Australian Government
Department of Health
Office of the Gene Technology Regulator

Technical Review of the Gene Technology Regulations 2001

Discussion paper:
Options for regulating new technologies

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1. Introduction

The Gene Technology Regulator (the Regulator) is undertaking a technical review of the Gene Technology Regulations 2001 (the GT Regulations). As with previous technical reviews undertaken by the Regulator, the purpose of this review is to ensure the GT Regulations reflect current technology and scientific knowledge. The technical review will not alter the policy settings of the regulatory scheme.

Purpose and scope of this review

The primary aim of this review is to provide clarity about whether organisms developed using a range of new technologies are subject to regulation as genetically modified organisms (GMOs) and ensure that new technologies are regulated in a manner commensurate with the risks they pose.

The technical review aims to focus on new technologies and examine:

- cases where the capture or exclusion of these techniques is not clear, and whether those new technologies should be regulated, and
- scientific evidence relating to risks posed as a result of using new technologies.

Since the Regulator last conducted a technical review of the GT Regulations several technologies have developed rapidly, in particular site-directed nuclease techniques and oligonucleotide-directed mutagenesis. As the legislation does not address technologies and techniques specifically in all cases, it has become apparent that it is not clear whether organisms produced using these techniques meet the definition of "genetically modified organism" in the *Gene Technology Act 2000* (the GT Act).

The Legislative and Governance Forum on Gene Technology, a body consisting of ministers from each jurisdiction, oversees the national gene technology regulatory scheme. A statutory function of the Regulator is to advise the Legislative and Governance Forum on Gene Technology about "the effectiveness of the legislative framework for the regulation of GMOs, including in relation to possible amendments of relevant legislation"[1]. The Regulator has previously undertaken technical reviews of the GT Regulations resulting in amendments in 2006 and 2011. These reviews addressed the interface between science and regulation, which needs to be kept up to date with current understanding and technology in this rapidly developing field.

What is not being reviewed

The separation of policy and regulation is a standard governance arrangement in place for most regulatory agencies of the Australian Government. The Regulator's technical review cannot alter the policy settings of the scheme. The policy settings are best described in the GT Act itself and in the explanatory material published with the legislation. For example, a central policy setting of the scheme is the process trigger built into the GT Act (discussed further in section 2). No changes to the GT Regulations will be recommended if organisms or

[1] Subparagraph 27 (g)(ii) of the GT Act, available at the Federal Register of Legislation.

techniques already receive clear treatment in the legislation, and if the scientific understanding of the risks they pose has not changed.

Any changes to the policy settings would need to be addressed in a review of the GT Act. The intergovernmental Gene Technology Agreement[2] requires the Legislative and Governance Forum on Gene Technology to review the scheme every five years. The next review is anticipated to commence in 2016-17, which is an opportunity to examine the scheme's policy settings. Any policy changes would be considered by the Legislative and Governance Forum on Gene Technology following the review.

Regulation of the application of new technologies to humans is outside the scope of this review. In Australia, altering the genome of an embryo and then attempting to achieve pregnancy is prohibited under the *Prohibition of Human Cloning for Reproduction Act 2002*. Research involving human embryos is regulated under the *Research Involving Human Embryos Act 2002*, with both Acts administered through the National Health and Medical Research Council (NHMRC). In the context of this review it is important to note that regardless of how techniques are described in the GT Act and GT Regulations, NHMRC's oversight of research and reproductive applications in human embryos will continue.

The options

In accordance with the Australian Government Office of Best Practice Regulation's guidance on consultation, this discussion paper offers options to provide clarity in relation to new technologies. OGTR is seeking your submissions in support of your favoured option. The proposed options are:

Option 1: no amendment to the GT Regulations

Option 2: regulate certain new technologies

Option 3: regulate some new technologies based on the process used

Option 4: exclude certain new technologies from regulation on the basis of the outcomes they produce

These options are discussed in detail in section 3. Details on how you can make a submission are below.

Next steps in the review process

This consultation is open to the public through the Office of the Gene Technology Regulator (OGTR) website. The Regulator is also directly seeking submissions from states and territories, relevant Australian Government agencies, regulated stakeholders (accredited organisations and institutional biosafety committees) and those subscribed to OGTR News.

[2] The intergovernmental Gene Technology Agreement is available on the Legislative and Governance Forum on Gene Technology web page.

After the consultation period closes the Regulator will consider the submissions received and decide whether to recommend amendments to the GT Regulations, ensuring that any proposed changes are consistent with the policy settings of the scheme. In making this decision the Regulator will consider scientific understanding, potential risks, the regulatory burden implications for stakeholders and whether regulatory burden would be commensurate with risks. The Regulator will also consider the policy intent of the GT Act.

If implementing the Regulator's recommended option requires amendments to the GT Regulations, the Regulator will publicly consult on any amendments before they are finalised. The Regulator will also formally examine the change in regulatory burden that might result from any proposed changes to the GT Regulations, in accordance with the requirements of the Office of Best Practice Regulation.

Any amendments to the legislation forming the scheme, including the GT Regulations, must be formally agreed by a majority of states and territories through the Legislative and Governance Forum on Gene Technology. The Regulator would seek this agreement after proposed amendment regulations are finalised and, once agreed, begin the process to have the Governor General make the amendment regulations[3].

Making a submission

This discussion paper canvases four broad options for how clarity about regulation of specific new technologies could be achieved. The Regulator is seeking submissions on the merits of these options, in particular in response to the consultation questions below. As this review is technical in nature submissions should be based on scientific arguments or supported by published research. Several questions seek information on the regulatory burden implications for stakeholders, in keeping with the requirements of the Office of Best Practice Regulation.

While the Regulator will consider all submissions and proposals put forward, those that are not well supported or raise policy issues are unlikely to be addressed in this technical review.

Submissions can be made by email to ogtr@health.gov.au or by mail to the Regulations Review, Office of the Gene Technology Regulator (MDP 54), GPO Box 9848, Canberra ACT 2601. **Submissions must be made by 2 December 2016.**

Submissions will be published on the OGTR website after the consultation period closes, however, OGTR can treat information of a confidential nature as such. Please ensure that material supplied in confidence is clearly marked 'IN CONFIDENCE' and is in a separate attachment to non-confidential material.

[3] The Regulator would seek the Minister's agreement that amendments to the GT Regulations be proposed to the Executive Council. Amendment regulations are made by the Governor-General on the recommendation of the Executive Council, and are then tabled in both houses of Parliament for scrutiny and potential disallowance.

