technology are immense and could lead to significant beneficial changes for Australia, such as the control of infectious diseases, the control of pests or improvements in agricultural productivity and the safety of agricultural products. It is clear that the status quo needs to change quickly to prevent the current Scheme becoming a barrier to such innovation.

Term of Reference 2: *Existing and potential mechanisms to facilitate an agile and effective Scheme which ensures continued protection of health and safety of people and the environment*

One of the bottlenecks for an agile and effective regulatory scheme arises because of limited resourcing of the OGTR. Funding arrangements are one obvious limiting factor, and these are addressed under Term of Reference 4. Another limiting factor is the regulatory burden that

needs to be managed by the OGTR. Mechanisms should be considered that would reduce regulatory burden to enable more efficient utilisation of the resources available to the OGTR. For example, approval of PC1 and PC2 NLRDs have already been devolved to IBCs, thereby reducing the regulatory burden imposed on the OGTR and distributing the workload among the organisations that benefit from these approvals. The same could be done for certification
of facilities. IBCs are already responsible for ensuring that PC1 and PC2 facilities meet the infrastructural requirements for certification and that people working in these facilities meet the behavioural requirements for certification. Why not introduce a system of notification of certifications similar to that for notification of NLRDs? Similarly, approval of some PC2 DNIRs e.g. those that do not involve a risk to personnel conducting the DNIR, could be devolved to IBCs. IBCs already play a major role in the preparation and vetting of DNIRs before they are submitted to the OGTR for approval. The OGTR itself would probably be well placed to identify other tasks that could be devolved to IBCs and would enable the OGTR to focus more effectively on matters of greater regulatory importance. New technologies have the potential to increase regulatory burden on both the OGTR and IBCs significantly if action is not taken to bring clarity to the Gene Technology Act and Regulations with respect to dealings based on gene-editing technologies.

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

Gene editing technologies such as those using CRISPR RNPs, should fall under the Gene Technology Act given that these techniques are used for the modification of genes. However, the current definition of a GMO in the legislation is outdated. Unlike legislation in Europe or the USA, Australia's legislation considers the process used to create the modification rather than the end product, in determining whether an organism is defined as a GMO. New legislation should consider the end product rather than the process. For instance, after editing with a CRISPR RNP, the RNP is rapidly degraded in the cell and does not integrate into the genome. An organism with a gene edited by a CRISPR RNP without the use of a repair template should not be considered a GMO. By contrast organisms edited using delivery and retention of foreign nucleic acids should continue to be classified as GMOs.

New legislation relating to gene-editing or "gene drive" technologies should align with the guidelines developed by the Australian Academy of Science and the National Academy of Science in the US for the implementation and regulation of this technology. It is essential that the Gene Technology Agreement be retained and extended to include new legislation dealing with gene-editing or "gene drive" technologies.

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

The ANU already provides considerable support to the Gene Technology Scheme through direct and indirect funding of regulatory activities. The ANU employs academic and support staff who serve on the ANU IBC and devote a significant portion of their time to undertake activities that underpin the regulatory scheme at the organisational level. The ANU employs an IBC secretary specifically to support the activities of the ANU IBC. The ANU also employs support staff that act as liaison officers to the ANU IBC and are important for regulatory implementation within local areas of the ANU. The ANU IBC has a number of roles. It is responsible for assisting individuals within the ANU, and spin out companies, to correctly identify proposed dealings with GMOs as Exempt, NLRDs or DNIRs (the ANU does not currently have any DIRs). It approves applications for Exempt dealings and NLRDs and assists in the preparation of DNIR applications for licencing by the Gene Technology Regulator. It monitors dealings and carries out inspections of certified containment facilities (plant, animal and invertebrate houses, and laboratories). It maintains a register of approved projects and containment facilities, and liaises with the OGTR in ensuring the ANU continues to meet the requirements of the Gene Technology Act and Regulations, and Guidelines issued by the OGTR. The ANU IBC considers matters of policy relevant to GM research at the ANU. It reports annually to the ANU Council, the OGTR and the National Institute of Health in the USA. The ANU provides IBC services to two spin out companies. Undertaking these activities represents a significant regulatory investment by the ANU. Given that the vast majority of the activities related to GM work at the ANU are self-regulated by the ANU at its own cost and are conducted for research purposes (i.e. not for profit), it would be unreasonable to impose any further financial burden on the ANU through a fee for OGTR service or other regulatory cost recovery mechanism. The same would apply to other research organisations. However, devolving some additional regulatory activities to IBCs, as outlined in the response to Term of Reference 3, could in effect reduce regulatory costs to the OGTR without significantly increasing regulatory burden on IBCs.

DIRs involve a significantly greater regulatory burden and a disproportionately high number of personnel and amount of time for the OGTR, and arguments could be presented for cost recovery from commercial organisations wishing to undertake DIRs. However, these organisations also bear a significant regulatory cost in establishing field trials/clinical trials and associated safeguards and monitoring regimes. It would be counterproductive to innovation to increase this financial burden further. In the case of GM crops, one possible solution might be to set aside part of the industry levy already imposed on sales for that crop to fund an extra position at the OGTR to offset the extra workload generated by DIRs related to that crop. Industry levies are used to fund crop-related Research and Development Corporations and, given that field trials of GM crops can be viewed as a legitimate Research and Development activity, it would not be unreasonable to use a small part of the income from that levy to offset the cost to the OGTR in assessing, licencing and monitoring the associated DIRs. For example, part of the levy allocated to the Cotton Research and Development Corporation could be used to employ an additional member of OGTR staff to offset the extra workload imposed on the OGTR by cotton DIRs. Similarly, part of the levy allocated to the Grains Research and Development Corporation could be used to

employ one or more additional members of OGTR staff to offset the extra workload imposed on the OGTR by canola DIRs and future wheat or legume DIRs. Perhaps a similar solution could be found to

offset the extra workload imposed by approvals for GM vaccines. The provision of additional OGTR staff (without increasing Department of Health or Commonwealth Government funding) would help expedite other OGTR processes and contribute to a more agile and flexible administration of the Scheme.