Consultation questions

1. Which option/s do you support, and why?
2. Are there other risks and benefits of each option that are not identified in this document?
3. Is there any scientific evidence that any of options 2-4 would result in a level of regulation not commensurate with risks posed by gene technology?
4. How might options 2-4 change the regulatory burden on you from the gene technology regulatory scheme?
5. How do you use item 1 of Schedule 1, and would it impact you if this item was changed?
6. Might contained laboratory research on GM gene drive organisms pose different risks to other contained research with GMOs, and how could these risks be managed? Supporting information and science-based arguments should be provided where possible.
7. What RNA interference techniques are you using, and are there RNA interference techniques that you believe have unclear regulatory status? Please provide details of the techniques and science-based arguments for whether these techniques pose risks to human health or the environment.
8. Do you have proposals for amendments to any other technical or scientific aspects of the GT Regulations? All proposals should be supported by a rationale and a science-based argument.

2. Background

The gene technology regulatory scheme

The object of the GT Act is:

> "to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs."[4]

Australia's gene technology regulatory scheme was set up in 2000 in response to a growing community view that GMOs posed potential risks which should be managed through regulation of particular activities with GMOs. While the object of the scheme is to protect human health and safety and the environment, the framework to achieve this also provides a clear regulatory pathway from research to market for GMOs[5].

The gene technology scheme was designed to fill the gaps between regulatory schemes for human food, human therapeutics, veterinary medicines, agricultural chemicals and industrial chemicals. The scheme focuses on live and viable GMOs and managing any risks they pose as a result of gene technology.

The national gene technology regulatory scheme is overseen by the Legislative and Governance Forum on Gene Technology, a body made up of ministers from each jurisdiction, in accordance with the intergovernmental Gene Technology Agreement[6].

Definitions of GMO and gene technology

If an organism meets the definition of a GMO then defined dealings with the organism are regulated under the GT Act[7]. The definition of gene technology is central in determining whether an organism is a GMO. Importantly, the definitions of 'GMO' and 'gene technology' allow the GT Regulations to specify exclusions to these definitions[8]. Clarification of the exclusions to regulation listed in the GT Regulations is the focus of the technical review and this discussion paper.

The definitions categorise organisms modified by the process of gene technology as GMOs, regardless of the outcomes of modification. Because of this focus the Australian regulatory scheme is commonly described as having a process trigger. The process trigger is a central policy setting for the Australian gene technology regulatory scheme.

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[4] Section 3 of the GT Act.
[5] Paragraph 4 (a) of the GT Act provides that the regulatory framework will provide "an efficient and effective system for the application of gene technologies".
[6] Further information about the Legislative and Governance Forum on Gene Technology is available on their web page.
[7] While it is dealings with GMOs that are regulated by the GT Act, for simplicity this paper will largely refer to organisms and techniques being regulated. These references should be taken to mean that dealings with organisms, or dealings with organisms modified by particular techniques, are regulated.
[8] See Appendix 1 for the full text of the definitions and exclusions. For additional information about general biotechnology terms please refer to Biotechnology Australia's comprehensive online glossary available on the Department of Industry, Innovation, Science, Research and Tertiary Education historical web archive.

Exclusions to the definitions of gene technology and GMO

The Explanatory Statement to the 2001 GT Regulations (the 2001 Explanatory Statement)[9] states that "The definition of 'genetically modified organism' in the GT Act was intentionally cast very broadly to ensure that the definition did not become outdated and ineffectual in response to rapidly changing technology." That is to say, as gene technology develops, the intended default setting of the scheme is to regulate new technology.

At the outset it was recognised that the definition was so broad it included things that were not intended to be regulated under the scheme[10]. To address this, a list of "organisms that are not GMOs" was included as Schedule 1 to the GT Regulations to remove these organisms from the scheme. These organisms will be described throughout this paper as being excluded from regulation.

The 2001 Explanatory Statement summarised the organisms excluded from regulation as those that:

- "have been exempt or excluded from the voluntary Genetic Manipulation Advisory Committee (GMAC) system of controls on GMOs for many years (some since the late 1970s); and/or
- exchange genetic material in nature, and as such do not pose any unique biosafety risks to the environment or human health and safety; and/or
- are commonly used in biological research; and/or
- have a very long history of usage in Australia and overseas."[11]

Schedule 1 was amended in 2006 and a list of "techniques that are not gene technology" was inserted as Schedule 1A to "provide for a clearer distinction between 'techniques' and 'organisms' that are not regulated under the Act"[12].

The wording of some exclusions in Schedule 1, particularly item 1 which remains unchanged from the original GT Regulations, now raises uncertainty about whether or not some new technologies are subject to regulation as GMOs. This is as a result of technological development beyond what was imagined in 2001 and changes in scientific terminology since that time.

Original scope and intent of the regulatory scheme

A broad generalisation of the original scope of the scheme is that moving and rearranging genes between species is gene technology and results in GMOs, whereas techniques which mimic natural processes and work through natural mechanisms do not result in GMOs. While in 2000 this was a clear distinction, technology has since developed so that a continuum of techniques now exists.

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[9] Explanatory Statement for the Gene Technology Regulations 2001 available at the Federal Register of Legislation.
[10] The Regulation Impact Statement to the GT Regulations outlines the policy decision to list some organisms as not being GMOs, see section 4(a), Organisms that are not genetically modified organisms. The Regulation Impact Statement is part of the Explanatory Statement.
[11] Stated in relation to Regulation 5, which is supported by Schedule 1.
[12] Explanatory Statement for the Gene Technology Amendment Regulations 2006 (No. 1) available at the Federal Register of Legislation.

The explanatory material from 2000 and 2001 provides insights into the intention of Parliament at the commencement of the scheme[13]. The ideas guiding the original list of organisms declared not to be GMOs are relevant to this discussion paper, even though they cannot be directly applied to the technologies available in 2016. The principle that organisms should be regulated commensurate with the risks they pose as a result of gene technology remains a central consideration for this review.

The 2001 Explanatory Statement elaborates on the idea of risks from gene technology in relation to the list of organisms that are not GMOs in Schedule 1:

- "organisms resulting from such technology [chemical and radiation mutagenesis] are not considered to be GMOs for the purposes of the legislation because the process mimics natural mutation processes and the organisms have not had genes inserted or deleted by virtue of gene technology." [14]
- the techniques "give rise to organisms that can occur in nature, and as such do not pose a particular biosafety risk to the environment or human health and safety". [15]

The 2001 Explanatory Statement also raises the practical need to be able to detect those organisms defined to be GMOs:

- "…it would be impossible for government to effectively regulate some of the organisms [listed in Schedule 1], as these changes to their genetic make-up can occur in nature (i.e. without human intervention)."[16]

Reliably detecting organisms that might be indistinguishable from naturally occurring mutants or the products of techniques that are not gene technology presents a great challenge for enforcing compliance with the scheme. The GMOs approved for commercial release in Australia to date can be easily detected with genetic tests for introduced gene sequences or tests for particular novel proteins. Should the legislation require the regulation of organisms that cannot be reliably distinguished from naturally occuring organisms, this could lead to difficulties in enforcing compliance.

Reviewing coverage of new technologies in the GT Regulations

A variety of biotechnology techniques have been described as new technologies or new techniques. In relation to plants, these are often referred to as new plant breeding techniques[17], however this paper will generally use the term new technologies to reflect that these processes can be applied to plants, animals and microbes. The new technologies relevant to this review are:

- oligo-directed mutagenesis (see Appendix 2)
- site-directed nuclease techniques (see Appendix 2)

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[13] The 2001 Explanatory Statement and the Explanatory Memorandum to the Gene Technology Bill 2000, available at the Federal Register of Legislation.
[14] 2001 Explanatory Statement in relation to Schedule 1 item 1.
[15] GT Regulations Regulation Impact Statement Section 4 part (a), discussion of listing a limited class of organisms as not being GMOs, published as part of the 2001 Explanatory Statement.
[16] GT Regulations Regulation Impact Statement Section 4 part (a), discussion of the impact of having no list of organisms that are not GMOs, published as part of the 2001 Explanatory Statement.
[17] Food Standards Australia New Zealand has published two reports from workshops on new plant breeding techniques; the European Commission's Joint Research Centre has also published on new plant breeding techniques, including a report by Maria Lusser *et al.* in 2011 and a journal article by Maria Lusser *et al.* in 2012.

- RNA interference
- grafting
- agro-infiltration
- breeding techniques producing null segregants (including reverse breeding, particular proprietary seed production technology and induction of early flowering).

The focus of this review is on those techniques often referred to as genome editing; specifically, oligo-directed mutagenesis and site-directed nuclease (SDN) techniques. Some consideration will also be given to RNA interference, gene drives, and to providing greater clarity on the current regulatory status of grafting, agro-infiltration and techniques producing null segregants (see section 4).

3. Regulatory options for new technologies

Option 1: No amendments to the GT Regulations

This option is being put forward for consultation to ask whether the current situation is better than any of the other options being proposed.

Pros of option 1

None identified.

Cons of option 1

- The *status quo* is considered to lack legal clarity and does not provide certainty for OGTR's stakeholders. Amendments are necessary to resolve uncertainty for stakeholders about whether or not new technologies are regulated.
- Stakeholders would continue to have differences of opinion on how to interpret the exclusions from regulation.
- This option could inhibit the commercialisation of products developed in Australia using these new technologies because stakeholders may consider the regulatory path to market is uncertain.
- The potential for dispute between the Regulator and stakeholders in terms of what should be regulated is increased as the use of new technologies becomes more prevalent.
- There might be trade implications for option 1 although these are somewhat unclear because few products developed with these technologies have come to market to date. In time the uncertainty about what is regulated could also impact importers and exporters.

Option 2: Regulate certain new technologies

Option 2 proposes to amend the GT Regulations so that dealings with all organisms developed using oligo-directed mutagenesis and all site-directed nuclease techniques are regulated under the GT Act.

Pros of option 2

This option would give legal clarity as to which technologies are subject to regulation, and so provide certainty for researchers and industry. Some of the general arguments that could be made to support option 2[18] are:

- These techniques were developed very recently and, because there is not enough scientific understanding of how they work or possible unintentional effects, full regulatory oversight is needed to protect human health and safety and the environment.
- These techniques might unintentionally interfere with the functioning of an organism's genome, for example through unforseen interactions between altered

[18] Reports arguing for regulation of the application of new technologies in plant breeding have been published by Friends of the Earth Australia, GenØk – Centre for Biosafety in Norway, Test Biotech in Germany, Econexus in the United Kingdom, and the Environment Agency Austria (commissioned by the Swiss Federal Ethics Committee on Non-Human Biotechnology).

genes and native genes, or through the altered genes having unexpected effects on biochemical pathways. Because such effects might pose risks, the techniques should be regulated as gene technology.

- The precision of oligo-directed mutagenesis and site-directed nucleases is not established. The processes involved can give rise to unintended changes to the genome. Because such effects might pose risks, the techniques should be regulated as gene technology.

Cons of option 2

Capturing oligo-directed mutagenesis and all site-directed nuclease techniques under regulation may not be commensurate with the risks posed by these technologies. For example, some applications of these techniques can give rise to changes identical to those that occur from processes that are excluded from regulation, namely natural mutations and chemical or radiation mutagenesis techniques. The Gene Technology Technical Advisory Committee has advised the Regulator that organisms altered by some site-directed nuclease techniques and oligo-directed mutagenesis are unlikely to pose risks that are different to natural mutations, conventional breeding or mutagenesis[19]. Chemical and radiation mutagenesis were excluded from regulation at the inception of the scheme on the basis of a long history of safe use.

Reliably detecting organisms that might be indistinguishable from naturally occurring mutants or the products of techniques that are not gene technology presents a great challenge for enforcing compliance with the scheme. Some new technologies can result in changes as small as altering, deleting or adding a single nucleotide, and these changes are not easily detected. With prior knowledge of the expected change it can be detected by gene sequencing. However, sequencing would not reveal whether such a change resulted from a new technology or a natural mutation.

This option is likely to inhibit the commercialisation of products developed using these new techniques, and potentially also innovation in early-stage research. The level and type of regulation and public perception may influence the decisions of researchers developing products or industry commercialising products.

The trade implications of option 2 are somewhat unclear at present because many countries have not yet determined whether, or which, new technologies will be regulated as gene technology according to the varying definitions in their legislation[20]. New Zealand has recently amended its legislation to clarify that techniques developed after 1998, including genome editing, are within the scope of regulation as GMOs[21], whereas regulatory decisions in the USA[22] have the result that some applications of site-directed nucleases and oligo-

[19] See Gene Technology Technical Advisory Committee Communique of 6 June 2016 meeting.
[20] For example, the European Commission is yet to publish a widely anticipated legal interpretation of the regulatory status of products generated by new techniques (the European Parliamentary Research Service recently published a briefing on the European situation).
[21] Amendments to New Zealand's Hazardous Substances and New Organisms (Organisms Not Genetically Modified) Regulations 1998 were approved in April 2016.
[22] The United States Department of Agriculture Animal and Plant Health Inspection Service publishes letters requesting clarification of regulatory status and their responses. In 2015 the White House directed US regulatory

directed mutagenesis are not subject to regulation as GMOs. Option 2 could lead to trade disruptions, for example where imports are not considered GMOs in their country of origin (and so are not separated from non-genetically modified) but are considered GMOs in Australia. Australia would remain involved in international fora seeking to harmonise regulation of new technologies[23].

Option 3: Regulate some new technologies based upon the process used

Option 3 proposes that the use or absence of nucleic acid template to guide DNA repair determines whether techniques are regulated under the GT Act. That is, techniques where nucleic acid template is applied to guide DNA repair (i.e. oligo-directed mutagenesis and the site-directed nuclease techniques known as SDN-2, SDN-3) would result in GMOs, whereas some specific techniques which do not involve the application of nucleic acid template (i.e. the site-directed nuclease technique known as SDN-1) would not result in GMOs[24].

Site-directed nucleases are designed enzymes that cut DNA at a chosen sequence. In SDN-1 the DNA break created by a site-directed nuclease is allowed to repair naturally, which can result in random repair errors. These errors can include single nucleotide changes, also known as point mutations, or deletion of nucleotides. SDN-2 and SDN-3 involve an introduced template guiding repair of DNA breaks made by site-directed nucleases. This incorporates desired sequence changes into the genome at the target sequence through a process known as homology-directed recombination or homology-directed repair. The difference between SDN-2 and SDN-3 lies in the extent of the nucleotide sequence difference between the native target sequence and the repair template. It is generally accepted that SDN-2 involves changes to one or a few nucleotides, whereas SDN-3 involves inserting a new gene or other genetic elements. Mutagenesis and natural mutations can give rise to organisms with sequence changes of one or a few nucleotides. Figure 1 provides an overview of the product and process features of site-directed nuclease techniques and oligo-directed mutagenesis.

Option 3 is compared to options 2 and 4 in Figure 2.

Pros for option 3

Option 3 would clarify which technologies are subject to regulation, and so provide certainty for researchers and industry. To best achieve legal clarity, amendments to the GT Regulations to implement this option would exclude specific techniques or organisms from regulation rather than providing descriptive exclusions which may become ambiguous as technology develops further.

Option 3 seeks to maintain the policy settings by reflecting the concepts guiding the scope of the regulatory scheme at its inception. The process trigger for regulation is a central policy

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agencies to review the Coordinated Framework for the Regulation of Biotechnology in light of technological changes. This review is ongoing, and it is not clear how the scope of regulation may change as a result.

[23] The statutory functions of the Regulator, as described in section 27 of the GT Act, include "(j) to monitor international practice in relation to the regulation of GMOs; (k) to maintain links with international organisations that deal with the regulation of gene technology and with agencies that regulate GMOs in countries outside Australia".

[24] Refer to appendix 2 for further information on SDN-1, SDN-2 and SDN-3.

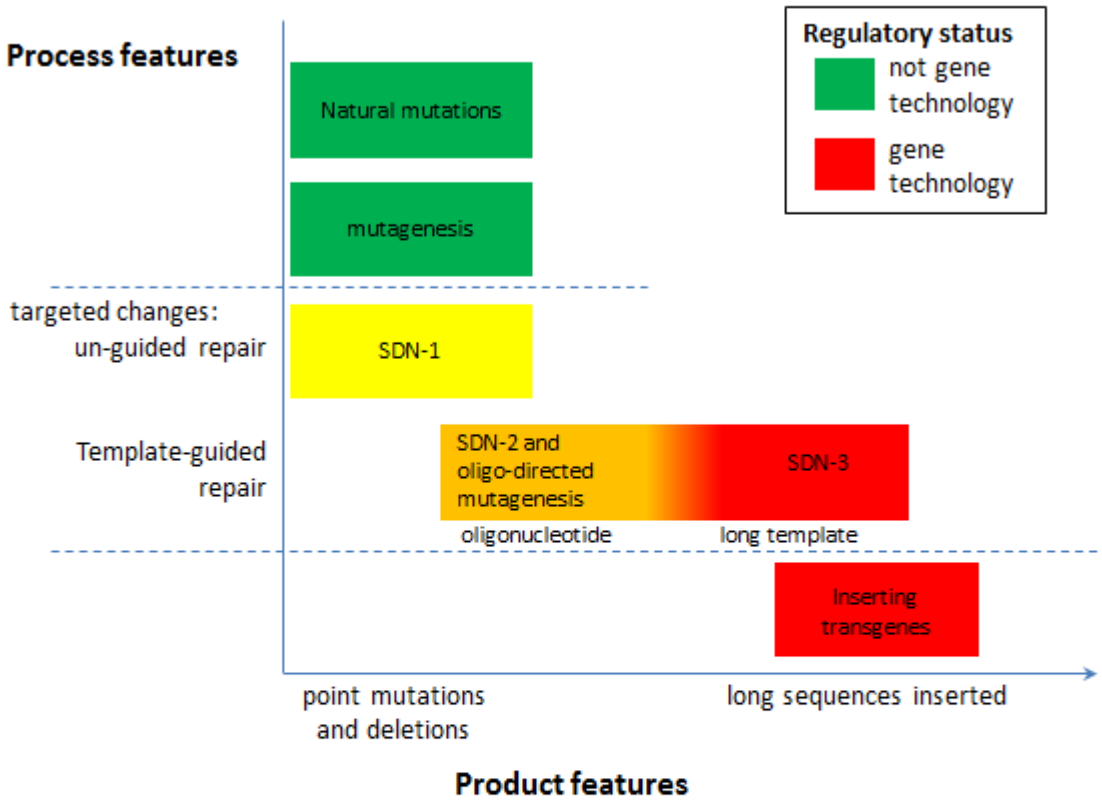

Figure 1: Comparison of process and product features of some new technologies.
Site-directed nuclease (SDN) techniques and oligo-directed mutagenesis are represented according to their process and product features, relative to unregulated techniques (natural mutations, chemical mutagenesis and radiation mutagenesis) and regulated techniques (inserting transgenes). SDN-1 involves the un-guided repair of a targeted double-strand break, producing sequence changes similar to natural mutations and mutagenesis. SDN-2 and SDN-3 involve template-guided repair of a targeted double-strand break. SDN-2 and oligo-directed mutagenesis use an oligonucleotide to guide small sequence changes that may be identical to the outcomes of SDN-1. SDN-3 uses a long template to insert new sequences, with similar outcomes to inserting transgenes by other gene technology techniques.

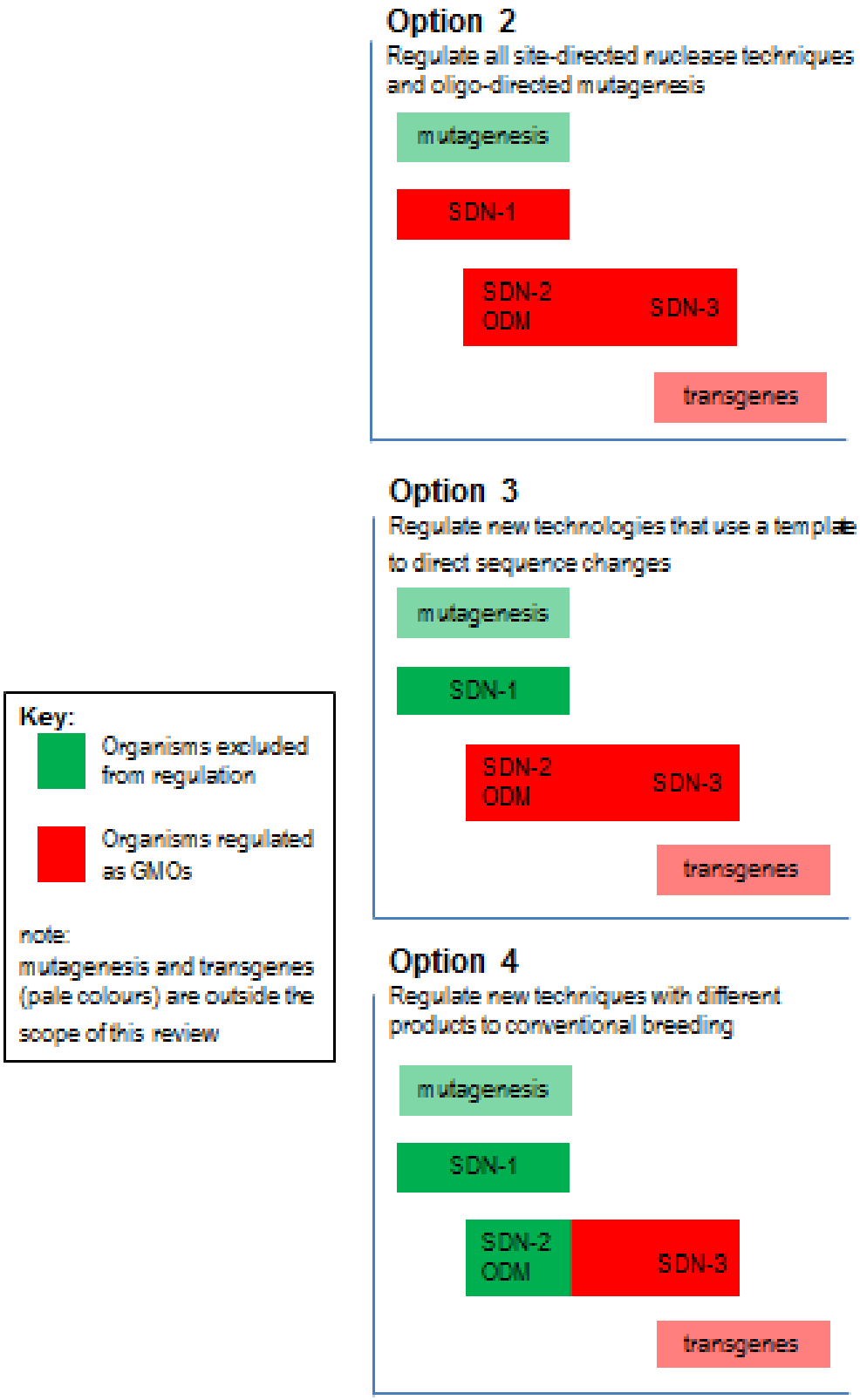

Figure 2: Comparison of technologies that would be regulated under options 2, 3 and 4. Site-directed nuclease (SDN) techniques and oligo-directed mutagenesis are represented according to their process and product features, as in Figure 1. How organisms produced using these techniques would be regulated in accordance with options 2, 3 and 4 is indicated. Mutagenesis and transgenes, which are outside the scope of this review, are shown in pale colours for comparison.

setting of the scheme, and this option retains the process by which organisms are modified as a central consideration in whether or not the resulting organisms would be regulated as GMOs. Using a nucleic acid template to direct genetic changes is a hallmark of the techniques generally considered to be gene technology since the inception of the regulatory scheme, and Option 3 focuses on this process feature. Importantly, changes achieved using a template to direct repair can be substantially different from naturally occurring mutations. For example, homology-directed repair using a template can be used to introduce gene sequences from other organisms.

Exclusion of SDN-1 from regulation would be consistent with the exclusion of chemical and radiation mutagenesis techniques from the scheme in 2001. In both mechanism and outcomes, SDN-1 bears strong similarity to radiation mutagenesis techniques. As with radiation mutagenesis, SDN-1 involves inducing DNA breakage and allowing the cell to repair the break without any externally supplied template to guide the repair. In both cases, the natural repair process can result in localised nucleotide insertions or rearrangements, or deletions from single nucleotides to sizeable parts of chromosomes. A significant difference to radiation and chemical mutagenesis techniques is that the site of DNA breakage is not random but designed in SDN-1, that is, the DNA breakage occurs at a selected nucleotide sequence through careful design of the site-directed nuclease enzyme. This results in the genetic change from SDN-1 being much more predictable than chemical or radiation mutagenesis techniques, noting that SDN-1 can lead to off-target genetic changes if the nuclease cleaves sequences that do not exactly match the target sequence. The Gene Technology Technical Advisory Committee has advised the Regulator that the risks posed by organisms altered by SDN-1 are unlikely to be different to naturally mutated organisms[25]

Cons of option 3

There is rapid progress towards commercial applications of new technologies in Australia, with some applications commercialised overseas. Because option 3 would result in the products of oligo-directed mutagenesis and SDN-2 being regulated as GMOs, this may impede commercialisation of some products, and potentially also innovation in early-stage research.

Option 3 may subject some genetically identical but differently derived organisms to different regulatory requirements because they were made by different processes. For example, a single nucleotide change from chemical mutagenesis would not result in a GMO whereas the same sequence change from oligo-directed mutagenesis would result in a GMO. Reliably detecting organisms that might be indistinguishable from naturally occurring mutants or the products of techniques that are not gene technology presents a great challenge for enforcing compliance with the scheme. However, this would be to a lesser extent for option 3 than for option 2, which would additionally require organisms produced using SDN-1 to be regulated.

There might be trade implications for option 3 although these are somewhat unclear at present. This is because few products developed with these technologies have come to market to date, and regulators overseas are also determining how new technologies will be regulated.

[25] See Gene Technology Technical Advisory Committee Communique of 6 June 2016 meeting.

Australia would remain involved in international fora seeking to harmonise regulation of new technologies.

Option 4: Exclude certain new technologies from regulation based on the outcomes they produce

Option 4 proposes to exclude organisms from regulation as GMOs if the genetic changes they carry are similar to or indistinguishable from the products of conventional breeding (e.g. chemical and radiation mutagenesis methods and natural mutations). This would have the effect that dealings with organisms produced by oligo-directed mutagenesis and SDN-1 and SDN-2 would be excluded from regulation. Option 4 is compared to options 2 and 3 in Figure 2.

The technical review must maintain the current policy settings, and so cannot alter the process-triggered definition of 'GMO' in the GT Act. However it is within the scope of the technical review to add to the list of "techniques that are not gene technology" in Schedule 1A of the GT Regulations or the list of "organisms that are not GMOs" in Schedule 1,if they were not given a clear treatment at the inception of the scheme or if scientific understanding of the risks they pose has since changed.

Pros of option 4

This option would result in clarity as to what technologies are subject to regulation, and so provide certainty for researchers and industry. To best achieve legal clarity, amendments to the GT Regulations to enact this option would exclude specific techniques or organisms from regulation rather than providing descriptive exclusions which may become ambiguous as technology develops further. In recent years it has been discussed at both the national and international level that the scope of GMO regulation could exclude organisms indistinguishable from conventionally bred organisms as they do not pose different risks to conventionally bred organisms. This argument has been made most broadly for plants[26], but these issues have also been explored in relation to animals[27].

The following arguments could be made to support excluding organisms from regulation if they carry small modifications resulting from new technologies:

- The organisms produced using oligo-directed mutagenesis, SDN-1 and SDN-2 are genetically indistinguishable from organisms which could have occurred naturally, and so do not pose different risks; they do not differ from organisms produced by mutagenesis techniques which are already excluded from regulation on the basis of a long history of safe use. The Gene Technology Technical Advisory Committee has advised the Regulator that SDN-1, SDN-2 and oligo-directed mutagenesis are unlikely to pose risks that are different to naturally mutated organisms[28].

[26] See Hartung and Schiemann (2014) on the European context, Comacho *et al*. (2014) on the US context and Podevin *et al* (2013). Documents supporting excluding new technologies from regulation if their outcomes are similar to conventional breeding have been published by CropLife Australia, the European New Breeding Techniques Platform, CropLife International (on site directed nucleases and oligo-directed mutagenesis)

[27] In December 2015 the National Academy of Sciences (USA) held a workshop on the scientific and ethical considerations around genome editing to modify animal genomes, summarised by Science magazine.

[28] See Gene Technology Technical Advisory Committee Communique of 6 June 2016 meeting.

- Organisms which are indistinguishable should be regulated in the same way, regardless of how they were derived, because they present the same risks.
- Because it may not be possible to detect these organisms without prior knowledge of the modification, it may not be possible to enforce compliance if these technologies were subject to regulation.
- These techniques are more specific and targeted than mutagenesis techniques and so are much less prone to off-target effects; chemical and radiation mutagenesis result in many untargeted mutations throughout the genome, whereas genome editing techniques result in discrete, targeted changes.

Cons of option 4

It is beyond the scope of a technical review of the GT Regulations to change the process regulatory trigger in the GT Act to instead focus on properties of the final organism. Implementing option 4 would therefore need amendments to the GT Regulations to exclude specific techniques or organisms, rather than provide broad exclusions based on properties of the final organism. However, any changes to the GT Regulations from this review must be within the policy settings. The extent to which the features of the resulting organism become the regulatory trigger raises the question of whether option 4 is appropriate within the policy settings. It may be more appropriate to consider regulation on the basis of the properties of the final organism in the context of the upcoming review of the scheme, to be conducted for the Legislative and Governance Forum on Gene Technology.

In order to draft amendments to the GT Regulations to exclude SDN-2 from regulation without also excluding SDN-3, a precise distinction between these techniques is required. It is a challenging task to provide convincing, risk-based arguments to support a clear legal distinction between these techniques, especially so when it must apply equally to all types of organisms.

Exclusion of a particular technique from regulation would result in all plants, animals or microbes modified by that technique being excluded. To date there has been a focus on plant applications of new technologies because these applications are closest to commercialisation. However, for pests or disease-causing organisms, for example pathogenic microorganisms, small sequence changes might give rise to significant risks. Blanket exclusions may not be commensurate with the level of risk posed by these techniques. Alternatively, drafting exclusions that do not apply to all organisms is potentially complex, and it is questionable whether such a departure from the current framing of exclusions could be achieved within current policy settings.

Successive rounds of modification using SDN-2 or oligo-directed mutagenesis could result in substantial changes which would not be subject to regulatory oversight. The Gene Technology Technical Advisory Committee has advised the Regulator that successive rounds of modifications using SDN-2 and oligo-directed mutagenesis may pose risks similar to inserting new genes or SDN-3[29].

[29] See Gene Technology Technical Advisory Committee Communique of 6 June 2016 meeting.

There may be trade implications from option 4 for Australian exports of commodities that are not GMOs in Australia but are GMOs according to the legislation of an importing country. To date, no countries have explicitly excluded all organisms developed using oligo-directed mutagenesis, SDN-1 and SDN-2 from their GMO regulatory schemes and many countries have not yet determined whether, or which, new technologies will be regulated as gene technology. Australia would remain involved in international fora seeking to harmonise regulation of new technologies.

4. Other considerations for this review

The Regulator's technical review is an opportunity for the Regulator to examine a range of issues with a view to improving the efficiency and effectiveness of the GT Regulations. Separately to the options for regulation of genome editing techniques detailed in section 3, other issues to be considered in the review include:

- improving clarity around the regulatory status of some other techniques
- examining whether item 1 of Schedule 1 should be changed
- whether containment requirements for gene drive research should be increased
- whether or not organisms that have undergone some RNA interference applications should be regulated as GMOs.

These issues are described further in this section.

Other amendments under consideration

The legislation can be clearly interpreted for a range of the techniques sometimes described as new technologies:

- plants comprised of genetically modified (GM) parts grafted to non-GM parts are GMOs
- null segregants (offspring of GMOs that have not inherited the genetic modification or a trait from genetic modification) are not GMOs
- organisms that are genetically modified in a transient manner (e.g. using agro-infiltration) are GMOs while the genetic modification or trait is present, and are no longer GMOs once both the trait and genetic modification are no longer present.

OGTR would seek to make the regulatory status of the techniques listed above clearer to stakeholders in any amendments that result from this review. Any amendments to achieve this would not alter the current regulatory status of these organisms.

Schedule 1 item 1

The experience of the OGTR has been that item 1 of Schedule 1 of the GT Regulations can be a source of much uncertainty. This is in large part because it was drafted in 2001 before many of the new technologies existed. Key terms in item 1, including "mutational event", "introduction", "foreign nucleic acid" and "non-homologous" are not defined. These terms can be interpreted in different ways, and the ambiguity has increased as technology and scientific terminology has changed in the last 15 years. In the absence of a clear meaning for this item stakeholders may have interpreted it in a variety of ways.

Depending on the option pursued following consultation, item 1 may need to be changed to improve clarity of the legislation. Stakeholders who use item 1 are requested to provide submissions addressing the consultation question on this topic.

Gene drives

Gene drives are genetic elements that are favoured for inheritance. This results in gene drives spreading through populations at a greater rate than genes with standard Mendelian inheritance. Genetically modified gene drives can only spread from sexually reproducing parents to their offspring, and not by transmission between organisms. Research into gene drives began over 50 years ago after the discovery of natural gene drives.

Internationally, there is rapidly growing research interest in using site-directed nucleases to create gene drives for a variety of purposes. Potential applications include:

- Reducing or eliminating populations of invasive animals, for example exotic rodents, to protect natural environments
- Reducing transmission of diseases from insects to humans, for example malaria from mosquitoes, by modifying the ability of insects to carry the disease or by reducing insect populations
- Controlling weeds of natural or agricultural environments.

Organisms carrying GM gene drives, which involve stably integrated transgenes, would be regulated as GMOs under the GT Act, both in contained research settings or if dealings involving intentional release into the environment were proposed. As with any GMO, the Regulator can only grant a licence for dealings involving environmental release if satisfied that any risks posed can be managed so as to protect human health and safety and the environment[30].

Recently, some researchers have questioned whether laboratory research on gene drives requires more stringent containment than other GMOs, because the potential consequences of escaped GM gene drive organisms are greater. For example, a recent report from the United States National Academies of Sciences, Medicine and Engineering on gene drives states:

> …[I]t is the goal of using a gene drive to spread a genetic trait through a population. Intentional spread challenges current governing systems for biotechnology predicated on managing risk by containing genetically modified organisms through physical, biological, or environmental methods. A mechanism designed to spread genetic information has consequences associated with accidental release that differ from other genetically modified organisms." [31]

GM gene drive organisms are a novel application of site-directed nucleases, and were unknown when the GT Regulations were last reviewed. Under the gene technology legislation, most GM gene drive research in contained facilities could be undertaken as a Notifiable Low Risk Dealing in standard certified facilities suitable for other GM animal or plant research. Notifiable Low Risk Dealings must be assessed by an Institutional Biosafety Committee before any work commences, and organisations must notify the Regulator annually about new Notifiable Low Risk Dealings.

This review will consider whether the current requirements for contained GM gene drive research are appropriate to manage any risks posed. The review would consider whether different containment requirements should apply and whether case-by-case assessment of such work by the Regulator (i.e. as a licensable Dealing Not involving Intentional Release) is more appropriate.

Stakeholders with information or opinions on gene drives are requested to provide submissions addressing the consultation question on this topic.

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[30] Subsection 56(1) of the GT Act.

[31] Page 139, *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*, published June 2016, available from the National Academies of Sciences, Medicine and Engineering website.

RNA interference

RNA interference, commonly referred to as RNAi or gene silencing, is a natural cellular mechanism that modulates expression of native genes and protects cells from viruses. RNA interference can be harnessed to reduce or eliminate expression of proteins from targeted native genes. RNA interference is triggered by the presence of short RNA sequences, and can take effect through degradation of a targeted messenger RNA, inhibition of translation of a targeted messenger RNA, or methylation of a targeted gene resulting in reduced expression (also known as RNA-dependent or RNA-directed DNA methylation).

Research into the mechanisms now known as RNA interference began in the 1980s, with widespread applications beginning in the early 2000s. Early RNA interference applications unambiguously involved GMOs as they involved insertion of transgenes that expressed RNA suitable to induce RNA interference. However, since that time a variety of ways to trigger RNA interference have been developed, including the direct application of short RNAs identical to sequences in the native target gene, without the presence of transgenes.

In light of scientific and technical developments, this review will consider the need for amendments to clarify whether or not organisms that have undergone some RNA interference applications are GMOs. However, there will be no change to the regulatory status of those RNA interference techniques where regulatory status is already clear, for example those involving transgenes. Stakeholders with information or opinions on RNA interference are requested to provide submissions addressing the consultation question on this topic.

5. Conclusion

The Regulator's technical review of the GT Regulations marks an important opportunity for the Regulator and stakeholders to consider how the GT Regulations can be brought up to date with current technology and scientific understanding. This discussion paper has outlined four options for how specific new technologies could be addressed in the GT Regulations to provide legal clarity and ensure regulatory burden is commensurate with risk.

OGTR invites submissions from stakeholders on the issues raised in this paper, particularly in response to the consultation questions below. Submitters are encouraged to provide information on the possible impacts these options might have on their activities to inform OGTR's assessment of the regulatory burden implications.

As this review is technical in nature submissions should be based on scientific arguments or supported by published research. While the Regulator will consider all submissions and proposals put forward, those that are not well supported or raise policy issues are unlikely to be addressed in this technical review.

Submissions can be made by email to ogtr@health.gov.au or by mail to the Regulations Review, Office of the Gene Technology Regulator (MDP 54), GPO Box 9848, Canberra ACT 2601. **Submissions must be made by 2 December 2016.**

Consultation questions

1. Which option/s do you support, and why?
2. Are there other risks and benefits of each option that are not identified in this document?
3. Is there any scientific evidence that any of options 2-4 would result in a level of regulation not commensurate with risks posed by gene technology?
4. How might options 2-4 change the regulatory burden on you from the gene technology regulatory scheme?
5. How do you use item 1 of Schedule 1, and would it impact you if this item was changed?
6. Might contained laboratory research on GM gene drive organisms pose different risks to other contained research with GMOs, and how could these risks be managed? Supporting information and science-based arguments should be provided where possible.
7. What RNA interference techniques are you using, and are there RNA interference techniques that you believe have unclear regulatory status? Please provide details of the techniques and science-based arguments for whether these techniques pose risks to human health or the environment.
8. Do you have proposals for amendments to any other technical or scientific aspects of the GT Regulations? All proposals should be supported by a rationale and a science-based argument.

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Appendix 1 – Definitions of GMO and gene technology

Gene Technology Act 2000

Section 10 Definitions

genetically modified organism means:

(a) an organism that has been modified by gene technology; or

(b) an organism that has inherited particular traits from an organism (the initial organism), being traits that occurred in the initial organism because of gene technology; or

(c) anything declared by the regulations to be a genetically modified organism, or that belongs to a class of things declared by the regulations to be genetically modified organisms;

but does not include:

(d) a human being, if the human being is covered by paragraph (a) only because the human being has undergone somatic cell gene therapy; or

(e) an organism declared by the regulations not to be a genetically modified organism, or that belongs to a class of organisms declared by the regulations not to be genetically modified organisms.

gene technology means any technique for the modification of genes or other genetic material, but does not include:

(a) sexual reproduction; or

(b) homologous recombination; or

(c) any other technique specified in the regulations for the purposes of this paragraph.

Gene Technology Regulations 2001

Section 4 Techniques not constituting gene technology

For paragraph (c) of the definition of gene technology in section 10 of the Act, gene technology does not include a technique mentioned in Schedule 1A.

Section 5 Organisms that are not genetically modified organisms

For paragraph (e) of the definition of genetically modified organism in section 10 of the Act, an organism mentioned in Schedule 1 is not a genetically modified organism.

Schedule 1A Techniques that are not gene technology (regulation 4)

Item	Description of technique
1	Somatic cell nuclear transfer, if the transfer does not involve genetically modified material.
2	Electromagnetic radiation-induced mutagenesis.
3	Particle radiation-induced mutagenesis.
4	Chemical-induced mutagenesis.
5	Fusion of animal cells, or human cells, if the fused cells are unable to form a viable whole animal or human.

Item	Description of technique
6	Protoplast fusion, including fusion of plant protoplasts.
7	Embryo rescue.
8	*In vitro* fertilisation.
9	Zygote implantation.
10	A natural process, if the process does not involve genetically modified material. Examples Examples of natural processes include conjugation, transduction, transformation and transposon mutagenesis.

Schedule 1 Organisms that are not genetically modified organisms (regulation 5)

Item	Description of organism
1	A mutant organism in which the mutational event did not involve the introduction of any foreign nucleic acid (that is, non-homologous DNA, usually from another species).
2	A whole animal, or a human being, modified by the introduction of naked recombinant nucleic acid (such as a DNA vaccine) into its somatic cells, if the introduced nucleic acid is incapable of giving rise to infectious agents.
3	Naked plasmid DNA that is incapable of giving rise to infectious agents when introduced into a host cell.
6	An organism that results from an exchange of DNA if: (a) the donor species is also the host species; and (b) the vector DNA does not contain any heterologous DNA.
7	An organism that results from an exchange of DNA between the donor species and the host species if: (a) such exchange can occur by naturally occurring processes; and (b) the donor species and the host species are micro-organisms that: (i) satisfy the criteria in AS/NZS 2243.3:2010 for classification as Risk Group 1; and (ii) are known to exchange nucleic acid by a natural physiological process; and (c) the vector used in the exchange does not contain heterologous DNA from any organism other than an organism that is involved in the exchange.

Appendix 2 – Oligo-directed mutagenesis and site-directed nuclease techniques

Oligo-directed mutagenesis

Oligo-directed mutagenesis (ODM) is a process for making small, precise changes to a genomic DNA sequence using a short piece of single stranded synthetic nucleic acid (DNA or RNA) called an oligonucleotide (oligo) as a template. The oligo is designed so that the majority of the sequence is identical to the target gene sequence. However, the middle of the oligo contains the desired sequence change. Oligos typically range from around 20 nucleotides to 100 nucleotides in length, and the longer the oligo, the more changes it can contain.

For organisms with large genomes, e.g. plants, the oligo is introduced into a cell and binds to the matching sequence in the target gene[32]. The cell's proof-reading enzymes then recognise that the two sequences are not a perfect match and changes one of them so that they match. If the oligo is changed to match the original strand then the cell's DNA is not changed. However, if the cell's DNA is changed to match the oligo then the cell's DNA will contain the new sequence.

For plants, ODM is carried out on cells in tissue culture, and whole plants are grown from these cells. For organisms with small genomes, such as viruses and bacteriophages, the reaction can take place in a tube with a mixture of oligos, nucleotides and enzymes rather than in a cell.

The small change(s) made via ODM can switch off a gene, change how much of the gene product is made, or change the function of a protein by changing the amino acid sequence produced from a gene.

Site-directed nuclease techniques

Site-directed nucleases (SDNs) such as zinc finger nucleases, TALENs (transcriptional activator-like effector nucleases), CRISPR/Cas9 (clustered regularly-interspaced short palindromic repeats/CRISPR-associated protein 9) and meganucleases are becoming widely used in biological research. These are specially designed proteins, or protein/nucleic acid combinations, that are capable of cutting DNA at a specific nucleotide sequence.

Once the DNA has been cut, there are two main pathways by which the cut can be repaired, both of which involve natural repair mechanisms:

1. Non-homologous end-joining, which joins the two ends back together. This can be an error prone process with the potential for nucleotides to be added, lost or changed at the cut site. If the cut is repaired correctly, then there is no sequence change and the sequence may be cut again by the SDN. However, if a mistake is made during non-homologous end-joining, a small random sequence change may alter how the gene

[32] DNA is most stable as a double stranded molecule and therefore single strands of DNA will naturally seek out and bind to the best match available.

functions. Additionally, repair of two nearby cuts can delete the sequence between them, creating substantial deletions. This technique is known as SDN-1.

2. Homology-directed repair can be used to deliver predetermined sequence changes. The cellular process for homology-directed repair is very similar to ODM, where an oligo acts as a template to direct modifications. Without human intervention, homology-directed repair can occur using sequences available naturally within the cell. The process can be directed by providing a piece of DNA with ends matching the sequence surrounding the DNA cut site to achieve a predetermined sequence change. This piece of DNA can be an oligo to guide a specific small modification of one or several nucleotides (SDN-2) or a large DNA cassette which includes new sequences such as additional genes, regulatory sequences or selectable markers (SDN-3).

One of the earliest uses of the SDN-1/2/3 terminology was by Lusser *et al* in their 2011 report for the European Commission's Joint Research Centre, New Plant Breeding Techniques; state-of-the-art and prospects for commercial development. Lusser *et al.* described the outcomes of modification using zinc finger nucleases as ZFN-1, ZFN-2 and ZFN-3.

SDN techniques can be used on animal embryos so that germline tissues carry the resulting sequence changes and offspring of that animal will uniformly carry the sequence change. SDN techniques can be used on plant cells in tissue culture, from which whole plants can be grown.

Successive rounds of modification using SDNs can be used to accumulate sequence changes to a genome. Alternatively, multiple sequences can be targeted at once by using a variety of SDNs (with or without different repair templates) at the same time.